Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018;378:615-24. DOI: 10.1056/NEJMoa1711948

Contents

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Inclusion Criteria

Adult subjects presenting with VTE associated with cancer (other than basal-cell or squamous-cell carcinoma of the skin) for whom long-term treatment with LMWH is intended are eligible to participate in the study.

Subjects must satisfy all of the following criteria to be included in the study:

1. Male or female subjects with age ≥ 18 years or the otherwise legal lower age according to the country of residence;
2. Confirmed symptomatic or unsuspected lower extremity proximal DVT (ie, popliteal, femoral, iliac or inferior vena cava (IVC) vein thrombosis), or confirmed symptomatic PE, or unsuspected PE of a segmental or larger pulmonary artery;
3. Cancer (other than basal-cell or squamous-cell carcinoma of the skin), either active or diagnosed within 2 years prior to randomization. [Note: Diagnosis of cancer must be objectively documented];
4. Intention for long-term treatment (at least 6 months) with parenteral LMWH;
5. Able to provide written informed consent.

Exclusion Criteria

Subjects who meet any of the following criteria are not eligible for enrollment:

1. Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current (index) episode of DVT and/or PE;
2. More than 72 hours pre-treatment with therapeutic dosages of anticoagulant treatment (LMWH, unfractionated heparin, and fondaparinux per local labeling), oral direct anticoagulants or VKA prior to randomization to treat the current (index) episode;
3. Treatment with therapeutic doses of an anticoagulant including dalteparin for an indication other than VTE prior to randomization;
4. Active bleeding or any contraindication for treatment with LMWH/dalteparin or edoxaban;
5. An Eastern Cooperative Oncology Group (ECOG) Performance Status of 3 or 4 at the time of randomization
6. Calculated CrCL < 30 mL/min;
7. History of heparin associated thrombocytopenia;
8. Acute hepatitis, chronic active hepatitis, liver cirrhosis;
9. Hepatocelullar injury with concurrent transaminase (ALT/AST > 3 x ULN) and bilirubin (> 2 x ULN) elevations in the absence of a clinical explanation;
10. Life expectancy < 3 months;
11. Platelet count < 50,000/mL;
12. Uncontrolled hypertension as judged by the Investigator (eg, systolic blood pressure (BP) > 170 mmHg or diastolic blood pressure > 100 mmHg despite antihypertensive treatment);
13. Women of childbearing potential without proper contraceptive measures, and women who are pregnant or breast feeding;

Note: Childbearing potential without proper contraceptive measures (ie, a method of contraception with a failure rate < 1 % during the course of the study including the observational period). These methods of

contraception according to the note for guidance on nonclinical safety studies for the conduct of human trials for pharmaceuticals (CPMP/ICH/286/95, modification) include consistent and correct use of hormone containing implants and injectables, combined oral contraceptives, hormone containing intrauterine devices, surgical sterilization, sexual abstinence, and vasectomy for the male partner).

14. Chronic treatment with non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) including both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibitors for ≥ 4 days/week anticipated to continue during the study;
15. Treatment with aspirin in a dosage of more than 100 mg/per day or dual antiplatelet therapy (any 2 antiplatelet agents including aspirin plus any other oral or intravenous [IV] antiplatelet drug) anticipated to continue during the study;
16. Treatment with the P-gp inhibitors ritonavir, nelfinavir, indinavir, or saquinavir anticipated to continue during the study;
17. Systemic use of the P-gp inhibitors ketoconazole, itraconazole, erythromycin, azithromycin or clarithromycin at the time of randomization; subsequent use is permitted (with appropriate dose reduction of edoxaban);
18. Subjects with any condition that as judged by the Investigator would place the subject at increased risk of harm if he/she participated in the study.

Secondary Objectives and Secondary Outcomes

Secondary Objectives: To compare LMWH/edoxaban with dalteparin with regards to rates of:

1. Recurrent VTE;

2. Major bleeding;

3. Clinically relevant non-major (CRNM) bleeding;

4. Major + CRNM bleeding;

5. Event-free survival, defined as the proportion of subjects over time free of recurrent VTE, major bleeding events, and death;

6. VTE-related death;

7. Mortality from all causes;

8. Recurrent deep vein thrombosis (DVT);

9. Recurrent pulmonary embolism (PE);

10. Healthcare resource utilization for potential recurrent VTE and bleed events. (not addressed in current manuscript)

Exploratory Objectives (not addressed in current manuscript)

To compare LMWH/edoxaban with dalteparin with regards to:

1. Cardiovascular events (myocardial infarction [MI], stroke, systemic embolic events [SEE);

2. Thrombotic events at other locations

3. Reason for permanent early discontinuation of study drug.

Index event and outcome event definitions

Symptomatic DVT

Symptomatic proximal vein thrombosis (of the leg) will be confirmed if there are typical symptoms of DVT associated with

- non-compressible vein segment on ultrasonography or
- an intra-luminal filling defect on venography, CT venography or MRI venography,
  located in the inferior vena cava (IVC), the iliac vein, the common femoral vein, the femoral or the popliteal vein.

Unsuspected DVT

Unsuspected proximal DVT is a thrombus that is detected during imaging testing performed for other reasons (e.g., computed tomography (CT) for cancer staging) and not for suspicion of DVT. A thrombus detected in the inferior vena cava (IVC) or iliac veins on a (staging) abdominal or pelvic CT will be considered diagnostic. Because of potential flow artefacts and layering of contrast, a suspected thrombus detected in the common femoral vein or more distal veins can only be considered if confirmatory compression ultrasound (CUS) or (CT) contrast venography diagnostic criteria are also met (see above).

Criteria will be:

- An intraluminal filling defect on (staging) CT scan or MR venography in the IVC or iliac veins;
- A non-compressible venous segment in the popliteal vein or above on ultrasonography or a filing defect on venography or CTV in the inferior vena cava (IVC), the iliac vein, the common femoral vein, the femoral or the popliteal vein.

