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ORIGINAL RESEARCH

Comparing Major Gastrointestinal Bleeding in Patients Receiving Edoxaban Versus Warfarin After Transcatheter Aortic Valve Replacement: Results From the Randomized ENVISAGE-TAVI AF Trial

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BACKGROUND: Non–vitamin K oral anticoagulants are recommended over vitamin K antagonists in patients with nonvalvular atrial fibrillation (AF). However, the risk of gastrointestinal bleeding may be higher with non–vitamin K oral anticoagulants versus vitamin K antagonists. Patients after successful transcatheter aortic valve replacement (TAVR) who are elderly and frail have worse outcomes with major gastrointestinal bleeding (MGIB), including death. This study evaluated incidence, predictors, and impact of MGIB among patients with AF after successful TAVR.

METHODS: This on-treatment analysis of ENVISAGE-TAVI AF (Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation) included patients who received ≥1 dose of the study drug. Demographic, clinical, and procedural characteristics were compared between patients with versus without an MGIB event. Cox multivariable regression analysis identified predictors of MGIB.

RESULTS: Of 1377 patients in this analysis, 83 (6.0%) experienced MGIB, with 56 (67.5%) of these patients receiving edoxaban. Patients with versus without MGIB were more likely to have undergone percutaneous coronary intervention ≤30 days before TAVR (9.6% versus 4.2%; *P*=0.03), a higher ejection fraction (mean±SD, 58.0±10.4 versus 55.3±11.5; *P*=0.04), and carotid artery disease (13.3% versus 6.6%; *P*=0.04). Edoxaban without dose adjustment versus vitamin K antagonist use (*P*=0.003), smoking (*P*=0.01), low hemoglobin levels (*P*<0.0001), and percutaneous coronary intervention ≤30 days before TAVR (*P*=0.01) emerged as predictors of MGIB.

CONCLUSIONS: In this ENVISAGE-TAVI AF subanalysis, MGIB occurred in 6.0% of patients with prevalent or incident AF undergoing TAVR, and those receiving edoxaban versus vitamin K antagonists had a higher risk of MGIB. A priori identification of risk factors for MGIB may help optimize outcomes for patients with AF undergoing TAVR.

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Key Words: atrial fibrillation ■ edoxaban ■ major gastrointestinal bleeding ■ transcatheter aortic valve implantation

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CLINICAL PERSPECTIVE

What Is New?

- Predictors of major gastrointestinal bleeding (MGIB) in patients with prevalent or incident atrial fibrillation after transcatheter aortic valve replacement (TAVR) receiving edoxaban or vitamin K antagonists included edoxaban without dose adjustment versus vitamin K antagonist use, smoking, low hemoglobin levels, and recent percutaneous coronary intervention before TAVR.
- Most MGIB events in the ENVISAGE-TAVI AF (Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation) trial occurred during the first 6 months after randomization.
- Of patients who experienced an MGIB event, 34.9% died during follow-up. However, only 1 MGIB event was fatal, and the other deaths were not related to MGIB events.

What Are the Clinical Implications?

- Patients with atrial fibrillation after TAVR receiving edoxaban versus vitamin K antagonists had a higher risk of MGIB.
- Patients with a recent percutaneous coronary intervention before TAVR may be at higher risk of MGIB due to antiplatelet therapy on top of oral anticoagulant therapy, suggesting the need for physicians to consider patient-specific oral antithrombotic strategies.
- A priori identification of risk factors of MGIB in patients with atrial fibrillation may help to optimize outcomes after TAVR.

Nonstandard Abbreviations and Acronyms

DAPT	dual antiplatelet therapy
ENVISAGE-TAVI AF	Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation
MGIB	major gastrointestinal bleeding
NOAC	non–vitamin K oral anticoagulant
TAVR	transcatheter aortic valve replacement
VKA	vitamin K antagonist

