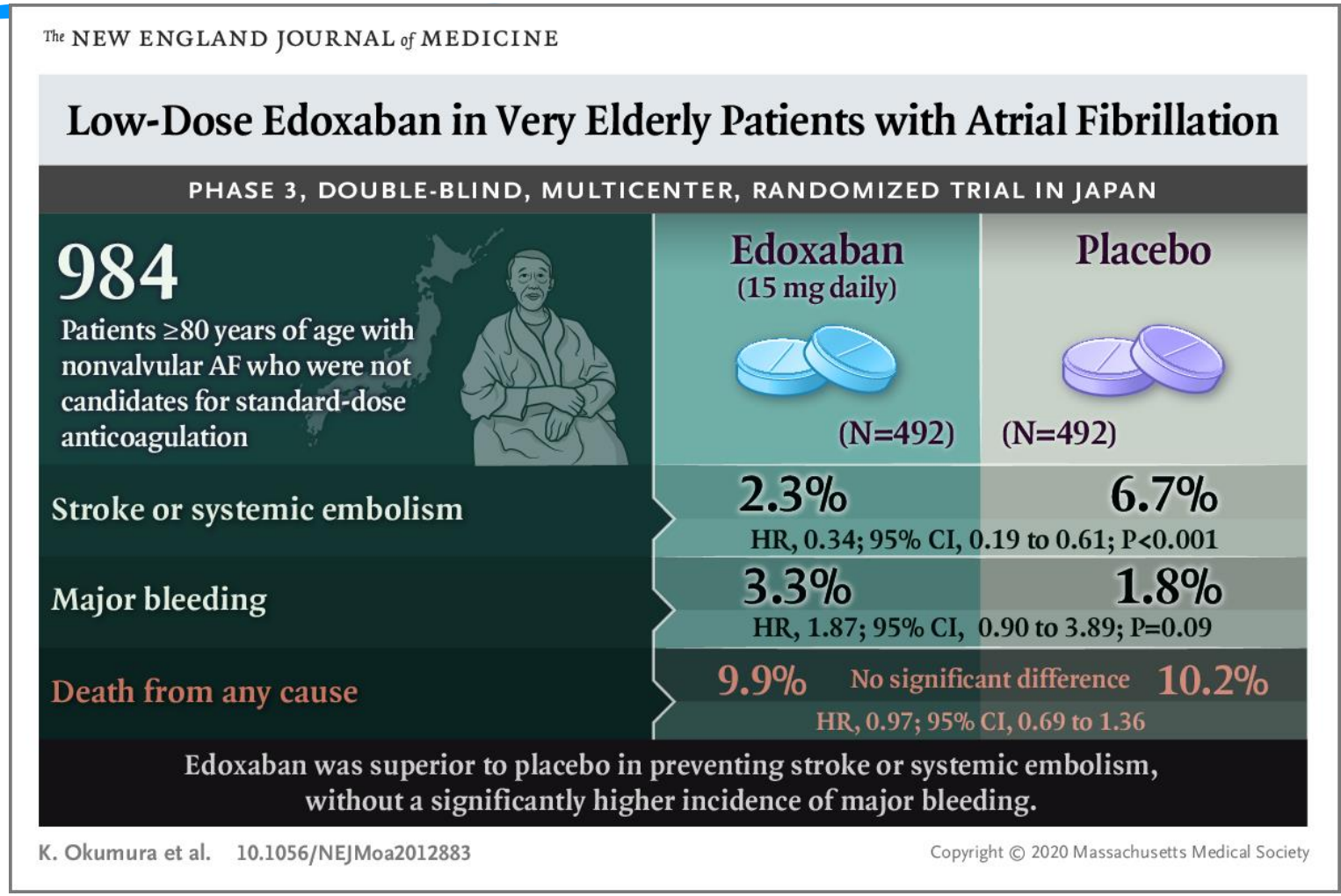
Efficacia e sicurezza di Edoxaban 15 mg in base al peso corporeo nei pazienti anziani con fibrillazione atriale

subanalisi del trial ELDERCARE-AF Trial

Background

- Elderly status, low body weight, and renal impairment are known risk factors for bleeding with OACs.
- In patients at high risk of bleeding who are ineligible for OAC treatment, the ELDERCARE-AF trial showed a significant reduction of stroke or systemic embolism with edoxaban 15 mg compared with placebo, without a significant increase in major bleeding.
- In addition, subgroup analyses of ELDERCARE-AF confirmed the consistent benefit of edoxaban 15 mg irrespective of age (80–84 years, 85–89 years, and ≥90 years) and renal function (creatinine clearance 15–<30 mL/min, 30–50 mL/min, and >50 mL/min).



