Association of Edoxaban Concentration with Major Bleeding in Very Elderly Patients with Atrial Fibrillation Treated by Edoxaban 15 mg

A post-hoc analysis of ELDERCARE-AF trial

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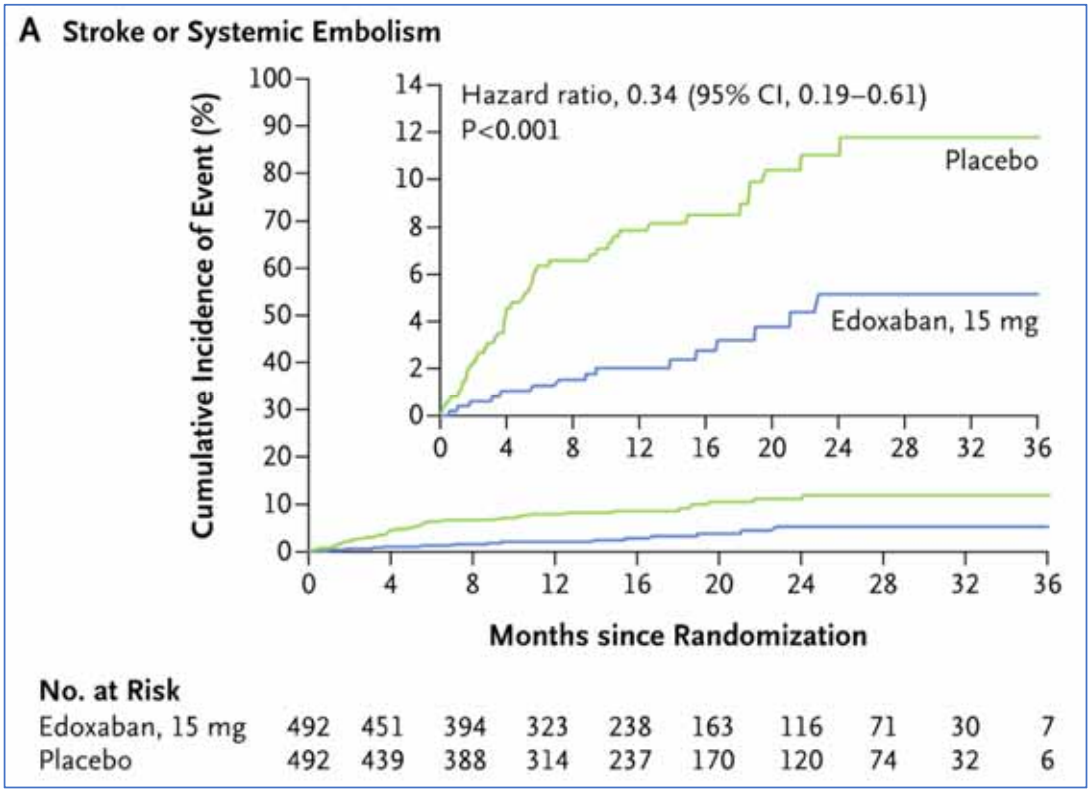
ELDERCARE-AF Trial

A randomized, placebo-controlled, double-blind ELDERCARE-AF trial demonstrated that low-dose (15 mg) edoxaban was superior to placebo in reducing stroke/systemic embolism (SE) in the Japanese very elderly AF patients at high-bleeding risk[1].



[1]*Okumura K, et al. N Engl J Med. 2020;383:1735-1745.*

Backgrounds

- The pharmacokinetics (PK) subanalysis of the ELDERCARE-AF showed that very elderly AF patients with severe renal impairment (CrCL, 15 to <30 mL/min) and low body weight (≤45 kg) had higher edoxaban plasma concentrations than those without, at trough after edoxaban administration[1].
- Another previous study showed that the once-daily regimen had lower trough edoxaban plasma concentrations and was associated with fewer bleeding events than the twice-daily regimen[2].
- Therefore, the higher trough edoxaban concentrations might be associated with the higher major bleeding risk in the ELDERCARE-AF.
- However, the relationships among pharmacokinetics of low-dose edoxaban, major bleeding events, and pharmacodynamics such as prothrombin time (PT) in the ELDERCARE-AF were undetermined.

