Confronto tra Edoxaban e antagonisti della vitamina K nei pazienti con fibrillazione atriale sottoposti a TAVI

Risultati del trial ENVISAGE-TAVI AF

Background

- Atrial fibrillation occurs in approximately 33% of patients after transcatheter aortic-valve replacement (TAVR), and oral anticoagulation is generally recommended as treatment.
- The effects of various antithrombotic strategies to prevent thromboembolic events with atrial fibrillation after TAVR have not been well studied.
- A randomized trial showed that the addition of clopidogrel to oral anticoagulation in patients undergoing TAVR who had established indications for anticoagulation, predominantly atrial fibrillation, resulted in more bleeding complications. Non–vitamin K oral anticoagulants were prescribed in less than 33% of the patients in that trial; there was no comparison between regimens, and medications were mostly initiated before TAVR.

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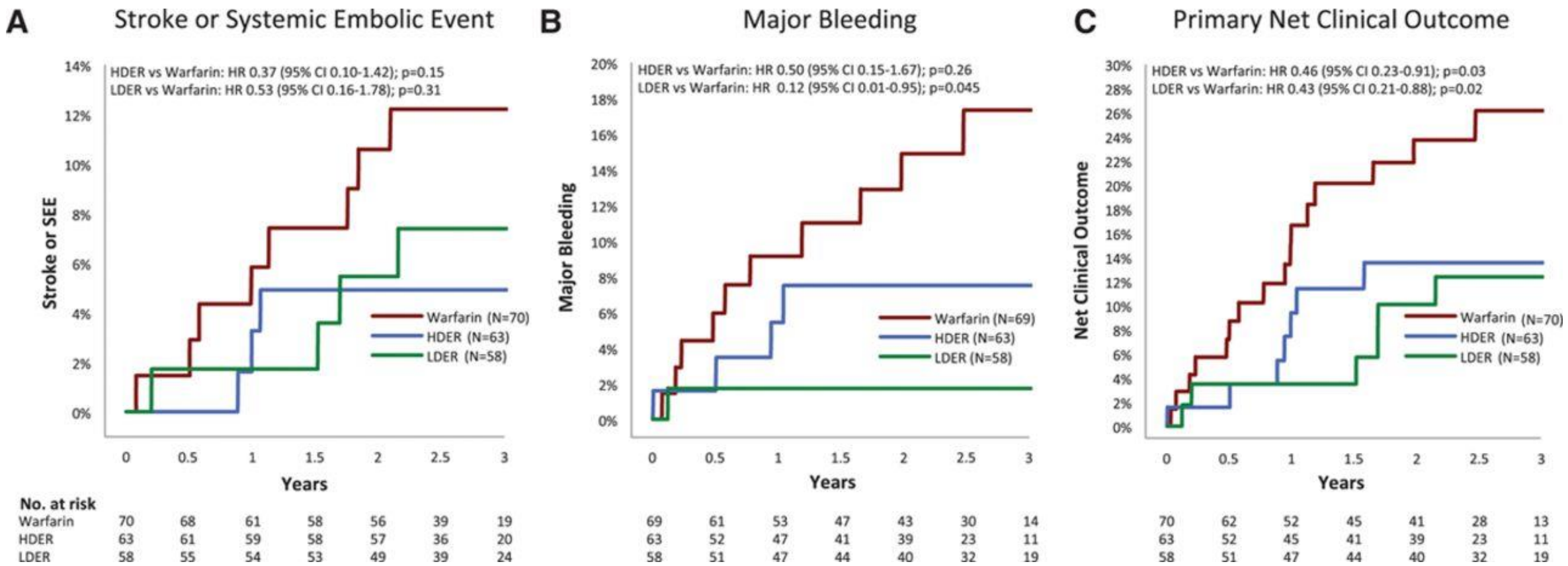
ENGAGE AF-TIMI 48 trial subanalysis: 191 pts with previous bioprosthetic valve implantation (131 mitral, 60 aortic)



Circulation. 2017;135:1273–1275

ORIGINAL ARTICLE

Edoxaban versus Vitamin K Antagonist for Atrial Fibrillation after TAVR

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Aim

The aim of 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 was to compare the efficacy and safety of edoxaban with those of vitamin K antagonists in patients with prevalent or incident atrial fibrillation after successful TAVR.

