Edoxaban for 3 months versus 12 months in cancer patients with isolated distal deep vein thrombosis: ONCO DVT Study

Yugo Yamashita

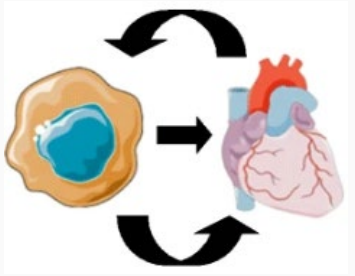
Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University

HOT LINE 9; 28 August 2023; 16:50-

Declaration of interest

- Research contracts : Funding was provided by Daiichi Sankyo Company, Limited, which had no role in the study design, data collection, analysis, interpretation, or writing of the report.
- Others : Dr. Yamashita received lecture fees from Bayer Healthcare, Bristol-Myers Squibb, Pfizer, and Daiichi Sankyo, and grant support from Bayer Healthcare and Daiichi Sankyo.

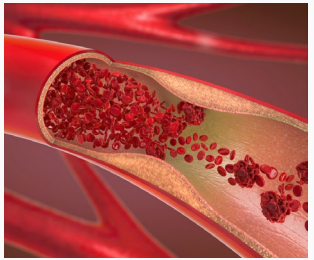
Background



- **Cancer** patients: Surviving longer

---> **Cardiovascular complications ↑↑**: **cardio-oncology**.

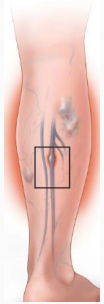
(Eur Heart J. 2022;43:4229-4361.)



- **Venous thromboembolism** (VTE): Risk of **recurrence**.

---> Can be **prevented** by **anticoagulation therapy**.

(Lancet. 2010;376:2032-9.)



- Isolated **distal** deep vein thrombosis (**DVT**): Common

---> More benign or not than a **proximal** DVT?

(Thromb Res. 2014;134:36-40. J Vasc Surg. 2012;55:550-61.)

Background

- **Guidelines recommendations** for isolated distal DVT (ACCP/CHEST)

---> **Anticoagulation of prolonged** duration for **cancer** patients

(**Weak** recommendation, **Low-certainty** evidence)

(Chest. 2021;160:e545-e608.)

- **Previous RCTs** for distal DVT (CACTUS [2016], RIDTS [2022])

---> **Excluded** patients with **active cancer**

(Lancet Haematol. 2016;3:e556-e562. BMJ. 2022;379:e072623.)

- **No RCT** for optimal duration of anticoagulation therapy for **cancer patients**

Purpose of the ONCO DVT study

To compare 12-month edoxaban treatment with 3-month edoxaban treatment in cancer patients with isolated distal DVT in a randomized clinical trial.