Symptomatic PE

Symptomatic PE will be confirmed if there are typical symptoms of PE associated with

- an intra-luminal filling defect in (sub) segmental or more proximal branches on spiral computed tomography scan (CT) or computerized tomographic pulmonary angiography (CTPA);
- a considerable perfusion defect (~ 75% of a segment) with a local normal ventilation result (high probability) during perfusion-ventilation lung scan (PLS, VLS or V/Q scan);
- an intraluminal filling defect or a sudden cut-off of vessels (~more than 2.5 mm in diameter) on a catheter guided pulmonary angiogram.

In case of an inconclusive CTPA, inconclusive V/Q scan (including perfusion scan only) or inconclusive angiography demonstration of DVT in the lower extremities e.g. by compression ultrasound or venography will be required.

Unsuspected PE

Unsuspected PE is a clot that is detected during imaging testing performed for other reasons (e.g., computed tomography (CT) for cancer staging) and not for suspicion of PE. This incidental finding will only be considered diagnostic if the clot is in a segmental or more proximal artery. Clots in sub-segmental or more peripheral arteries detected during staging in an asymptomatic subject will not be classified as PE (due to risk of a false positive result).

Criterion will be: an intraluminal filling defect in segmental or more proximal branches on spiral CT or MR scan.

Recurrent venous thromboembolism (VTE)

Recurrent VTE is either:

- symptomatic confirmed (recurrent) DVT or (recurrent) PE;
- unsuspected (new) proximal DVT of the legs or unsuspected (new) PE located in segmental or more proximal arteries:
  - Unsuspected DVT or PE are thrombi that are detected during imaging testing performed for other reasons (e.g., computed tomography (CT) for cancer staging) and not for suspicion of DVT or PE.
- fatal PE.

Symptomatic confirmed (recurrent) DVT or (recurrent) PE

Confirmation of (recurrent) symptomatic DVT requires symptoms of DVT and the following criteria:

In the absence of previous DVT investigations at baseline:

- A non-compressible venous segment on ultrasonography or
- An intraluminal filling defect on venography. CT –scan or MR venography located in the deep veins of the leg or IVC.

If there were previous DVT investigations at baseline:

Abnormal CUS where compression had been normal or, if previously non-compressible, a substantial increase (≥ 4 mm) in diameter of the thrombus during full compression, or

- An extension of an intraluminal filling defect, or a new intraluminal filling defect, or an extension of non-visualization of veins in the presence of a sudden cut-off on venography CT-scan or MR- venography.

Confirmation of (recurrent) symptomatic PE requires symptoms of PE and one of the following findings

- A (new) intraluminal filling defect in (sub) segmental or more proximal branches on spiral CT scan;
- A (new) intraluminal filling defect or an extension of an existing defect or a new sudden cut-off of vessels on the pulmonary angiogram;
- A (new) considerable perfusion defect (~ 75% of a segment) with a local normal ventilation result (high-probability) on ventilation/perfusion lung scintigraphy (V/Q scan);
- An inconclusive lungscan accompanied by documentation of (new) DVT in the lower extremities e.g., by compression ultrasound or venography.

Diagnosis of fatal PE is based on one or more of the following:

- Objective diagnostic testing;
- Autopsy;
- Death which cannot be attributed to a documented cause and for which PE/DVT cannot be ruled out.

Unsuspected (new) DVT or (new) PE

Unsuspected DVT is only considered an outcome if located in popliteal or more proximal veins. For the 2 scenarios when previous imaging was normal or when previous objective imaging was abnormal unsuspected DVT will be considered an outcome if it meets criteria as defined in below table.

Previous objective imaging normal	Previous objective imaging abnormal
An intraluminal filling defect on (staging) CT scan or MR venography in the IVC or iliac veins.	An extension of an intraluminal filling defect, or a new intraluminal filling defect, or an extension of non-visualization of the iliac IVC in the presence of a sudden cut-off on staging CT-scan (or MR- venography).

Unsuspected PE will be considered an outcome if it is a (new) intraluminal filling defect in segmental or more proximal branches on spiral CT or MR scan.

Bleeding events

Major bleeding event

A major bleeding event will be confirmed when it is a clinically overt bleeding event that meets at least one of the following:

a) Fatal bleeding

b) Bleeding in a critical area or organ such as:

- Retroperitoneal
- Intracranial
- Intraocular
- Intraspinal
- Intra-articular
- Pericardial
- Intramuscular with compartment syndrome

c) A clinically overt bleeding event

- that is associated with a fall in hemoglobin of 2.0 g/dL (>1.24 mMol/L) or more, or
- leading to a transfusion of ≥ 2 units of packed red blood cells or whole blood.

Separately a sub-classification of the clinical presentation of the major bleeding will be done according to pre-specified criteria:

Category Description

1. Bleeding events presenting without any clinical emergency
2. All bleeding events that could not be classified to any of the other three categories, as they presented with the need for some measures but without clear urgency
3. Bleeding events presenting with great medical emergency; e.g. with hemodynamic instability, or cerebral major bleeding presenting with neurologic symptoms
4. Bleeding events already fatal before or almost immediately upon entering the hospital

Clinically Relevant non-major bleeding

A bleeding event will be classified as a clinically relevant non-major bleeding event if it is overt (i.e. is symptomatic or visualized by examination) not meeting the criteria for major bleeding, requires medical attention or is associated with discomfort for the subject such as pain, or impairment of activities of daily life.

Nuisance (not clinically relevant) bleeding events

Other overt bleeding events that do not fulfill the criteria of a major bleeding event or a clinically relevant non-major bleeding event will be classified as a nuisance bleeding event.

NOTE: All other notified suspected bleeding events (e.g., decline in hemoglobin with no overt bleeding, or bleeding that is detected on examinations that are done for follow-up of cancer (e.g., brain CT scan in patient with brain tumor, or brain metastases) and not clinically overt) will be classified as “no bleeding event.”

Death Classification

Death will be classified in 5 categories with respect to cause.