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Methods

- Multicenter, prospective, randomized, open-label, adjudicator-masked trial comparing edoxaban with vitamin K antagonists in patients with prevalent or incident atrial fibrillation as the indication for oral anticoagulation after successful TAVR.
- **Primary efficacy outcome**: composite of adverse events consisting of death from any cause, myocardial infarction, ischemic stroke, systemic thromboembolism, valve thrombosis, or major bleeding.
- **Primary safety outcome:** major bleeding.
- On the basis of a hierarchical testing plan, the primary efficacy and safety outcomes were tested sequentially for noninferiority, with noninferiority of edoxaban established if the upper boundary of the 95% confidence interval for the hazard ratio did not exceed 1.38.
- Superiority testing of edoxaban for efficacy would follow if noninferiority and superiority were established for major bleeding.

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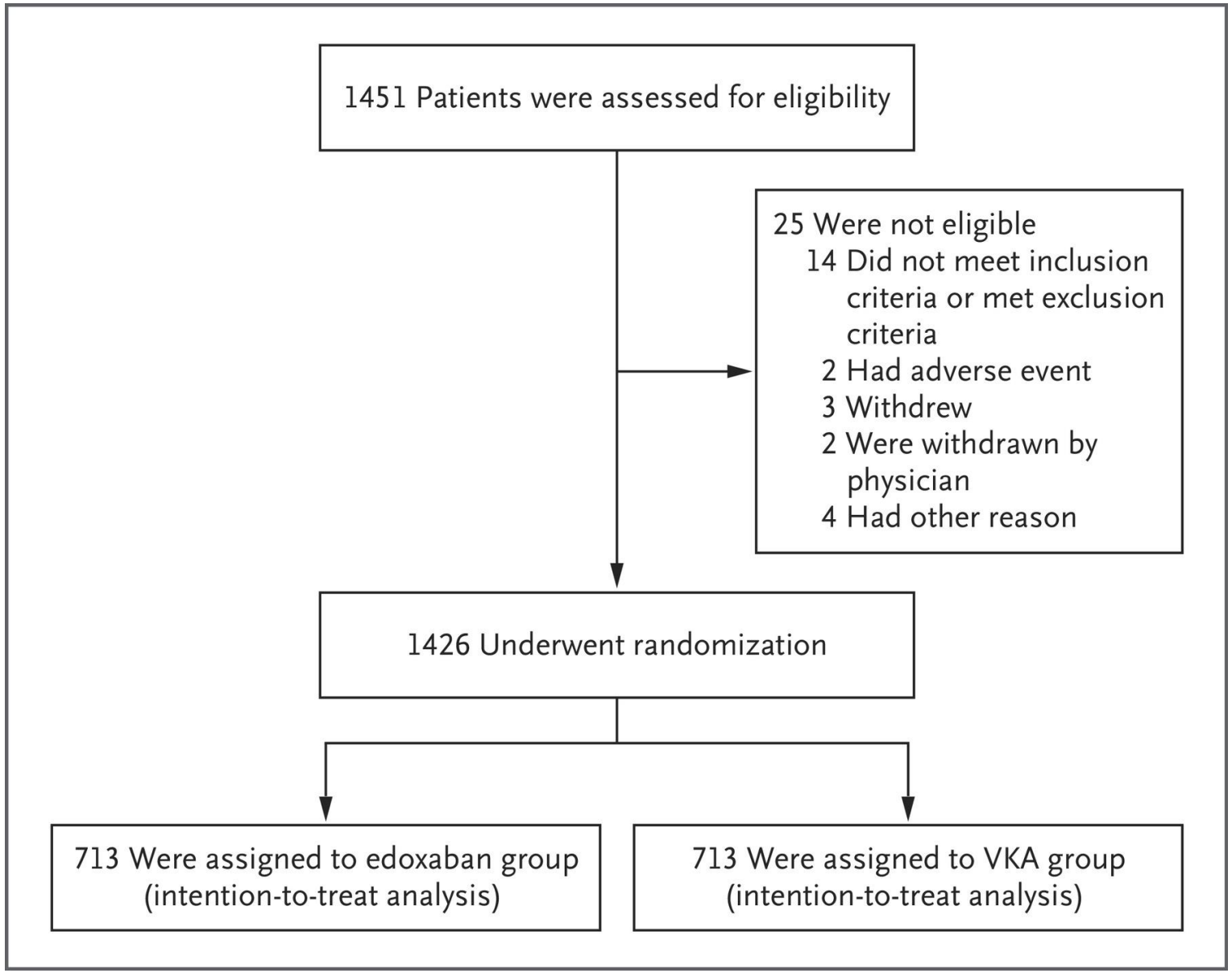
Screening, Randomization, and Treatment