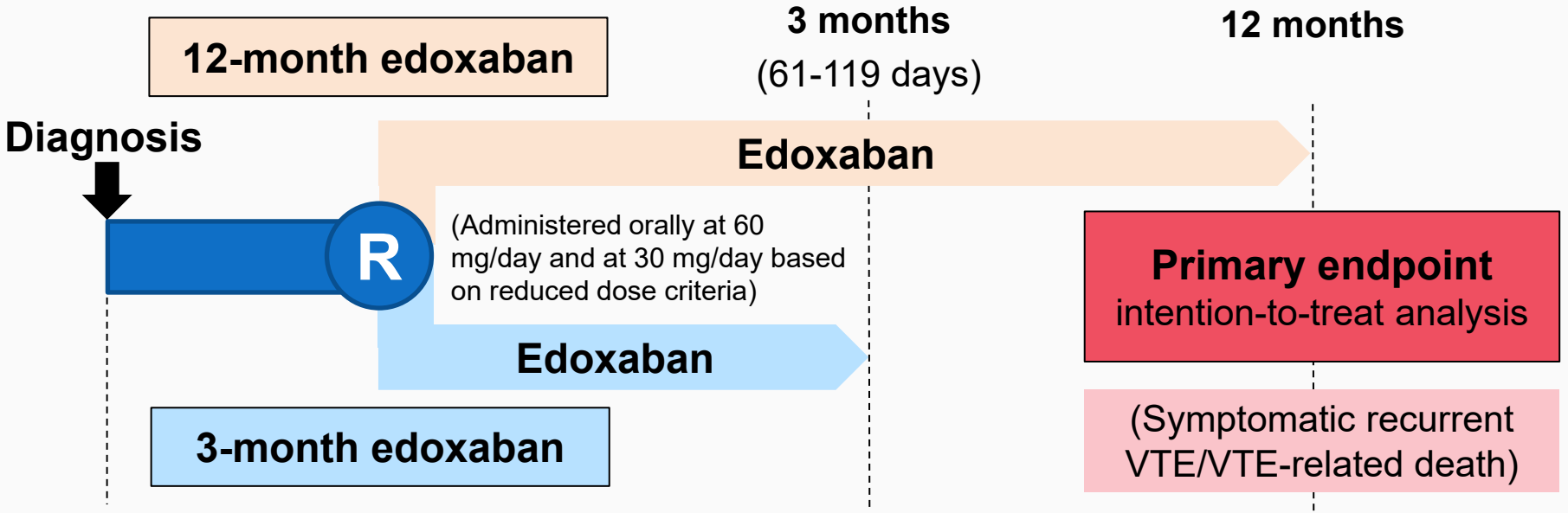
ONCO DVT Study: NCT03895502

(Optimal duration of anticoagulation therapy for isolated distal deep vein thrombosis in patients with cancer study)

Study design: ONCO DVT study

(A multicenter, open-label, adjudicator-blinded, randomized clinical trial)

Patients with active cancer who were newly diagnosed with isolated distal DVT confirmed by ultrasonography were eligible for inclusion.



Inclusion and Exclusion Criteria

Key Inclusion Criteria

- ✓ A new diagnosis of DVT objectively confirmed by ultrasonography
- ✓ With active cancer at randomization
- ✓ Scheduled for DVT treatment with anticoagulation therapy

Key Exclusion Criteria

- ✓ Already on anticoagulation therapy at the time of the diagnosis
- ✓ With pulmonary embolism
- ✓ Expected to have a life prognosis of 3 months or less

Endpoints

- **Primary endpoint (ITT analysis)**
  - ✓ Symptomatic recurrent VTE or VTE-related death at 12 months
- **Major secondary endpoint (ITT analysis)**
  - ✓ A major bleeding event (ISTH criteria definition) at 12 months

Sample Size Calculation

- **Hypothesis: Superiority of 12-month to 3-month edoxaban for the primary endpoint at 12 months**
- Assumption: Event rate at 12-month: 6% (12-month group)
  13% (3-month group)
- Randomization ratio: 1:1
- Power: 80%
- Two-sided alpha: 0.05
- Sample size: 550 patients (275 in each arm)
- Considering the potential dropouts: **600** patients