Non–vitamin K oral anticoagulants (NOACs) offer several advantages over vitamin K antagonists (VKAs) in patients with atrial fibrillation (AF), including enhanced safety profiles, effectiveness, and practicality.[1] NOACs are associated with a reduced risk of hemorrhagic stroke, all-cause death, and intracranial hemorrhage when compared with VKAs.[2] As a result, NOACs are currently recommended over VKAs as first-line therapy in patients with nonvalvular AF.[3] A meta-analysis of 4 randomized trials comparing the efficacy and safety of NOACs versus warfarin revealed higher rates of major gastrointestinal bleeding (MGIB) with NOACs versus VKAs.[2] After successful transcatheter aortic valve replacement (TAVR), patients who are older and frail generally have worse outcomes with MGIB versus without MGIB, including death.[3–5]

The NOAC edoxaban is an oral, reversible, direct factor Xa inhibitor, recently shown in the ENVISAGE-TAVI AF (Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation) randomized trial to be noninferior to VKAs with regards to the composite primary efficacy end point of net adverse clinical events, including thromboembolic and bleeding complications, in patients with prevalent or incident AF who underwent successful TAVR.[4] However, edoxaban versus VKA use was associated with a higher rate of major bleeding, exclusively driven by a higher rate of MGIB.[4] This on-treatment analysis evaluated the incidence, predictors, and impact of MGIB among patients in the ENVISAGE-TAVI AF trial.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Patients

The detailed study design for the ENVISAGE-TAVI AF trial was previously reported.[4,6] Briefly, ENVISAGE-TAVI AF was a prospective, randomized, controlled, open-label, adjudicator-masked trial comparing edoxaban with VKAs in patients with prevalent or incident AF after successful TAVR. Eligible patients were aged ≥18 years with AF after successful TAVR for severe aortic stenosis. Successful TAVR was defined as the implantation of any approved transcatheter bioprosthetic aortic valve into the proper anatomic location with the intended valve performance and without unresolved periprocedural complications. Patients identified to be at high risk of bleeding due to existing conditions (active peptic ulcer with upper gastrointestinal bleeding within the 90 days before randomization, malignancy,

recent brain or spinal surgery, arteriovenous malformations) or dealing with serious unresolved periprocedural complications were excluded from this analysis. An indication for dual antiplatelet therapy (DAPT) for >3 months was also an exclusion criterion.

The trial was conducted in accordance with the International Council for Harmonization and the Declaration of Helsinki. The study was approved by the ethics committees and corresponding health authorities for all sites. All patients provided written informed consent before enrollment. An independent data and safety monitoring board reviewed all serious adverse events to ensure patients' safety.

Study Drug

Patients were randomized 1:1 to either edoxaban or VKAs 12 hours to 7 days after successful TAVR for severe aortic stenosis.[4] Patients randomized to edoxaban received 60 mg once daily or 30 mg once daily if any of the dose adjustment criteria were met (creatinine clearance of ≤50 mL/min, body weight ≤60 kg [not used as a dose reduction criterion in US patients], or concomitant therapy with certain P-glycoprotein inhibitors [not used as a dose reduction criterion in US patients]). The study sponsor supplied edoxaban to the sites, and VKAs were supplied according to local practice. The target international normalized ratio for patients randomized to the VKA arm was 2.0 to 3.0; this range was adjusted to 1.6 to 2.6 for patients aged ≥70 years in Japan. Prespecified use of an antiplatelet therapy in addition to edoxaban or VKAs was permitted and at the discretion of each treating physician.

End Points

This post hoc analysis focused on MGIB events, a subcategory of the ENVISAGE-TAVI AF primary safety end point, major bleeding, as defined by the International Society on Thrombosis and Hemostasis.[7] Patient follow-up occurred at 3 months after randomization and every 6 months thereafter (≥6 months to ≤36 months). The adjudication of all major adverse events was performed by an independent clinical events committee whose members were masked to the drug assignment.

Statistical Analysis

This on-treatment analysis included patients who received ≥1 dose of the study drug (safety cohort). The time period for the primary analysis was the time from randomization to an end-of-treatment visit at 36 months, an end-of-trial visit, the patient's last visit, or death, whichever occurred first. Baseline demographics and clinical characteristics were stratified by the occurrence of an MGIB event. Categorical variables were presented as frequencies and percentages, and continuous variables as means±SD. Statistical comparisons for baseline characteristics of patients with versus without an MGIB were made using analysis of variance for numerical parameters and Fisher's exact test for categorical parameters.