Background

- Previous studies have reported the effectiveness and safety of DOACs for preventing stroke in patients with AF and low body weight.
  - The ENGAGE AF-TIMI 48 trial reported similar efficacy of the DOACs regimen at the recommended dose across 3 body weight groups, including the low body weight group defined as <55 kg.

- The efficacy and safety of OACs in patients with AF who are very underweight (≤45 kg) have yet to be demonstrated.

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ORIGINAL RESEARCH

Efficacy and Safety of Low-Dose Edoxaban by Body Weight in Very Elderly Patients With Atrial Fibrillation: A Subanalysis of the Randomized ELDERCARE-AF Trial

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Aim of the study

- This subanalysis was conducted to evaluate the efficacy and safety of edoxaban in patients with AF with extremely low body weight.
- Data from the ELDERCARE-AF trial, and assessed clinical outcomes according to body weight (≤45 or >45 kg).

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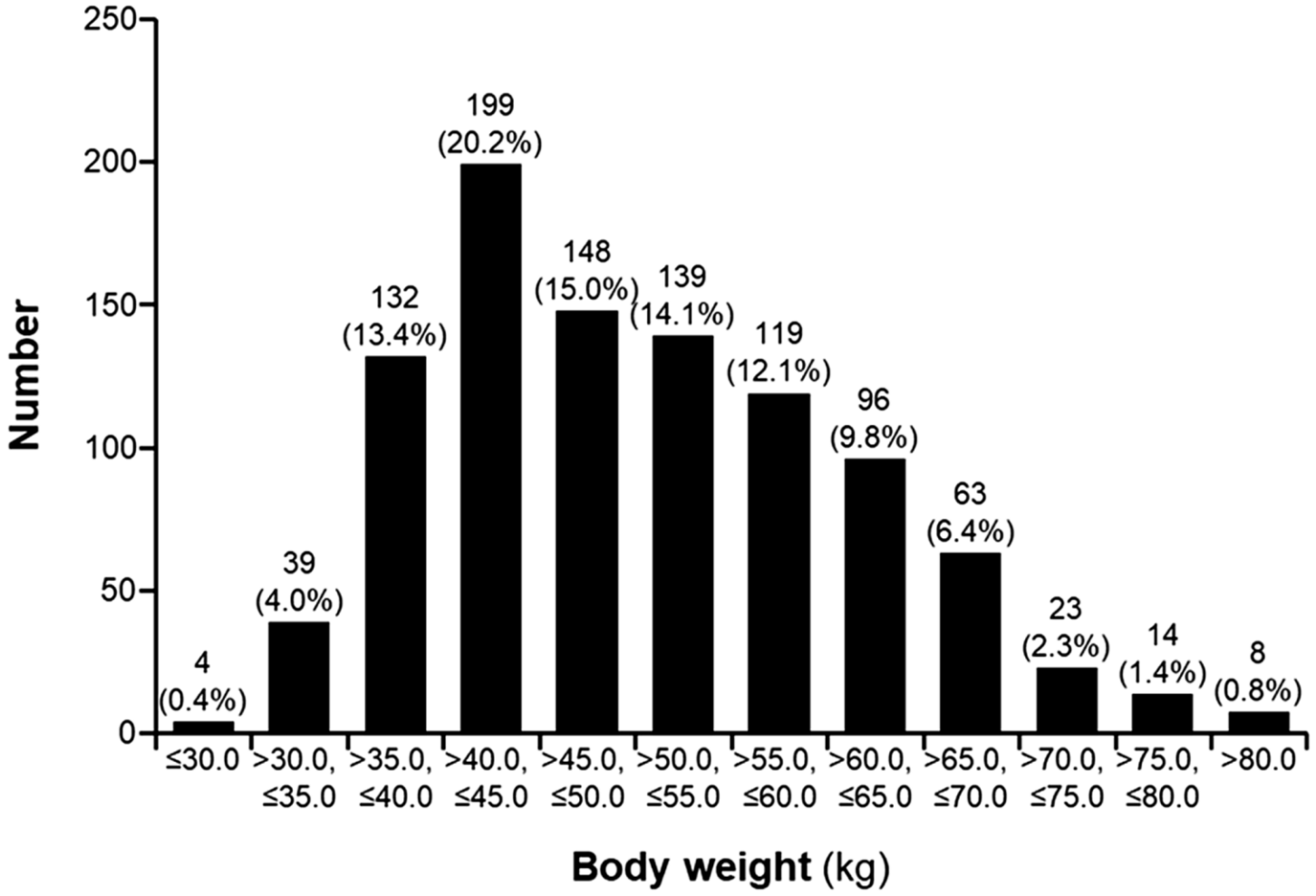
Methods