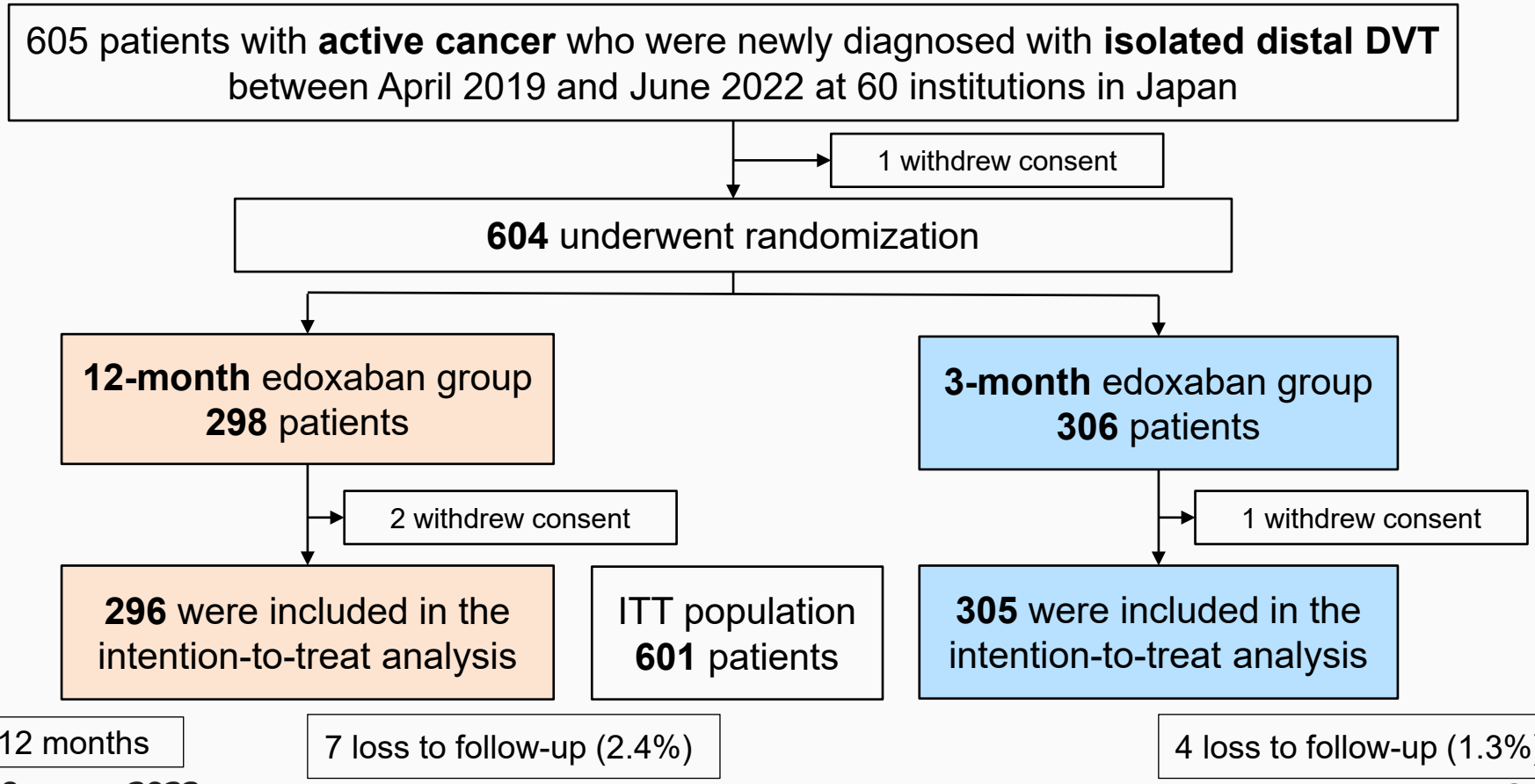
60 participating centers

Kyoto University Hospital
Osaka International Cancer Institute
Saiseikai Noe Hospital
Osaka Red Cross Hospital
Japanese Red Cross Otsu Hospital
Kakogawa Central City Clinics
Cancer Institute Hospital
Kansai Medical University Medical Center
Kyoto Prefectural University of Medicine
Kyorin University Faculty of Medicine
Kindai University Hospital
Kumamoto University Hospital
Kurashiki Central Hospital
Kurume University Hospital
Kuwana City Medical Center
Gunma University
Kobe City Medical Center General Hospital
Kobe University Hospital
Kohka Public Hospital
Fukushima Medical University Hospital
Kokura Memorial Hospital
National Cancer Center Hospital
NHO Okayama Medical Center
NHO Kyoto Medical Center
Saiseikai Yokohamashi Nanbu Hospital
Saiseikai Wakayama Hospital
Saku Central Hospital Advanced Care Center
Shiga General Hospital
Shizuoka Cancer Center
Shizuoka City Shizuoka Hospital
Shimane University Hospital
Shimada General Medical Center
St. Marianna University School of Medicine
Medical Research Institute Kitano Hospital
University of Tsukuba Hospital
Tenri Hospital
Tokyo Women's Medical University Hospital
Tokyo Metropolitan Tama Medical Center
Toho University Ohashi Medical Center
Toho University Omori Medical Center
Tohoku University Hospital
Nagasaki University Hospital
Nara Medical University Hospital
Nippon Medical School Hospital
Japanese Red Cross Wakayama Medical Center
Hyogo Prefectural Amagasaki General Medical Center
Hirakata Kohsai Hospital
Fukui Prefectural Hospital
Saiseikai Yahata General Hospital
Fujisawa City Hospital
Makiminato Central Hospital
Mie University Hospital
Mitsubishi Kyoto Hospital
Japanese Red Cross Musashino Hospital
Yokohama Minami Kyousai Hospital
Yokohama Rosai Hospital
Rakuwakai Otowa Hospital
Niigata University Graduate School of Medicine and Dentistry
Niigata Cancer Center Niigata Hospital
Hyogo College of Medicine

