Predictors of All-Cause Mortality After Successful Transcatheter Aortic Valve Implantation in Patients With Atrial Fibrillation

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Prevalent and incident atrial fibrillation are common in patients who undergo transcatheter aortic valve implantation and are associated with impaired postprocedural outcomes, including mortality. We determined predictors of long-term mortality in patients with atrial fibrillation after successful transcatheter aortic valve implantation. The EdoxabaN Versus standard of care and theIr effectS on clinical outcomes in pAtients havinG undergonE Transcatheter Aortic Valve Implantation−Atrial Fibrillation (ENVISAGE-TAVI AF) trial (NCT02943785) was a multicenter, prospective, randomized controlled trial in patients with prevalent or incident atrial fibrillation after successful transcatheter aortic valve implantation who received edoxaban or vitamin K antagonists. A Cox proportional hazard model was performed to identify predictors of all-cause mortality using a stepwise approach for multiple regression analysis. In addition, we assessed the performance of different risk scores and prediction models using ENVISAGE-TAVI AF data. Of 1,426 patients in ENVISAGE-TAVI AF, 178 (12.5%) died during the follow-up period (median 548 days). Our stepwise approach identified greater risk of mortality with older age, impaired renal function, nonparoxysmal atrial fibrillation, excessive alcohol use, New York Heart Association heart failure class III/IV, peripheral artery disease, and history of major bleeding or predisposition to bleeding. The present model (concordance statistic [c-statistic] 0.67) was a better discriminator than were other frequently used risk scores, such as the Society of Thoracic Surgeons score (c-statistic 0.56); Congestive heart failure, Hypertension, Age ≥75, Diabetes, Stroke, Vascular disease, Age 65 to 74 years, and Sex category (CHA_2DS_2-VASc) score (c-statistic 0.54); or Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, and Drugs/alcohol concomitantly (HAS-BLED) score (c-statistic 0.58). In ENVISAGE-TAVI AF, several modifiable and nonmodifiable clinical characteristics were significantly associated with greater long-term all-cause mortality. Improved risk stratification to estimate the probability of mortality after successful transcatheter aortic valve implantation in patients with atrial fibrillation may improve long-term patient prognosis. **(Am J Cardiol 2023;207:150−158)**

Keywords: risk scores, antithrombotic treatment, atrial fibrillation, aortic valve implantation

Over the last 2 decades, transcatheter aortic valve implantation (TAVI) has become a widely adopted alternative to surgical aortic valve replacement in patients with severe symptomatic aortic stenosis.[1,2] Advances in bioprosthetic valve technologies and transcatheter delivery techniques, coupled with increased operator experience, have

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facilitated the expansion of TAVI indications from patients at high risk to those at moderate and low risk. Despite this progress, short- and long-term complications after TAVI occur and may affect prognosis.[3] After TAVI, approximately 1/3 of patients present with atrial fibrillation (AF); the minority of these patients present with new-onset AF. Previous studies indicated that AF is a well-established risk factor for mortality after successful TAVI.[4−6] However, other predictors of mortality in patients with AF who undergo TAVI remain uncertain. A meta-analysis of 4 randomized trials investigated causes of mortality in patients with AF who received non−vitamin K antagonist (VKA) oral anticoagulants (NOACs) or warfarin for prevention of stroke and systemic embolism.[7] Older age, low creatinine clearance (CrCl), heart failure, diabetes, and male sex were significantly associated with a greater risk of mortality in patients with AF who were on anticoagulants.[7] Notably, this meta-analysis included a broad cohort of patients with AF and was not specific to patients with AF who undergo TAVI.[7] Risk stratification tools are instrumental in estimating the probability of post-TAVI complications in patients with AF and to inform decision making regarding the benefits and risks of undergoing TAVI. In the absence of a well-established risk score for TAVI, the Society of Thoracic Surgeons (STS) score is routinely used in the Heart Team evaluation of patients with symptomatic aortic stenosis. However, this score was derived from cohorts of patients who underwent surgical aortic valve replacement and may not accurately estimate the risk in candidates for TAVI. There have been several attempts to develop TAVI-specific risk scores; however, applicability was limited by their modest discriminative ability when applied to populations different from the cohorts from which the scores were originally derived.[8−12] The EdoxabaN Versus standard of care and theIr effectS on clinical outcomes in pAtients havinG undergonE Transcatheter Aortic Valve Implantation−Atrial Fibrillation (ENVISAGE-TAVI AF; NCT02943785) trial was a global, prospective, randomized, open-label, multicenter, adjudicator-masked trial that compared the efficacy and safety of edoxaban, a direct factor Xa inhibitor, with those of VKAs in patients with AF after successful TAVI.[13,14] The rate of all-cause mortality was 10.0 per 100 person-years for patients treated with edoxaban and 11.7 per 100 person-years for those treated with VKAs.[13] Further investigation is needed to understand the risk of death in this population and to elucidate strategies to minimize mortality rates. This subanalysis of ENVISAGE-TAVI AF aimed to identify the independent predictors of all-cause mortality after successful TAVI in patients with an indication for oral anticoagulation due to prevalent or incident AF.