- This was a prespecified subanalysis by body weight (≤45, >45 kg) of the phase 3, multicenter, randomized, double-blind, placebo-controlled, event-driven ELDERCARE-AF trial, which compared low-dose edoxaban (15 mg once daily) with placebo in Japanese patients considered ineligible for oral anticoagulants at the recommended therapeutic strength or the approved doses.
- The primary efficacy and safety end points were stroke or systemic embolism and major bleeding (International Society on Thrombosis and Hemostasis definition), respectively.

Distribution of participants by body weight

- Most of the patients in the ≤45-kg group weighed 40 to 45 kg (199/374 [53.2%]



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Patients' Baseline Characteristics by Body Weight Subgroup

Characteristic	≤45 kg (N=374)	>45 kg (N=610)
Age, y	87.8±4.4	85.8±4.0
Male sex	48 (12.8)	371 (60.8)
Paroxysmal atrial fibrillation	191 (51.1)	272 (44.6)
Weight, kg	39.8±3.9	57.2±8.4
BMI, kg/m²*	19.3±2.3	23.9±3.3
Creatinine clearance, mL/min		
Mean	31.2±11.4	39.4±15.1
<30	204 (54.5)	197 (32.3)
≥30	170 (45.5)	413 (67.7)
Coronary artery disease	61 (16.3)	196 (32.1)
Dementia	95 (25.4)	65 (10.7)
Dyslipidemia	129 (34.5)	321 (52.6)
History of falling within past year	150 (40.1)	190 (31.1)
$CHADS_2$ score†		
Mean	3.0±1.0	3.1±1.2
≤2	141 (37.7)	222 (36.4)
≥3	233 (62.3)	388 (63.6)
Risk factor for thromboembolism		
Congestive heart failure	227 (60.7)	306 (50.2)
Hypertension	290 (77.5)	520 (85.2)
Age ≥75 y	374 (100.0)	610 (100.0)
Diabetes	55 (14.7)	170 (27.9)
Previous stroke or TIA	84 (22.5)	152 (24.9)
CHA_2DS_2-VASc score‡	5.0±1.2	4.8±1.3
HAS-BLED score§	2.0±0.9	2.5±0.8

Characteristic	≤45 kg (N=374)	>45 kg (N=610)
Reason for OAC ineligibility		
Severe renal impairment (creatinine clearance <30 mL/min)	204 (54.5)	199 (32.6)
History of bleeding from critical area or organ	53 (14.2)	169 (27.7)
Intracranial	21 (5.6)	59 (9.7)
Gastrointestinal	29 (7.8)	98 (16.1)
Intraocular	2 (0.5)	5 (0.8)
Other‖	1 (0.3)	13 (2.1)
Continuous use of NSAIDs	77 (20.6)	240 (39.3)
Use of an antiplatelet drug	134 (35.8)	395 (64.8)
Aspirin	71 (19.0)	220 (36.1)
Clopidogrel	37 (9.9)	97 (15.9)
Other#	27 (7.2)	80 (13.1)
Frailty category**		
Robust	6 (1.6)	55 (9.0)
Prefrail	157 (42.0)	324 (53.1)
Frail	191 (51.1)	211 (34.6)
Could not be evaluated	9 (2.4)	8 (1.3)
Missing data	11 (2.9)	12 (2.0)

Characteristic	≤45 kg (N=374)	>45 kg (N=610)
History of oral anticoagulant therapy		
Yes	142 (38.0)	281 (46.1)
Warfarin	77 (20.6)	166 (27.2)
Direct oral anticoagulant	95 (25.4)	156 (25.6)
Unknown	1 (0.3)	0 (0.0)
No	232 (62.0)	329 (53.9)

The body mass index (BMI), creatinine clearance, prevalence of comorbidities (CAD, dyslipidemia, and diabetes), HAS-BLED score, continuous use of NSAIDs, and use of an antiplatelet drug all showed decreases with lower body weight.