with collaboration of
cardiologists and **oncologists**

ONCO DVT Study

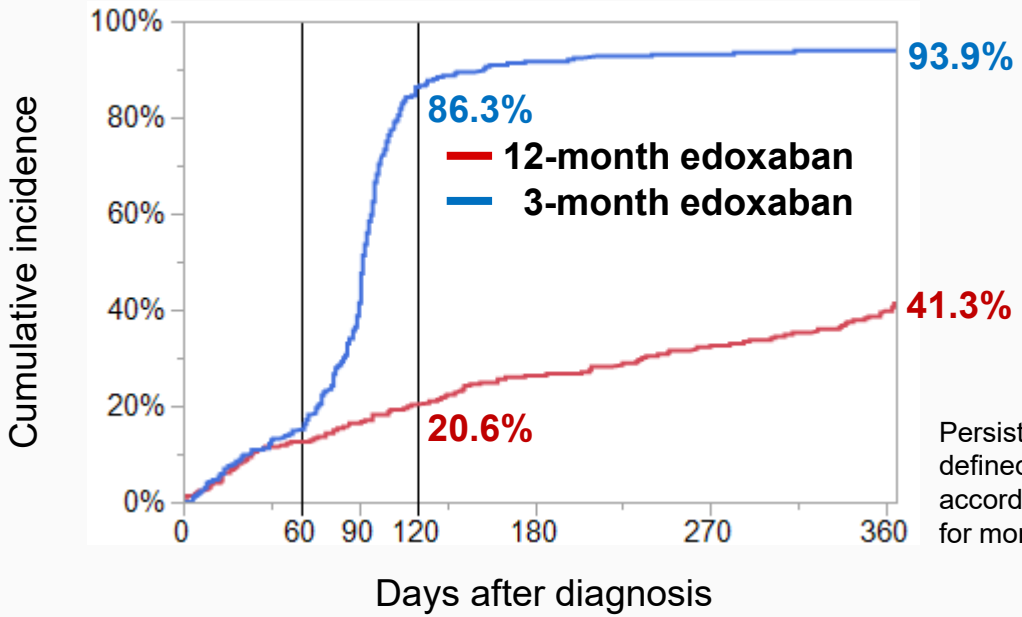
Study Flow


605 patients with **active cancer** who were newly diagnosed with **isolated distal DVT** between April 2019 and June 2022 at 60 institutions in Japan
1 withdrew consent
604 underwent randomization
12-month edoxaban group **298** patients
3-month edoxaban group **306** patients
2 withdrew consent
1 withdrew consent
296 were included in the intention-to-treat analysis
ITT population **601** patients
305 were included in the intention-to-treat analysis
At 12 months
7 loss to follow-up (2.4%)
4 loss to follow-up (1.3%)

Clinical characteristics at baseline

Variables, No. (%)	12-month edoxaban (N=296)	3-month edoxaban (N=305)
Age, years (Mean± SD)	71.6±9.4	70.1±10.3
Male sex	94 (32)	73 (24)
Body weight, kg	56.3±12.1	54.8±11.6
Symptoms at baseline	53 (18)	69 (23)
Lower dose of edoxaban (30 mg/day)	216 (73)	234 (77)
Cancer status		
Metastatic disease	67 (23)	80 (26)
ECOG performance status		
0	161 (54)	150 (49)
1	78 (26)	103 (34)
≥2	57 (19)	52 (17)
History of venous thromboembolism	20 (6.8)	13 (4.3)
Creatinine clearance ≤50 mL/min	69 (23)	62 (20)
Anemia (Hb <13 g/dL for men and <12 g/dL for women)	199 (67)	203 (67)
Platelet count <100,000 per μL	12 (4.1)	19 (6.2)

