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ORIGINAL RESEARCH

VALVULAR HEART DISEASE

Sex Differences Among Patients Receiving Edoxaban vs Vitamin K Antagonist for Atrial Fibrillation After TAVR

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ABSTRACT

BACKGROUND In the ENVISAGE-TAVI AF (Edoxaban vs Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation–Atrial Fibrillation) trial, edoxaban was noninferior to vitamin K antagonists (VKA) for a composite outcome of ischemic and bleeding complications but increased major bleeding in patients with atrial fibrillation after successful transcatheter aortic valve replacement. Women are at higher risk of bleeding and stroke than men after transcatheter aortic valve replacement. It is unclear whether the effect of edoxaban on these complications varies in relation to sex.

OBJECTIVES This study was to assess the effect of edoxaban vs VKA according to sex in the ENVISAGE-TAVI AF trial.

METHODS The primary outcomes were net adverse cardiovascular events (NACE) and major bleeding, assessed considering the effective time on study medication (safety analysis).

RESULTS Out of 1,377 patients, 658 (47.8%) were women. Risks for ischemic and major bleeding outcomes were similar between women and men. Edoxaban compared to VKA was associated with a similar risk of NACE in women (HR: 1.16; 95% CI: 0.81-1.65) and men (HR: 1.08; 95% CI: 0.76-1.53; *P* for interaction = 0.820) and a higher risk of major bleeding in both sexes (*P* for interaction = 0.170). The risk increase of major bleeding was attenuated in women (HR: 1.11; 95% CI: 0.69-1.79) as compared to men (HR: 1.75; 95% CI: 1.07-2.85). There were no treatment-related differences for ischemic complications in both sexes.

CONCLUSIONS Edoxaban compared to VKA was associated with a similar risk of NACE and higher risk of major bleeding in both sexes. The increase in bleeding complications with edoxaban was attenuated in women.
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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ISTH = International Society on Thrombosis and Haemostasis

MACCE = major adverse cardiac and cerebrovascular events

NACE = net adverse cardiovascular events

TAVR = transcatheter aortic valve replacement

VKA = vitamin K antagonist

Aortic stenosis is the most common valvular heart disease in high-income countries and has a relevant impact on morbidity and mortality.[1] Transcatheter aortic valve replacement (TAVR) emerged as an effective treatment option for elderly patients for which a valve intervention is indicated.[2] Approximately 50% of patients undergoing TAVR are women and up to 40% have atrial fibrillation (AF).[3-5] Among women undergoing TAVR, AF has been associated with an increased risk of death and stroke at 1 year.[6] In patients with AF not undergoing TAVR, edoxaban, an oral, reversible, direct factor Xa inhibitor, was noninferior to vitamin K antagonist (VKA), in the prevention of thromboembolic events, including stroke, and yielded lower rates of bleeding complications and cardiovascular fatalities.[7] In patients with AF who underwent successful TAVI, the ENVISAGE-TAVI AF (Edoxaban vs Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation-Atrial Fibrillation) showed that edoxaban was noninferior to VKA with respect to a composite of ischemic and bleeding adverse clinical events, but was associated with a higher risk of major bleeding.[8]

Women have been shown to be at higher risk of bleeding, vascular complications and stroke than men after TAVR irrespective of the concomitant anticoagulant treatment.[3,5,9] Among patients with AF not undergoing TAVR, women derived a greater benefit than men from edoxaban as compared to VKA with respect to bleeding risk reduction.[10] Whether the effect of edoxaban on outcomes may vary in relation to sex in patients with AF undergoing TAVR is unclear.

The aim of this secondary analysis of ENVISAGE-TAVI AF trial was to explore the impact of sex on safety and efficacy of edoxaban vs VKA in patients with AF after successful TAVR.

METHODS

TRIAL DESIGN AND OVERSIGHT. ENVISAGE-TAVI AF was a multicenter, prospective, randomized, open-label, adjudicator-masked trial conducted at 173 centers in 14 countries in Europe, North America, and Asia from April 2017 through January 2020.

The trial design and main results have been reported previously.[8,11] The trial was designed by 8 academic authors and 1 author employed by the sponsor, Daiichi Sankyo. The sponsor contributed also to the trial conduct and data analyses. The current manuscript was written by academic authors and approved by the sponsor before submission.

Ethics committees and corresponding health authorities for all sites approved the protocol. All the patients provided written informed consent before enrollment. An independent data and safety monitoring board reviewed all serious adverse events to ensure participants safety.

