Supplementary material

Supplementary Text 1.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

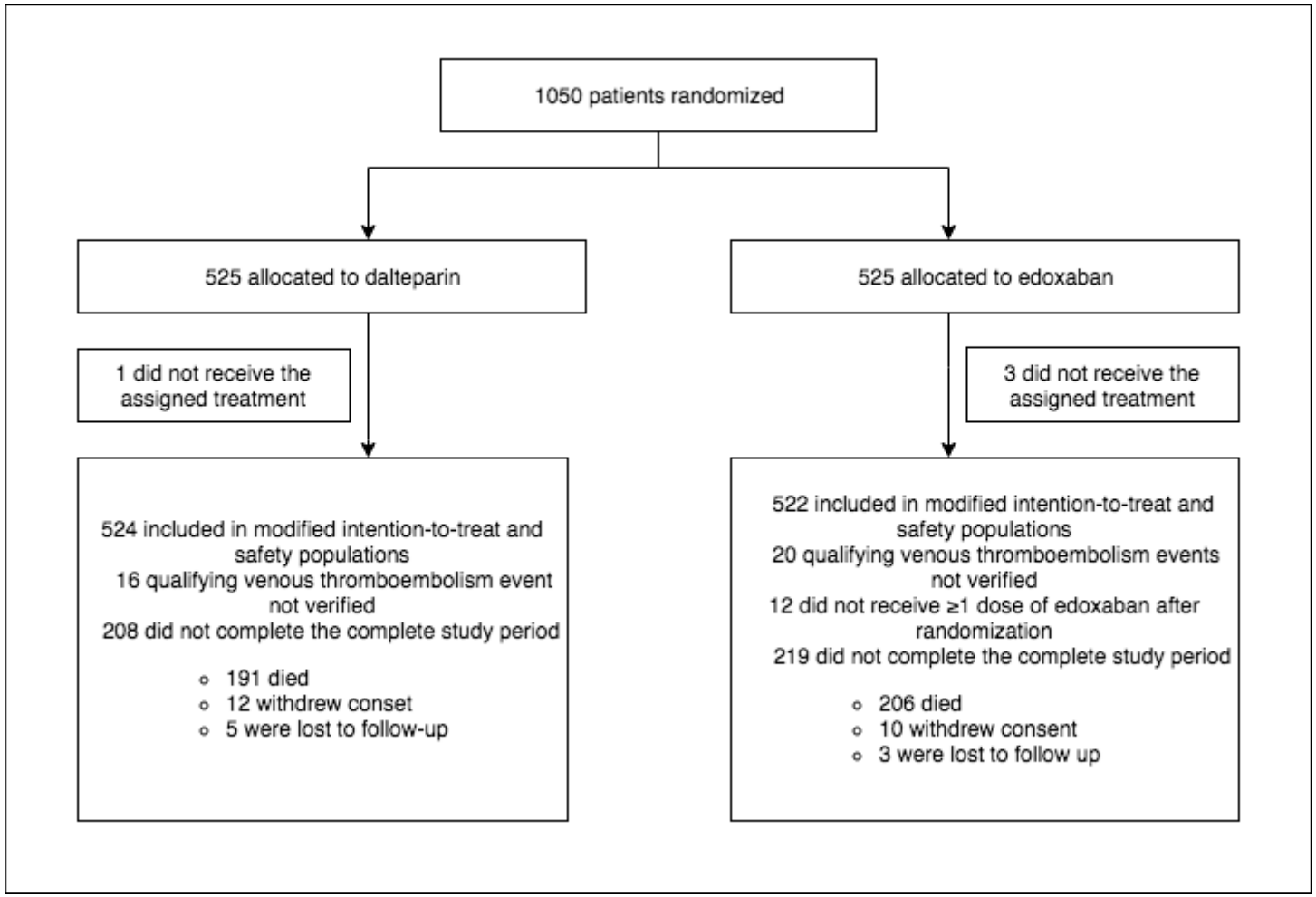
Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	6
Sample size	7a	How sample size was determined	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	6
Randomisation:			
	8a	Method used to generate the random allocation sequence	6

