Edoxaban 15 mg nei pazienti anziani con fibrillazione atriale

ELDERCARE-AF: Edoxaban 15 mg for elderly Japanese AF patients ineligible for standard anticoagulants

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Background and Purpose

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- Thromboprophylaxis with oral anticoagulants (OACs) for stroke prevention is challenging in very elderly AF patients at high risk of bleeding complications[1,2]
- Information regarding the use of direct oral anticoagulants in this population is limited
- To address this issue, we evaluated efficacy and safety of **edoxaban 15 mg once daily** vs **placebo** in very elderly (≥80 years) Japanese nonvalvular AF patients with high risk of bleeding

ClinicalTrials.gov: NCT02801669

1. Kato ET, et al. *Ageing Res Rev*. 2019;49:115–24; 2. Akao M, et al. *Circulation J*. 2014;78:2166–72.

Trial Design and Population

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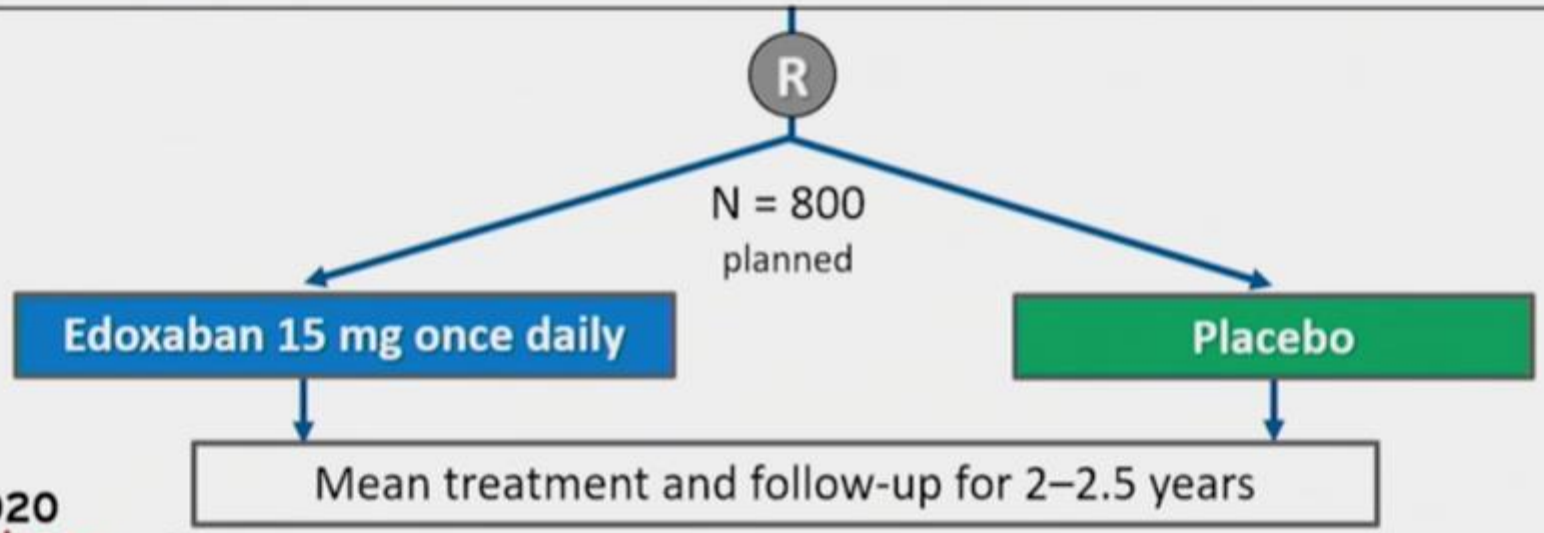
A phase 3, randomized, double-blind, placebo-controlled, event-driven, multicenter trial[1]

Patients ≥ 80 years with $CHADS_2$ score ≥2

Ineligible for standard OAC therapy at approved doses for ≥1 of the following reasons:

