2019
21-23 JUNE
SAN FRANCISCO
SUPPORTIVE CARE MAKES EXCELLENT CANCER CARE POSSIBLE

The safety and efficacy of oral Edoxaban administration without initial heparin therapy for venous thromboembolism in cancer patients

Risako Kogawa[1], Takayuki Sone[1], Chika Matsuda[1], Taichi Murai[1], Kazufumi Itaya[1], Yuta Koike[1], Ayana Endo[1], Yoko Tsukuda[1], Yuji Ono[1], Atsushi Nagasaka[1], Shuji Nishikawa[1], Michio Nakamura[1]

[1]Department of Gastroenterology, Sapporo City General Hospital

MASCC/ISOO
Annual Meeting on Suppportive Care in Cancer
www.mascc.org/meeting
Follow us on Twitter: @CancerCareMASCC

MASCC Multinational Association of Supportive Care in Cancer
ISOO International Society of Oral Oncology
#MASCC19

Conflict of Interest Disclosure

Risako Kogawa, MD.

There are no real or apparent conflicts of interest to report.

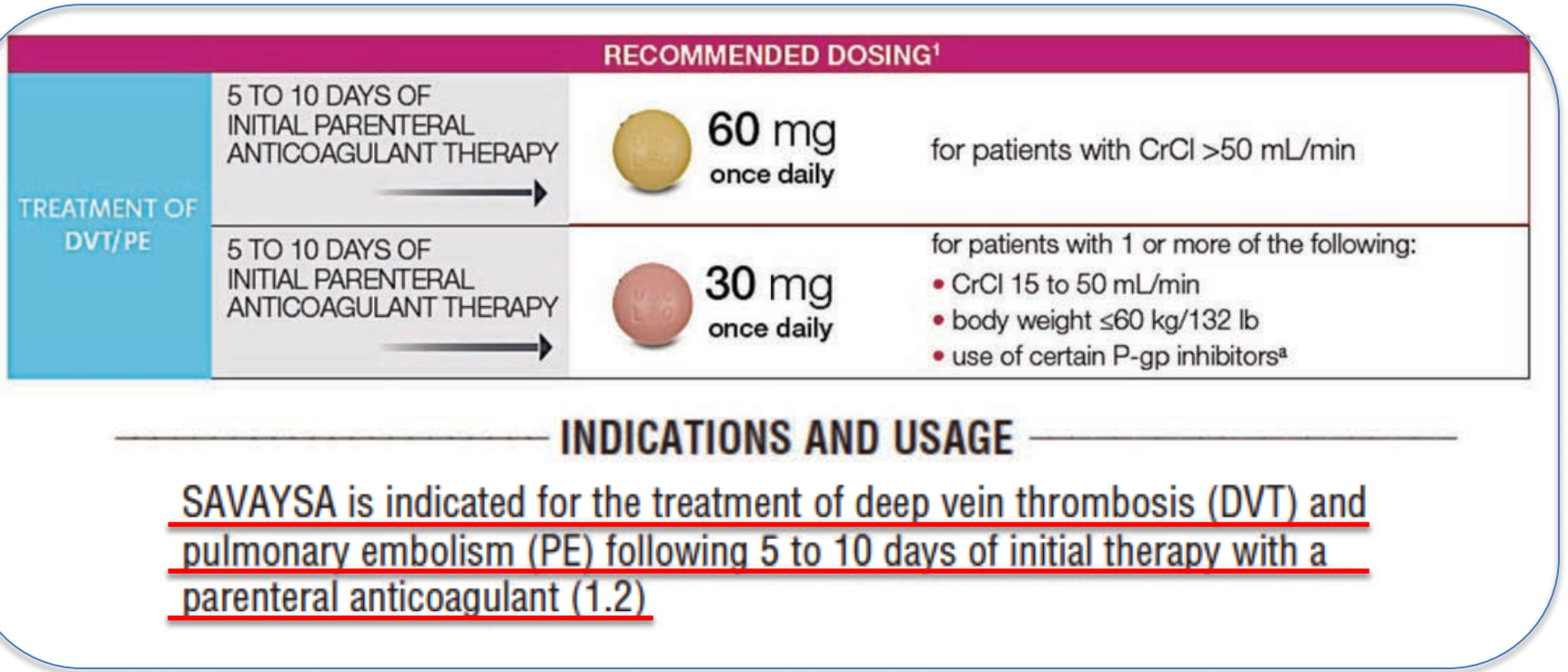
Background

- Approximately 10 - 20 % of cancer patients develop venous thromboembolism (VTE)