STUDY POPULATION. To be eligible for enrollment, patients of 18 years or older had to have either prevalent or incident AF lasting more than 30 seconds and a successful TAVR for severe aortic stenosis. Successful TAVR was defined as correct positioning of any approved transcatheter bioprosthetic aortic valve at the proper anatomical location with the intended valve performance and without unresolved periprocedural complications. Key exclusion criteria were percutaneous coronary intervention within 7 days prior to randomization, indication for dual antiplatelet therapy for >3 months or conditions associated with a high risk of bleeding, such as peptic ulcer or upper gastrointestinal bleeding within 90 days of randomization, prior intracranial hemorrhage, known or suspected esophageal varices. The complete list of inclusion and exclusion criteria is reported in Supplemental Table 1.

TRIAL TREATMENT AND FOLLOW-UP. Between 12 hours and 7 days after TAVR, patients were randomly assigned in a 1:1 ratio to receive edoxaban 60 mg once daily or a VKA (warfarin, phenprocoumon, acenocoumarol, or fluindione according to country availability). Patients with creatinine clearance ≤50 mL/min (Cockcroft-Gault formula), a body weight ≤60 kg or using certain P-glycoprotein inhibitors (ketoconazole, itraconazole, erythromycin, or clarithromycin) received an adjusted dose of 30 mg edoxaban once daily. For patients assigned to VKA regimen, the target international normalized ratio was

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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2.0 to 3.0 (adjusted to 1.6-2.6 for patients ≥70 years old in Japan). Concomitant antiplatelet therapy in either trial group was allowed at discretion of the treating physician. Dual antiplatelet therapy could be associated to the study regimen for up to 3 months after TAVR (ie, in patients with coronary stent deployment); single antiplatelet therapy indefinitely. Follow-up occurred at 3 months after randomization and thereafter every 6 months for a total duration of at least 6 months and up to 36 months.

OUTCOMES. The primary efficacy outcome was net adverse clinical event (NACE), a composite of death from any cause, myocardial infarction, ischemic stroke, systemic thromboembolism, valve thrombosis, or major bleeding according to International Society on Thrombosis and Haemostasis (ISTH) definition.[12] The primary safety outcome was ISTH major bleeding defined as clinically overt bleeding associated with a hemoglobin drop (>2 g/dL), blood transfusion of 2 or more units, symptomatic bleeding at a critical site (ie, intracranial, intraspinal, intraocular, retroperitoneal, pericardial, intra-articular, or intramuscular with compartment syndrome), or death.

Secondary outcomes were: NACE using Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries, Thrombolysis in Myocardial Infarction, or Bleeding Academic Research Consortium major or severe bleeding definitions; components of the composite primary efficacy outcome; major adverse cardiac and cerebrovascular events (MACCE, a composite of cardiovascular death, myocardial infarction, any stroke, or repeat coronary revascularization), and their single components; ISTH clinically relevant non-major bleeding; intracranial hemorrhage. An independent clinical events committee, whose members were masked with respect to the trial-group assignments, adjudicated all prespecified major adverse events. Further details on outcome definitions used for adjudication are provided in Supplemental Table 2.

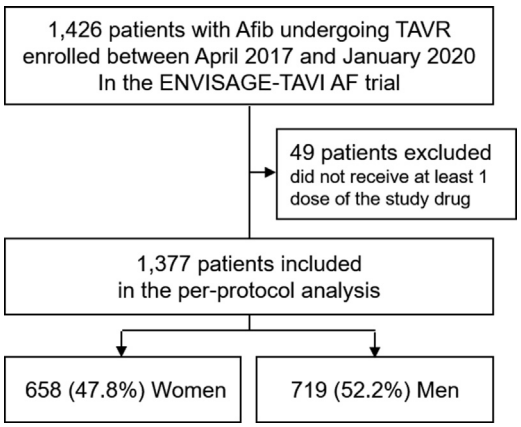
STATISTICAL ANALYSIS. The analyses were performed in the per protocol population, which included all randomized patients receiving ≥1 dose of the study drug. Baseline clinical and procedural characteristics were summarized by sex as well as by sex and randomized treatment assignment using mean ± SD for continuous variables and numbers and frequencies for categorical variables. *P* values for comparisons were obtained from analysis of variance for continuous variables and from Fisher exact test for categorical variables.