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Patients' Baseline Characteristics in the Edoxaban and Placebo Groups by Body Weight Subgroup

The characteristics of each weight subgroup did not differ between the edoxaban and placebo groups.

Characteristic	Edoxaban 15 mg		Placebo	
	≤45 kg (N=188)	>45 kg (N=304)	≤45 kg (N=186)	>45 kg (N=306)
Age, y	87.6±4.4	86.1±4.0	87.9±4.5	85.6±3.9
Male sex	21 (11.2)	191 (62.8)	27 (14.5)	180 (58.8)
Paroxysmal atrial fibrillation	98 (52.1)	139 (45.7)	93 (50.0)	133 (43.5)
Weight, kg	39.7±3.9	57.3±7.9	39.9±3.8	57.0±8.9
BMI, kg/m^2*	19.3±2.3	23.8±3.1	19.3±2.3	24.0±3.5
Creatinine clearance, mL/min				
Mean	31.6±10.7	39.3±15.4	30.8±12.1	39.6±14.9
<30	96 (51.1)	101 (33.2)	108 (58.1)	96 (31.4)
≥30	92 (48.9)	203 (66.8)	78 (41.9)	210 (68.6)
Coronary artery disease	30 (16.0)	100 (32.9)	31 (16.7)	96 (31.4)
Dementia	39 (20.7)	31 (10.2)	56 (30.1)	34 (11.1)
Dyslipidemia	71 (37.8)	155 (51.0)	58 (31.2)	166 (54.2)
History of falling within past year	63 (33.5)	91 (29.9)	87 (46.8)	99 (32.4)
$CHADS_2$ score†				
Mean	2.9±1.0	3.1±1.1	3.0±1.1	3.2±1.2
≤2	70 (37.2)	111 (36.5)	71 (38.2)	111 (36.3)
≥3	118 (62.8)	193 (63.5)	115 (61.8)	195 (63.7)
Risk factor for thromboembolism				
Congestive heart failure	115 (61.2)	144 (47.4)	112 (60.2)	162 (52.9)
Hypertension	152 (80.9)	260 (85.5)	138 (74.2)	260 (85.0)
Age ≥75 y	188 (100.0)	304 (100.0)	186 (100.0)	306 (100.0)
Diabetes	25 (13.3)	90 (29.6)	30 (16.1)	80 (26.1)
Previous stroke or TIA	37 (19.7)	73 (24.0)	47 (25.3)	79 (25.8)
CHA_2DS_2-VASc score‡	5.0±1.2	4.8±1.3	5.0±1.2	4.9±1.3
HAS-BLED score§	2.0±0.9	2.4±0.8	2.1±0.9	2.5±0.9

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Patients' Baseline Characteristics in the Edoxaban and Placebo Groups by Body Weight Subgroup

The characteristics of each weight subgroup did not differ between the edoxaban and placebo groups.

Characteristic	Edoxaban 15 mg		Placebo	
	≤45 kg (N=188)	>45 kg (N=304)	≤45 kg (N=186)	>45 kg (N=306)
History of oral anticoagulant therapy				
Yes	76 (40.4)	131 (43.1)	66 (35.5)	150 (49.0)
Warfarin	36 (19.1)	79 (26.0)	41 (22.0)	87 (28.4)
Direct oral anticoagulants	53 (28.2)	71 (23.4)	42 (22.6)	85 (27.8)
Unknown	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
No	112 (59.6)	173 (56.9)	120 (64.5)	156 (51.0)
Reasons for OAC ineligibility				
Severe renal impairment (creatinine clearance <30 mL/min)	96 (51.1)	102 (33.6)	108 (58.1)	97 (31.7)
History of bleeding from critical area or organ	30 (16.0)	80 (26.3)	23 (12.4)	89 (29.1)
Intracranial	12 (6.4)	29 (9.5)	9 (4.8)	30 (9.8)
Gastrointestinal	16 (8.5)	45 (14.8)	13 (7.0)	53 (17.3)
Intraocular	1 (0.5)	2 (0.7)	1 (0.5)	3 (1.0)
Other ‖	1 (0.5)	5 (1.6)	0 (0.0)	8 (2.6)
Low body weight (≤45 kg)	188 (100.0)	0 (0.0)	186 (100.0)	0 (0.0)
Continuous use of NSAIDs	41 (21.8)	108 (35.5)	36 (19.4)	132 (43.1)
Use of an antiplatelet drug	64 (34.0)	196 (64.5)	70 (37.6)	199 (65.0)
Aspirin	36 (19.1)	98 (32.2)	35 (18.8)	122 (39.9)
Clopidogrel	16 (8.5)	55 (18.1)	21 (11.3)	42 (13.7)
Other #	12 (6.4)	44 (14.5)	15 (8.1)	36 (11.8)
Frailty category**				
Robust	4 (2.1)	28 (9.2)	2 (1.1)	27 (8.8)
Prefrail	90 (47.9)	167 (54.9)	67 (36.0)	157 (51.3)
Frail	85 (45.2)	100 (32.9)	106 (57.0)	111 (36.3)
Could not be evaluated	3 (1.6)	4 (1.3)	6 (3.2)	4 (1.3)
Missing data	6 (3.2)	5 (1.6)	5 (2.7)	7 (2.3)