Timp JF et al. Blood 2013; 122: 1712-1723

- Newer treatments for VTE include direct oral anticoagulants, (DOACs) such as Edoxaban

Edoxaban



RECOMMENDED DOSING[1]			
TREATMENT OF DVT/PE	5 TO 10 DAYS OF INITIAL PARENTERAL ANTICOAGULANT THERAPY →	60 mg once daily	for patients with CrCl >50 mL/min
	5 TO 10 DAYS OF INITIAL PARENTERAL ANTICOAGULANT THERAPY →	30 mg once daily	for patients with 1 or more of the following: • CrCl 15 to 50 mL/min • body weight ≤60 kg/132 lb • use of certain P-gp inhibitors[a]

INDICATIONS AND USAGE

SAVAYSA is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant (1.2)

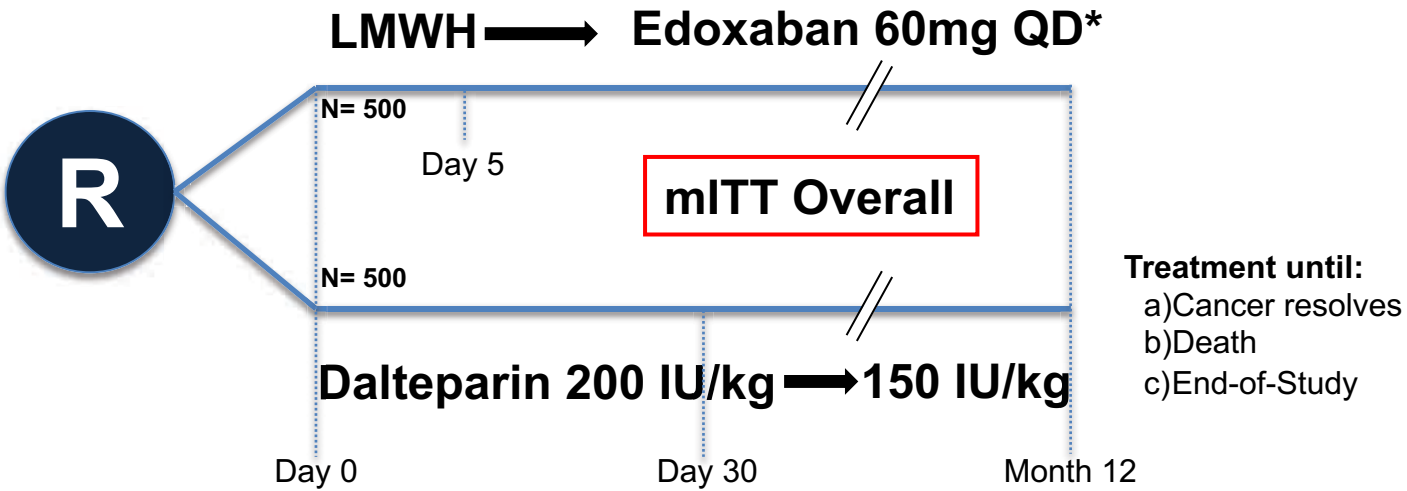
→ Edoxaban administration without other initial therapy is increasing

→ Further evaluation of safety and efficacy is needed

Hokusai VTE CANCER Study

Study Design

prospective, randomized, open label, blinded evaluation
LMWH / Edoxaban 60mg vs Dalteparin in N = 1000 cancer patients with VTE