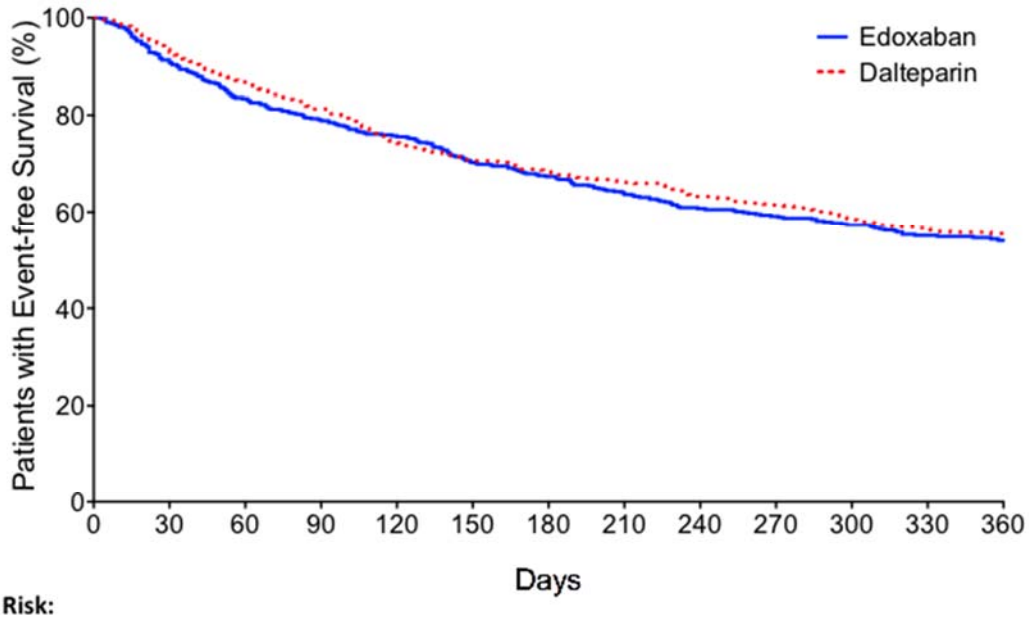
VTE, cardiovascular, cancer, bleeding, other known cause.

In general all deaths will be assumed to be due to PE or cancer in nature unless another cause is obvious.

- VTE death: is defined as death due to a documented PE (either an objective test prior to death of the subject or PE detected during autopsy) or unexplained death i.e. death without a clear alternate cause and not a primary consequence of subject’s underlying Cancer (see below)
- Cancer deaths**:** Death in which the mode of death can be attributed to the direct effects of a malignancy (e.g. a brain tumor that causes herniation, coma, and respiratory arrest) or death in a subject with progressive cancer who had a (gradual) decline in general condition or a complication (e.g. infection) or in whom palliative treatment only was decided
- Cardiovascular death: is defined as death due to documented cardiovascular cause : acute myocardial infarction, stroke, congestive heart failure, arrhythmia, cardiac surgery, systemic embolic other cardiovascular cause
- Bleeding: death in which a bleeding event directly led to death. Examples of fatal bleeding events are an intracranial hemorrhage that led to herniation of the brain and death within 24 hours, and a massive gastrointestinal hemorrhage that results in shock, hemodynamic collapse, and death.
- Other known cause: include those caused primarily by infection, accident, renal failure, or other non-cardiovascular organ system failure, trauma, non-cardiac surgery, suicide.

Figures

Figure S1. Event-free Survival



No. at Risk:													
Edoxaban:	522	472	429	407	388	360	345	328	310	295	270	237	161
Dalteparin:	524	485	449	420	385	364	352	340	324	313	276	241	171