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Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population)

Characteristic	Edoxaban (N=713)	Vitamin K Antagonist (N=713)
Age — yr	82.1±5.4	82.1±5.5
Female sex — no. (%)	347 (48.7)	331 (46.4)
Race — no. (%)†		
Asian	92 (12.9)	89 (12.5)
White	593 (83.2)	594 (83.3)
Other	28 (3.9)	30 (4.2)
Weight — kg	74.6±17.9	76.0±17.3
Body-mass index‡	27.5±5.7	27.9±5.4
Creatinine clearance by Cockcroft–Gault formula — ml/min	57.9±24.0	58.6±24.3
Hypertension — no. (%)	647 (90.7)	657 (92.1)
Diabetes mellitus — no. (%)	270 (37.9)	257 (36.0)
Congestive heart failure — no. (%)	591 (82.9)	619 (86.8)
NYHA class III or IV	314 (44.0)	328 (46.0)
Mitral-valve disease — no. (%)	57 (8.0)	60 (8.4)
History of stroke or TIA — no. (%)	123 (17.3)	116 (16.3)
History of coronary artery disease — no. (%)	293 (41.1)	297 (41.7)
Previous CABG	67 (9.4)	60 (8.4)
Previous PCI	176 (24.7)	192 (26.9)
PCI performed within 30 days before TAVR	34 (4.8)	28 (3.9)
Previous myocardial infarction	97 (13.6)	101 (14.2)
Incident (new onset) atrial fibrillation — no. (%)	7 (1.0)	8 (1.1)
CHA_2DS_2-VASc score§		
Mean	4.5±1.4	4.5±1.3
Median (IQR)	4 (4–5)	4 (4–5)
STS risk score¶		
Mean	4.8±3.5	5.0±4.1
Distribution — %‖		
<4	53.0	51.5
4–8	34.7	35.5
>8	12.3	13.0
Gastrointestinal disorder — no. (%)	264 (37.0)	242 (33.9)
Previous PPI use — no. (%)	406 (56.9)	393 (55.1)
Pre-TAVR use of non–vitamin K oral anticoagulant — no. (%)**	206 (28.9)	198 (27.8)
Pre-TAVR use of vitamin K antagonist — no. (%)	311 (43.6)	337 (47.3)
No pre-TAVR use of non–vitamin K oral anticoagulant or vitamin K antagonist — no. (%)	196 (27.5)	178 (25.0)
History of labile INR — no. (%)	53 (7.4)	61 (8.6)
Indication for dose adjustment — no. (%)††	330 (46.3)	331 (46.4)
Valve type — no. (%)‡‡		
Any balloon-expandable valve	342 (48.0)	335 (47.0)
Intraannular self-expanding valve	46 (6.5)	49 (6.9)
Supraannular self-expanding valve	325 (45.6)	328 (46.0)