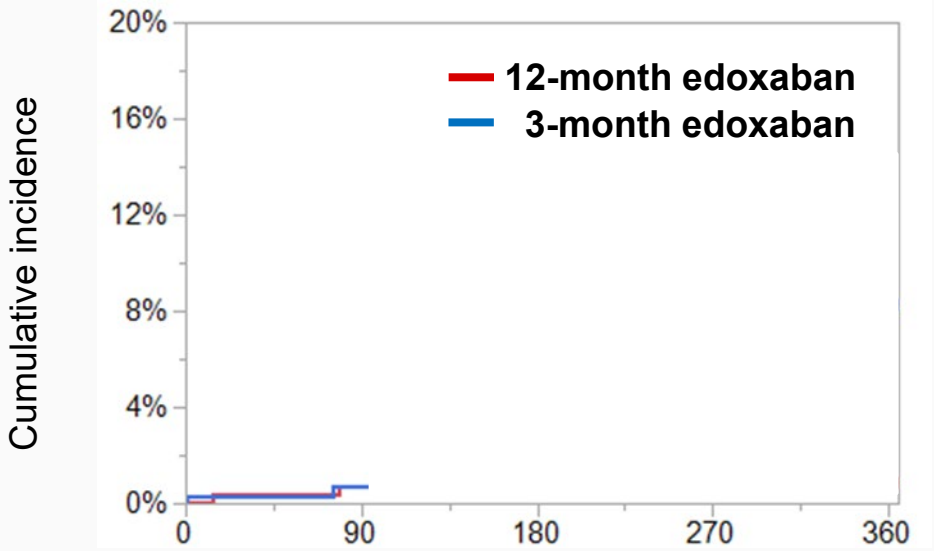
Persistent edoxaban discontinuation



Persistent edoxaban discontinuation was defined as a discontinuation of edoxaban according to the study protocol or lasting for more than 14 days for any reason.

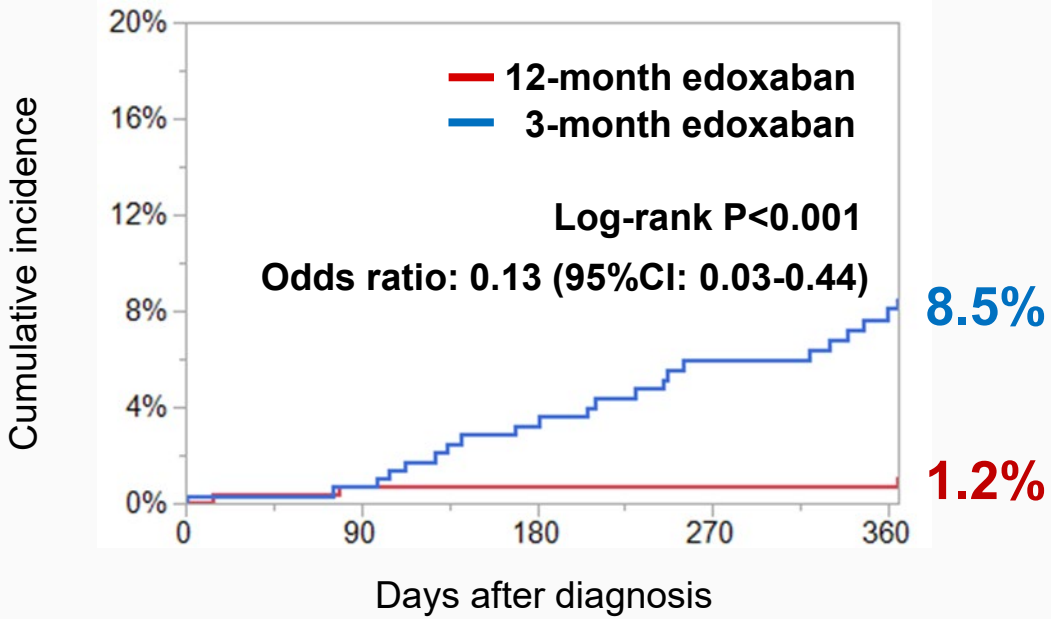
N of patients on edoxaban	0-day	60-day	90-day	120-day	180-day	365-day
12-month edoxaban	296	253	240	224	202	151
3-month edoxaban	305	255	173	40	23	15