- Low creatinine clearance (CrCl, 15–30 mL/minute)
- Low body weight (≤45 kg)
- History of bleeding from critical organs or areas, or gastrointestinal bleeding
- Concomitant use of NSAIDs or antiplatelet therapy



1. Okumura K, et al. *Am Heart J*. 2017;194:99–106.

Trial End Points and Enrollment

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Primary Efficacy End Point

- Composite of stroke or systemic embolism
- Conducted in the ITT population
- Time to first onset of stroke or systemic embolism was analyzed using the Cox proportional hazards

Primary Safety End Point

- Major bleeding (ISTH criteria)
- The safety analysis set included patients who received ≥1 dose of trial drug
- Bleeding events were analyzed for the on-treatment period

- Between August 5, 2016, and November 5, 2019, 984 patients were enrolled from 164 institutions in Japan
- Median (interquartile range) trial duration was 466.0 (293.5–708.0) days

Patient Disposition

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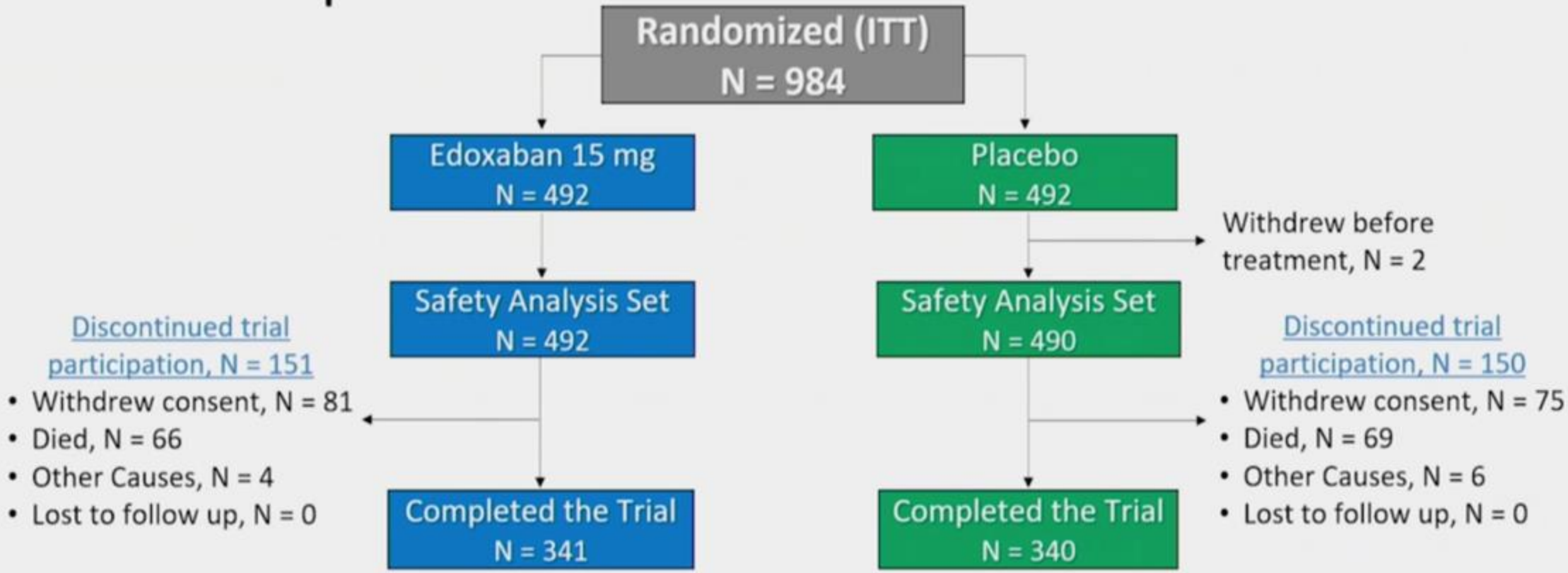

- Overall, 303 patients discontinued the trial
- There were no differences between arms in discontinuation rate or reasons for withdrawal