[1]*Yamashita T et al. Thromb Haemost. 2024;124:874–882.*
[2]*Weitz JI et al. Thromb Haemost. 2010;104:633–641.*

Objectives

This post-hoc analysis of the ELDERCARE-AF aimed to determine the relationship between the edoxaban (15 mg) PK data and bleeding events. Further, the role of PT in predicting the development of major bleeding in the very elderly AF patients was studied.

Methods

ELDERCARE-AF

Patients

- **Aged ≥80 years** with $CHADS_2$ score ≥2
- Inappropriate for standard oral anticoagulants (OAC) for: **low CrCl** (15 to <30 mL/min); **low body weight** (≤45 kg)**; history of bleeding** from critical organs or GI bleeding; concomitant use of **NSAIDs** or **antiplatelet therapy**.

Intervention and sample collection

- **15 mg of edoxaban** once daily
- Blood sampling before edoxaban administration (**trough**) at Week 8.
- Trough edoxaban concentrations were **divided into quarters**.

Key outcomes

- **Incidences of bleeding and stroke/SE events for each of trough concentration quartiles** and **by PT median value**.

Trough edoxaban concentration quartiles and patient characteristics in each quartile

ELDERCARE-AF

Quartiles by trough edoxaban concentration (EC, ng/mL)	1st quartile EC ≤9.24 (n = 107)	2nd quartile 9.24< EC ≤13.6 (n = 111)	3rd quartile 13.6< EC ≤21.6 (n = 103)	4th quartile 21.6< EC (n = 106)	*P* value[b]
Age, years	85.1 ± 3.5	86.7 ± 4.1	86.7 ± 4.3	88.7 ± 4.4	<0.0001
Sex, male	49 (45.8)	49 (44.1)	40 (38.8)	45 (42.5)	0.7675
Non-paroxysmal atrial fibrillation	33 (30.8)	47 (42.3)	61 (59.2)	71 (67.0)	<0.0001
Weight, kg	53.4 ± 11.8	51.8 ± 10.5	50.5 ± 9.8	46.8 ± 9.4	<0.0001
Creatinine clearance, mL/min	46.4 ± 17.2	38.1 ± 13.1	33.4 ± 10.7	28.3 ± 8.8	<0.0001
CHADS2 score	2.8 ± 1.1	2.9 ± 1.1	3.0 ± 1.0	3.3 ± 1.0	0.0153
Risk factor for thromboembolism					
Previous stroke or TIA	19 (17.8)	25 (22.5)	22 (21.4)	24 (22.6)	0.7990
Congestive heart failure	37 (34.6)	44 (39.6)	60 (58.3)	80 (75.5)	<0.0001
Diabetes mellitus	24 (22.4)	26 (23.4)	23 (22.3)	28 (26.4)	0.8448
Hypertension	95 (88.8)	96 (86.5)	84 (81.6)	84 (79.2)	0.2043
HAS-BLED score	2.2 ± 0.8	2.3 ± 0.8	2.4 ± 0.9	2.3 ± 1.0	0.4470
Frailty category	n = 106	n = 109	n = 100	n = 105	0.6982
Robust	13 (12.1)	9 (8.1)	5 (4.9)	2 (1.9)	0.0492
Pre-frail	61 (57.0)	65 (58.6)	53 (51.5)	51 (48.1)	
Frail	32 (29.9)	35 (31.5)	42 (40.8)	52 (49.1)	
Concomitant use of P-glycoprotein inhibitors	4 (3.7)	4 (3.6)	8 (7.8)	10 (9.4)	0.1859

Data are n (%) or mean ± standard deviation (SD). TIA=transient ischemic attack

[b]*P*-values were calculated using one way analysis of variance for continuous variables and chi square test for categorical variables.