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Efficacy and Safety End Points by Body Weight Subgroup

SSE, all-cause mortality, and net clinical outcome were significantly higher in the ≤45-kg group than in the >45-kg group

End point*	No. of patients with event/total no. of patients [event rate % per patient-y]		Hazard ratio (95% CI)†
	≤45 kg	>45 kg	
Efficacy end point	N=374	N=610	
Stroke/systemic embolism	29/374 [6.2]	30/610 [3.5]	1.71 (1.02–2.84)
All-cause mortality	64/374 [13.4]	71/610 [8.2]	1.64 (1.17–2.29)
Net clinical outcome	89/374 [19.3]	101/610 [12.0]	1.60 (1.20–2.13)
Safety end point	N=373	N=609	
Major bleeding	12/373 [2.8]	19/609 [2.4]	1.15 (0.56–2.38)
Major bleeding (gastrointestinal)	8/373 [1.8]	11/609 [1.4]	1.32 (0.53–3.31)
Major bleeding or clinically relevant nonmajor bleeding	59/373 [14.6]	100/609 [13.8]	1.05 (0.76–1.45)
Clinically relevant nonmajor bleeding	49/373 [12.0]	84/609 [11.5]	1.03 (0.72–1.46)
All bleeding	167/373 [56.8]	276/609 [51.4]	1.08 (0.89–1.31)

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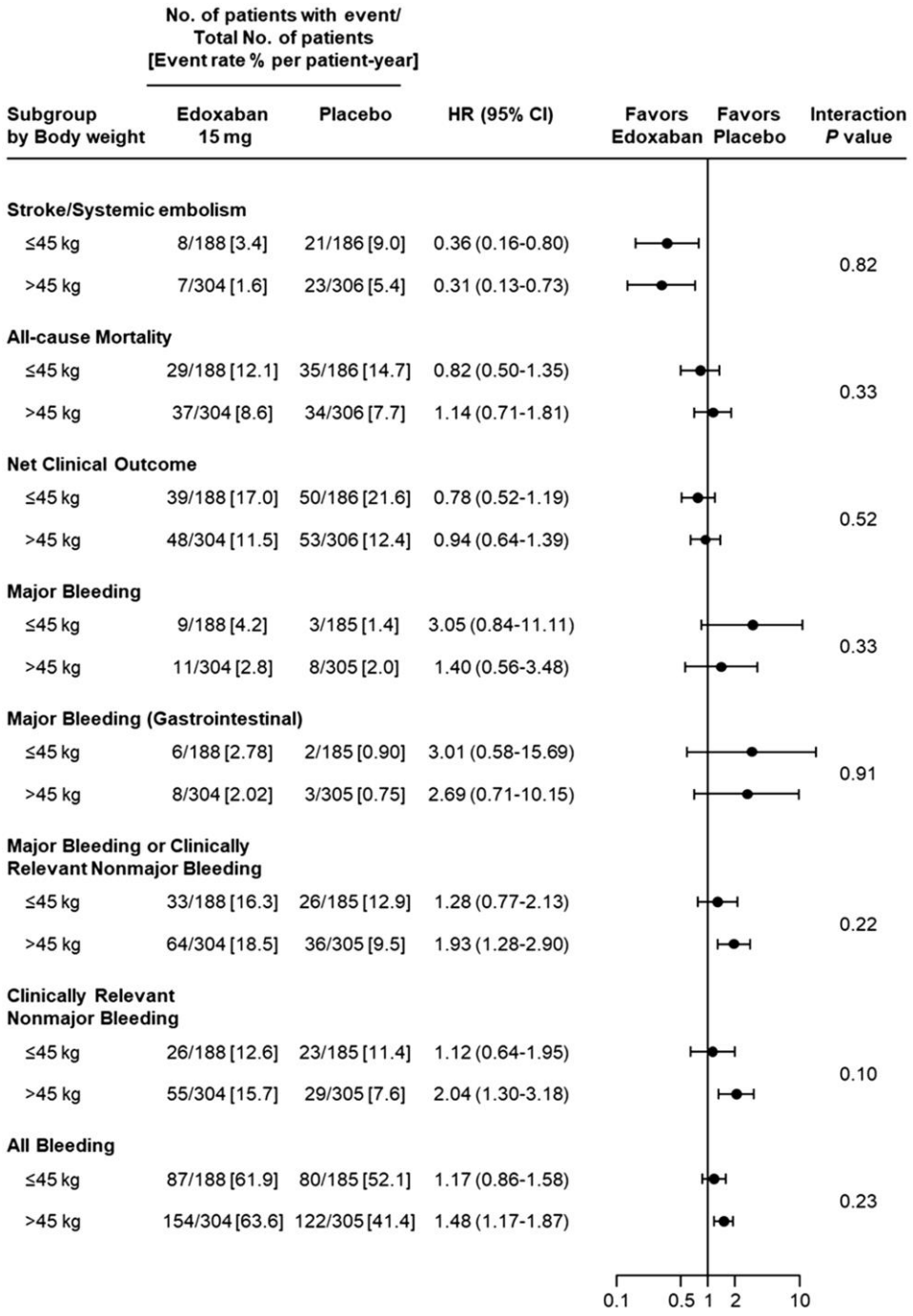
Effects of edoxaban on major efficacy and safety end points by body weight subgroup