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Baseline Characteristics (ITT population)

	Edoxaban 15 mg (n = 492)	Placebo (n = 492)
Age, year, mean ± SD	86.7 ± 4.2	86.4 ± 4.3
Sex, Male, n (%)	212 (43.1)	207 (42.1)
Type of AF, Paroxysmal, n (%)	237 (48.2)	226 (45.9)
Body weight, kg, mean ± SD	50.6 ± 10.9	50.6 ± 11.1
BMI [a], kg/m^2, mean ± SD	22.1 ± 3.6	22.2 ± 3.8
CrCl, mL/min, mean ± SD	36.3 ± 14.3	36.2 ± 14.5
$CHADS_2$ score, mean ± SD	3.0 ± 1.1	3.1 ± 1.1
CHA_2DS_2-VASc score, mean ± SD	4.9 ± 1.2	5.0 ± 1.3
HAS-BLED score, mean ± SD	2.3 ± 0.9	2.4 ± 0.9
Coronary artery disease, n (%)	130 (26.4)	127 (25.8)
Frailty assessment [1,2,b], n (%)		
• Robust or pre-frail (score 0, 1-2)	289 (58.7)	253 (51.4)
• Frail (score ≥3)	185 (37.6)	217 (44.1)
History of OAC therapy, n (%)	207 (42.1)	216 (43.9)

[a]Missing: 1 edoxaban; 2 placebo; were unable to measure height in these patients. [b]Unevaluable: 7 edoxaban, 10 placebo; Missing: 11 edoxaban, 12 placebo.

[1]Research Funding for Longevity Sciences from National Center for Geriatrics and Gerontology, General Report, 2014. http://www.ncgg.go.jp/ncgg-kenkyu/kadai26.html. [2]Makizako H, et al. *BMJ Open.* 2015;e008462.

Reasons for Ineligibility for Standard OACs (ITT population)

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	Edoxaban 15 mg (n = 492)	Placebo (n = 492)
Reasons for OAC ineligibility, n (%)		
Severe renal impairment (CrCl <30 mL/min)	198 (40.2)	205 (41.7)
History of bleeding	110 (22.4)	112 (22.8)
• Intracranial	41 (8.3)	39 (7.9)
• Gastrointestinal	61 (12.4)	66 (13.4)
• Other	9 (1.8)	12 (2.4)
Low body weight (≤45 kg)	188 (38.2)	186 (37.8)
Continuous use of NSAIDs	149 (30.3)	168 (34.1)
Use of an antiplatelet drug	260 (52.8)	269 (54.7)
• Aspirin	134 (27.2)	157 (31.9)
• Clopidogrel	71 (14.4)	63 (12.8)
• Other	56 (11.4)	51 (10.4)