Factors associated with trough edoxaban concentration by multiple regression analysis model

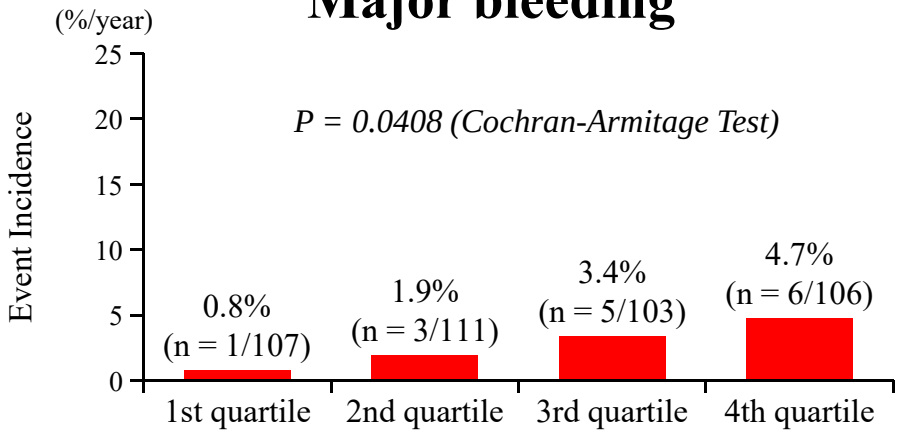
Factor	Freedom	Mean sum of squares	F-score	P-value (Pr >F)
Age	1	6.446	5.62	0.0182
Weight	1	4.093	3.57	0.0595
Creatinine clearance	1	10.272	8.96	0.0029
$CHADS_2$ score	1	0.539	0.47	0.4932
Presence or absence of congestive heart failure	1	8.188	7.14	0.0078

The event rates by trough edoxaban concentration quartiles

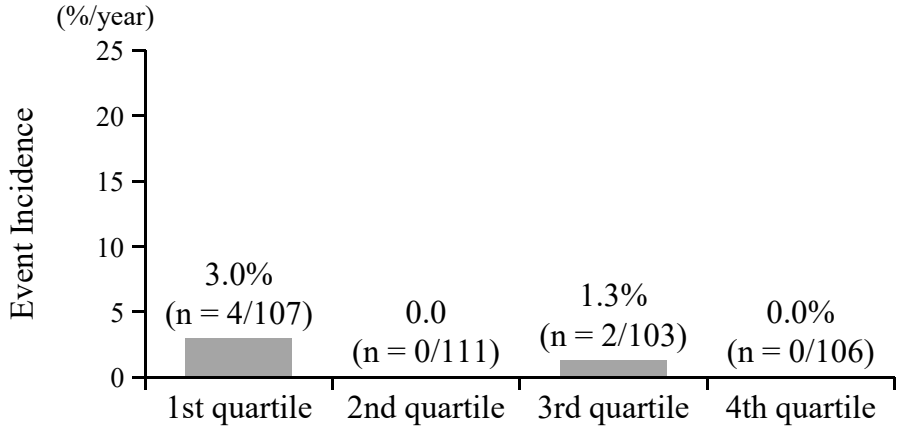
Edoxaban concentration quartiles:

- 1st quartile: ≤9.24 ng/mL
- 2nd quartile: 9.24< EC ≤13.6 ng/mL
- 3rd quartile: 13.6< EC ≤21.6 ng/mL
- 4th quartile: 21.6 ng/mL< EC.