Cox multivariable regression analysis was performed to identify predictors of MGIB events. The multivariable model was built by the stepwise selection method. Candidate variables for the model included all baseline characteristics, with parameters highly correlated with another existing parameter removed (Table S1). For a variable to remain in or enter into the model, a significance level of $P<0.1$ was required. After the final model was obtained, only those variables with a significance level of $P<0.05$ were included. Multivariable model results are presented as hazard ratios (HRs) with 2-sided 95% CIs. Receiver operating characteristic curves for the model with selected variables were analyzed. All analyses were performed using SAS software version 9.2 or newer (SAS Institute, Cary, NC).

The impact of MGIB events in patients receiving edoxaban versus VKAs was qualitatively evaluated using estimations of cumulative event-free survival by means of Kaplan–Meier analyses. A post hoc 30-day landmark analysis was performed due to the prevalence of DAPT use during this period.

RESULTS

Study Population

Of 1377 patients included in this on-treatment analysis, 83 (6.0%) experienced an MGIB event; of these, 56 (67.5%) patients received edoxaban whereas 27 (32.5%) received a VKA. Of the 83 MGIB events, 57 (68.7%) were upper and 26 (31.3%) were lower MGIB events. Patients with versus without an MGIB event were similar in age, sex, and body mass indices (). They also had similar prevalences of hypertension, coronary artery disease, hypercholesterolemia, and diabetes. In contrast, patients with versus without MGIB were more likely to have undergone percutaneous coronary intervention (PCI) ≤30 days before TAVR (9.6% versus 4.2%; $P=0.03$), a higher ejection fraction (mean±SD, 58.0±10.4 versus 55.3±11.5; $P=0.04$), and carotid artery disease (13.3% versus 6.6%; $P=0.04$). Importantly, oral antiplatelets were used more frequently by patients who underwent PCI ≤30 days before TAVR (54% on single antiplatelet therapy and 37% on DAPT) than by those who did not (43% on single antiplatelet therapy and 7% on DAPT) at randomization. Of the patients with MGIB, 61 (73.5%) had antiplatelet therapy, and 10 (12.1%) had triple therapy (study drug+DAPT) during the study. Of the patients without MGIB, 793 (59.1%) received antiplatelet therapy, and 137 (10.2%) received triple therapy. The HAS-BLED (hypertension, abnormal renal/liver

Table. Baseline Patient Characteristics

Parameter	MGIB n=83	No MGIB n=1294	*P* value
Age at enrollment, y, mean±SD	81.7±5.7	82.1±5.4	0.5
Age ≥75 y, n (%)	72 (86.7)	1189 (91.9)	
Sex, female, n (%)	42 (50.6)	616 (47.6)	0.7
Race, White, n (%)	73 (88.0)	1073 (82.9)	0.3
Weight, kg, mean±SD	77.5±19.4	75.2±17.5	0.2
BMI, kg/m^2, mean±SD	28.1±5.6	27.6±5.5	0.5
CrCL, mL/min, mean±SD	57.3±23.4	58.3±24.2	0.7
Hypertension, n (%)	75 (90.4)	1183 (91.4)	0.7
Diabetes, n (%)	31 (37.3)	475 (36.7)	0.9
Ischemic stroke/TIA, n (%)	15 (18.1)	218 (16.8)	0.8
Coronary artery disease, n (%)	51 (61.4)	690 (53.3)	0.2
Prior CABG, n (%)	8 (9.6)	116 (9.0)	0.8
PCI performed within 30 d before TAVR, n (%)	8 (9.6)	54 (4.2)	0.03*
Prior major bleeding or predisposition to bleeding, n (%)	12 (14.5)	107 (8.3)	0.07
Paroxysmal AF, n (%)	35 (42.2)	534 (41.3)	0.9
Hypercholesterolemia, n (%)	64 (77.1)	900 (69.6)	0.2
Hospitalization for bleeding, n (%)	6 (7.2)	54 (4.2)	0.2
Valvular heart disease, n (%)	83 (100.0)	1294 (100.0)	
Non-CNS systemic thromboembolic event, n (%)	6 (7.2)	64 (4.9)	0.3
Peripheral artery disease, n (%)	11 (13.3)	146 (11.3)	0.6
Carotid artery disease, n (%)	11 (13.3)	85 (6.6)	0.04*
Ejection fraction, mean±SD	58.0±10.4	55.3±11.5	0.04*
APT before randomization, n (%)	42 (50.6)	580 (44.8)	0.3
HAS-BLED score, mean±SD	1.9±0.9	1.6±0.8	<0.0001*
CHA_2DS_2-VASc score, mean±SD	4.5±1.4	4.5±1.3	1.0
Gastrointestinal disorder, n (%)	33 (39.8)	465 (35.9)	0.5
Previous PPI use, n (%)	37 (44.6)	563 (43.5)	0.9
Pre-TAVR use of VKA, n (%)	40 (48.2)	593 (45.8)	0.7
Pre-TAVR use of NOAC, n (%)	17 (20.5)	367 (28.4)	0.1
Labile INR, n (%)	5 (6.0)	103 (8.0)	0.7
Dose adjustment factor, n (%)	36 (43.4)	601 (46.4)	0.7
Stent requiring antiplatelet therapy, n (%)	18 (21.7)	200 (15.5)	0.2
STS score, mean±SD	5.0±3.5	4.9±3.8	0.8
EuroScore I, mean±SD	12.7±9.3	12.9±9.9	0.8
EuroScore II, mean±SD	4.6±4.1	4.6±5.6	0.9
Intracranial hemorrhage, n (%)	2 (2.4)	15 (1.2)	0.3