The rates of the primary and secondary outcomes were calculated considering the effective time on study medication (safety analysis). The annualized event rates were calculated as the number of subjects with events divided by the total time at risk (years) to the subjects' first event or censoring time. The time at risk was defined as the time during which the patient was on treatment, ie, adherent to the study drug regimen. The time not 'at risk' and the events occurring during the time not 'at risk' were therefore not counted. HRs and 95% CIs were obtained with Cox proportional-hazards regression models using the counting process approach. Each subject was included in the Cox-regression analysis only during the period of time during which the subject was on treatment. Further details about this method are available in the Supplemental Figure 1. The assumptions of this model were verified using log minus log plots. Differences in outcomes between sexes were assessed in the whole population, after stratification according to the fulfilment of edoxaban dose adjustment criteria and after stratification by study treatment regimen (edoxaban or VKA). To assess the independent association of sex with outcomes, Cox-regression models were adjusted for baseline differences or other known confounders, including: age, creatinine clearance, diabetes, coronary artery disease, AF pattern (paroxysmal vs non-paroxysmal), cigarette use, chronic obstructive pulmonary disease, prior non-central nervous system systemic thromboembolic events, peripheral artery disease, carotid artery disease, ejection fraction. Treatment outcomes of edoxaban vs VKA were evaluated by sex and formal interaction testing using Cox regression to assess for association modification. *P* values were 2-sided, and statistical significance was set at $P < 0.05$. Moreover, the effect of anticoagulation treatment by sex was assessed in the intention-to-treat analysis, in which all subjects were included and the entire time to event was taken into account and not only the time on treatment. Additionally, in the intention-to-treat analysis the risks of key outcomes were adjusted for the competing risk of all-cause death. All analyses were performed using SAS software, version 9.2 or newer (SAS Institute).

RESULTS

POPULATION CHARACTERISTICS. From the total population of 1,426 patients enrolled in ENVISAGE-TAVI AF trial, 49 individuals (3.4%), who did not receive at least 1 dose of the study drug, were excluded from the per-protocol analysis. Out of the 1,377 patients included in the per-protocol analysis, 658 (47.8%) were women (**Figure 1**). Women were slightly older, less likely to be smokers or to have

FIGURE 1 Flow Diagram of Patients Included in the Per-Protocol Analysis



Afib = atrial fibrillation; ENVISAGE-TAVI AF = Edoxaban vs Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation–Atrial Fibrillation; TAVR = transcatheter aortic valve replacement.

chronic obstructive pulmonary disease, diabetes, hypercholesterolemia, concomitant coronary, peripheral or carotid artery disease but more likely to have chronic kidney disease or a history of thromboembolic events not affecting the central nervous system. CHA2DS2-VASc, Society of Thoracic Surgeons score, and EuroScore I values were higher in women than in men. AF was diagnosed before TAVR in almost all patients (99%) and had a paroxysmal pattern more frequently in women than men. A supra-annular self-expandable valve was more often implanted in women, a balloon expandable device in the male counterpart (**Table 1**). Women met the criteria of edoxaban dose adjustment (57% vs 36.4%, $P < 0.001$) and discontinued the study treatment (46.7% vs 40.2%, $P = 0.017$) more frequently than men. In both sexes, VKA was more frequently interrupted than edoxaban (52.5% vs 41.1% in women and 45.9% vs 34.4% in men). The main reason for discontinuation in women was subject's withdrawal, in men adverse event (Supplemental Table 3). The proportion of patients receiving antiplatelet therapy in addition to the study regimen was similar in women and men (Supplemental Table 4). Baseline, procedural characteristics and medication were well balanced between the 2 treatment arms in both sexes (Supplemental Table 4).

CLINICAL OUTCOMES BY SEX. NACE occurred in 127 (16.2 per 100 person-years) women and 128 (14.1 per 100 person-years) men (HR: 1.12; 95% CI: 0.88-1.44), whereas ISTH major bleeding in 69 (8.7 per 100 person-years) and 70 (7.6 per 100 person-years), respectively (HR: 1.12; 95% CI: 0.80-1.56). There were no differences between sexes for the secondary outcomes (**Figure 2**, Supplemental Table 5). Risk of adverse outcomes remained similar between women and men also after stratification according to the fulfilment of edoxaban dose adjustment criteria (Supplemental Table 6), study regimen assignment (Supplemental Table 7), or after adjustment for baseline imbalances (**Figure 2**).

CLINICAL OUTCOMES BY SEX AND RANDOMIZED TREATMENT ASSIGNMENT. NACE occurred in 74 women on edoxaban and in 53 on VKA (17.1 vs 15.2 per 100 person-years; HR: 1.16; 95% CI: 0.81-1.65); among men, NACE events were 67 and 61 in the 2 treatment groups, respectively (14.7 vs 13.4 per 100 person-years, HR: 1.08; 95% CI: 0.76-1.53). The effect of edoxaban and VKA on NACE did not differ in both sexes (P value for interaction 0.820) (**Central Illustration**). The results for this composite endpoint remained concordant when other bleeding scales were applied (**Table 2**).

Among women, 40 suffered from ISTH major bleeding in the edoxaban group and 29 in the VKA group (9.1 vs 8.3 per 100 person-years; HR: 1.11; 95% CI: 0.69-1.79). Among men ISTH major bleeding occurred in 45 patients on edoxaban and 25 on VKA (9.8 vs 5.4 per 100 person-years, HR: 1.75; 95% CI: 1.07-2.85) (**Central Illustration**). Bleeding was consistently higher in patients treated with edoxaban than VKA irrespective of sex (P for interaction = 0.170). Consistently in both sexes (P for interaction >0.05), this risk difference was largely determined by an excess of non-fatal major bleeding in the edoxaban arm, whereas the rates of fatal bleeding, life-threatening bleeding, intracranial hemorrhage as well as clinically relevant non-major bleeding were similar in the 2 treatment arms (**Figure 3**, **Table 2**).