Methods

The study design of the ENVISAGE-TAVI AF trial is published in detail.[14] The trial was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice, and all applicable local laws and regulations pertaining to clinical research. The trial protocol was approved by the appropriate ethics committees and corresponding health authorities for all study sites. Before enrollment, all patients provided written informed consent.

Eligible patients were adults with prevalent or incident AF after successful TAVI. Coexisting conditions with increased bleeding risk, significant unresolved periprocedural complications, and contraindications to edoxaban and VKAs per local label were key patient exclusion criteria. Patients were enrolled from April 2017 through January 2020.

Patients were randomly assigned to receive edoxaban 60 mg once daily or a VKA between 12 hours and 7 days after TAVI. The edoxaban dose was adjusted to 30 mg if ≥1 of the following criteria were met: CrCl (Cockcroft-Gault formula) 15 to ≤50 ml/min, body weight ≤60 kg, and use of P-glycoprotein inhibitors.[13] For patients treated with VKAs, the target international normalized ratio was 2.0 to 3.0 (adjusted to 1.6 to 2.6 for patients aged ≥70 years in Japan).

Prespecified oral antiplatelet therapy was permitted at the discretion of the treating physician. Concomitant use of the following therapies was disallowed during the treatment period unless there was no clinically suitable alternative therapy: anticoagulants other than the assigned study medication by any route except for parenteral agents used as a bridge when starting or resuming the study drug as per approved local label; dual antiplatelet therapy, which was prohibited while on study medication except for rare occasions, such as for 3 months after coronary stenting; and concomitant treatment with other antithrombotic agents, such as aspirin >100 mg/d. Patients having undergone TAVI with percutaneous coronary intervention either before or during the study period were permitted to obtain single antiplatelet therapy indefinitely (i.e., any $P2Y_{12}$ inhibitor or acetylsalicylic acid).

Clinically relevant modifiable and nonmodifiable variables were evaluated for association with all-cause mortality after TAVI. These included age, race, body mass index, body weight, CrCl, type of AF (paroxysmal or nonparoxysmal), previous major bleeding or predisposition to bleeding (e.g., anemia), New York Heart Association (NYHA) heart failure class III (moderate-to-severe limitations of physical activity with less than ordinary activity causing symptoms of heart failure) or class IV (symptoms of heart failure at rest),[15] excessive alcohol use (≥8 drinks/week), current or former cigarette use, abnormal liver function (cirrhosis or bilirubin >2 × upper limit of normal with aspartate transaminase/alanine aminotransferase/alkaline phosphatase >3 × upper limit of normal), abnormal renal function (dialysis, transplant, or creatinine >2.26 mg/100 ml or >200 μmol/l), and labile international normalized ratio (unstable/high international normalized ratios, time in therapeutic range <60%). In addition to these variables, treatment arm (edoxaban vs VKAs), fulfillment of dose adjustment criteria for edoxaban, concomitant use of oral antiplatelet therapy, laboratory data (such as hemoglobin level and platelet count), and ejection fraction were assessed.

All analyses were performed in the intent-to-treat population, which included all patients randomized regardless of whether they received a single dose of the study drug. The period for the intent-to-treat analysis was the time from

randomization to whichever occurred first: the patient's last visit (including the end-of-treatment visit at 36 months), an end-of-trial visit, or death. Demographic and baseline characteristics were presented using descriptive statistics and compared between patients with and without mortality during the study. Differences were tested using the unpaired Student's *t* test or Fisher's exact test depending on the distribution of the variable.