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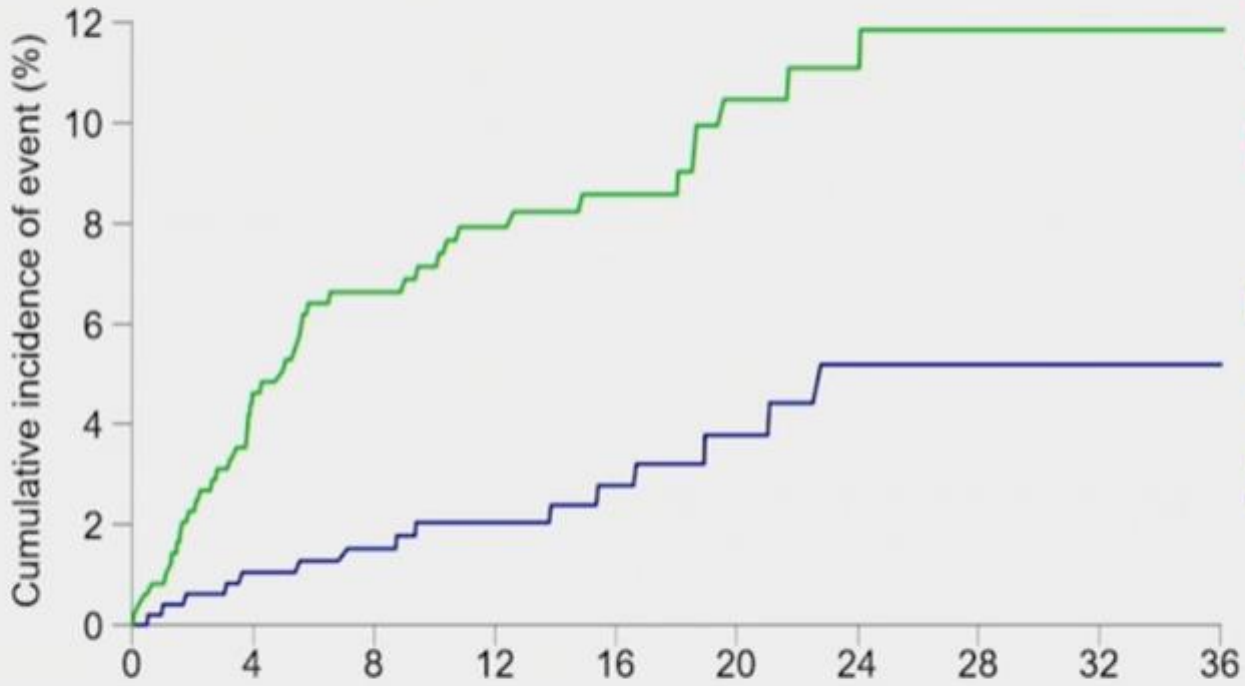
Primary Efficacy End Point

Stroke/Systemic Embolism



Placebo

44 events

6.7% per patient-year

Edoxaban 15 mg

15 events

2.3% per patient-year

HR, **0.34** (**0.19–0.61**)

P <0.001 (superiority)

Number at risk										
Edoxaban 15 mg	492	451	394	323	238	163	116	71	30	7
Placebo	492	439	388	314	237	170	120	74	32	6

Analysis was based on the ITT population.

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Efficacy End Points (ITT population)

	Edoxaban 15 mg (N = 492)		Placebo (N = 492)		
Primary efficacy end point	**N**	**% per patient-yr**	**N**	**% per patient-yr**	**Hazard ratio (95% CI)**
Stroke/systemic embolism	**15**	**2.3**	**44**	**6.7**	**0.34 (0.19–0.61)**
• Stroke	12	1.8	40	6.0	0.30 (0.16–0.57)
• Ischemic	12	1.8	39	5.9	0.31 (0.16–0.59)
• Hemorrhagic	0	0	2	0.3	-
• Fatal	1	0.1	3	0.4	0.34 (0.04–3.30)
• Systemic embolism	3	0.4	6	0.9	0.50 (0.13–2.01)
Secondary efficacy end points					
• All-cause mortality	66	9.9	69	10.2	0.97 (0.69–1.36)
• Stroke/systemic embolism/CV mortality	52	7.8	72	10.9	0.72 (0.50–1.03)
• Stroke/systemic embolism/all-cause mortality	74	11.1	98	14.8	0.75 (0.56–1.02)
• Major adverse cardiovascular events [a]	51	7.7	72	11.0	0.70 (0.49–1.01)
• Net clinical benefit outcome [b]	87	13.5	103	15.6	0.86 (0.65–1.15)

[a] Major adverse cardiovascular events include nonfatal myocardial infarction, nonfatal stroke, nonfatal systemic embolism, or deaths due to cardiovascular causes or bleeding. [b] Net clinical benefit outcome, stroke/systemic embolism/major bleeding/all-cause mortality