Concerning the ischemic endpoints, MACCE occurred in 36 (8.0 per 100 person-years) women treated with edoxaban and 24 (6.7 per 100 person-years) on VKA (HR: 1.29; 95% CI: 0.76-2.18); among men, 29 (6.1 per 100 person-years) and 33 (7.1 per 100 person-years) experienced this outcome in the 2 study treatment groups, respectively (HR: 0.86; 95% CI: 0.52-1.43). Risk of MACCE did not differ between edoxaban and VKA in both sexes (P for interaction = 0.295).

All-cause mortality did not differ between the 2 treatment groups consistently in women (HR: 0.77; 95% CI: 0.44-1.33) and men (HR: 1.37; 95% CI: 0.75-2.50; P for interaction = 0.169).

Cardiovascular death was higher with Edoxaban than VKA in women (HR: 2.32; 95% CI: 0.99-5.45) but not in men (HR: 0.63, 95% CI: 0.30-1.33; *P* for interaction = 0.030). The risk for the other ischemic events was similar with edoxaban vs VKA in female and male patients (*P* for interaction >0.05) (**Figure 3**, **Table 2**). No cases of valve thrombosis occurred.

In the intention-to-treat analysis, men treated with edoxaban were at higher hazard for ISTH major bleeding due to an excess of non-fatal occurrences than those in the VKA arm. Otherwise, no differences were observed between the 2 treatments for the other outcomes in women and men (Supplemental Table 8), also after taking into account the competing risk of all-cause death (Supplemental Table 9).

DISCUSSION

The results of this secondary analysis of the ENVISAGE-TAVI AF trial, assessing the impact of sex on the efficacy and safety of edoxaban vs VKA in 1,377 patients with AF after successful TAVR can be summarized as follows

- Women as compared to men were older, less likely to have cardiovascular risk factors or comorbidities, but had higher thromboembolic and surgical preoperative risks;
- Women and men had a similar unadjusted and adjusted risk of ischemic and bleeding complications after TAVR;
- Consistently in both sexes, Edoxaban and VKA had a similar effect on the primary composite endpoint of ischemic and bleeding events;
- Edoxaban was associated with higher risk of major bleeding irrespective of sex; however, the risk increase was attenuated in women

Women represent roughly half of patients undergoing TAVR and are at higher risk of major procedural and post-procedural bleeding, vascular complications and stroke, but have a better survival after TAVR.[3-5,9] AF, which is observed in up to 40% of women undergoing TAVR, is associated with an increased hazard of death and stroke.[6] The primacy of oral anticoagulation over antiplatelet agents or placebo in reducing stroke in patients with AF has been established in the context of nonvalvular AF.[13] New oral anticoagulants showed a similar efficacy to VKAs in reducing ischemic events but superior safety, given the lower rate of intracranial bleeding associated with these new agents.[14] With edoxaban, all types of bleeding, including major, intracranial, and life-threatening bleeding were reduced in the setting of

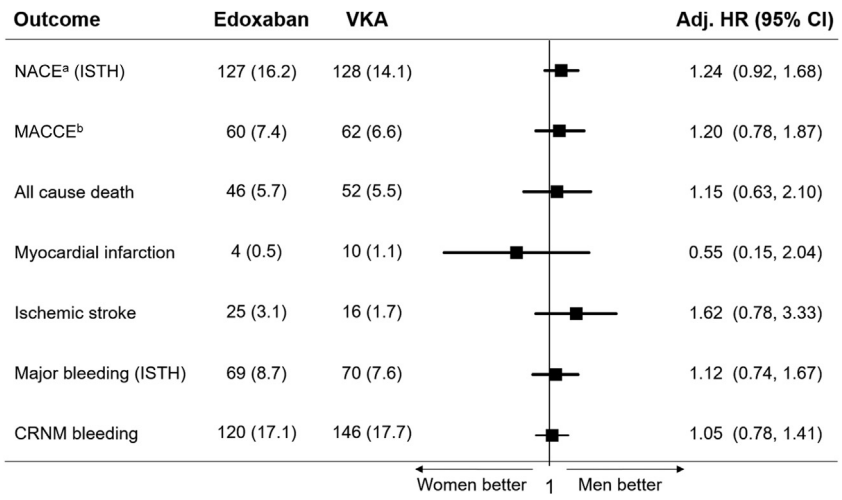
TABLE 1 Baseline and Procedural Characteristics