Proportional hazard regression analyses were performed to obtain the hazard ratio of each variable for predicting all-cause mortality after TAVI. A Cox proportional hazard model was performed to identify predictors of all-cause mortality using a stepwise approach for the multiple regression analysis. A significance level of $p < 0.05$ was required for inclusion of a variable in the model and for a variable to remain in the model. Results are presented as hazard ratios (HRs) with 2-sided 95% confidence intervals (CIs). Receiver operating characteristic (ROC) curves for the model with selected variables were analyzed. Furthermore, we assessed the performance of published risk scores and prediction models using the ENVISAGE-TAVI AF data. These included the STS score; Congestive heart failure, Hypertension, Age ≥75, Diabetes, Stroke, Vascular disease, Age 65 to 74 years, and Sex category (CHA_2DS_2-VASc) score; Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly, and Drugs/alcohol concomitantly (HAS-BLED) score; French Aortic National CoreValve and Edwards (FRANCE-2) score[9] Observational Study of Appropriateness Efficacy and Effectiveness of AVR-TAVR Procedures for the Treatment of Severe Symptomatic Aortic Stenosis (OBSERVANT) score;[16] and German Aortic Valve Score (GAVS) II score.[17]

The ENVISAGE mortality risk score was subsequently derived from the present stepwise model. The beta coefficients from the Cox proportional hazard model were multiplied by 10 and rounded to the nearest integer to derive weights for each model component. A patient's risk score was calculated on the basis of the model component weights and patient's observed predictor values. Patients were grouped into low-, moderate-, and high-risk categories. The number and percentage of patients who died and 1-year survival rates for each risk category were calculated. The 1-year mortality rate was calculated as 1 − (1-year survival rate). All statistical analyses were performed using SAS version 9.04 (SAS Institute, Cary, North Carolina).

Results

Of the 1,426 patients with AF after successful TAVI enrolled in ENVISAGE-TAVI AF, a total of 178 patients (12.5%) died during the trial follow-up period (median, 548 days). The baseline characteristics for patients who died and those who remained alive are listed in Table 1. The patients who died were older than those who remained alive (mean ± standard deviation [SD], 83.1 ± 5.6 vs 81.9 ± 5.4 years, $p = 0.0085$), with lower CrCl (mean ± SD, 52.9 ± 22.5 vs 59.0 ± 24.3 ml/min, $p = 0.0020$), had a greater prevalence of coronary artery disease (61.8% vs 52.6%, $p = 0.0243$) and chronic obstructive pulmonary disease (20.2% vs 13.6%, $p = 0.0226$), and had higher STS (mean ± SD, 5.6 ± 4.9 vs 4.8 ± 3.6, $p = 0.0065$) and HAS-BLED (mean ± SD, 1.8 ± 0.8 vs 1.6 ± 0.8, $p = 0.0022$) scores. In addition, patients who died were more likely than those who remained alive to have a history of current or former cigarette use (38.8% vs 31.3%, $p = 0.0491$). CHA_2DS_2-VASc score was similar between the 2 groups (mean ± SD, 4.6 ± 1.4 vs 4.5 ± 1.3, $p = 0.1985$). At the time of randomization, 53.4% of patients who died and 45.4% of patients who remained alive met ≥1 of the criteria for edoxaban dose adjustment to 30 mg.

Clinical variables associated with long-term all-cause mortality were identified by univariate analysis (Table 2). Age ($p = 0.0037$), CrCl ($p = 0.0005$), history of a non−central nervous system systemic thromboembolic event ($p = 0.0407$), history of peripheral artery disease ($p = 0.0471$), NYHA class III or IV ($p = 0.0227$), indication for dose adjustment ($p = 0.0102$), type of AF ($p = 0.0076$), excessive alcohol use ($p = 0.0103$), chronic obstructive pulmonary disease ($p = 0.0343$), ejection fraction ($p = 0.0156$), and hemoglobin level ($p = 0.0034$) were significantly associated with all-cause mortality.

Multiple regression analysis (Table 3) revealed that the independent predictive factors of long-term all-cause mortality were age (≥90 vs ≤80; HR 2.37, 95% CI 1.27 to 4.43, $p = 0.0069$), CrCl (<30 vs >45; HR 2.13, 95% CI 1.31 to 3.45, $p = 0.0023$), type of AF (HR 1.42, 95% CI 1.02 to 1.98, $p = 0.0376$), excessive alcohol use (HR 3.78, 95% CI 1.64 to 8.73, $p = 0.0089$), NYHA class III or IV (HR 1.36, 95% CI 1.01 to 1.85, $p = 0.0444$), history of peripheral artery disease (HR 1.63, 95% CI 1.04 to 2.54, $p = 0.0312$), and previous major bleeding or predisposition to bleeding (HR 1.63, 95% CI 1.02 to 2.61, $p = 0.0399$).

A prediction model for all-cause mortality was created with the clinical variables identified by multiple regression analysis as significant predictors of mortality. The 1-year ROC curve is shown in Figure 1. The concordance statistic (c-statistic) for our model was 0.67 (95% CI 0.62 to 0.71).