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Efficacy and Safety Outcomes (Intention-to-Treat Population)

Outcome	Edoxaban (N=713)	Vitamin K Antagonist (N=713)	Hazard Ratio (95% CI)
	no. of patients (rate per 100 person-yr)		
Primary efficacy outcome: net adverse clinical events†	170 (17.3)	157 (16.5)	1.05 (0.85–1.31)‡
Primary safety outcome: major bleeding§	98 (9.7)	68 (7.0)	1.40 (1.03–1.91)¶
Secondary outcomes			
Death from any cause	85 (7.8)	93 (9.1)	0.86 (0.64–1.15)
Death from cardiovascular causes	49 (4.5)	46 (4.5)	1.00 (0.67–1.50)
Ischemic stroke	22 (2.1)	28 (2.8)	0.75 (0.43–1.30)
Myocardial infarction	12 (1.1)	7 (0.7)	1.65 (0.65–4.14)
Systemic thromboembolic event	2 (0.2)	3 (0.3)	Not calculated
Valve thrombosis§	0	0	Not calculated
Any stroke	29 (2.7)	35 (3.5)	0.78 (0.48–1.28)
Major adverse cardiac or cerebrovascular event‖	86 (8.2)	80 (8.1)	1.02 (0.76–1.39)
Major adverse cardiac event**	61 (5.7)	53 (5.2)	1.10 (0.76–1.58)
Fatal bleeding§	11 (1.0)	10 (1.0)	Not calculated
Life-threatening bleeding	17 (1.6)	19 (1.9)	Not calculated
Intracranial hemorrhage	16 (1.5)	21 (2.1)	0.72 (0.38–1.39)
Clinically relevant nonmajor bleeding§	164 (18.2)	142 (16.4)	1.13 (0.90–1.14)

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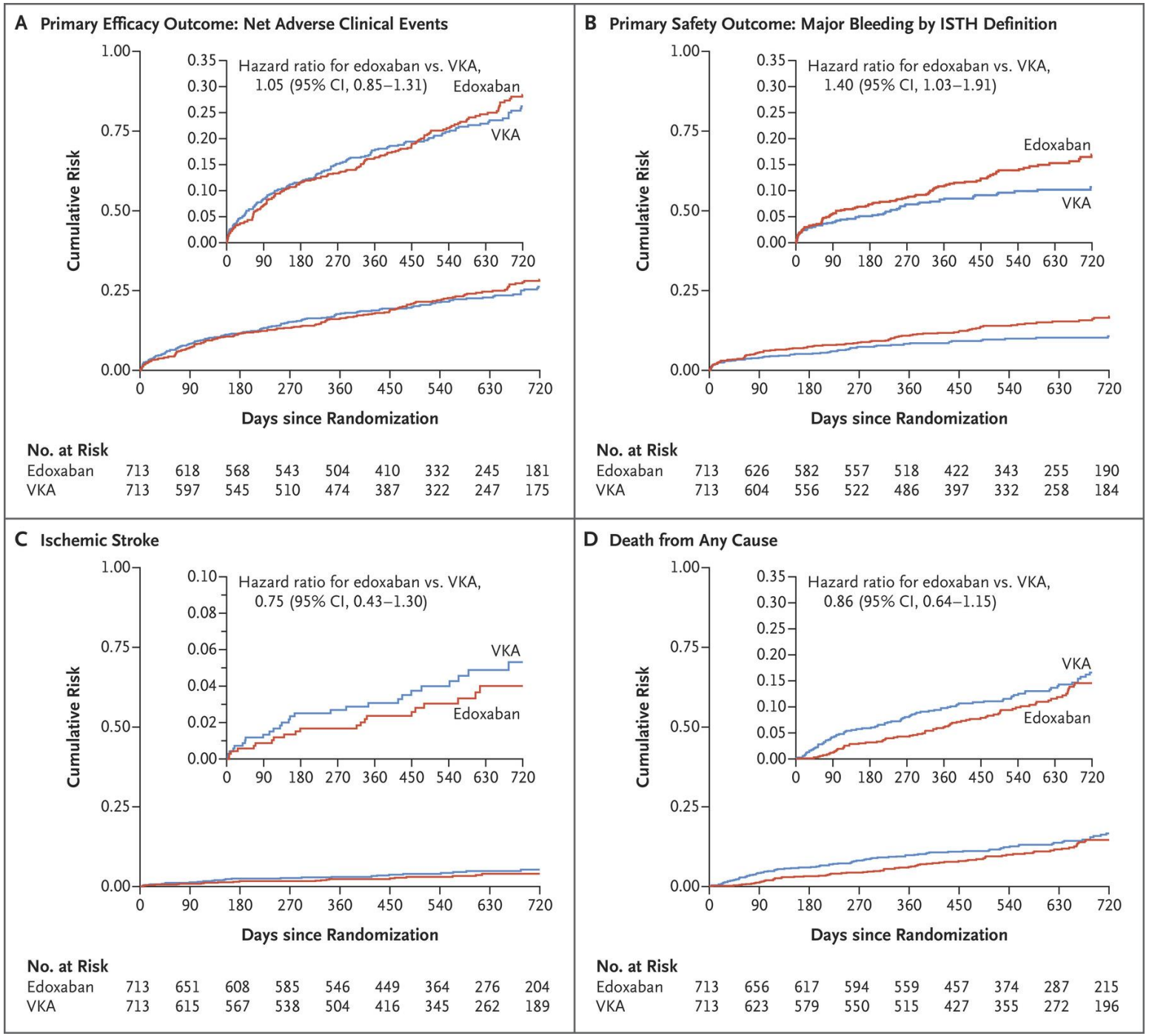
Kaplan–Meier Curves for the Primary Outcomes and Other Outcomes (Intention-to-Treat Population)