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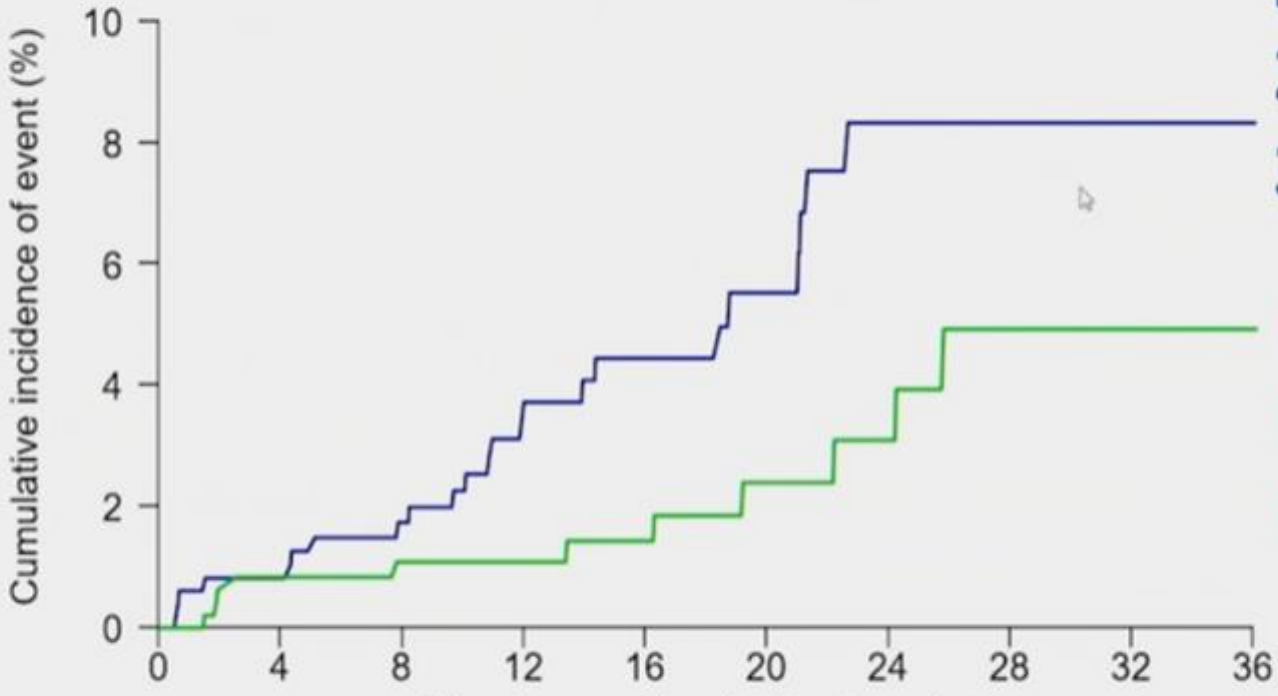
Primary Safety End Point
Major Bleeding



Edoxaban 15 mg

20 events

3.3% per patient-year

Placebo

11 events

1.8% per patient-year

HR, **1.87** (**0.90–3.89**)

P = 0.09

Number at risk										
Edoxaban 15 mg	492	452	391	314	231	158	107	64	28	7
Placebo	490	451	398	322	243	173	122	74	33	7

Analysis was based on the safety analysis set.