Prediction models were created based on STS score, CHA_2DS_2-VASc score, HAS-BLED score, FRANCE-2 score, OBSERVANT score, and GAVS II score (Figure 1). The c-statistic for the present model was highest, followed by the HAS-BLED score model (c-statistic: 0.58; 95% CI 0.54 to 0.62), STS score model (c-statistic: 0.56; 95% CI 0.52 to 0.61), and the CHA_2DS_2-VASc score model (c-statistic: 0.54; 95% CI 0.49 to 0.58). The integrated time-dependent area under the curve (AUC) for the present stepwise model (AUC 0.70) was also greater than that of models based on the STS score (AUC 0.58), CHA_2DS_2-VASc score (AUC 0.53), HAS-BLED score (AUC 0.59), FRANCE-2 score (AUC 0.60), OBSERVANT score (AUC 0.62), and GAVS II score (AUC 0.61). Two-year ROC curves for these models are presented in Supplementary Figure 1.

The ENVISAGE mortality risk score subsequently derived from the current model is presented in Figure 2; excessive alcohol use had the largest weight, followed by age ≥90 years and CrCl <30 ml/min. Patients were categorized into 3 groups based on their risk score: 0 to 10 (low risk), 11 to 15 (moderate risk), and ≥16 (high risk). One-

Table 1
Key baseline patient demographics and clinical characteristics

	Mortality		
	Yes (n = 178)	No (n = 1,248)	p value
Age, (years), mean ± SD	83.1 ± 5.6	81.9 ± 5.4	**0.009**
<65	2 (1.1)	8 (0.6)	
≥65 to <75	10 (5.6)	98 (7.9)	
≥75	166 (93.3)	1,142 (91.5)	
Sex, male	104 (58.4)	644 (51.6)	0.09
Weight (kg), mean ± SD	77.7 ± 17.5	74.9 ± 17.6	0.05
BMI (kg/m^2), mean ± SD	28.2 ± 5.5	27.6 ± 5.5	0.2
Race, White	158 (88.8)	1,029 (82.5)	**0.04**
CrCl (CG formula ml/min), mean ± SD	52.9 ± 22.5	59.0 ± 24.3	**0.002**
CrCl ≤50	85 (47.8)	485 (38.9)	**0.03**
AF, paroxysmal	56 (31.5)	529 (42.4)	**0.006**
Hypertension	167 (93.8)	1,137 (91.1)	0.3
Coronary artery disease	110 (61.8)	657 (52.6)	**0.02**
Diabetes mellitus	65 (36.5)	462 (37.0)	0.9
Chronic obstructive pulmonary disease	36 (20.2)	170 (13.6)	**0.02**
Peripheral artery disease	27 (15.2)	138 (11.1)	0.1
History of stroke/TIA	35 (19.7)	204 (16.3)	0.3
Abnormal renal function	12 (6.7)	17 (1.4)	**<0.0001**
Non-CNS systemic thromboembolic event	15 (8.4)	57 (4.6)	**0.04**
Prior PCI	51 (28.7)	317 (25.4)	0.4
Prior myocardial infarction	29 (16.3)	169 (13.5)	0.4
Prior major bleeding or predisposition to bleeding	22 (12.4)	103 (8.3)	0.09
CHA_2DS_2-VASc, mean ± SD	4.6 ± 1.4	4.5 ± 1.3	0.2
HAS-BLED, mean ± SD	1.8 ± 0.8	1.6 ± 0.8	**0.002**
STS score, mean ± SD	5.6 ± 4.9	4.8 ± 3.6	**0.007**
Indication for dose adjustment*	95 (53.4)	566 (45.4)	0.05
Edoxaban arm	85 (47.8)	628 (50.3)	0.6
Excessive alcohol use	7 (3.9)	21 (1.7)	0.07

Data are presented as n (%) unless otherwise indicated.

* Indications for adjustment of the edoxaban dose included CrCl ≤50 ml/min, body weight ≤60 kg (not used as an indication in US patients), and concomitant therapy with a P-glycoprotein inhibitor (not used as an indication in US patients).

AF = atrial fibrillation; BMI = body mass index; CG = Cockcroft-Gault; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Stroke-Vascular disease, Age 65 to 74 years, Sex category; CNS = central nervous system; CrCl = creatinine clearance; HAS-BLED = Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol concomitantly; INR = international normalized ratio; PCI = percutaneous coronary intervention; SD = standard deviation; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack.

year mortality rates by risk score category are shown in Figure 2. A numeric increase in 1-year mortality rates was observed moving from low- to moderate- and high-risk score categories.