	Women (n = 658)	Men (n = 719)	*P* Value
Age at enrollment	82.6 ± 5.4	81.5 ± 5.4	<0.001
Non-White ethnicity	115 (17.4)	116 (16.2)	0.380
Body mass index	27.9 ± 6.3	27.5 ± 4.7	0.137
Hypertension	610 (92.7)	648 (90.1)	0.103
Diabetes mellitus	215 (32.7)	291 (40.5)	0.003
Hypercholesterolemia	440 (66.9)	524 (72.9)	0.016
Cigarette use (current or former)	90 (13.7)	355 (49.4)	<0.001
Coronary artery disease	313 (47.6)	428 (59.5)	<0.001
Prior CABG	33 (5.0)	91 (12.7)	<0.001
Prior PCI	126 (19.1)	228 (31.7)	<0.001
Within 30 d before TAVR	36 (5.5)	26 (3.6)	0.118
Prior myocardial infarction	63 (9.6)	128 (17.8)	<0.001
Peripheral artery disease	54 (8.2)	103 (14.3)	<0.001
Carotid artery disease	29 (4.4)	67 (9.3)	<0.001
Prior stroke/TIA	114 (17.3)	119 (16.6)	0.719
Non-CNS systemic thromboembolic event	44 (6.7)	26 (3.6)	0.010
Left ventricular ejection fraction	58.0 ± 10.3	53.2 ± 11.9	<0.001
Congestive heart failure	549 (83.4)	614 (85.4)	0.333
NYHA class III or IV	294 (44.7)	319 (44.4)	0.914
Mitral-valve disease	289 (43.9)	310 (43.1)	0.786
Creatinine clearance ≤50 mL/min	325 (49.4)	245 (34.1)	<0.001
COPD	74 (11.2)	125 (17.4)	0.001
Prior major bleeding or predisposition to bleeding	61 (9.3)	58 (8.1)	0.444
Prior hospitalization for bleeding	27 (4.1)	33 (4.6)	0.693
Labile INR prior to randomization	61 (9.3)	47 (6.5)	0.071
Atrial fibrillation/flutter pattern			0.002
Paroxysmal	300 (45.6)	269 (37.4)	
Persistent (>7 d but <1 y)	65 (9.9)	93 (12.9)	
Persistent (>1 y)	52 (7.9)	58 (8.1)	
Permanent	230 (35.0)	288 (40.1)	
Flutter	9 (1.4)	9 (1.3)	
Criteria for dose adjustment fulfilled[a]	375 (57.0)	262 (36.4)	<0.001
HAS-BLED score	1.6 ± 0.7	1.6 ± 0.8	0.687
CHA2DS2-VASc score	4.9 ± 1.2	4.1 ± 1.3	<0.001
STS Score	5.7 ± 4.1	4.2 ± 3.4	<0.0001
EuroScore I	13.6 ± 9.8	12.3 ± 9.9	0.014
EuroScore II	4.8 ± 5.5	4.4 ± 5.5	0.131
Procedural characteristics			
Balloon expandable valves	261 (39.7)	392 (54.5)	<0.001
Self-expandable valve supra-annular	346 (52.6)	284 (39.5)	
Self-expandable valve intra-annular	51 (7.8)	42 (5.8)	
Coronary stenting requiring APT	90 (13.7)	128 (17.8)	0.039
Treatment after randomization			
Aspirin or P2Y12 inhibitor	388 (59.0)	436 (60.6)	0.545
SAPT	373 (56.7)	423 (58.8)	0.445
DAPT followed by SAPT	15 (2.3)	16 (2.2)	1.000
Any DAPT	90 (13.7)	87 (12.1)	0.420

Values are mean ± SD or n (%). [a]Fulfilment of any of the following criteria: creatinine clearance ≤50 mL/min (Cockcroft-Gault formula), a body weight ≤60 kg or using certain P-glycoprotein inhibitors (ketoconazole, itraconazole, erythromycin, and clarithromycin).

APT = antiplatelet treatment; CABG = coronary artery bypass graft; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; DAPT = dual antiplatelet therapy; INR = international normalized ratio; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SAPT = single antiplatelet therapy; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement; TIA = transient ischemic attack.