Primary endpoint (Symptomatic recurrent VTE or VTE-related death)



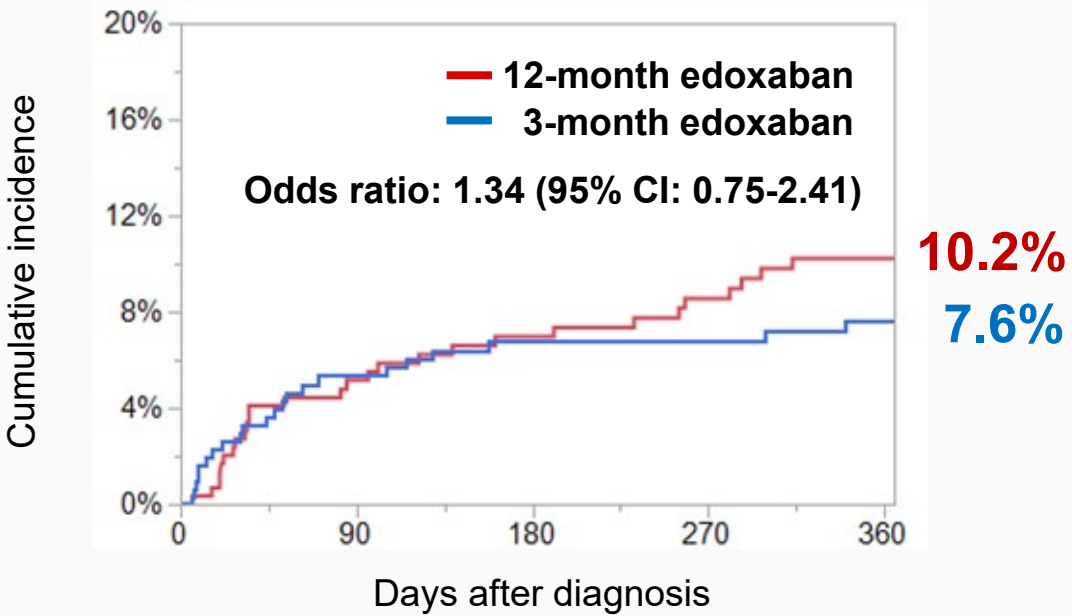
N of patients at risk	0-day	60-day	90-day
12-month edoxaban	296	283	274
3-month edoxaban	305	289	280

Primary endpoint (Symptomatic recurrent VTE or VTE-related death)



N of patients at risk	0-day	60-day	90-day	120-day	180-day	365-day
12-month edoxaban	296	283	274	269	253	222
3-month edoxaban	305	289	280	275	256	210

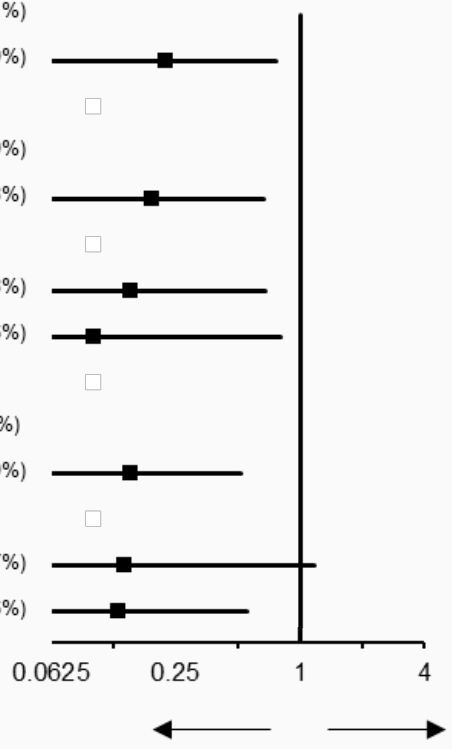
Major secondary endpoint (Major bleeding)