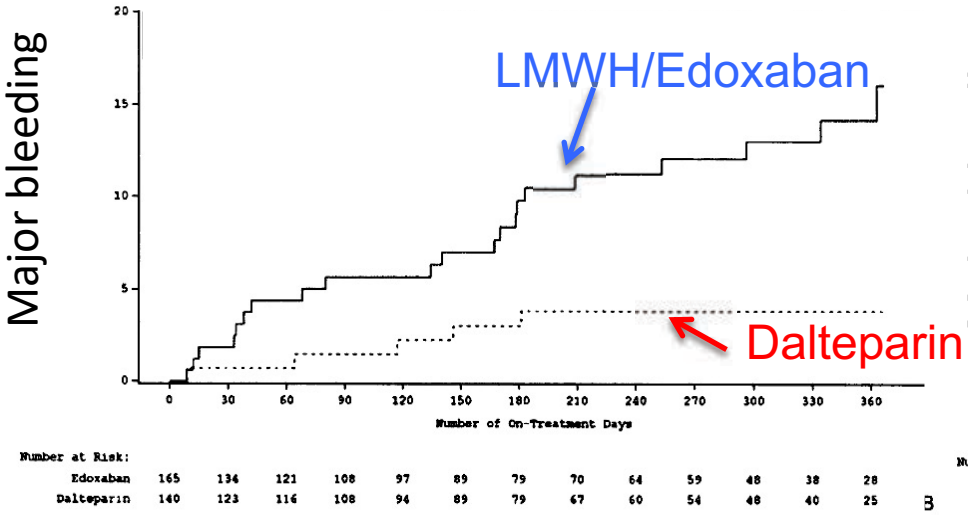


Primary outcome:
Composite of ISTH **major bleeding** and **recurrent VTE**

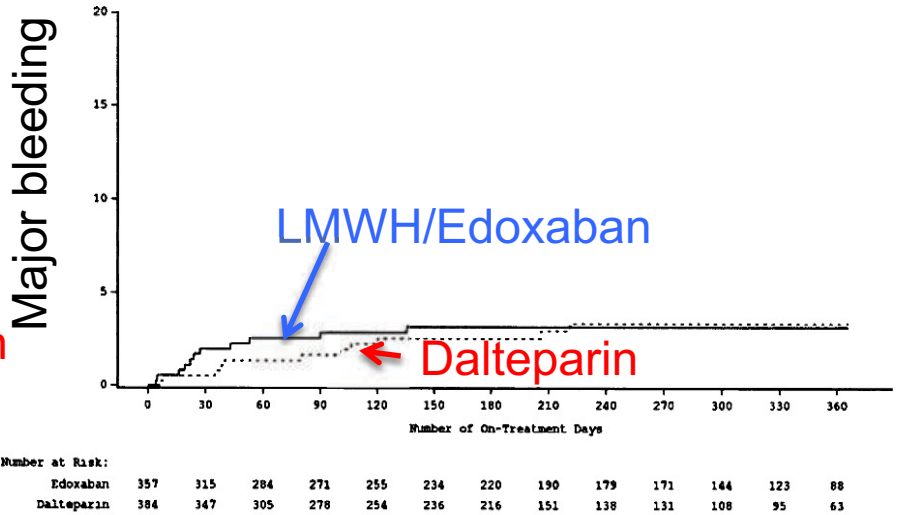
Raskob GE, et al.：N Engl J Med 2017 （doi:10.1056/NEJMoa1711948）

Clinical Impact of Bleeding in Cancer-Associated Venous Thromboembolism: Results from the Hokusai VTE Cancer Study

Gastrointestinal Cancer



Non-Gastrointestinal Cancer



Thromb Haemost 2018;118:1439-1449.

Objective

To investigate the safety and efficacy of
Edoxaban monotherapy for VTE patients with cancer

Patients and Methods

Study design

- a single-institutional retrospective review

Study Population

- All the patients administered with Edoxaban in our institution from January 2008 to Dec 2017 were identified.
- Cancer patients who administered Edoxaban for treatment VTE were enrolled.

Data Collection

- Eligible patients were identified through electronic medical record-review extracted by our hospital data warehouse.
- VTE was diagnosed by contrast-enhanced computed tomography (CT) images or ultrasonography performed during the follow-up periods.
- Data cut-off : Dec 31 2017

Patients and Methods

Group E

Patients treated with 60 mg or 30 mg **Edoxaban** (dose reduction criteria) from the beginning of DVT treatment

Group I + E

Patients who received **initial treatments (UFH, Warfarin)** for VTE before using Edoxaban

UFH : Unfractionated heparin

Initial Anticoagulant

Initial Anticoagulant	Group E (N = 60)	Group I+E (N = 22)
No initial treatment— no. (%)	60 (100)	0 (0.0)
Heparin only— no. (%)	—	8 (36.4)
Warfarin only— no. (%)	—	8 (36.4)
Heparin + Warfarin— no. (%)	—	3 (13.6)
Others— no. (%)	—	3 (13.6)