FIGURE 2 Adjusted Risk of Adverse Outcomes in Women vs Men



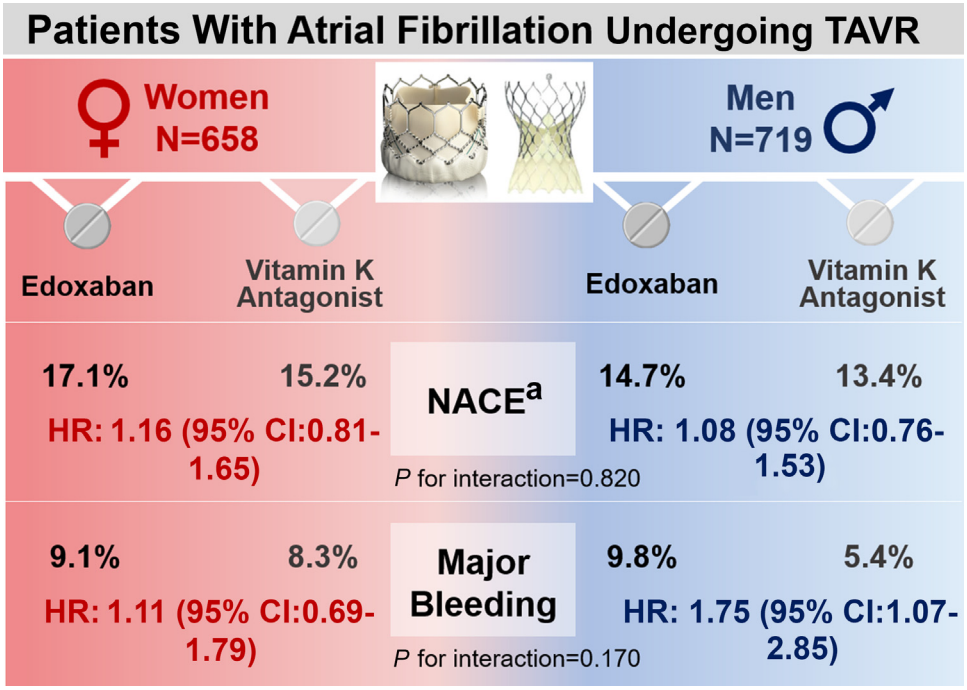
Bleeding is classified according to ISTH (International Society on Thrombosis and Haemostasis) definitions. CRNM = clinically relevant non-major; MACCE = major adverse cardiac and cerebrovascular events; NACE = net adverse cardiac events. [a]Composite of all-cause death, myocardial infarction, ischemic stroke, systemic embolic event, valve thrombosis and major bleeding. [b]Composite of cardiovascular death, myocardial infarction, any stroke or repeat coronary revascularization.

non-valvular AF[7] and the extent of these benefits was even larger in women.[10] Yet, an advantage of edoxaban over VKA was not observed in patients with AF after successful TAVR; indeed, in this population edoxaban was noninferior to VKA with regard to the composite outcome of bleeding and ischemic events but was associated with more major bleedings.

In accordance with previous TAVR reports, women in our analysis were older, with less cardiovascular comorbidities, a higher left ventricular ejection fraction, and a higher thromboembolic (ie, higher CHA2DS2-VASc score) and surgical preoperative (based on Society of Thoracic Surgeons Score, EuroScore I and II) risk than men.[15] Women and men had a similar risk of ischemic and bleeding outcomes after TAVR. These findings are in contrast with previous studies, showing an increased occurrence of bleeding, vascular complications, and stroke, but a better survival rate in women than in men. However, in these previous reports less than one-half of patients had AF, only one third was treated with oral anticoagulants and, at variance with our study, outcomes after non-successful TAVR and peri-procedural events were taken into account[3-5,9]; moreover, prior reports had a shorter follow-up duration.

We observed that edoxaban compared to VKA had a similar effect in preventing the composite ischemic and bleeding endpoint but was associated with higher rates of ISTH major bleeding. These effects were consistent in women and men. However, the increase in bleeding complications with edoxaban appeared to be attenuated in women (10% risk increase; absolute risk difference <1%) than in men (75% risk increase; absolute risk difference >4%). The risk of major bleeding was largely due to non-fatal occurrences; fatal, life-threatening, or intracranial bleeding were not increased in the edoxaban arm. Adherence to oral anticoagulation was generally modest (around 60%), lower in women than men by about 7% and lower in the VKA than edoxaban arm by roughly 10% in both sexes. It is unlikely that this latter finding explains the bleeding risk increase associated with edoxaban, since adherence to oral anticoagulation was taken into account in the safety analysis. Causes and impact of low adherence to anticoagulation treatment, as well as measures to improve it, should be further investigated. While the concomitant intake of antiplatelet therapy was similar in the 2 treatment arms in both sexes, women were more likely to receive an adjusted dose of edoxaban. This latter observation could at least in part explain the mitigated increase of bleeding with edoxaban in women. Interestingly, edoxaban appeared to be safer than VKA in terms of bleeding complications in women also in the

CENTRAL ILLUSTRATION **Primary Outcomes in Women and Men Treated With Edoxaban vs Vitamin K Antagonist**



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Major bleeding was defined according to ISTH (International Society on Thrombosis and Haemostasis). Interaction was not significant for any of the outcomes. [a]Net adverse cardiovascular events: composite of all-cause death, myocardial infarction, ischemic stroke, systemic embolic event, valve thrombosis, and major bleeding. TAVR = transcatheter aortic valve replacement.

secondary sex-based analysis of the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48).[10] However, in this latter trial edoxaban reduced bleeding events compared to VKA in both sexes and to a larger extent in women. The mechanism explaining the lower rates of bleeding in women than men taking edoxaban is not fully understood.