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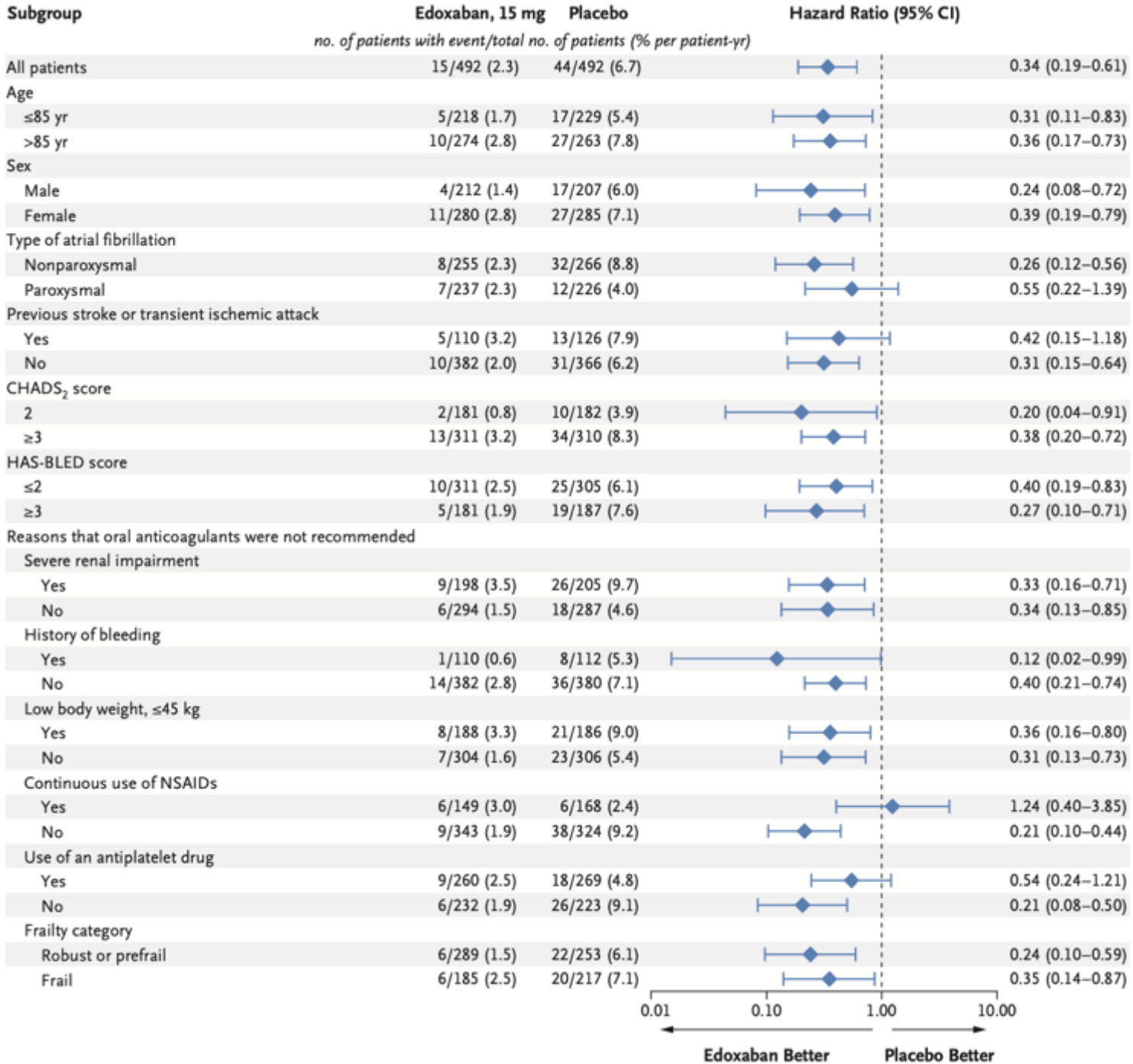
Safety End Points (Safety analysis set, On-treatment period)

	Edoxaban 15 mg (N = 492)		Placebo (N = 490)		
Primary safety end point	**N**	**% per patient-yr**	**N**	**% per patient-yr**	**Hazard ratio (95% CI)**
Major bleeding	**20**	**3.3**	**11**	**1.8**	**1.87 (0.90–3.89)**
• Intracranial hemorrhage	2	0.3	4	0.6	0.50 (0.09–2.72)
• Gastrointestinal bleeding	14	2.3	5	0.8	2.85 (1.03–7.88)
Secondary safety end points					
CRNM bleeding [a]	81	14.5	52	8.9	1.62 (1.14–2.30)
Major/CRNM bleeding	97	17.7	62	10.7	1.65 (1.20–2.27)
Any bleeding	241	63.0	202	45.0	1.35 (1.12–1.63)

[a] CRNM bleeding, clinically relevant non-major bleeding

- Edoxaban did not increase intracranial hemorrhage or fatal bleeding vs placebo
- Edoxaban caused more gastrointestinal bleeding and bleeding defined as secondary safety end points

Primary Efficacy End Point in Selected Subgroups.