Outcomes

Primary Outcome - Safety

- Major bleeding events , All bleeding events and Early bleeding events

Major bleeding events

1) decrease in the hemoglobin level by ≧2 g/dL
2) the need for at least 2 units of packed RBC transfusion
3) bleeding at one or more intracranial, intraspinal, intraocular, intra-pericardial, intra-articular, intramuscular(with compartmental syndrome), or retroperitoneal sites
4) clinically apparent acute bleeding, equivalent to lethal bleeding

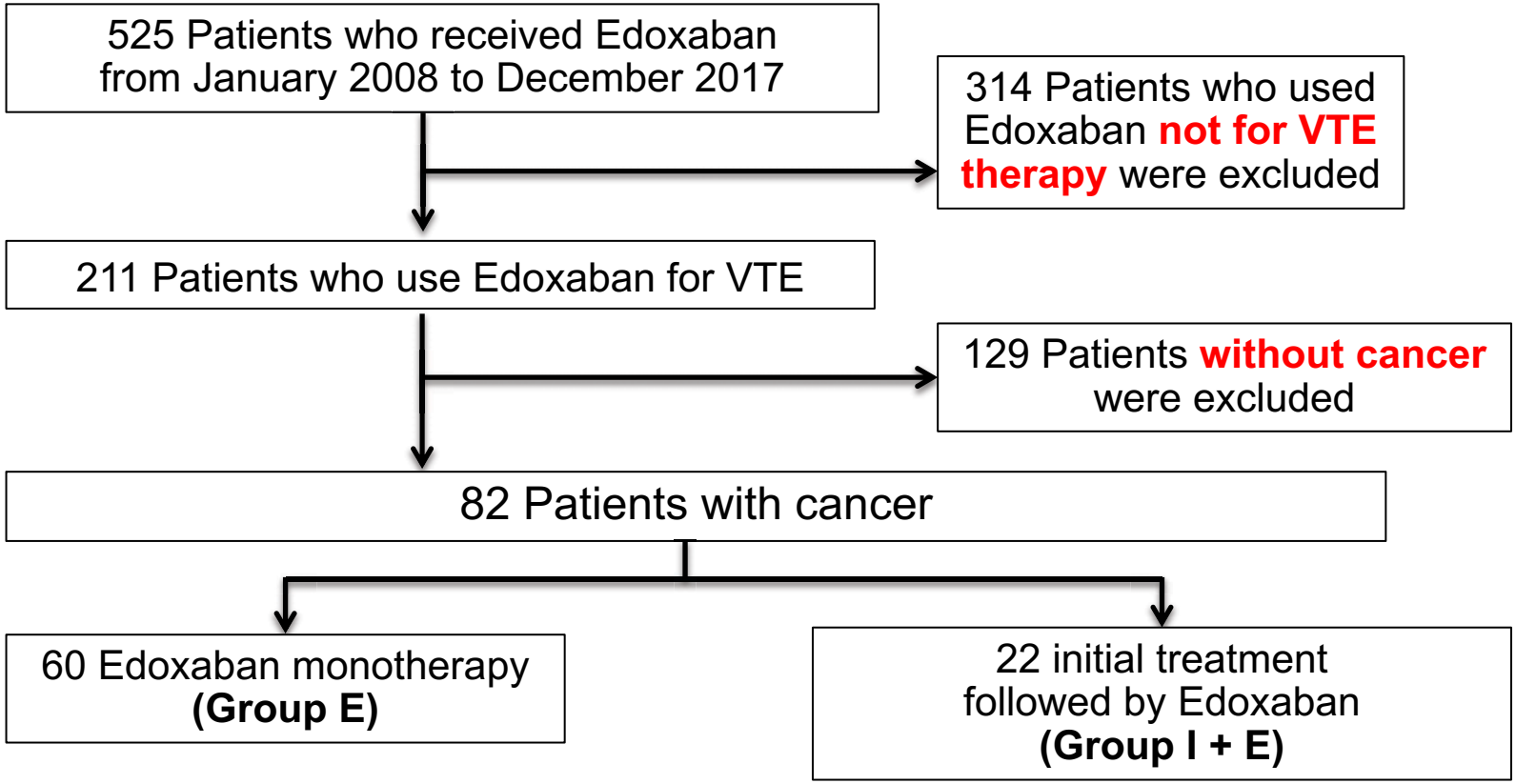
Early bleeding events

Bleeding event within a month from the beginning of anticoagulation therapy

Secondary Outcome - Efficacy

- Disappearance of VTE, Recurrence of VTE

CONSORT


525 Patients who received Edoxaban from January 2008 to December 2017
314 Patients who used Edoxaban not for VTE therapy were excluded
211 Patients who use Edoxaban for VTE
129 Patients without cancer were excluded
82 Patients with cancer
60 Edoxaban monotherapy (Group E)
22 initial treatment followed by Edoxaban (Group I + E)