In both sexes, rates of MACCE, all-cause death and the single non-fatal ischemic components did not differ in patients treated with edoxaban vs VKA. However, there was an increase of cardiovascular death in women on edoxaban. The absolute number of this complication was low; in addition this effect was not present in the intention to treat population and in prior studies comparing edoxaban with VKA. Except for a single observational study,[16] the rates of fatal and non-fatal ischemic events in patients treated with edoxaban vs VKA were similar in non-randomized studies[17] and in the ENGAGE AF-TIMI 48 trial,[10] which compared these 2 treatments in 21,105 patients with non-valvular AF. In the ATLANTIS (Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis) study, among the 451 TAVR patients (>50% women) with an indication for oral anticoagulant, no differences could be observed for any of the ischemic or bleeding outcomes between apixaban and standard of care.[18] For these reasons, the increase in cardiovascular fatalities observed in women treated with edoxaban is probably a result of chance.

In summary, our analysis showed that the effect of edoxaban vs VKA on NACE and major bleeding was consistent in women and men with AF after successful TAVR. However, a different effect of

TABLE 2 Other Secondary Outcomes by Sex and Treatment: Kaplan-Meier Estimate Rates and Risk

	Edoxaban	Vitamin K Antagonist	HR (95% CI)	*P* for Interaction
NACE[a] (TIMI)				
Women[b]	66 (15.0)	45 (12.6)	1.23 (0.84-1.80)	0.766
Men[c]	58 (12.6)	51 (11.1)	1.12 (0.76-1.64)	
NACE[a] (BARC)				
Women[b]	73 (16.9)	50 (14.3)	1.22 (0.85-1.76)	0.818
Men[c]	64 (14.0)	56 (12.3)	1.14 (0.79-1.64)	
NACE[a] (GUSTO)				
Women[b]	71 (16.3)	48 (13.7)	1.23 (0.85-1.78)	0.830
Men[c]	62 (13.5)	53 (11.6)	1.15 (0.80-1.67)	
Repeat coronary revascularization				
Women[b]	1 (0.2)	0 (0.0)	n.a.	-
Men[c]	3 (0.6)	0 (0.0)	n.a.	
Cardiovascular death				
Women[b]	20 (4.4)	7 (1.9)	2.32 (0.99-5.45)	0.030
Men[c]	12 (2.5)	18 (3.8)	0.63 (0.30-1.33)	
Any stroke				
Women[b]	13 (2.9)	17 (4.8)	0.67 (0.32-1.41)	0.394
Men[c]	13 (2.7)	13 (2.6)	1.06 (0.48-2.33)	
Systemic embolic event				
Women[b]	1 (0.2)	2 (0.6)	0.41 (0.04-4.08)	0.656
Men[c]	1 (0.2)	1 (0.2)	0.93 (0.05-16.44)	
Fatal major bleeding (ISTH)				
Women[b]	3 (0.7)	4 (1.1)	0.69 (0.15-3.08)	0.660
Men[c]	5 (1.0)	5 (1.1)	0.98 (0.28-3.39)	
Life-threatening major bleeding (ISTH)				
Women[b]	4 (0.9)	8 (2.2)	0.43 (0.13-1.44)	0.208
Men[c]	9 (1.9)	8 (1.7)	1.12 (0.43-2.94)	
Intracranial hemorrhage				
Women[b]	5 (1.1)	8 (2.2)	0.53 (0.17-1.63)	0.613
Men[c]	9 (1.9)	12 (2.6)	0.74 (0.31-1.76)	
Non-fatal major bleeding (ISTH)				
Women[b]	38 (8.7)	27 (7.7)	1.13 (0.69-1.85)	0.096
Men[c]	42 (9.1)	20 (4.3)	2.04 (1.20-3.47)	

Values are n (%). *P* value for interaction is not significant for any of the outcomes. [a]Composite of all-cause death, myocardial infarction, ischemic stroke, systemic embolic event, valve thrombosis, and major bleeding. [b]Edoxaban n = 338, VKA n = 320. [c]Edoxaban n = 355, VKA n = 364.

BARC = Bleeding Academic Research Consortium; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; ISTH = International Society on Thrombosis and Haemostasis; NACE = net adverse clinical event; TIMI = Thrombolysis In Myocardial Infarction.

edoxaban in function of sex is not excluded and has to be verified in an adequately powered RCT.