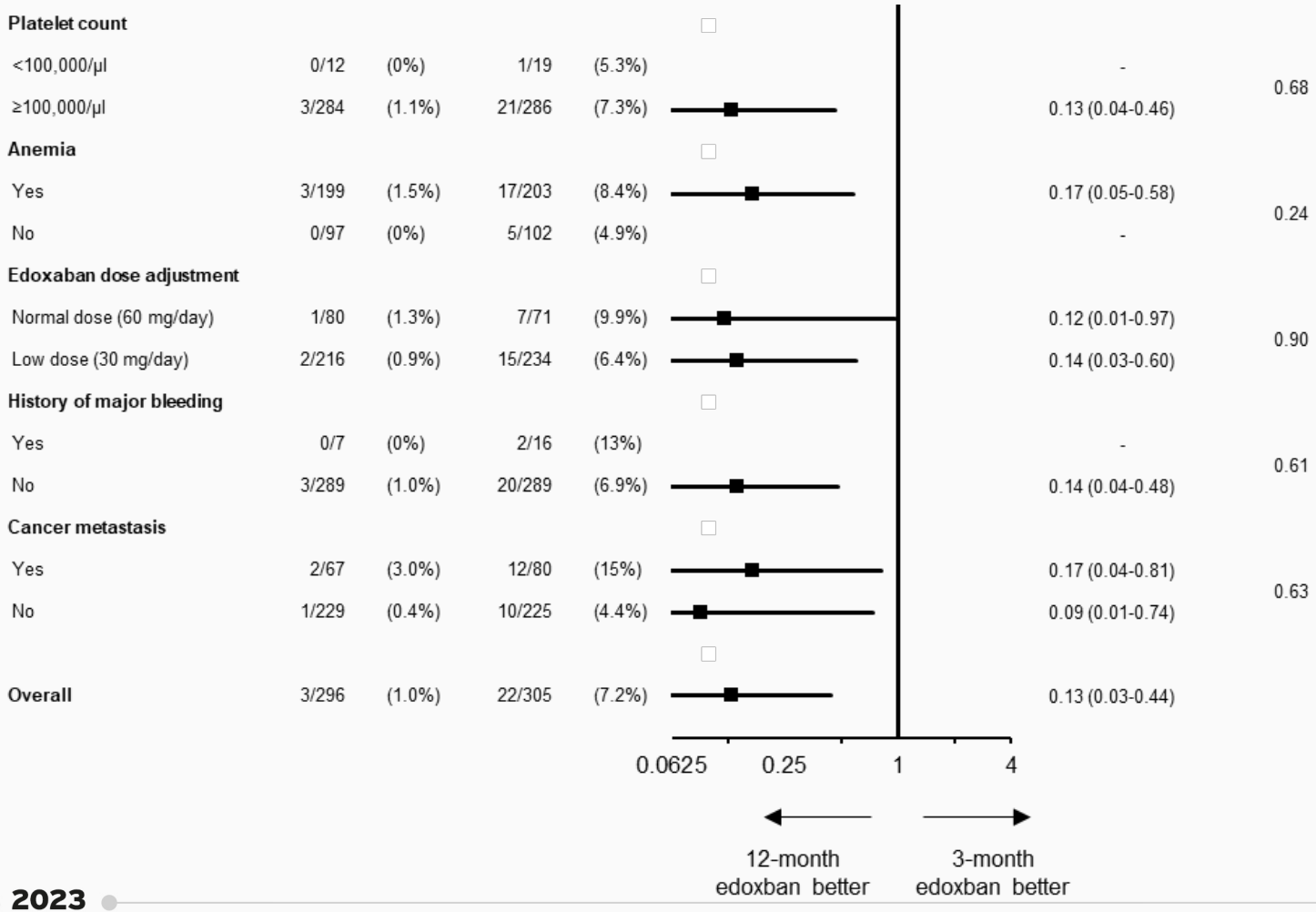


N of patients at risk	0-day	60-day	90-day	120-day	180-day	365-day
12-month edoxaban	296	273	267	261	245	210
3-month edoxaban	305	279	271	264	250	217