Figure S2. Forest Plot for Primary Outcome - mITT

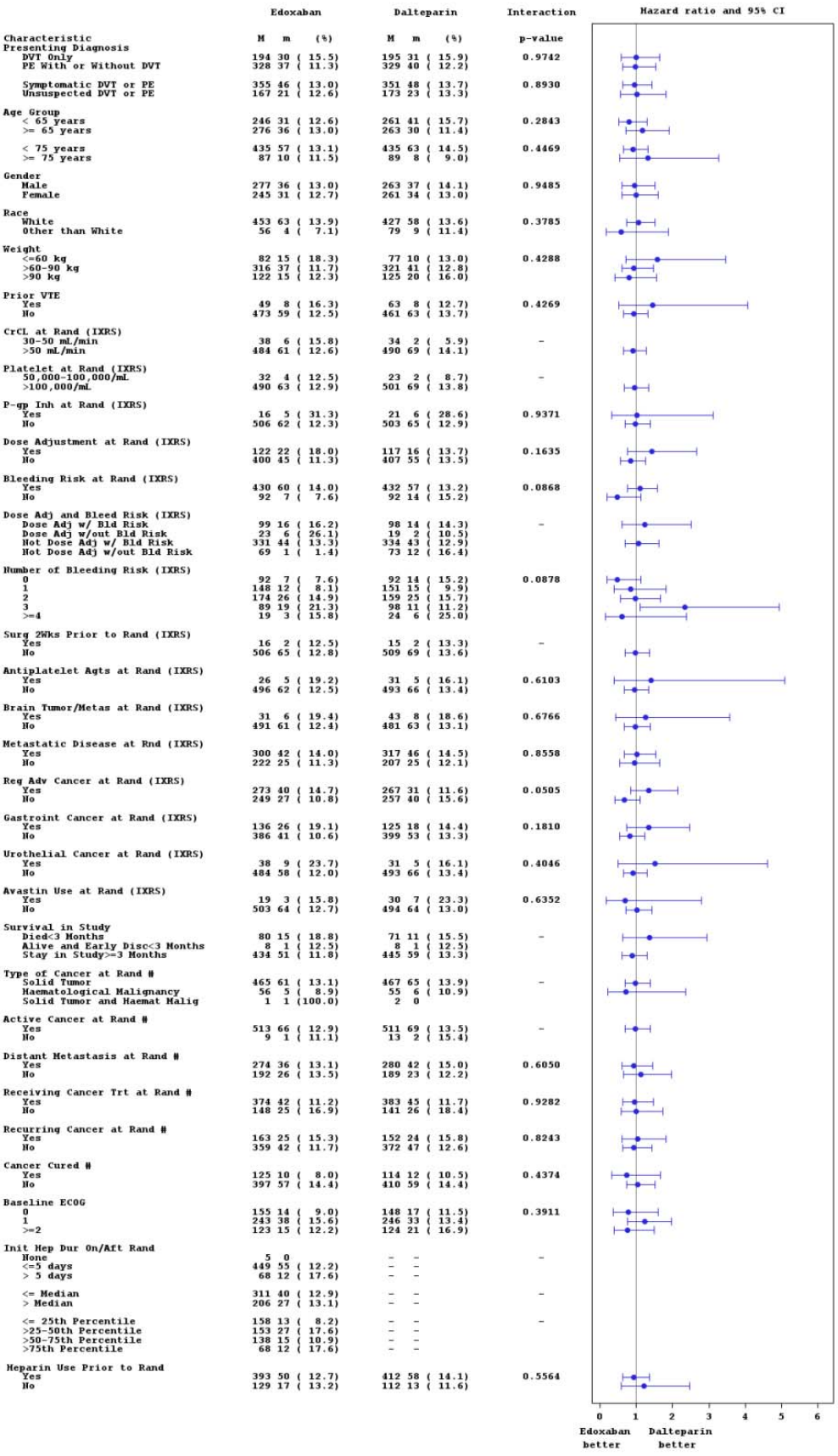


Figure S3. Forest Plot for Recurrent VTE – mITT

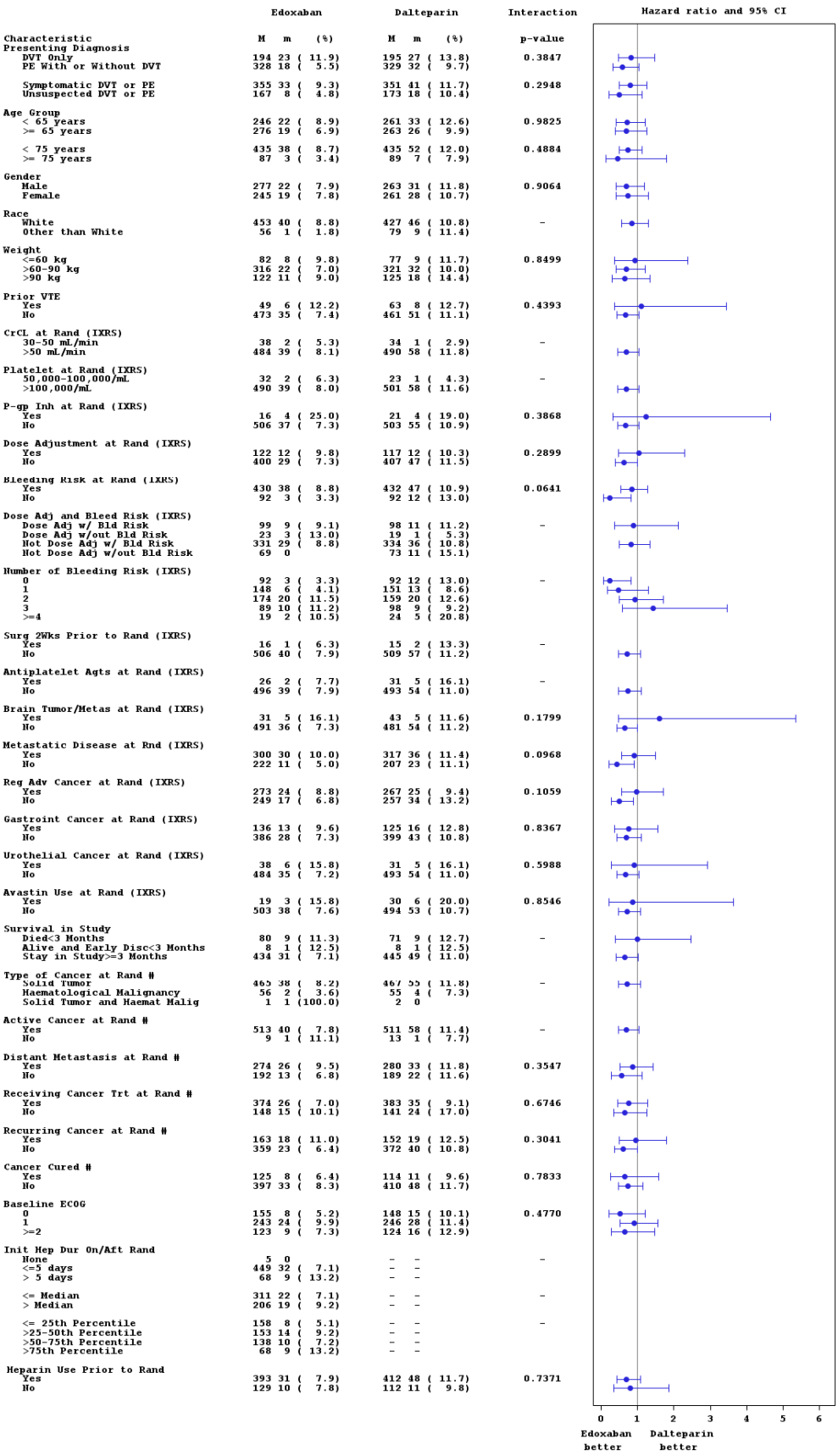


Figure S4. Forest Plot for Major Bleeding Safety Population (mITT)