STUDY LIMITATIONS. This is a secondary analysis and was not powered to assess the effect of edoxaban vs VKA in women or men. Therefore, the results have to be considered exploratory. Additional caution is needed when interpreting the results of single bleeding or ischemic outcomes because of the low number of events. Moreover, the ENVISAGE-TAVI AF had an open-label design that entailed a risk of reporting bias regarding the trial outcomes. The modest and asymmetric adherence to the experimental and control regimen might have affected the results. Finally, these results apply only to patients after successful TAVR with AF, intermediate operative risk, and symptomatic aortic stenosis.

CONCLUSIONS

In women and men with AF undergoing successful TAVR, edoxaban was consistently associated with a similar risk of net adverse cardiovascular events and an increase of major bleeding as compared to VKA. The increase of bleeding complications with edoxaban was attenuated in women.

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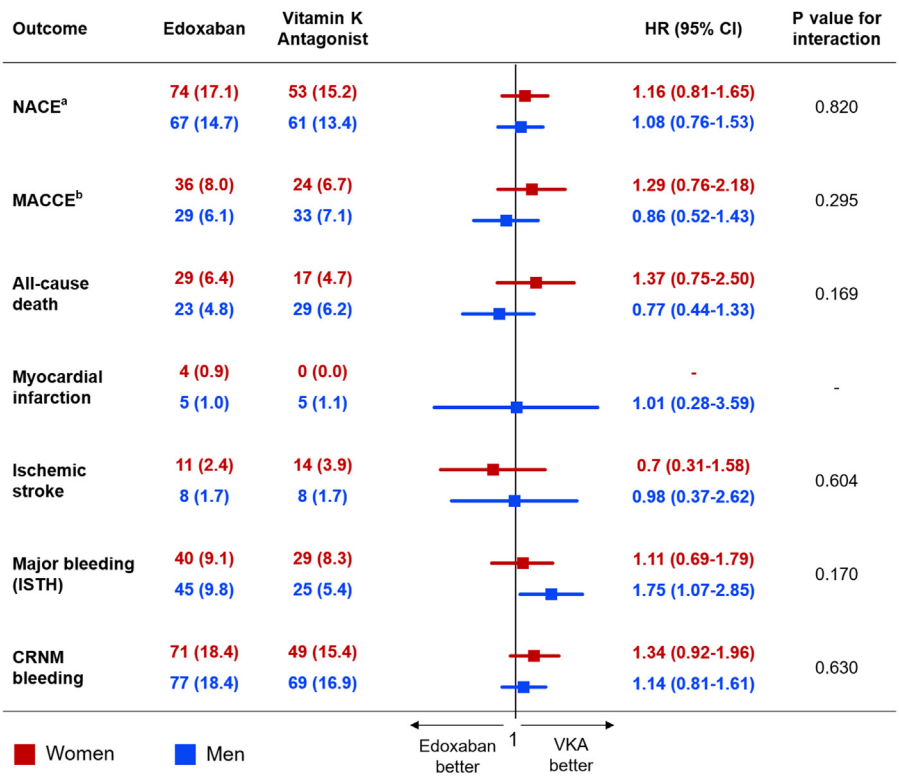
FIGURE 3 Rates and Risk of Adverse Outcomes in Women and Men Treated With Edoxaban vs Vitamin K Antagonist



CRNM = clinically relevant non-major; ISTH = International Society on Thrombosis and Haemostasis; MACCE = major adverse cardiac and cerebrovascular events; NACE = net adverse cardiac events; VKA = vitamin K antagonist. [a]Composite of all-cause death, myocardial infarction, ischemic stroke, systemic embolic event, valve thrombosis, and major bleeding. [b]Composite of cardiovascular death, myocardial infarction, any stroke, or repeat coronary revascularization.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among patients with AF after successful TAVR, edoxaban compared to VKA has a similar impact on net adverse cardiac events but increases the risk of major bleeding. These effects are consistent in women and men, even though the increase in bleeding complications with edoxaban is attenuated in women.

COMPETENCY IN PATIENT CARE: In women and men with AF after successful TAVR, VKA should be preferred over edoxaban to reduce the risk of bleeding complications, especially in men.

TRANSLATIONAL OUTLOOK 1: Adequately powered randomized controlled trials are needed to verify possible sex-related differences in the efficacy and safety of edoxaban vs VKA in patients with AF after successful TAVR.

TRANSLATIONAL OUTLOOK 2: Discontinuation of oral anticoagulant is frequent in patients with AF after successful TAVR. Causes of anticoagulant discontinuation and interventions to reduce it should be further investigated.

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KEY WORDS atrial fibrillation, edoxaban, outcomes, sex, TAVR

APPENDIX For supplemental tables and a figure, please see the online version of this paper.