AF indicates atrial fibrillation; APT, antiplatelet treatment; BMI, body mass index; CABG, coronary artery bypass graft; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65 to 74, and Sex Category (female); CNS, central nervous system; CrCL, creatinine clearance; INR, international normalized ratio; MGIB, major gastrointestinal bleeding; NOAC, non–vitamin K oral anticoagulant; PCI, percutaneous coronary intervention; PPI, proton pump inhibitor; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack; and VKA, vitamin K antagonist.

**P* values were significant (<0.05).

function, stroke history, bleeding history or predisposition, labile international normalized ratio, elderly, drug/alcohol usage) score was significantly higher in patients with versus without MGIB (mean±SD, 1.9±0.9 versus 1.6±0.8; *P*<0.0001). The use of proton pump inhibitors was similar between patients with (44.6%) versus without (43.5%) a MGIB event and between patients receiving edoxaban (68%) versus VKAs (64%).

Predictors of MGIB

Multivariable analysis identified baseline characteristics that were significant predictors of MGIB (Figure 1), including edoxaban without dose adjustment versus VKA use (HR, 2.63 [95% CI, 1.38–5.01]; *P*=0.003), smoking (yes versus no; HR, 1.78 [95% CI, 1.13–2.79]; *P*=0.01), low hemoglobin levels (per 10-unit decrease; HR, 1.13 [95% CI, 1.08–1.19]; *P*<0.001), and PCI ≤30 days before TAVR (yes versus no; HR, 2.51 [95% CI, 1.22–5.18]; *P*=0.01). A prediction model for MGIB was created including the identified clinical variables that were significant predictors of MGIB. Figures 2A and 2B illustrate the receiver operating characteristics for predicting MGIB at 1 (concordance statistic, 0.68 [95% CI, 0.62–0.74]) and 2 years (concordance statistic, 0.68 [95% CI, 0.62–0.74]).

Impact of MGIB

The MGIB events in the edoxaban arm occurred in 3 phases: (1) the most rapid rate during the first 30 days after randomization; (2) a steady rate up to ≈6 months after randomization; and (3) a near plateau thereafter (Figure 3A). A 30-day landmark analysis further illustrated the rapid increase in MGIB events in the edoxaban arm over this time period (Figure 3B). In contrast, MGIB events in the VKA arm occurred at a steady rate from randomization to 4 months. Among the 83 patients who experienced an MGIB event, death occurred in 29 (34.9%) patients. The mean±SD time from first MGIB to all-cause death was 132.9±160.8 days