Discussion

To the best of the authors' knowledge, this subanalysis in the ENVISAGE-TAVI AF intent-to-treat population is the first to report predictors of long-term mortality after successful TAVI in patients with an indication for oral anticoagulation owing to prevalent or incident AF. Overall, death occurred in 12.5% of patients throughout the study period. Independent predictors of long-term all-cause mortality were modifiable (i.e., excessive alcohol use) and nonmodifiable (i.e., age, CrCl, paroxysmal AF [PAF], NYHA class III or IV, peripheral artery disease, and previous major bleeding or predisposition to bleeding) risk factors. The study drug (edoxaban or VKA) did not emerge as an independent predictor of mortality. Lastly, evaluation of several other previously published risk scores yielded inferior results to the present ENVISAGE mortality risk score.

The prediction of post-TAVI mortality based on the presence of certain risk factors is essential to guide clinical decision making between the physician and patient. Although our all-cause mortality risk evaluation is not sufficiently validated in this cohort of patients with AF after TAVI, the 7 variables identified may be considered as surrogate markers for predicting increased risk of mortality in these patients. Contemporary risk models are derived from surgical aortic valve replacement cohorts and are routinely used for mortality risk assessment; however, they have suboptimal predictive ability in TAVI populations, especially in high-risk subsets of patients, such as those with AF.

In this study focusing on patients who underwent TAVI with an indication for oral anticoagulation due to prevalent or incident AF, several clinical predictors of long-term mortality were identified. These include age, decreased renal function, heart failure, peripheral artery disease, and bleeding. These results are consistent with previously published

Table 2
Univariate analysis of baseline variables

	HR	95% CI	p value
Age*	1.05	(1.02, 1.08)	**0.004**
Weight*	1.00	(1.00, 1.01)	0.3
CrCl*	0.99	(0.98, 0.99)	**0.0005**
Sex, female vs male	0.81	(0.60, 1.09)	0.2
Race, White vs non-White	1.39	(0.87, 2.21)	0.2
History of stroke/TIA	1.17	(0.81, 1.69)	0.4
Hypertension	1.39	(0.75, 2.57)	0.3
Diabetes mellitus	0.90	(0.66, 1.22)	0.5
APT prior to randomization	0.92	(0.68, 1.23)	0.6
Non-CNS systemic thromboembolic event	1.73	(1.02, 2.94)	**0.04**
Peripheral artery disease	1.52	(1.00, 2.30)	**0.05**
NYHA, class III or IV	1.41	(1.05, 1.88)	**0.02**
Intracranial hemorrhage	1.97	(0.75, 5.15)	0.2
Previous PPI use	0.98	(0.73, 1.31)	0.9
Labile INR	0.68	(0.38, 1.23)	0.2
Pre-TAVI use of VKAs	1.01	(0.75, 1.36)	0.9
Pre-TAVI use of NOACs†	0.84	(0.59, 1.20)	0.3
No pre-TAVI use of VKAs or NOACs†	1.15	(0.83, 1.59)	0.4
PCI performed within 30 days before TAVI	1.06	(0.52, 2.18)	0.9
Gastrointestinal disorder	1.07	(0.79, 1.46)	0.6
Prior major bleeding or predisposition to bleeding	1.55	(1.00, 2.42)	0.05
Coronary artery disease	1.30	(0.96, 1.76)	0.09
Indication for dose adjustment‡	1.47	(1.10, 1.98)	**0.01**
AF, paroxysmal vs nonparoxysmal	0.65	(0.47, 0.89)	**0.008**
Cigarette use	1.30	(0.96, 1.75)	0.09
Abnormal liver function	2.45	(0.30, 20.02)	0.4
Major bleed, anemia	1.55	(1.00, 2.42)	0.05
Excessive alcohol use	2.87	(1.28, 6.42)	**0.01**
Chronic obstructive pulmonary disease	1.49	(1.03, 2.16)	**0.03**
Ejection fraction*	0.98	(0.97, 1.00)	**0.02**
Hemoglobin, g/l*	0.99	(0.99, 1.00)	**0.003**
Platelet, 10^9/l*	1.00	(1.00, 1.00)	0.4

Analyses were Yes vs No unless otherwise indicated.

* Numerical variable, 1 unit increase.

† NOACs included rivaroxaban, apixaban, dabigatran, and edoxaban.

‡ Indications for adjustment of the edoxaban dose included CrCl ≤50 ml/min, body weight ≤60 kg (not used as an indication in US patients), and concomitant therapy with a P-glycoprotein inhibitor (not used as an indication in US patients).