Sequence generation	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6
	11b	If relevant, description of the similarity of interventions	6
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Supp. file
	13b	For each group, losses and exclusions after randomisation, together with reasons	Supp. file
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	16
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	16
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	16
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	16
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	16
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11-14

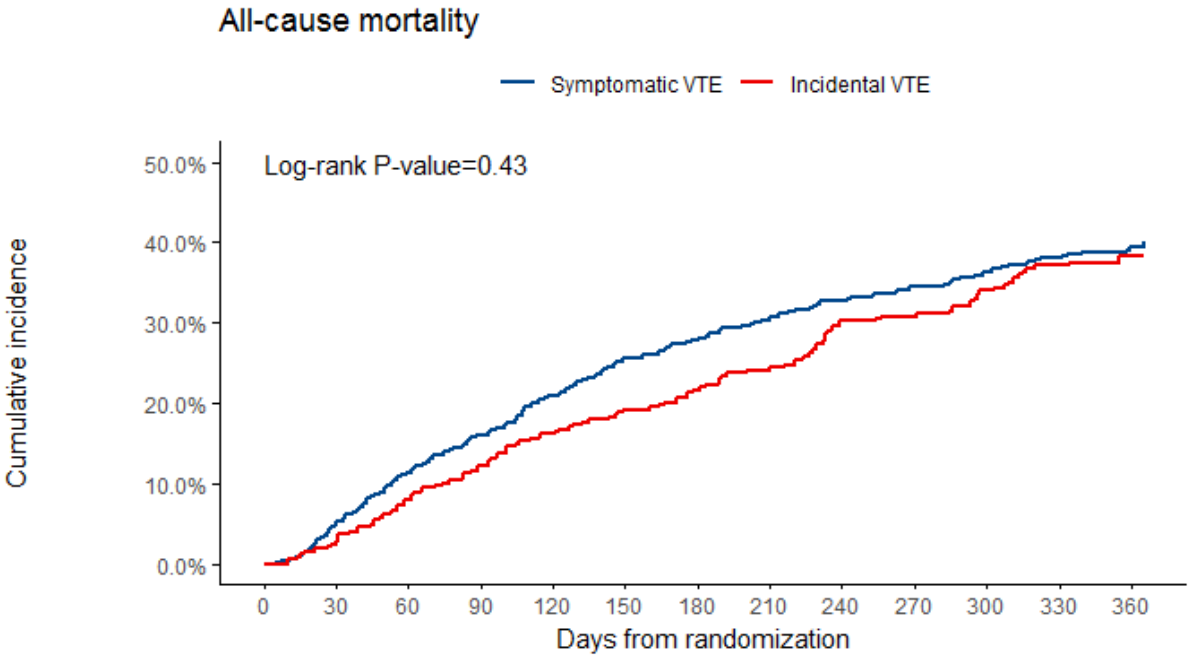
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11-14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11-14
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	2