Subgroup	Edoxaban, 15 mg	Placebo	Hazard Ratio (95% CI)
	no. of patients with event/total no. of patients (% per patient-yr)		
All patients	15/492 (2.3)	44/492 (6.7)	0.34 (0.19–0.61)
Age			
≤85 yr	5/218 (1.7)	17/229 (5.4)	0.31 (0.11–0.83)
>85 yr	10/274 (2.8)	27/263 (7.8)	0.36 (0.17–0.73)
Sex			
Male	4/212 (1.4)	17/207 (6.0)	0.24 (0.08–0.72)
Female	11/280 (2.8)	27/285 (7.1)	0.39 (0.19–0.79)
Type of atrial fibrillation			
Nonparoxysmal	8/255 (2.3)	32/266 (8.8)	0.26 (0.12–0.56)
Paroxysmal	7/237 (2.3)	12/226 (4.0)	0.55 (0.22–1.39)
Previous stroke or transient ischemic attack			
Yes	5/110 (3.2)	13/126 (7.9)	0.42 (0.15–1.18)
No	10/382 (2.0)	31/366 (6.2)	0.31 (0.15–0.64)
$CHADS_2$ score			
2	2/181 (0.8)	10/182 (3.9)	0.20 (0.04–0.91)
≥3	13/311 (3.2)	34/310 (8.3)	0.38 (0.20–0.72)
HAS-BLED score			
≤2	10/311 (2.5)	25/305 (6.1)	0.40 (0.19–0.83)
≥3	5/181 (1.9)	19/187 (7.6)	0.27 (0.10–0.71)
Reasons that oral anticoagulants were not recommended			
Severe renal impairment			
Yes	9/198 (3.5)	26/205 (9.7)	0.33 (0.16–0.71)
No	6/294 (1.5)	18/287 (4.6)	0.34 (0.13–0.85)
History of bleeding			
Yes	1/110 (0.6)	8/112 (5.3)	0.12 (0.02–0.99)
No	14/382 (2.8)	36/380 (7.1)	0.40 (0.21–0.74)
Low body weight, ≤45 kg			
Yes	8/188 (3.3)	21/186 (9.0)	0.36 (0.16–0.80)
No	7/304 (1.6)	23/306 (5.4)	0.31 (0.13–0.73)
Continuous use of NSAIDs			
Yes	6/149 (3.0)	6/168 (2.4)	1.24 (0.40–3.85)
No	9/343 (1.9)	38/324 (9.2)	0.21 (0.10–0.44)
Use of an antiplatelet drug			
Yes	9/260 (2.5)	18/269 (4.8)	0.54 (0.24–1.21)
No	6/232 (1.9)	26/223 (9.1)	0.21 (0.08–0.50)
Frailty category			
Robust or prefrail	6/289 (1.5)	22/253 (6.1)	0.24 (0.10–0.59)
Frail	6/185 (2.5)	20/217 (7.1)	0.35 (0.14–0.87)

Limitations

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- A substantial number of patients discontinued the trial due to withdrawal of consent (N = 158, 16.1% [edoxaban, N = 81; placebo, N = 77]), due to their high-risk backgrounds
- These results were obtained from Japanese AF patients and therefore may not be replicated in other populations

Summary and Conclusion

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- In very elderly Japanese nonvalvular AF patients with high risk of bleeding considered ineligible for standard OAC therapy, edoxaban 15 mg significantly reduced stroke/systemic embolism compared with placebo.
- The incidence of major bleeding was nonsignificantly higher with edoxaban, with no increase in intracranial hemorrhage or fatal bleeding observed with edoxaban.
- However, there was substantially more gastrointestinal bleeding, as well as bleeding defined as secondary safety end points, with edoxaban
- Edoxaban 15 mg may be an acceptable treatment option for stroke prevention in this high-risk population