Characteristic	Edoxaban M	Edoxaban m	Edoxaban (%)	Dalteparin M	Dalteparin m	Dalteparin (%)	Interaction p-value
Presenting Diagnosis							
DVT Only	194	11	5.7	195	8	4.1	0.5126
PE With or Without DVT	328	25	7.6	329	13	4.0	
Symptomatic DVT or PE	355	20	5.6	351	13	3.7	0.5198
Unsuspected DVT or PE	167	16	9.6	173	8	4.6	
Age Group							
< 65 years	246	14	5.7	261	10	3.8	0.6835
>= 65 years	276	22	8.0	263	11	4.2	
< 75 years	435	28	6.4	435	19	4.4	-
>= 75 years	87	8	9.2	89	2	2.2	
Gender							
Male	277	20	7.2	263	10	3.8	0.6190
Female	245	16	6.5	261	11	4.2	
Race							
White	453	32	7.1	427	20	4.7	-
Other than White	56	4	7.1	79	1	1.3	
Weight							
<=60 kg	82	7	8.5	77	2	2.6	-
>60-90 kg	316	24	7.6	321	15	4.7	
>90 kg	122	5	4.1	125	4	3.2	
Prior VTE							
Yes	49	2	4.1	63	1	1.6	-
No	473	34	7.2	461	20	4.3	
CrCL at Rand (IXRS)							
30-50 mL/min	38	4	10.5	34	1	2.9	-
>50 mL/min	484	32	6.6	490	20	4.1	
Platelet at Rand (IXRS)							
50,000-100,000/mL	32	4	12.5	23	1	4.3	-
>100,000/mL	490	32	6.5	501	20	4.0	
P-gp Inh at Rand (IXRS)							
Yes	16	3	18.8	21	3	14.3	0.6104
No	506	33	6.5	503	18	3.6	
Dose Adjustment at Rand (IXRS)							
Yes	122	12	9.8	117	5	4.3	0.4794
No	400	24	6.0	407	16	3.9	
Bleeding Risk at Rand (IXRS)							
Yes	430	32	7.4	432	16	3.7	0.1647
No	92	4	4.3	92	5	5.4	
Dose Adj and Bleed Risk (IXRS)							
Dose Adj w/ Bld Risk	99	9	9.1	98	4	4.1	-
Dose Adj w/out Bld Risk	23	3	13.0	19	1	5.3	
Not Dose Adj w/ Bld Risk	331	23	6.9	334	12	3.6	
Not Dose Adj w/out Bld Risk	69	1	1.4	73	4	5.5	
Number of Bleeding Risk (IXRS)							
0	92	4	4.3	92	5	5.4	-
1	148	9	6.1	151	4	2.6	
2	174	9	5.2	159	7	4.4	
3	89	12	13.5	98	4	4.1	
>=4	19	2	10.5	24	1	4.2	
Surg 2Wks Prior to Rand (IXRS)							
Yes	16	1	6.3	15	0		-
No	506	35	6.9	509	21	4.1	
Antiplatelet Agts at Rand (IXRS)							
Yes	26	3	11.5	31	1	3.2	-
No	496	33	6.7	493	20	4.1	
Brain Tumor/Metas at Rand (IXRS)							
Yes	31	2	6.5	43	4	9.3	-
No	491	34	6.9	481	17	3.5	
Metastatic Disease at Rnd (IXRS)							
Yes	300	19	6.3	317	14	4.4	0.4281
No	222	17	7.7	207	7	3.4	
Reg Adv Cancer at Rand (IXRS)							
Yes	273	22	8.1	267	11	4.1	0.4886
No	249	14	5.6	257	10	3.9	
Gastroint Cancer at Rand (IXRS)							
Yes	136	18	13.2	125	3	2.4	0.0169
No	386	18	4.7	399	18	4.5	
Urothelial Cancer at Rand (IXRS)							
Yes	38	5	13.2	31	0		-
No	484	31	6.4	493	21	4.3	
Avastin Use at Rand (IXRS)							
Yes	19	1	5.3	30	1	3.3	-
No	503	35	7.0	494	20	4.0	
Survival in Study							
Died<3 Months	80	10	12.5	71	3	4.2	-
Alive and Early Disc<3 Months	8	1	12.5	8	0		
Stay in Study>=3 Months	434	25	5.8	445	18	4.0	
Type of Cancer at Rand #							
Solid Tumor	465	32	6.9	467	18	3.9	-
Haematological Malignancy	56	3	5.4	55	3	5.5	
Solid Tumor and Haemat Malig	1	1	100.0	2	0		
Active Cancer at Rand #							
Yes	513	36	7.0	511	19	3.7	-
No	9	0		13	2	15.4	
Distant Metastasis at Rand #							
Yes	274	17	6.2	280	13	4.6	0.1943
No	192	16	8.3	189	5	2.6	
Receiving Cancer Trt at Rand #							
Yes	374	24	6.4	383	12	3.1	0.4644
No	148	12	8.1	141	9	6.4	
Recurring Cancer at Rand #							
Yes	163	12	7.4	152	7	4.6	0.8741
No	359	24	6.7	372	14	3.8	
Cancer Cured #							
Yes	125	3	2.4	114	2	1.8	-
No	397	33	8.3	410	19	4.6	
Baseline ECOG							
0	155	6	3.9	148	5	3.4	0.1284
1	243	20	8.2	246	6	2.4	
>=2	123	10	8.1	124	10	8.1	
Init Hep Dur On/Aft Rand							
None	5	0		-	-		-
<=5 days	449	31	6.9	-	-		
> 5 days	68	5	7.4	-	-		
<= Median	311	23	7.4	-	-		-
> Median	206	13	6.3	-	-		
<= 25th Percentile	158	10	6.3	-	-		-
>25-50th Percentile	153	13	8.5	-	-		
>50-75th Percentile	138	8	5.8	-	-		
>75th Percentile	68	5	7.4	-	-		
Heparin Use Prior to Rand							
Yes	393	25	6.4	412	19	4.6	-
No	129	11	8.5	112	2	1.8	