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

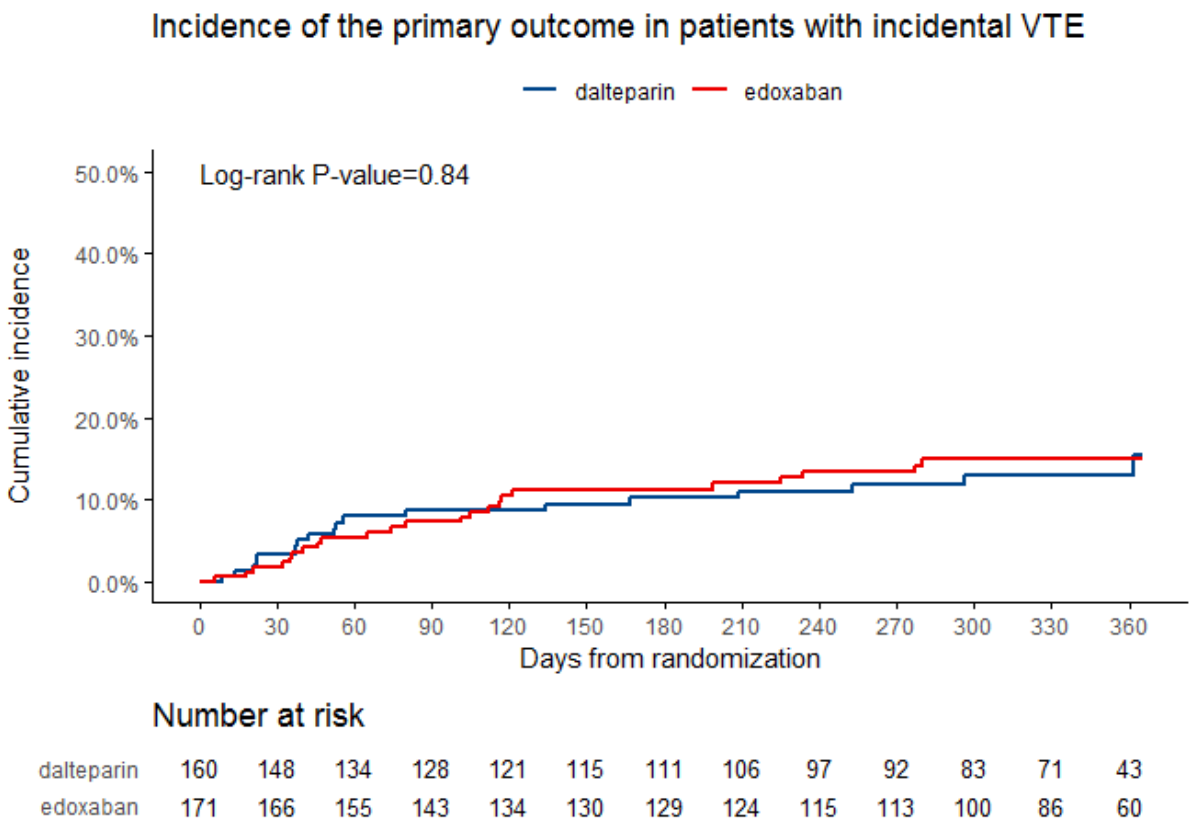
Supplementary Figure 1. CONSORT flow diagram