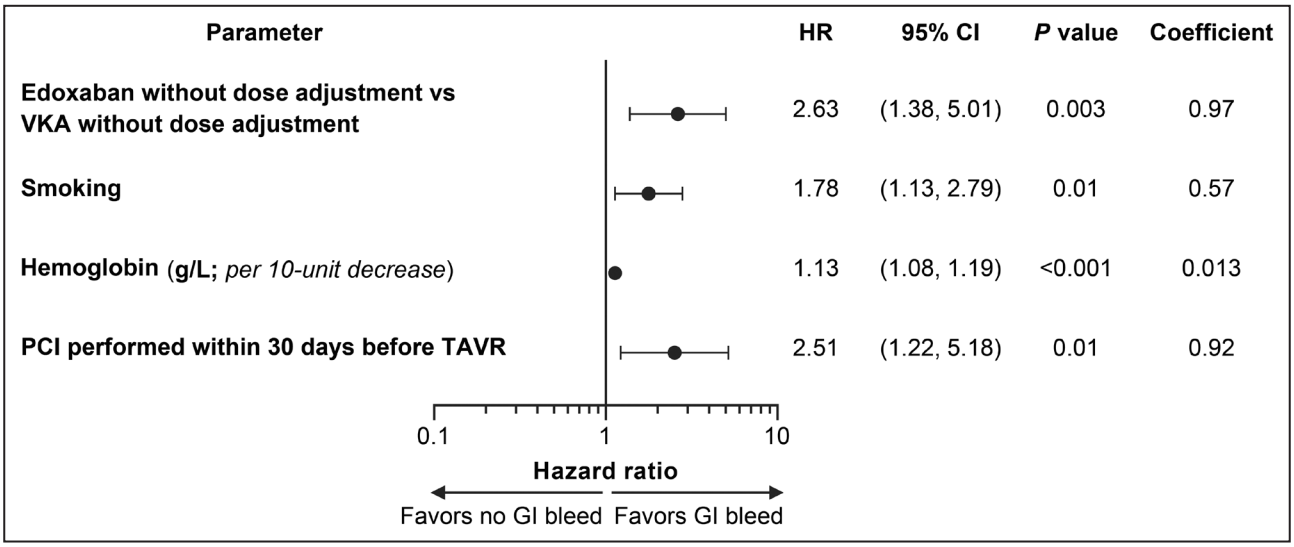

Figure 1. Multivariable predictors of major gastrointestinal bleeding.
Variables included in the model: age, weight, creatinine clearance, hemoglobin level, platelet level, sex, race, history of stroke/transient ischemic attack, hypertension, diabetes, non-CNS systemic thromboembolic event, peripheral artery disease, PCI within ≤30 days of TAVR, history of coronary artery bypass graft surgery, congestive heart failure (New York Heart Association class III or IV), history of intracranial hemorrhage, previous proton pump inhibitor use, labile international normalized ratio, pre-TAVR use of VKAs, pre-TAVR use of NOACs, no pre-TAVR use of VKAs or NOACs, GI disorder, prior major bleeding or predisposition to bleeding, coronary artery disease, atrial fibrillation type, abnormal renal function, smoking, anemia, excessive alcohol use, chronic obstructive pulmonary disease, and treatment arm with or without dose adjustment factor. CNS indicates central nervous system; GI, gastrointestinal; HR, hazard ratio; NOAC, non–vitamin K oral anticoagulant; PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement; and VKA, vitamin K antagonist.

after the MGIB event. One MGIB event was fatal; the other deaths were not related to MGIB events.

DISCUSSION

This on-treatment analysis of the ENVISAGE-TAVI AF trial investigated the incidence, predictors, and impact of gastrointestinal bleeding among patients with AF after successful TAVR. To the authors' knowledge, this is the first study designed specifically to identify predictors of MGIB in the very high-risk population of patients with AF on oral anticoagulants after successful TAVR. Consistent with the main ENVISAGE-TAVI AF trial, the current analysis found that MGIB occurred in 6.0% of patients, the majority (67.5%) of whom were in the edoxaban arm.[4] Additionally, the principal findings of this study were that predictors of MGIB included edoxaban use without dose adjustment, smoking, low hemoglobin level, and DAPT use in the setting of recent PCI ≤30 days before TAVR; MGIB events occurred mostly during the first 6 months after randomization.