AF = atrial fibrillation; APT = antiplatelet therapy; CI = confidence interval; CrCl = creatinine clearance; CNS = central nervous system; HR = hazard ratio; INR = international normalized ratio; NOAC = non−vitamin K antagonist oral anticoagulant; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PPI = proton-pump inhibitor; TAVI = transcatheter aortic valve implantation; TIA = transient ischemic attack; VKA = vitamin K antagonist.

multivariate analyses in patients with AF and analyses in patients who undergo TAVR.[6,7] Generally, aging is associated with increased risk of mortality irrespective of the presence of AF and the procedure.[18,19] Renal impairment, advanced heart failure, and atherosclerotic peripheral disease are well-established risk factors for adverse events after TAVI.[19,20] In contrast, the association between excessive alcohol intake and mortality after aortic valve intervention has not been well studied. Nonetheless, several studies show that alcohol consumption increases the risk of cardiovascular diseases and death.[21−23] Because excessive alcohol use was the only modifiable risk factor identified by our analysis, treatment of alcohol use disorder before TAVI may optimize postprocedural outcomes and improve long-term prognosis.

Another important predictor of mortality identified in our study and frequently reported in patients who undergo another type of catheter-based intervention, namely, percutaneous coronary intervention, is a history of bleeding or bleeding diathesis. Major bleeding complications are strongly associated with death after coronary interventions.[24,25] Similarly, studies show a direct impact of bleeding complications on mortality after TAVI.[26,27] Furthermore, history of bleeding is an important component of the HAS-BLED score, which is frequently used to predict bleeding risk in patients with AF.[28] Consequently, physicians may consider a high bleeding risk status as a corollary for mortality in patients with AF who undergo TAVI. Lastly, the type of AF had a significant impact on mortality after TAVI, with nonparoxysmal AF (NPAF) being a stronger predictor of mortality than was PAF. This observation agrees with a previous meta-analysis that showed NPAF was associated with a significantly greater risk of death than was PAF;[29] however, clinical guidelines explicitly recommend decisions regarding oral anticoagulation be made independently of AF type.[30]

ENVISAGE-TAVI AF included patients with prevalent or incident AF after successful TAVI who were randomly

Table 3
Predictors of mortality from multiple regression analysis

Variable	Regression coefficient	HR (95% CI)	p value
Age, years			
80−89 vs ≤80	0.354	1.42 (0.96, 2.12)	0.08
≥90 vs ≤80	0.863	2.37 (1.27, 4.43)	**0.007**
CrCl, ml/min			
30−45 vs >45	0.240	1.27 (0.88, 1.83)	0.2
<30 vs >45	0.755	2.13 (1.31, 3.45)	**0.002**
Peripheral artery disease	0.488	1.63 (1.05, 2.54)	**0.03**
NYHA, class III or IV	0.312	1.37 (1.01, 1.85)	**0.04**
Prior major bleeding or predisposition to bleeding	0.491	1.63 (1.02, 2.61)	**0.04**
AF, nonparoxysmal vs paroxysmal	0.351	1.42 (1.02, 1.98)	**0.04**
Excessive alcohol use	1.331	3.79 (1.64, 8.73)	**0.002**

Analyses were Yes vs No unless otherwise indicated.
AF = atrial fibrillation; CI = confidence interval; CrCl = creatinine clearance; HR = hazard ratio; NYHA = New York Heart Association.

assigned to receive edoxaban or VKA. Although several studies show the efficacy of NOACs over VKAs for the prevention of thromboembolic events and death in patients with AF,[31,32] similar all-cause mortality rates were indicated for patients treated with edoxaban and VKAs in the ENVISAGE-TAVI AF trial.[13] The present subanalysis found the study drug (edoxaban or VKAs) was not an independent predictor of all-cause mortality, despite the significantly higher rate of major bleeding events observed with edoxaban than with VKAs in the primary trial (9.7 per 100 person-years vs 7.0 per 100 person-years; HR 1.40, 95% CI 1.03 to 1.91).[13] A randomized trial of apixaban vs VKAs in patients with AF after TAVI also showed similar mortality rates between treatment groups.[33] Furthermore, a recent meta-analysis revealed no significant differences in all-cause mortality between patients receiving NOACs and those receiving VKAs.[34]

Finally, a risk score for 1-year mortality after successful TAVI was derived from the model in the present investigation. This ENVISAGE risk score is the first risk assessment tool in patients receiving long-term oral anticoagulation for AF after a successful TAVI. This model had greater