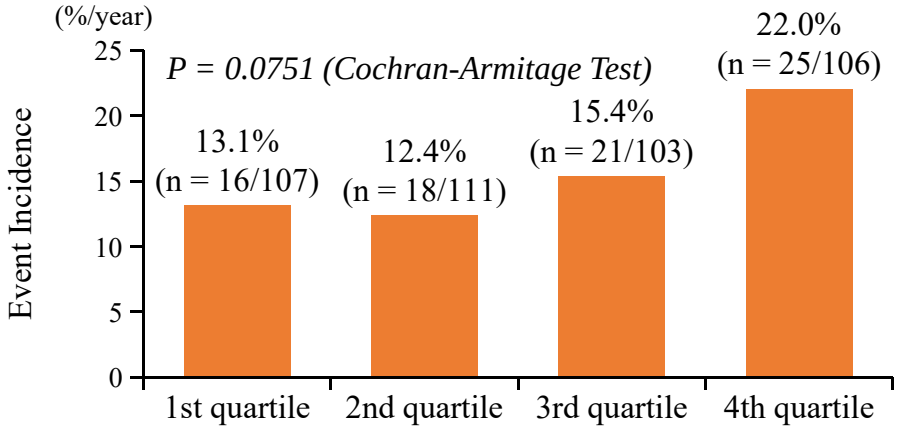
Major bleeding



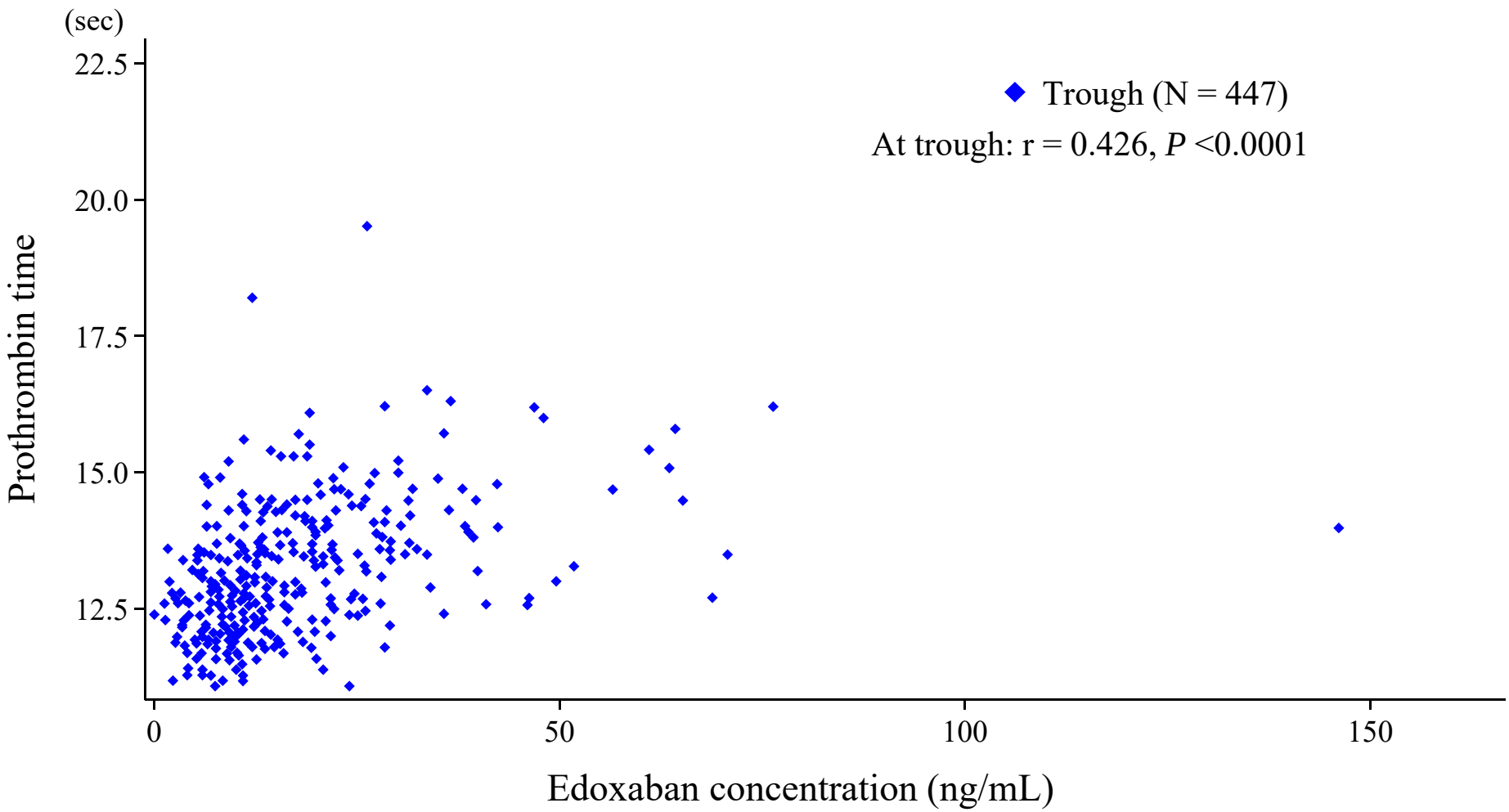