Clinical Characteristics -1

Characteristic	Group E (N = 60)	Group I+E (N = 22)	P-value
Age — year± SD	65.9 ± 12.1	64.5 ± 10.5	
Male sex — no. (%)	31 (51.7)	12 (54.5)	0.817†
Weight (kg)			
Mean ± SD (kg)	57.9 ± 13.5	57.1 ± 18.9	
≦60 kg — no. (%)	23 (38.3)	14(63.6)	0.041†
CCR of 30-50 ml/min — no. (%)	8 (13.3)	2 (9.1)	0.722*
Met criteria to receive lower dose of edoxaban — no. (%)	36 (60.0)	16 (72.7)	0.289†
Qualifying diagnosis of VTE — no. (%)			0.025*
PE with/without DVT	19 (31.7)	14 (63.6)	
DVT only	40 (66.7)	8 (36.4)	
Others	1 (1.7)	0 (0.0)	
Symptom of VTE — no. (%)			0.00001†
Symptomatic DVT or PE	7 (11.7)	14 (63.6)	
Incidental DVT or PE	53 (88.3)	8 (36.4)	

PE : Pulmonary embolism, DVT : Deep vein thrombosis

† Chi-square test * Fisher's exact test

Clinical Characteristics -1

Characteristic	Group E (N = 60)	Group I+E (N = 22)	P-value
Age — year± SD	65.9 ± 12.1	64.5 ± 10.5	
Male sex — no. (%)	31 (51.7)	12 (54.5)	0.817†
Weight (kg)			
Mean ± SD (kg)	57.9 ± 13.5	57.1 ± 18.9	
≦60 kg — no. (%)	23 (38.3)	14(63.6)	0.041†
CCR of 30-50 ml/min — no. (%)	8 (13.3)	2 (9.1)	0.722*
Met criteria to receive lower dose of edoxaban — no. (%)	36 (60.0)	16 (72.7)	0.289†
Qualifying diagnosis of VTE — no. (%)			0.025*
PE with/without DVT	19 (31.7)	14 (63.6)	
DVT only	40 (66.7)	8 (36.4)	
Others	1 (1.7)	0 (0.0)	
Symptom of VTE — no. (%)			0.00001†
Symptomatic DVT or PE	7 (11.7)	14 (63.6)	
Incidental DVT or PE	53 (88.3)	8 (36.4)	

PE : Pulmonary embolism, DVT : Deep vein thrombosis

† Chi-square test * Fisher's exact test

Clinical Characteristics -2

Characteristic	Group E (N = 60)	Group I+E (N = 22)	P-value
Active cancer— no. (%)	48 (80.0)	13 (59.1)	0.055†
Metastatic disease — no. (%)	44 (73.3)	12 (54.5)	0.105†
ECOG performance status — no. (%)			0.0002*
0	45 (75.0)	6 (27.3)	
1	11 (18.3)	10 (45.5)	
≥2	4 (6.7)	6 (27.3)	
Risk factors for bleeding — no. (%) †			0.089*
0	4 (6.7)	5 (22.7)	
1	15 (25.0)	8 (36.4)	
2	26 (43.3)	5 (22.7)	
≥3	15 (25.0)	4 (18.1)	
Follow-up period — Mean(day) ± SD	198.7 ± 224.0	241.6 ± 320.1	

† Risk factors for bleeding include surgery within 2 weeks before edoxaban administration, the use of antiplatelet agents, a primary or metastatic brain tumor, regionally advanced or metastatic cancer, gastrointestinal or urothelial cancer that had been diagnosed within 6 months before edoxaban administration, and treatment with bevacizumab within the 6-week period before edoxaban administration.