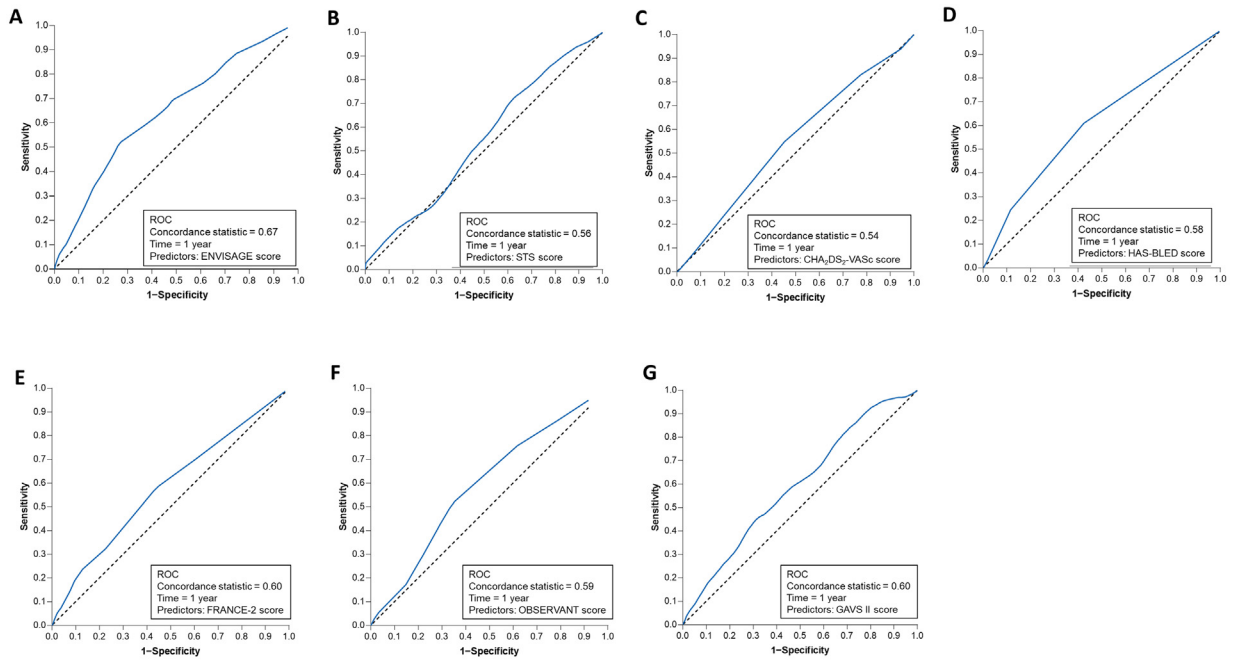

Figure 1. One-year ROC curves for models based on the present analysis (*A*), STS score (*B*), CHA_2DS_2-VASc score (*C*), HAS-BLED score (*D*), FRANCE-2 score (*E*), OBSERVANT score (*F*), and GAVS II score (*G*). Variables included in the current model are age (category), CrCl (category), type of AF, excessive alcohol use, NYHA class III or IV, peripheral artery disease, previous major bleeding or predisposition to bleeding; CHA_2DS_2-VASc includes Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Stroke-Vascular disease, Age 65 to 74 years, and Sex category; HAS-BLED includes Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, and Drug/alcohol concomitantly; FRANCE-2 includes age, body mass index, pulmonary hypertension severe, pulmonary edema, NYHA class IV, respiratory insufficiency, and critical state; OBSERVANT includes glomerular filtration rate, critical preoperative state, pulmonary hypertension, diabetes mellitus, NYHA class IV, and left ventricular ejection fraction; GAVS II includes sex, age, body mass index, NYHA class IV, pulmonary hypertension, left ventricular ejection fraction, coronary artery disease, diabetes mellitus, coronary artery bypass graft, and preoperative hemodialysis or creatinine >2.3 mg/100 ml. AF = atrial fibrillation; CrCl = creatinine clearance; INR = international normalized ratio; NYHA = New York Heart Association; ROC = receiver operating characteristic; TIA = transient ischemic attack; STS = Society of Thoracic Surgeons.

Risk score component	Weight
Age, years	
<80 years	0
80–89 years	4
≥90	9
CrCl, ml/min	
<30	8
30–45	2
>45	0
Type of AF	
Non-paroxysmal	4
Paroxysmal	0
NYHA, class III or IV	3
Excessive alcohol use	13
Peripheral artery disease history	5
Prior major bleeding or predisposition to bleeding	5

Analyses were Yes vs No unless otherwise indicated.