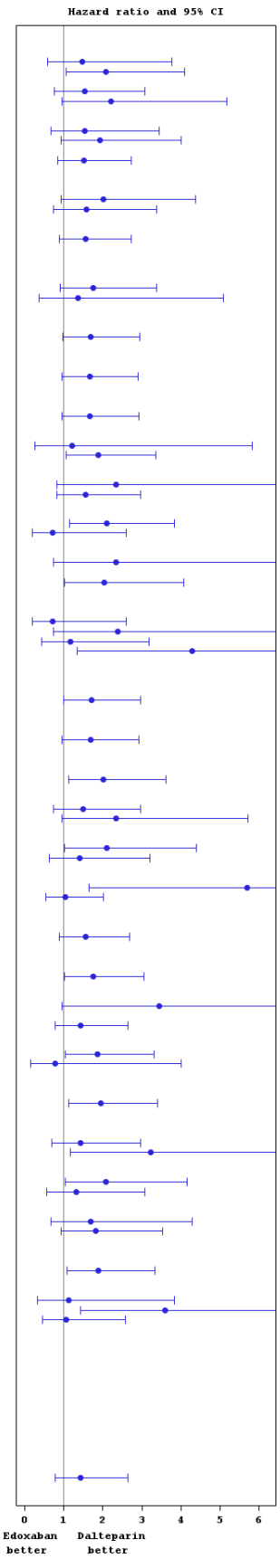
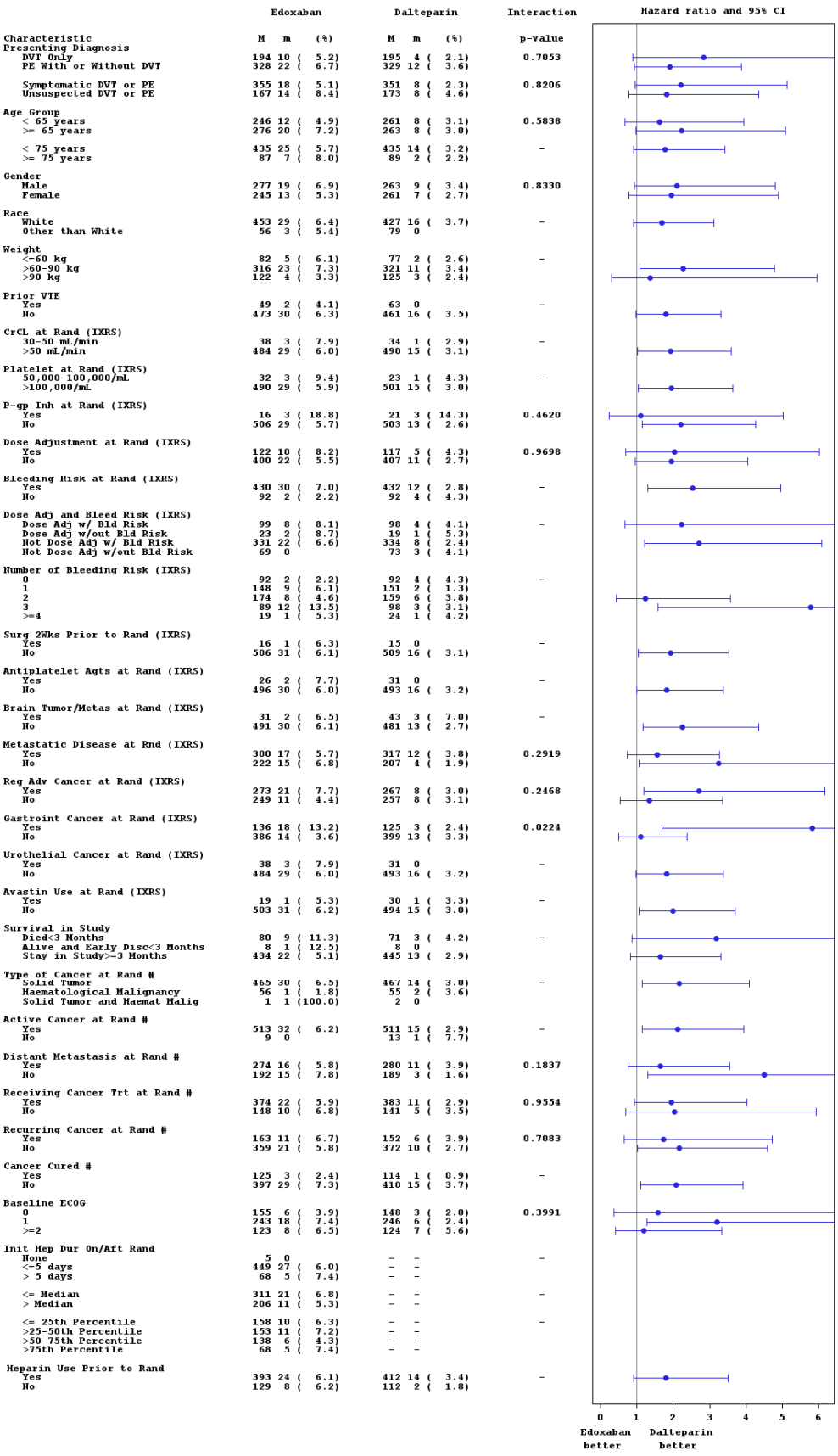


Figure S5. Forest Plot for Major Bleeding On-Treatment Safety Population



Tables

Table S1. Types of Cancer at Baseline

	Edoxaban (N=522)	**Dalteparin (N=524)**
Solid tumor – no. (%)	465 (89.1)	467 (89.1)
Colorectal	83 (15.9)	79 (15.1)
Lung	77 (14.8)	75 (14.3)
Genitourinary	65 (12.5)	71 (13.5)
Breast	64 (12.3)	60 (11.5)
Pancreatic or hepatobiliary	49 (9.4)	40 (7.6)
Gynecological	47 (9.0)	63 (12.0)
Upper gastrointestinal	33 (6.3)	21 (4.0)
Other	48 (9.2)	60 (11.5)
Hematological malignancy – no. (%)	56 (10.7)	55 (10.5)

Table S2. Anticancer Drug Therapies Continuing after Randomization*

	Edoxaban (N=522)	**Dalteparin (N=524)**
Antimetabolites – no. (%)	124 (23.8)	118 (22.5)
Platinum-based chemotherapy – no. (%)	105 (20.1)	107 (20.4)
Monoclonal antibodies – no. (%)	42 (8.0)	54 (10.3)
Bevacizumab – no. (%)	13 (2.5)	17 (3.2)
Taxanes – no. (%)	40 (7.7)	47 (9.0)
Hormonal therapy – no. (%)	41 (7.9)	37 (7.1)
Topoisomerase inhibitors – no. (%)	30 (5.7)	48 (9.2)
Alkylating agents – no. (%)	30 (5.7)	38 (7.3)
Anthracyclines – no. (%)	22 (4.2)	25 (4.8)
Vinca alkaloids – no. (%)	16 (3.1)	18 (3.4)
Kinase inhibitors – no. (%)	18 (3.4)	18 (3.4)
Immunomodulating agents – no. (%)	16 (3.1)	9 (1.7)
Proteasome inhibitors – no. (%)	7 (1.3)	8 (1.5)
Antitumor antibiotics – no. (%)	5 (1.0)	5 (1.0)
Miscellaneous – no. (%)	14 (2.7)	14 (2.7)

*Patients could receive more than one anticancer drug. Treatment does not include anticancer therapy initiated after randomization.