Stroke or Systemic embolism



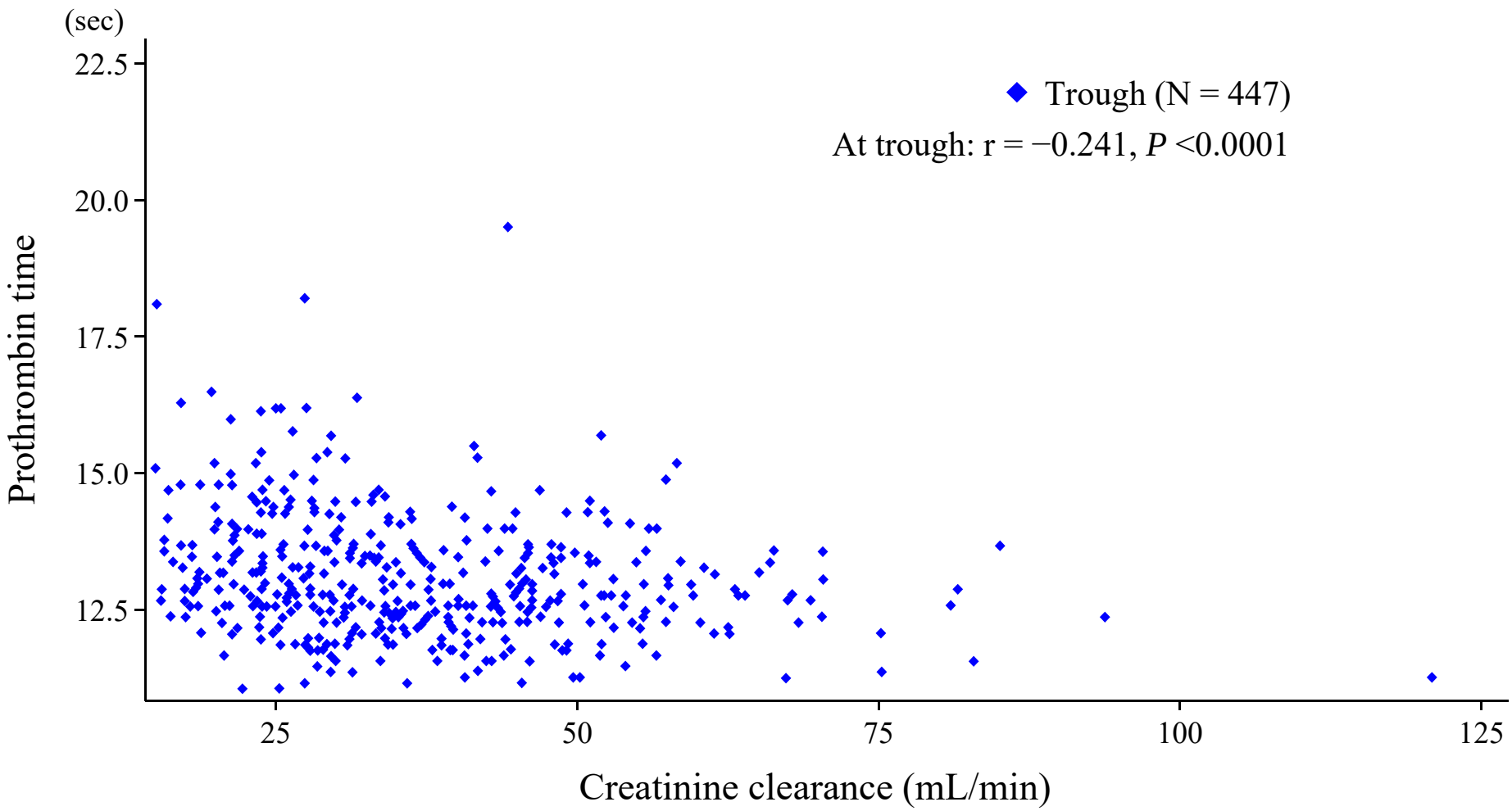
Major bleeding + clinically relevant non-major bleeding