Edoxaban use without dose adjustment (60 mg) versus VKA use was identified as a significant predictor of MGIB in patients with AF after successful TAVR. In accordance with prescribing information, edoxaban dose should be adjusted when patients are indicated.[8,9] Edoxaban dose adjustment decreases bleeding risk in patients with impaired kidney function or low body weight, and in those on potent P-glycoprotein inhibitors, as each of these factors are reported to elevate the blood concentration of edoxaban.[10] Bleeding risk may increase if patients meet >1 of the dose adjustment criteria. A retrospective analysis of patients receiving 30 mg/d of edoxaban found that the incidences of major bleeding were 7.3% and 20.0% when patients met 2 or 3 dose adjustment factors, respectively.[10] Additionally, edoxaban dose reduction in older patients (aged ≥75 years) with AF decreased major bleeding risk with edoxaban versus warfarin.[11]

A low baseline hemoglobin level was associated with increased risk of MGIB in the current study. A systematic review and meta-analysis of patients undergoing TAVR found baseline anemia was associated with an increased risk of complications after TAVR, such as postprocedural transfusion, acute kidney injury, and death.[12] With anemia being a well-established predictor of bleeding, low hemoglobin levels may be indicators of patients with increased risk of MGIB in the setting of underlying gastrointestinal pathology, particularly in frail patients undergoing TAVR.[12]

The concomitant use of DAPT in the setting of recent coronary stenting increases the risk of MGIB due to stacking of antithrombotic agents.[13] A nationwide cohort study of Danish patients with AF found that those on triple therapy (DAPT+oral anticoagulation) experienced higher rates of MGIB compared with patients

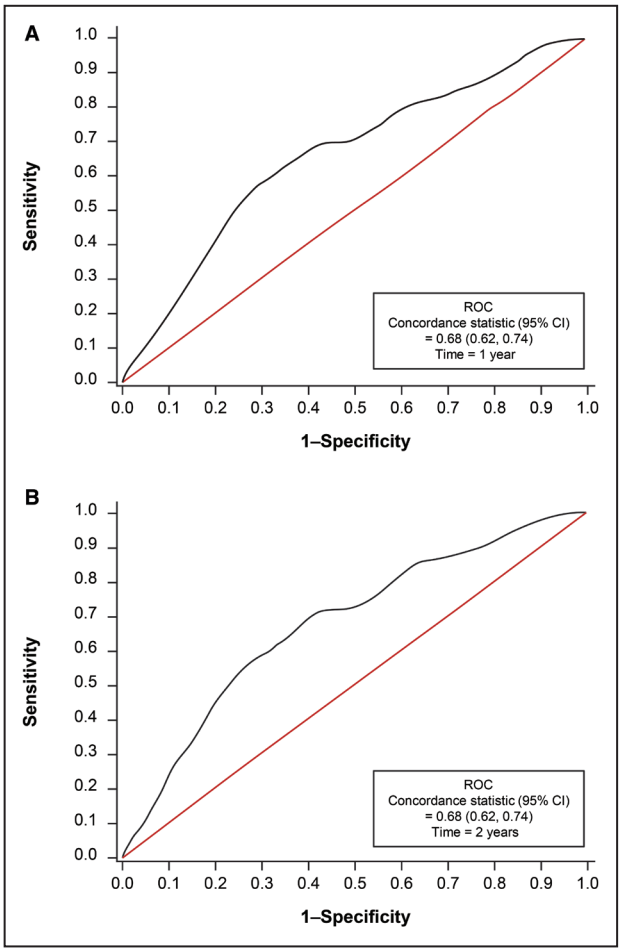

Figure 2. One- (A) and 2-year (B) receiver operating characteristic curves for the prediction of major gastrointestinal bleeding.
Predictors included in receiver operating characteristic curves included PCI performed within 30 days before TAVR, cigarette use (current or former), hemoglobin, and arm/dose adjustment. PCI indicates percutaneous coronary intervention; ROC, receiver operating characteristic; and TAVR, transcatheter aortic valve replacement.