Table S3. Duration of Study Drug Treatment and Reasons for Treatment Discontinuation

	Edoxaban (N=522)	**Dalteparin (N=524)**
LMWH lead-in days – median (IQR)	5.0 (5-6)	-
Drug exposure days - median (IQR)	211 (76-357)*	184 (85-341)*
<3 months – no. (%)	139 (26.6)	137 (26.1)
3 months to ≤6 months – no. (%)	80 (15.3)	102 (19.5)
>6 months – no (%)	303 (58.0)	285 (54.4)
Completed treatment for 12 months or until study closure	200 (38.3)	154 (29.4)
Reason for permanent study drug discontinuation		
Death	86 (16.5)	100 (19.1)
Clinical outcome/adverse event	79 (15.1)	62 (11.8)
Cancer progression	53 (10.2)	33 (6.3)
Cancer resolved	10 (1.9)	15 (2.9)
Investigator decision: benefit/risk judgement	32 (6.1)	46 (8.8)
Investigator decision: palliative treatment only	10 (1.9)	7 (1.3)
Investigator decision: patient non-compliance	1 (0.2)	2 (0.4)
Platelet count <50,000 per mL	1 (0.2)	2 (0.4)
Start of new chemotherapy	6 (1.1)	3 (0.6)
Patient decision: inconvenience of dosing	21 (4.0)	78 (14.9)
Withdrawal of study consent	6 (1.1)	8 (1.5)
Other reason	17 (3.3)	14 (2.7)

IQR denotes interquartile range

* Refers to the time from initiating study drug treatment until permanent discontinuation of study drug. P = 0.0143 (by log rank test).

Table S4. Types of Outcomes Contributing to the Primary Outcome

Clinical Outcomes	**Edoxaban (N=522)**	**Dalteparin (N=524)**
Primary outcome: first recurrent VTE or major bleeding – no. (%)	67 (12.8)	71 (13.5)
Recurrent VTE – no. (%)	34 (6.5)	54 (10.3)
Fatal PE	0	0
Death, with PE not ruled out	3 (0.6)	3 (0.6)
Nonfatal PE with or without DVT	18 (3.4)	21 (4.0)
DVT only	13 (2.5)	30 (5.7)
Symptomatic nonfatal VTE	22 (4.2)	40 (7.6)
Incidental nonfatal VTE	9 (1.7)	11 (2.1)
Major bleeding – no. (%)	33 (6.3)	17 (3.2)
Fatal†	0	2 (0.4)
Intracranial	2 (0.4)	4 (0.8)†
Gastrointestinal	20 (3.8)	6 (1.1)
Upper	17 (3.3)	3 (0.6)
Lower	3 (0.6)	3 (0.6)†
Urogenital	5 (1.0)	0

Other	6 (1.1)	7 (1.3)
Severity of clinical presentation of major bleeding – no. (% of patients with major bleeding) ‡		
1	0	0
2	21/33 (63.6)	5/17 (29.4)
3	12/33 (36.4)	11/17 (64.7)
4	0	1/17 (5.9)

DVT denotes deep-vein thrombosis, PE pulmonary embolism, and VTE venous thromboembolism.

† The site of fatal bleeding was intracranial in one patient and lower gastrointestinal in one patient.

‡ The severity of clinical presentation of major bleeding was adjudicated without knowledge of treatment assignment according to the predefined categories 1: Bleeding events presenting without any clinical emergency, 2: Bleeding events that could not be classified to any of the other three categories, as they presented with the need for some measures but without clear urgency, 3: Bleeding events presenting with great medical urgency, such as bleeding with hemodynamic instability or intracranial bleeding presenting with neurologic symptoms, and 4: Bleeding events already fatal before or almost immediately upon entering the hospital. [1]

Table S5. Clinical Outcomes during First Six Month-Study Period

Clinical Outcomes	Edoxaban (N=522)	Dalteparin (N=524)	Hazard Ratio with Edoxaban (95% CI)
Primary outcome: first recurrent VTE or major bleeding – no. (%)	55 (10.5)	56 (10.7)	1.01 (0.69-1.46) P=0.0176 for noninferiority P=0.9755 for superiority
Secondary outcomes – no. (%)			
Recurrent VTE*	34 (6.5)	46 (8.8)	0.75 (0.48-1.17) P=0.2090
Recurrent DVT	15 (2.9)	25 (4.8)	0.61 (0.32-1.15)
Recurrent PE **	23 (4.4)	24 (4.6)	0.99 (0.56-1.75)
Major bleeding	29 (5.6)	17 (3.2)	1.74 (0.95-3.18) P=0.0707
Clinically relevant nonmajor bleeding	64 (12.3)	43 (8.2)	1.55 (1.05-2.28)
Major or clinically relevant nonmajor bleeding¶	83 (15.9)	56 (10.7)	1.54 (1.10-2.16)
Deaths from all causes	140 (26.8)	127 (24.2)	1.14 (0.90-1.45)
Event-free survival (i.e., free of recurrent VTE, major bleeding, or death)	354 (67.8)	360 (68.7)	0.94 (0.76-1.17)

CI denotes confidence interval, DVT deep-vein thrombosis, PE pulmonary embolism, and VTE venous thromboembolism.