* Fisher's exact test
† Chi-square test

Clinical Characteristics -2

Characteristic	Group E (N = 60)	Group I+E (N = 22)	P-value
Active cancer— no. (%)	48 (80.0)	13 (59.1)	0.055†
Metastatic disease — no. (%)	44 (73.3)	12 (54.5)	0.105†
ECOG performance status — no. (%)			0.0002*
0	45 (75.0)	6 (27.3)	
1	11 (18.3)	10 (45.5)	
≥2	4 (6.7)	6 (27.3)	
Risk factors for bleeding — no. (%) †			0.089*
0	4 (6.7)	5 (22.7)	
1	15 (25.0)	8 (36.4)	
2	26 (43.3)	5 (22.7)	
≥3	15 (25.0)	4 (18.1)	
Follow-up period — Mean(day) ± SD	198.7 ± 224.0	241.6 ± 320.1	

† Risk factors for bleeding include surgery within 2 weeks before edoxaban administration, the use of antiplatelet agents, a primary or metastatic brain tumor, regionally advanced or metastatic cancer, gastrointestinal or urothelial cancer that had been diagnosed within 6 months before edoxaban administration, and treatment with bevacizumab within the 6-week period before edoxaban administration.

* Fisher's exact test
† Chi-square test

Primary Cancer Site

Site of primary malignancy	Group E (N = 60) no. (%)	Group I+E (N = 22) no. (%)
Head and Neck	0 (0.0)	2 (9.1)
Esophagus / Stomach	5 (8.3)	0 (0.0)
Colon / Rectum	25 (41.7)	6 (27.3)
Pancreas / Bile duct	10 (16.7)	1 (4.5)
Lung	4 (6.7)	5 (22.7)
Kidney / Bladder	1 (1.7)	0 (0.0)
Prostate	1 (1.7)	1 (4.5)
Uterus / Ovary	7 (25.0)	2 (9.1)
Lymphoma	3 (5.0)	3 (13.6)
Others	4 (6.7)	2 (9.1)

Primary Cancer Site

Site of primary malignancy	Group E (N = 60) no. (%)	Group I+E (N = 22) no. (%)
Head and Neck	0 (0.0)	2 (9.1)
Esophagus / Stomach	5 (8.3)	0 (0.0)
Colon / Rectum	25 (41.7)	6 (27.3)
Pancreas / Bile duct	10 (16.7)	1 (4.5)
Lung	4 (6.7)	5 (22.7)
Kidney / Bladder	1 (1.7)	0 (0.0)
Prostate	1 (1.7)	1 (4.5)
Uterus / Ovary	7 (25.0)	2 (9.1)
Lymphoma	3 (5.0)	3 (13.6)
Others	4 (6.7)	2 (9.1)

36 / 82
43.9 %

Results: Safety – Major bleeding events

Outcome	Group E (N = 60)	Group I+E (N = 22)	P-value*
Major bleeding — no. (%)	6 (10.0)	3 (13.6)	0.696
Upper GI	1 (1.7)	1 (4.5)	
Lower GI	4 (6.7)	2 (9.1)	1.000
Liver met	1 (1.7)	0(0.0)	
Bleeding Category			0.523
Category 1	0 (0.0)	0 (0.0)	
Category 2	4 (6.7)	1 (4.5)	
Category 3	2 (3.3)	2 (9.1)	
Category 4	0 (0.0)	0 (0.0)	
VTE related death	0(0.0)	0(0.0)	

* Fisher's exact test

Results: Safety – All bleeding events

	Group E (N = 60)	Group I+E (N = 22)	P-value*
All Bleeding events‡	15 (25.0)	7 (31.8)	0.537
Bleeding site			
Intracranial	0(0.0)	0(0.0)	
Gastrointestinal	10 (16.7)	3 (13.6)	
Genitourinary	1 (1.7)	4 (18.2)	0.006
Other	8 (13.3)	0(0.0)	
Early Bleeding events#	10 (16.7)	4 (18.2)	1.000
Blood transfusion	3 (5.0)	2 (9.1)	0.61

‡ Some percentages may not total 100 because of rounding.

* Fisher's exact test

Results: Safety – All bleeding events

	Group E (N = 60)	Group I+E (N = 22)	P-value*
All Bleeding events‡	15 (25.0)	7 (31.8)	0.537
Bleeding site			
Intracranial	0(0.0)	0(0.0)	
Gastrointestinal	10 (16.7)	3 (13.6)	0.006
Genitourinary	1 (1.7)	4 (18.2)	
Other	8 (13.3)	0(0.0)	
Early Bleeding events#	10 (16.7)	4 (18.2)	1.000
Blood transfusion	3 (5.0)	2 (9.1)	0.61

‡ Some percentages may not total 100 because of rounding.