Subgroup analyses for the primary endpoint

	12-month edoxaban (N=296)		3-month edoxaban (N=305)		OR (95%CI)	P interaction
Age						
≥75 years	0/131	(0%)	7/114	(6.1%)	-	0.11
<75 years	3/165	(1.8%)	15/191	(7.9%)	0.22 (0.06-0.76)	
Sex						
Male	0/94	(0%)	5/73	(6.9%)	-	0.16
Female	3/202	(1.5%)	17/232	(7.3%)	0.19 (0.06-0.66)	
Weight						
<60 kg	2/199	(1.0%)	14/222	(6.3%)	0.15 (0.03-0.67)	0.74
≥60 kg	1/97	(1.0%)	8/83	(9.6%)	0.10 (0.01-0.80)	
History of VTE						
Yes	0/20	(0%)	2/13	(15%)	-	0.35
No	3/276	(1.1%)	20/292	(6.9%)	0.15 (0.04-0.51)	
Creatinine clearance						
≤50 mL/min	1/69	(1.5%)	6/62	(9.7%)	0.14 (0.02-1.17)	0.95
>50 mL/min	2/227	(0.9%)	16/243	(6.6%)	0.13 (0.03-0.55)	




Platelet count
<100,000/μl 0/12 (0%) 1/19 (5.3%) - 0.68
≥100,000/μl 3/284 (1.1%) 21/286 (7.3%) 0.13 (0.04-0.46)
Anemia
Yes 3/199 (1.5%) 17/203 (8.4%) 0.17 (0.05-0.58) 0.24
No 0/97 (0%) 5/102 (4.9%) -
Edoxaban dose adjustment
Normal dose (60 mg/day) 1/80 (1.3%) 7/71 (9.9%) 0.12 (0.01-0.97) 0.90
Low dose (30 mg/day) 2/216 (0.9%) 15/234 (6.4%) 0.14 (0.03-0.60)
History of major bleeding
Yes 0/7 (0%) 2/16 (13%) - 0.61
No 3/289 (1.0%) 20/289 (6.9%) 0.14 (0.04-0.48)
Cancer metastasis
Yes 2/67 (3.0%) 12/80 (15%) 0.17 (0.04-0.81) 0.63
No 1/229 (0.4%) 10/225 (4.4%) 0.09 (0.01-0.74)
Overall 3/296 (1.0%) 22/305 (7.2%) 0.13 (0.03-0.44)
0.0625
0.25
1
4
12-month edoxban better
3-month edoxban better

Study limitations

- Open-label design (although blinded endpoint adjudication)
- Lower event rates of the primary endpoints than expected
- Not-high adherence to the study protocol as to edoxaban treatment
- Differences of races and a variety of cancer types (generalizability)

Conclusions

In cancer patients with isolated distal DVT, edoxaban treatment for 12 months was superior to 3 months with respect to the composite outcome of a symptomatic recurrent VTE or VTE-related death.

ONCO DVT Study

Circulation

ORIGINAL RESEARCH ARTICLE

Edoxaban for 12 Months versus 3 Months in Cancer Patients with Isolated Distal Deep Vein Thrombosis (ONCO DVT study): An Open-label, Multicenter, Randomized Clinical Trial

Yugo Yamashita, Takeshi Morimoto, Nao Muraoka, Takuya Oyakawa, Michihisa Umetsu, Daijirou Akamatsu, Yuji Nishimoto, Yukihito Sato, Takuma Takada, Kentaro Jujo, Yuichiro Minami, Yoshito Ogihara, Kaoru Dohi, Masashi Fujita, Tatsuya Nishikawa, Nobutaka Ikeda, Go Hashimoto, Kazunori Otsui, Kenta Mori, Daisuke Sueta, Yukari Tsubata, Masaaki Shoji, Ayumi Shikama, Yutaka Hosoi, Yasuhiro Tanabe, Ryuki Chatani, Kengo Tsukahara, Naohiko Nakanishi, Kitae Kim, Satoshi Ikeda, Makoto Mo, Yusuke Yoshikawa, Takeshi Kimura;
On behalf of the ONCO DVT Study Investigators.

Circulation. 2023; DOI: 10.1161/CIRCULATIONAHA.123.066360
https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.123.066360