*One patient can have more than one event

** Among the patients with recurrent PE 5 (1.0%) patients in the edoxaban group and 3 (0.6%) patients in the dalteparin group had unexplained death (pulmonary embolism could not be ruled out) but none of the patients had objectively confirmed fatal pulmonary embolism

¶ For patients who had more than one event, only the first event was counted

Table S6. Clinical Outcomes On-Treatment in the Per-Protocol-Population

Clinical Outcomes	Edoxaban (N=490)	Dalteparin (N=508)	Hazard Ratio with Edoxaban (95% CI)
Primary outcome: first recurrent VTE or major bleeding – no. (%)	51 (10.4)	53 (10.4)	0.99 (0.68 - 1.46) P=0.0177 for noninferiority P=0.9685 for superiority
Safety outcomes – no. (%)			
Major bleeding	29 (5.9)	16 (3.1)	1.83 (0.99 - 3.39) P= 0.0535
Clinically relevant nonmajor bleeding	64 (13.1)	48 (9.4)	1.35 (0.93 - 1.97)
Major or clinically relevant nonmajor bleeding¶	82 (16.7)	59 (11.6)	1.42 (1.01 - 1.98)

CI denotes confidence interval, DVT deep-vein thrombosis, PE pulmonary embolism, and VTE venous thromboembolism.

¶ For patients who had more than one event, only the first event was counted.

Table S7. Bleeding Outcomes on Treatment in the Safety Population

Outcome	Edoxaban (N=522)	Dalteparin (N=524)
Major Bleeding – no. (%)	32 (6.1)	16 (3.1)
Clinically relevant nonmajor bleeding	70 (13.4)	48 (9.2)
Major or clinically relevant nonmajor bleeding	91 (17.4)	59 (11.3)
Any Bleeding	137 (26.2)	104 (19.8)

Table S8. Deaths at 3, 6, and 12 months, and Causes of Death overall study period

Cause of Death	Edoxaban (N=522)	Dalteparin (N=524)
Deaths from all causes at 3 months – no. (%)	80 (15.3)	71 (13.5)
Deaths from all causes at 6 months – no. (%)	140 (26.8)	127 (24.2)
Death from all causes at 12 months – no. (%)	206 (39.5)	192 (36.6)
Cause of Death		
VTE related	6 (1.1)	4 (0.8)
Bleeding	0	2 (0.4)
Cancer related	181 (34.7)	172 (32.8)
Cardiovascular	8 (1.5)	3 (0.6)
Other	11 (2.1)	11 (2.1)

VTE denotes venous thromboembolism

Table S9 Summary of Adverse Events

All reported Adverse Events (including study outcomes) Safety Analysis Set - On-Treatment Study Period

	Edoxaban (N=522)	**Dalteparin (N=524)**
All Adverse Events	308 (59.0)	286 (54.6)
Serious Adverse Events	217 (41.6)	195 (37.2)
Drug-Related Adverse Events	118 (22.6)	100 (19.1)
Adverse Events that caused study drug discontinuation	101 (19.3)	109 (20.8)
Adverse Events with Fatal Outcome	116 (22.2)	126 (24.0)

Note: Targeted adverse reporting was a priori defined in the protocol : Adverse Events needed to be reported when they 1) met seriousness criteria or resulted in interruption or discontinuation of study drug Events that were assessed by the investigator to be related to the underlying cancer or treatment of the underlying cancer did not meet criteria for targeted AE reporting, unless patients would die (death is a study outcome) or were associated with another outcome) 2) met criteria as a study outcome or 3) were an event of special interest

Table S10. Most frequent reported Adverse Events

Type of Adverse Event	Edoxaban (N=522)	Dalteparin (N=524)
Malignant neoplasm progression	68 (13.0)	67 (12.8)
Neoplasm progression	23 (4.4)	21 (4.0)
Pneumonia	16 (3.1)	14 (2.7)
Dyspnoea	9 (1.7)	6 (1.1)
Lung neoplasm malignant	8 (1.5)	6 (1.1)
Respiratory failure	7 (1.3)	6 (1.1)
Cachexia	4 (0.8)	2 (0.4)
Disease progression	4 (0.8)	2 (0.4)
Pancreatic carcinoma	4 (0.8)	0
Peripheral swelling	4 (0.8)	3 (0.6)
Renal failure	4 (0.8)	0
Sepsis	4 (0.8)	7 (1.3)
Hepatic enzyme increased	4 (0.8)	4 (0.8)
Atrial fibrillation	3 (0.6)	1 (0.2)
Gastric cancer	3 (0.6)	0
Lung adenocarcinoma metastatic	3 (0.6)	2 (0.4)
Lung cancer metastatic	3 (0.6)	4 (0.8)
Prostate cancer metastatic	3 (0.6)	0
Pyrexia	3 (0.6)	1 (0.2)
Septic shock	3 (0.6)	1 (0.2)
Adenocarcinoma	2 (0.4)	3 (0.6)
Pancreatic carcinoma metastatic	2 (0.4)	3 (0.6)
Urinary tract infection	2 (0.4)	4 (0.8)
Cardiac arrest	1 (0.2)	3 (0.6)
Chest pain	1 (0.2)	4 (0.8)

Type of Adverse Event	Edoxaban (N=522)	Dalteparin (N=524)
Endometrial cancer metastatic	1 (0.2)	3 (0.6)
Multi-organ failure	1 (0.2)	3 (0.6)
Breast cancer metastatic	0	4 (0.8)
Fall	0	3 (0.6)
Heparin-induced thrombocytopenia	0	3 (0.6)
Injection site bruising	0	3 (0.6)
Injection site pain	0	3 (0.6)
Ovarian cancer	0	3 (0.6)
Prostate cancer	0	3 (0.6)
Pyelonephritis	0	3 (0.6)

Table S11 Hepatic events of special interest

	Edoxaban (N=522)	Dalteparin (N=524)
Subjects with blood samples available for (ALT or AST) and Total Bilirubin	N=482	N=487
ALT or AST>=3*ULN With Total Bilirubin>=2*ULN	5 (1.0)	8(1.6)

Reference

1. Bleker SM, A Brekelmans MP, Eerenberg ES, et al. Clinical impact of major bleeding in patients with venous thrombo - embolism treated with factor Xa inhibitors or vitamin K antagonists An individual patient data meta-analysis. Thromb Haemost 2017;117:1944–51.