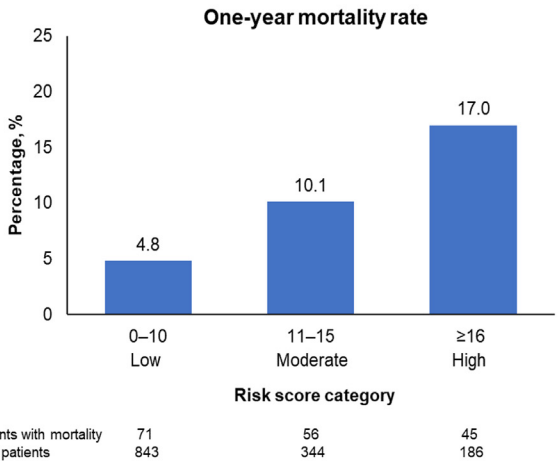

Figure 2. One-year mortality rate by risk score category and components of the derived risk score with corresponding weights. AF = atrial fibrillation; CrCl = creatinine clearance; NYHA = New York Heart Association; No. = number.

predictive ability of mortality than did other previously published risk scores and risk prediction models in patients with AF and those in patients who undergo TAVI. This may largely be explained by differences in baseline characteristics of the cohort used to develop the STS score and the ENVISAGE-TAVI AF cohort. Therefore, our findings further reiterate the need for TAVI-specific risk scores, especially for patients with an indication for oral anticoagulation due to AF.

There are several limitations of this study to be considered. First, patients enrolled in the ENVISAGE-TAVI AF were older and at intermediate surgical risk. Therefore, the present results may not apply to a younger population at lower surgical risk. In addition, the predictors are only applicable to patients with an indication for oral anticoagulation because of AF. Second, this analysis focused on clinical variables that are easily assessed by clinicians; however, there may be other procedural characteristics not assessed in this study that may affect the incidence of mortality. Furthermore, although the information of new-onset AF is important to consider for prognosis after TAVI,[35] data concerning the timing of PAF before or after TAVI are limited. Lastly, results from this study must be validated both in other TAVI cohorts including patients without an indication for oral anticoagulation due to AF and in other populations with AF.

In patients with AF after successful TAVI, several modifiable (excessive alcohol use) and nonmodifiable (age, CrCl, PAF, NYHA class III or IV, peripheral artery disease, and previous major bleeding or predisposition to bleeding) clinical risk factors were significantly associated with greater long-term all-cause mortality. A priori identification of these risk factors may be useful for risk stratification of patients with AF who undergo TAVI.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Declaration of Competing Interest

Dr. Yamamoto is a clinical proctor for Edwards Lifesciences and Medtronic. Dr. Hayashida is a clinical proctor for Edwards Lifesciences, Medtronic, and Abbott. Dr. Hengstenberg is a clinical proctor for Edwards Lifesciences and Boston Scientific, and reports payment for speaker bureaus, support for attending meetings, and advisory board participation from Daiichi Sankyo, Inc. Dr. Watanabe is a consultant for Edwards Japan, Medtronic Japan, and Abbott Japan. Dr. Van Mieghem reports grants or contracts from Abbott; Abiomed; Boston Scientific; Daiichi Sankyo, Inc.; Edwards Lifesciences; Medtronic; PulseCath BV; and Siemens. Dr. Jin is an employee of Daiichi Sankyo, Inc. Dr. Saito is a clinical proctor for Edwards Lifesciences and Medtronic. Dr. Valgimigli declares personal fees from AstraZeneca, Alvimedica/CID, Vifor, Bristol Myers Squibb SA, Boston Scientific, Medtronic, Novartis, and Chiesi; grants and personal fees from Terumo; and consultancy fees from Abbott Vascular; Daiichi Sankyo, Inc.; Bayer; CoreFLOW; IDORSIA PHARMACEUTICALS LTD; Universität Basel; Biotronik; Vesalio; and PhaseBio. Dr. Mehran reports research grants to institution; support for attending meetings from Bayer and Daiichi Sankyo, Inc.; and consulting fees from Daiichi Sankyo, Inc. Dr. Moreno reports payments for personal fees from Abbott Vascular; Amgen; Biosensors; Boston Scientific; Daiichi Sankyo, Inc.; Edwards Lifesciences; Ferrer; Medtronic; Philips; and Terumo. Mr. Kimura is an employee of Daiichi Sankyo Co., Ltd. Dr. Chen is an employee of Daiichi Sankyo, Inc. Dr. Unverdorben is an employee of Daiichi Sankyo, Inc. Dr. Dangas reports research grants to institution; support for attending meetings from Bayer and Daiichi Sankyo, Inc.; and consulting fees from Daiichi Sankyo, Inc. Dr. Nicolas has no competing interest to declare.

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Supplementary Materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2023.08.067.

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