- There were no significant differences between the edoxaban and placebo groups and no interaction with body weight



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Kaplan–Meier curves for stroke/systemic embolism (A), all-cause mortality (B), net clinical outcome (C), and major bleeding by body weight subgroup (D)

In the ≤45-kg group, major bleeding occurred in 9 of 188 patients (4.2% per patient-year) and 3 of 185 patients (1.4% per patient-year) in the edoxaban group and placebo group, respectively; though the rate of major bleeding was numerically higher in the edoxaban group, it was not significant (HR, 3.05 [95% CI, 0.84–11.11]).
In the >45-kg group, major bleeding occurred in 11 of 304 patients (2.8% per patient-year) and 8 of 305 patients (2.0% per patient-year) in the edoxaban group and placebo group, respectively

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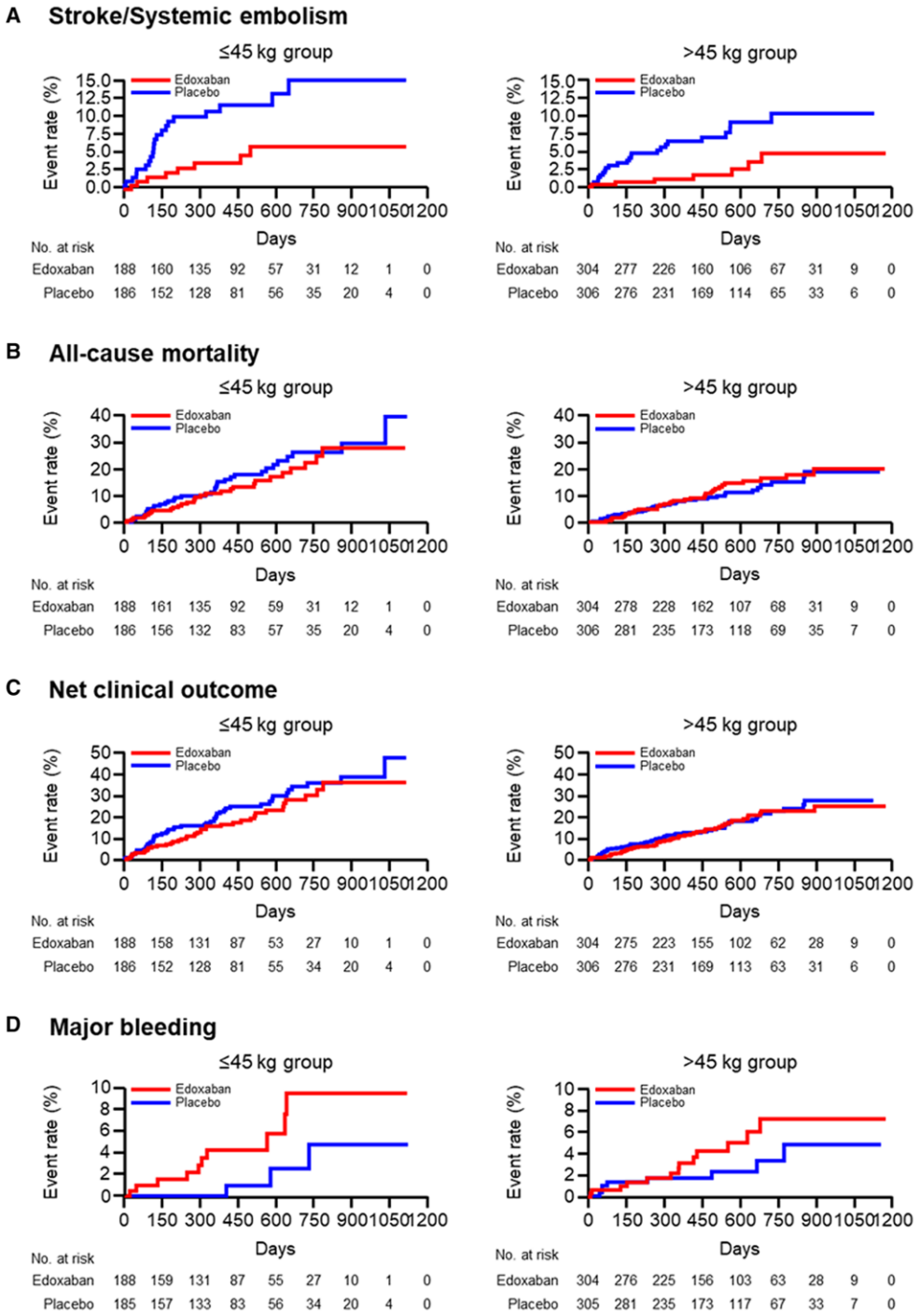

Major bleeding

- The most common major bleeding event was gastrointestinal bleeding in the edoxaban group and placebo group (n=6/9 and n=2/3 for the ≤45-kg group; n=8/11 and n=3/8 for the >45-kg group, respectively).
- In the ≤45-kg patient group, the incidence of gastrointestinal bleeding was 2.8% per patient-year (6/188) in the edoxaban group and 0.9% per patient-year (2/185) in the placebo group.
- In the ≤45-kg group, there were no cases of intracranial hemorrhage in either the edoxaban or the placebo groups.

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Limitations

- A substantial number of patients discontinued the trial because of their high-risk backgrounds, but no patients were lost to follow-up, and only 6 withdrew consent because of bleeding-related concerns. Of the patients who did withdraw, most did so due to adverse events that were unrelated to bleeding or participation was no longer possible.