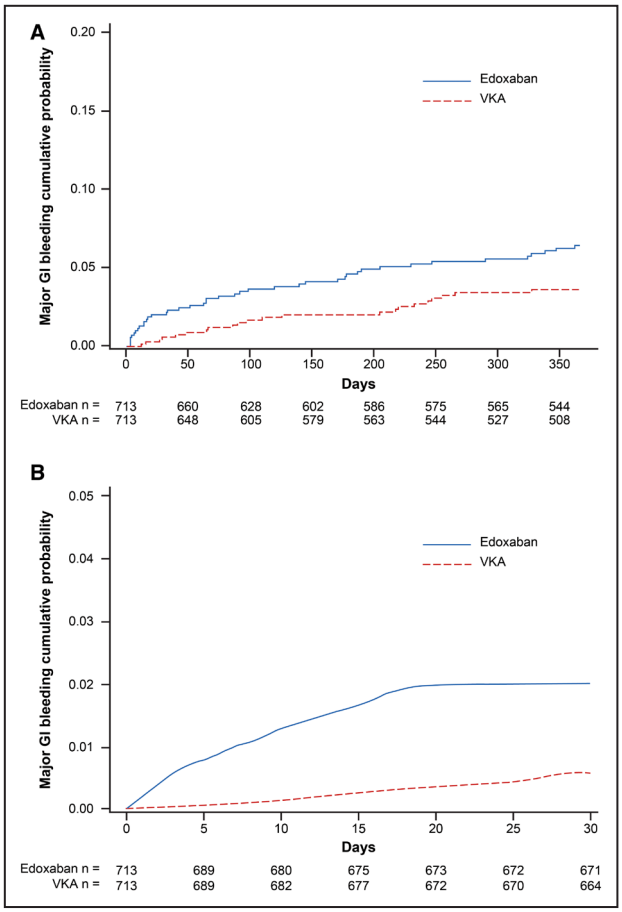

Figure 3. Incidence of major gastrointestinal bleeding over 350 days (A) and 30 days (B) after randomization.
GI indicates gastrointestinal; and VKA, vitamin K antagonist.

on dual therapy or monotherapy.[14] In the current study, 12.1% of patients with an MGIB event during the study received triple therapy. Most MGIB events occurred in the first 6 months after randomization, which may be due in part to concomitant antiplatelet therapy and oral anticoagulant therapy. Additionally, arteriovenous malformations and acquired von Willebrand disease may contribute to the incidence of MGIB in patients with severe aortic stenosis.[4,15] Potential strategies that can be used in clinical practice to mitigate stroke and bleeding risk in this vulnerable population include avoiding the use of concomitant oral antiplatelets whenever possible, strict adherence to the edoxaban dose reduction criteria per label instructions, and nonpharmacological approaches.[16]

Finally, smoking is a well-known risk factor for both stroke and cardiovascular death. Smoking status is also associated with a number of adverse events in patients with AF, including major bleeding and MGIB, irrespective of use of oral anticogulation.[13,17,18] In an analysis of the ENGAGE AF-TIMI 48 trial that investigated predictors, outcomes, and laboratory variables associated with first-time MGIB events, smoking was one of the strongest independent predictors of MGIB events.[19] This highlights the importance of identifying risk factors to optimize treatment.

Study Limitations

The limitations of the ENVISAGE-TAVI AF trial are published and should be taken into account when interpreting the results of the current subanalysis.[4] Key limitations include the open-label design, which may have introduced reporting bias, and follow-up visits affected by the SARS-CoV-2 pandemic since 2020 possibly resulting in unaddressed mild to moderate clinical events. Additionally, the predictors of MGIB identified in this analysis are applicable only to patients with an indication for oral anticoagulation because of AF after successful TAVR. Furthermore, the on-treatment

approach taken in this analysis may fail to capture some drug-related adverse events that occur after stopping the drug. Finally, it is unknown whether the resumption of oral anticoagulation after MGIB may lead to recurrent bleeding and will require further studies.

CONCLUSIONS

In this subanalysis of the ENVISAGE-TAVI AF trial, MGIB occurred in 6.0% of patients with prevalent or incident AF after successful TAVR, with only 1 MGIB event being fatal. There was a higher risk of MGIB events in patients with AF receiving edoxaban compared with those receiving VKAs after TAVR, and most MGIB events occurred during the first 6 months after randomization. Patients with a recent PCI are at a higher risk of MGIB due to use of antiplatelet therapy on top of oral anticoagulant therapy, so physicians may need to tailor oral anticoagulant therapy to each patient. Given its impact on morbidity and death, a priori identification of predictors of MGIB may help with the optimization of TAVR outcomes.

ARTICLE INFORMATION

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Supplemental Material

Table S1

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