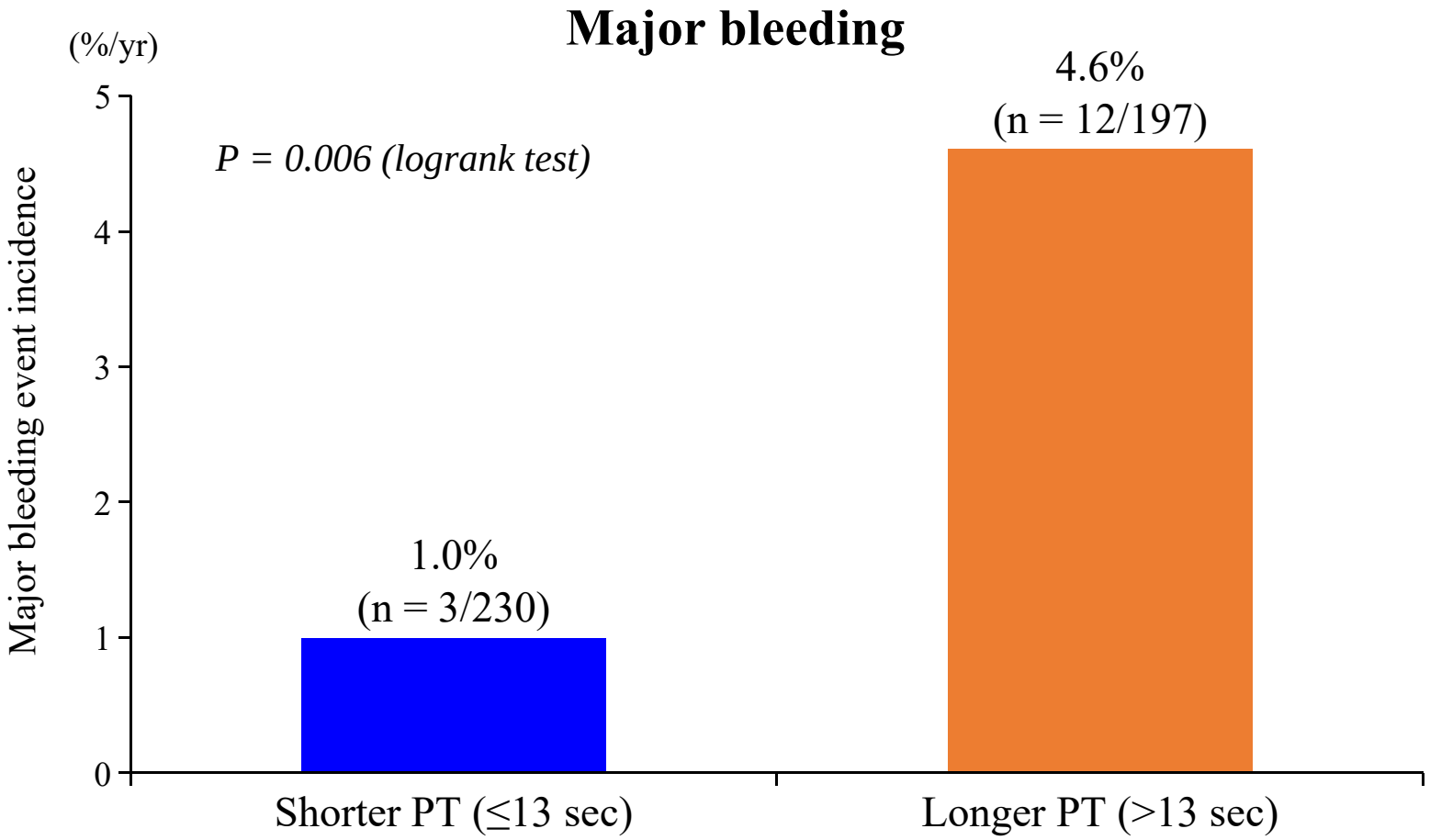
Scatter plot of prothrombin time vs edoxaban plasma concentration at trough