* Fisher's exact test

Subgroup Analysis – All bleeding events

Variable	Univariate analysis		Mutivariate analysis	
	OR (95%CI)	*p*	OR (95%CI)	*p*
Age ≥60	1.929 (0.572 – 6.506)	0.290		
Sex Male	2.449 (0.874 – 6.864)	0.088		
PS ≥1	0.919 (0.334 – 2.531)	0.871		
CCR <50	0.650 (0.127 – 3.328)	0.605		
Edoxaban 60mg vs 30mg	1.007 (0.353 – 2.875)	0.990		
Group E only vs IE	0.714 (0.245 – 2.084)	0.538		
Primary Site GI vs Others	3.980 (1.403 – 11.285)	0.009	4.095 (1.376 – 12.188)	0.011
Cancer Status Active vs Inactive	10.500 (1.316 – 83.766)	0.026	10.853 (1.316 – 89.515)	0.027

Subgroup Analysis – All bleeding events

Variable	Univariate analysis		Mutivariate analysis	
	OR (95%CI)	*p*	OR (95%CI)	*p*
Age ≥60	1.929 (0.572 – 6.506)	0.290		
Sex Male	2.449 (0.874 – 6.864)	0.088		
PS ≥1	0.919 (0.334 – 2.531)	0.871		
CCR <50	0.650 (0.127 – 3.328)	0.605		
Edoxaban 60mg vs 30mg	1.007 (0.353 – 2.875)	0.990		
Group E only vs IE	0.714 (0.245 – 2.084)	0.538		
Primary Site GI vs Others	3.980 (1.403 – 11.285)	0.009	4.095 (1.376 – 12.188)	0.011
Cancer Status Active vs Inactive	10.500 (1.316 – 83.766)	0.026	10.853 (1.316 – 89.515)	0.027

Subgroup Analysis – Early bleeding events

Variable	Univariate analysis	
	OR (95%CI)	*p*
Age ≥60	5.809 (0.713 – 47.339)	0.100
Sex Male	1.800 (0.546 – 5.929)	0.334
PS ≥1	1.290 (0.401 – 4.147)	0.669
CCR <50	1.250 (0.236 – 6.633)	0.793
Edoxaban 60mg vs 30mg	1.243 (0.371 – 4.162)	0.724
Group E only vs IE	0.900 (0.251 – 3.232)	0.872
Primary Site GI vs Others	2.733 (0.826 – 9.041)	0.099
Cancer Status Active vs Inactive	5.417 (0.663 – 44.224)	0.115

Subgroup Analysis – GI bleeding events

Variable	Univariate analysis	
	OR (95%CI)	*p*
Age ≥60	1.267 (0.314 – 5.107)	0.740
Sex Male	2.316 (0.651 – 8.238)	0.194
PS ≥1	1.034 (0.306 – 3.497)	0.958
CCR <50	0.556 (0.064 – 4.803)	0.593
Edoxaban **60mg vs 30mg**	0.600 (0.150 – 2.394)	0.469
Group **E only vs IE**	1.267 (0.314 – 5.107)	0.740
Primary Site **GI vs Others**	2.343 (0.694 – 7.906)	0.170
Cancer Status **Active vs Inactive**	4.898 (0.597 – 40.208)	0.139

Results: Efficacy

	Group E (N = 60)	Group I+E (N = 22)	P-value
Disappearance of VTE — no. (%)	29 (48.3)	8 (36.4)	0.453
PE with/without DVT — no. (%)	11 (18.3)	5 (13.6)	
DVT only — no. (%)	17 (28.3)	3 (22.7)	
Others — no. (%)	1 (1.7)	0 (0.0)	
Recurrent VTE— no. (%)	8/29 (27.6)	2/8 (25.0)	1.000
PE with/without DVT — no. (%)	1 (1.7)	2 (9.1)	
DVT only — no. (%)	7 (11.7)	0 (0.0)	

Limitations

- A single institutional retrospective review
- Dose and Periods of initial therapy before Edoxaban in group I+E were not the same
- The intervals of follow-up CT scan were also different among patients
- Combination therapy may have been given for severe patients

Conclusions

- Safety: no differences in incidence of bleeding between Group E and Group I + E
- GI cancer and active cancer were risk factors of all bleeding events
- Efficacy, rate of recurrence and disappearance of VTE between both groups: no significant difference between groups

Acknowledgements

- Thanks to all the patients and their families

- I am grateful to Ichiro Iwanaga for assistance with data collection and statistical analysis

- Thanks to Adam Tucker for review of this presentation