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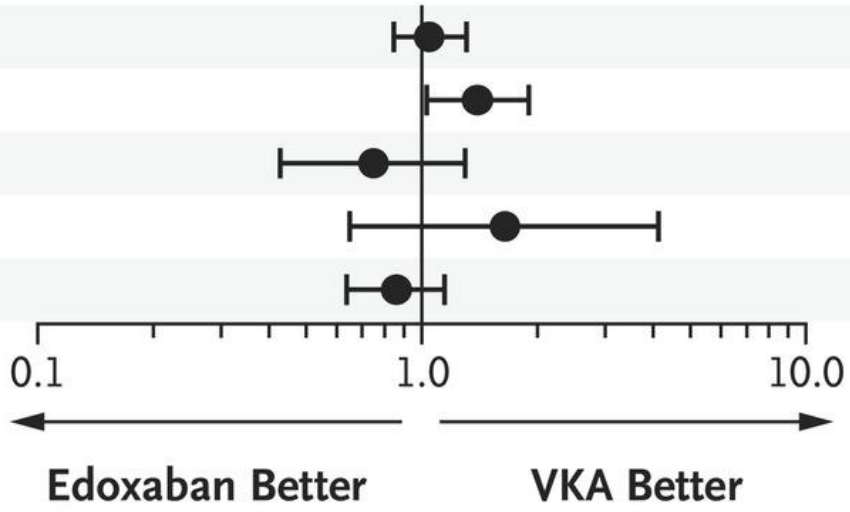
Hazard Ratio for the Primary Efficacy Outcome and Its Components (Intention-to-Treat Population)

Event	Edoxaban	VKA
	rate per 100 person-yr (no. of patients/total no.)	
Net adverse clinical events	17.3 (170/713)	16.5 (157/713)
Major bleeding	9.7 (98/713)	7.0 (68/713)
Ischemic stroke	2.1 (22/713)	2.8 (28/713)
Myocardial infarction	1.1 (12/713)	0.7 (7/713)
Death from any cause	7.8 (85/713)	9.1 (93/713)



the difference between groups was mainly due to more gastrointestinal bleeding with edoxaban
(56 [5.4 per 100 person-years] vs. 27 [2.7 per 100 person-years]; hazard ratio, 2.03; 95% CI, 1.28 to 3.22),