- The trial involved Japanese patients with AF; therefore, the results may not be applicable to other populations with AF.
- The sample size of the trial was not powered for any of the subgroup analyses, resulting in relatively low event rates; therefore, the statistical power of the subgroup analyses was limited. The results of the subgroup analyses should be interpreted with caution.

Conclusions

- The results of the present study, which compared the placebo group and the edoxaban 15-mg groups in ELDERCARE-AF stratified by body weight (≤45 and >45 kg), suggest that edoxaban 15 mg may be considered in elderly high-risk patients with AF with low body weight, while remaining vigilant about the risk of major bleeding, especially gastrointestinal bleeding.

CLINICAL PERSPECTIVE

What Is New?

- Among elderly patients with nonvalvular atrial fibrillation who were considered ineligible for standard oral anticoagulants due to their high bleeding risk, treatment with edoxaban (15 mg) reduced the incidence of stroke/systemic embolism compared with placebo in both body weight groups (≤45 and >45 kg).
- The incidence of major bleeding events (predominantly gastrointestinal bleeding) was numerically higher in the edoxaban group than in the placebo group, but there was no interaction with body weight.

What Are the Clinical Implications?

- The benefit of edoxaban 15 mg was consistent in elderly patients with atrial fibrillation and a very low body weight; however, clinicians must remain vigilant about the risk of major bleeding, particularly gastrointestinal bleeding.

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