Scatter plot of prothrombin time vs creatinine clearance

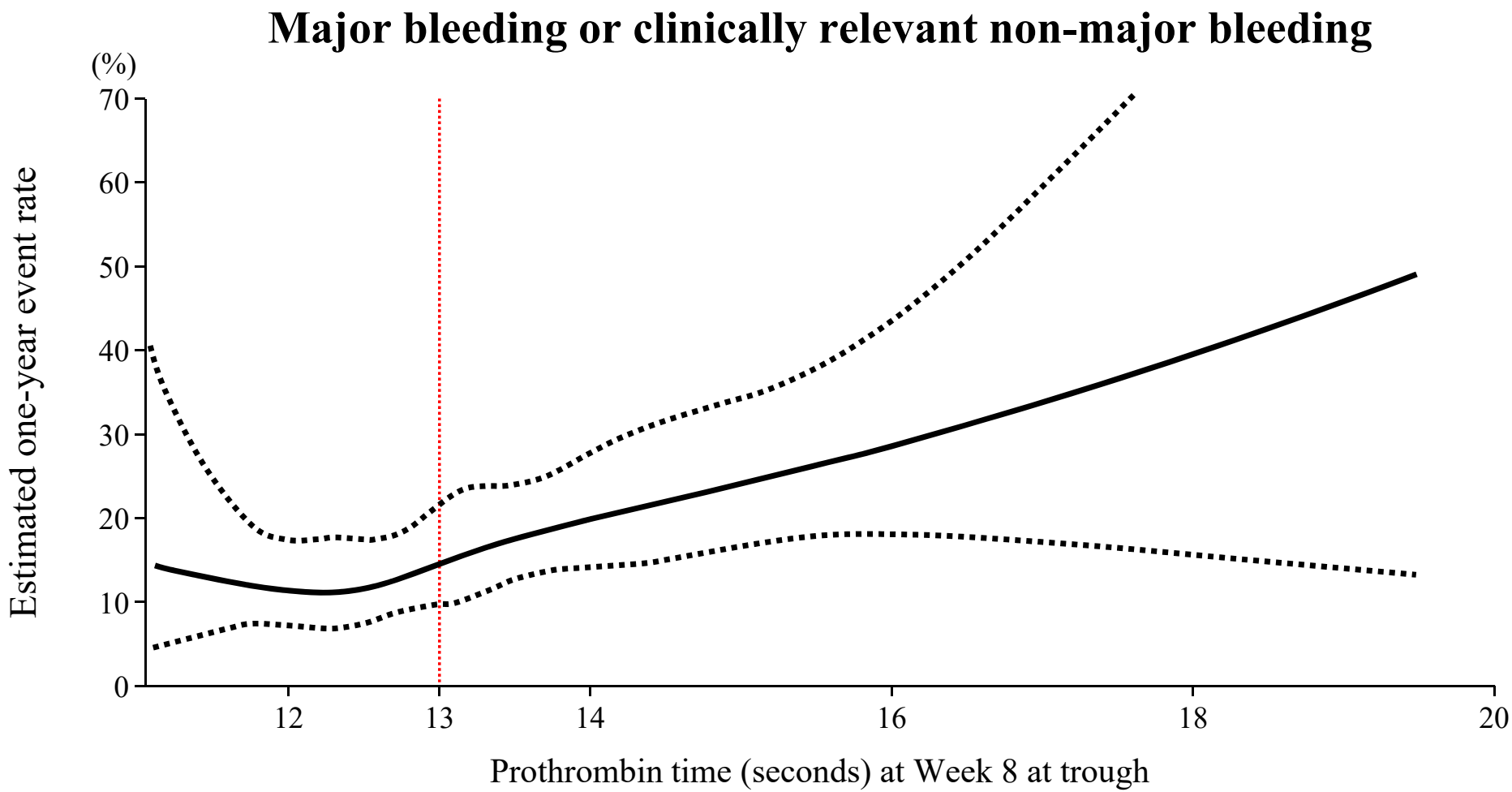


The incidence of major bleeding by PT subgroups

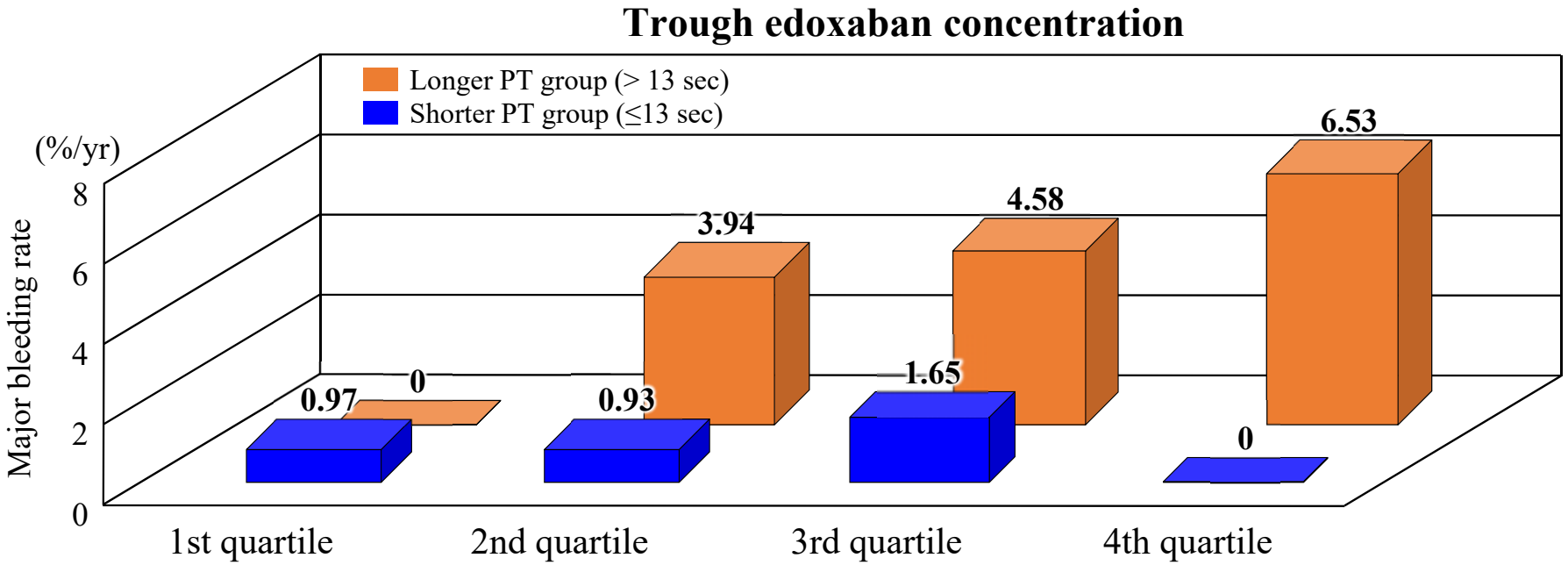


PT, Prothrombin time.

One-year bleeding rate by PT at trough



Incidence of major bleeding events by PT median across edoxaban plasma concentration quartiles



	1st quartile	2nd quartile	3rd quartile	4th quartile
Longer PT >13 sec (n)	27	34	56	80
Major bleeding (n)	0	2	4	6
CrCl, mL/min (mean ± SD)	44.8 ± 15.6	37.5 ± 15.3	33.6 ± 10.3	28.0 ± 8.9
Shorter PT≤13 sec (n)	80	77	47	26
Major bleeding (n)	1	1	1	0
CrCl, mL/min (mean ± SD)	47.0 ± 17.7	38.4 ± 12.1	33.1 ± 11.2	29.1 ± 8.4

CrCl, creatinine clearance; PT, Prothrombin time; SD, standard deviation.

Summary

- Higher trough edoxaban concentrations occurred in patients with higher age, lower body weight, lower CrCl and heart failure.
- The higher the trough edoxaban concentration, the greater the incidence of major bleeding.
- PT was positively correlated with trough edoxaban concentration and was negatively with CrCl.
- The incidence of major bleeding was higher in patients with longer PT (>13 seconds) than shorter PT (≤13 seconds) at trough.

Limitation

- This post hoc analysis included only patients from the main ELDERCARE-AF study who consented to have their blood drawn for PK analyses.
- The sample size of the main trial was not pre-specified for the PK subanalysis.
- There were only a few bleeding events.
- The small number of blood sampling may limit the ability to assess variations in PK data and its relationship to safety outcomes.
- PT data was derived from a limited number of blood sample and was known to be sensitive to reagents and measurement equipment, which may affect the generalizability of the findings.

Conclusions

In the very elderly, high-bleeding risk AF patients treated with edoxaban (15 mg):

- Higher trough edoxaban concentration, which occurs in patients with higher age, lower body weight, lower CrCl and heart failure, is associated with increased risk of major bleeding.
- PT >13 seconds may be useful to predict the development of major bleeding.