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Trial Drug Discontinuation

	Edoxaban n=713	VKA n=713
Discontinued study treatment	215 (30.2)	289 (40.5)
Primary reason for discontinuation		
AE/suspected clinical event	112 (15.7)	97 (13.6)
By patient	63 (8.8)	126 (17.7)
By physician	23 (3.2)	47 (6.6)
Patients lost to follow-up	1 (0.1)	0
Other	16 (2.2)	19 (2.7)

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Concomitant Use of Oral Antiplatelet Drugs Throughout the Trial Period

	Edoxaban n=713	VKA n=713
No OAP from randomization to end of study	290 (40.7)	282 (39.6)
Any OAP after randomization	423 (59.3)	431 (60.4)
Any SAPT after randomization	409 (57.4)	415 (58.2)
Acetylsalicylic acid only	196 (27.5)	197 (27.2)
P2Y12 inhibitor only	191 (26.8)	196 (27.5)
Acetylsalicylic acid or P2Y12 in sequence	22 (3.1)	22 (3.1)
Any DAPT after randomization	86 (12.1)	94 (13.2)
DAPT followed by SAPT in sequence	72 (10.1)	78 (10.9)

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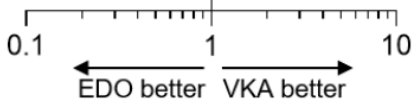
Hazard Ratio of Clinical Events by Specified Antiplatelet Therapy (Intention-to-Treat)

Endpoint	Event rate, %/yr (No. of patients/Total no.) Edoxaban	VKA	Hazard ratio (95% CI)
NACE			
OAP Yes	19.01 (85/328)	17.89 (86/359)	
OAP No	15.82 (85/385)	15.08 (71/354)	
Major bleeding*			
OAP Yes	11.85 (54/328)	7.26 (36/359)	
OAP No	7.92 (44/385)	6.68 (32/354)	
Major GI bleeding*			
OAP Yes	6.79 (32/328)	3.74 (19/359)	
OAP No	4.21 (24/385)	1.62 (8/354)	
Ischemic stroke			
OAP Yes	2.04 (10/328)	2.72 (14/359)	
OAP No	2.08 (12/385)	2.86 (14/354)	
ICH			
OAP Yes	2.03 (10/328)	2.32 (12/359)	
OAP No	1.02 (6/385)	1.82 (9/354)	
All-cause mortality			
OAP Yes	7.84 (39/328)	9.33 (49/359)	
OAP No	7.79 (46/385)	8.81 (44/354)	
CV mortality			
OAP Yes	4.82 (24/328)	5.14 (27/359)	
OAP No	4.24 (25/385)	3.81 (19/354)	
Non-CV mortality			
OAP Yes	3.01 (15/328)	4.19 (22/359)	
OAP No	3.56 (21/385)	5.01 (25/354)	



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Study limitation

- Open-label design that entailed a risk of reporting bias regarding the trial outcomes.
- The coronavirus disease 2019 pandemic affected the outpatient clinic follow-up routine and may have resulted in underassessment of laboratory data and mild-to-moderate clinical events.
- The outcomes of death and trial-drug discontinuation may have been competing risks in relation to the outcomes studied (competing-risk analyses not permormed).
- The trial results apply only to patients with AF, intermediate operative risk, and symptomatic aortic stenosis, and the trial involved a population of older adults who were undergoing TAVR.

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Conclusion

- In patients with mainly prevalent atrial fibrillation who underwent successful TAVR, edoxaban was noninferior to vitamin K antagonists as determined by a hazard ratio margin of 38% for a composite primary outcome of adverse clinical events.
- The incidence of major bleeding was higher with edoxaban than with vitamin K antagonists.

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