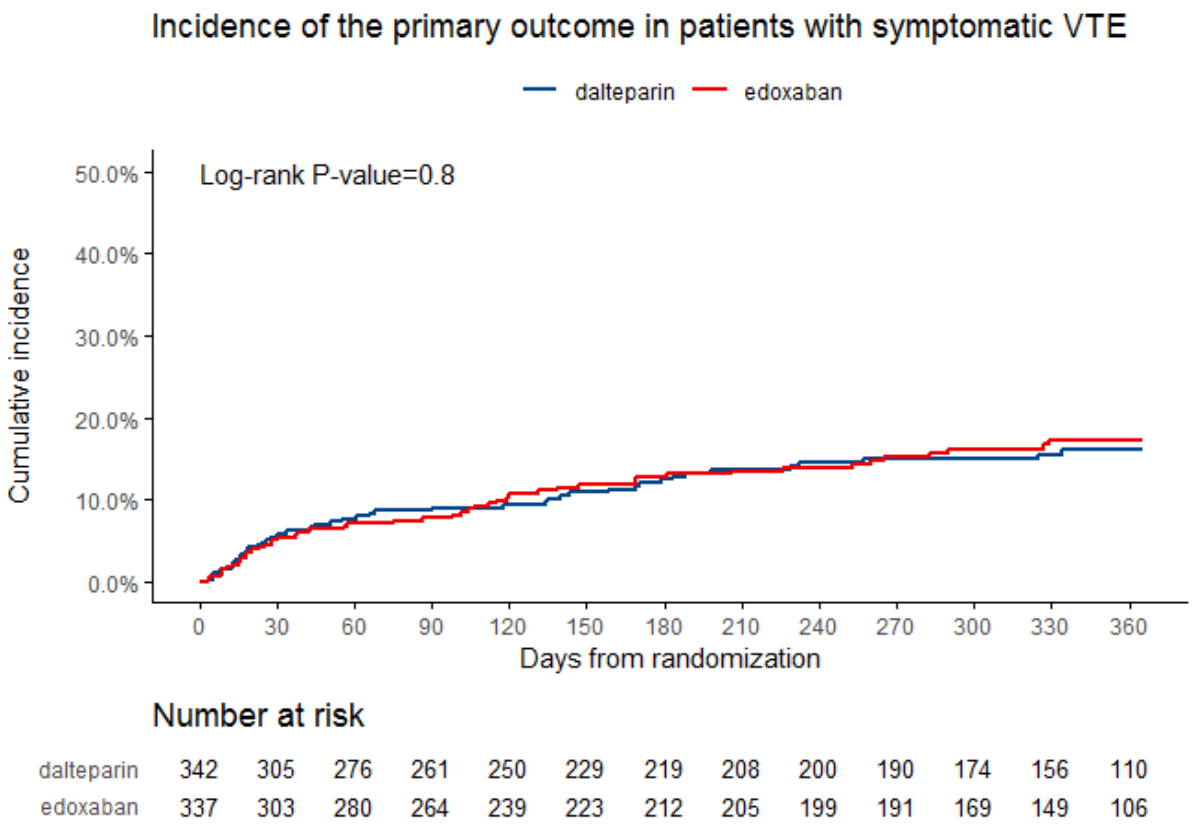
Supplementary Figure 2. The cumulative incidence of all-cause mortality in patients with incidental and symptomatic venous thromboembolism.



Supplementary Figure 3. Occurrence of the primary outcome in patients with incidental VTE randomized to edoxaban and dalteparin.



Supplementary Figure 4. Occurrence of the primary outcome in patients with symptomatic VTE randomized to edoxaban and dalteparin.



Supplementary Table 1. Outcomes in patients with incidental and symptomatic venous thromboembolism during the 6-month study period.

			Incidental vs symptomatic VTE	
	Incidental VTE (n=331)	**Symptomatic VTE** (n=679)	**Crude hazard ratio** (95% CI)	**Adjusted hazard ratio*** (95% CI)
Primary outcome				
First recurrent VTE or major bleeding	33 (10.0%)	76 (11.2%)	0.85 (0.57-1.28)	0.85 (0.54-1.33)
Secondary outcomes				
Recurrent VTE	21 (6.3%)	59 (8.7%)	0.70 (0.42-1.15)	0.68 (0.40-1.17)
Recurrent PE with or without DVT	13 (3.9%)	34 (5.0%)	0.76 (0.40-1.43)	0.73 (0.37-1.45)
Incidental	4 (30.8%)	10 (29.4%)		
Symptomatic	6 (46.2%)	19 (55.9%)		
Death for which PE could not be ruled out	3 (23.1%)	5 (14.7%)		
Recurrent DVT only	8 (2.4%)	25 (3.7%)	0.63 (0.28-1.40)	0.66 (0.27-1.58)
Incidental	3 (37.5%)	2 (8.0%)		
Symptomatic	5 (62.5%)	23 (92.0%)		
On-treatment recurrent VTE	16 (4.8%)	50 (7.4%)	0.63 (0.36-1.10)	0.63 (0.34-1.15)
Major bleeding	17 (5.1%)	27 (4.0%)	1.25 (0.68-2.30)	1.31 (0.67-2.59)
On-treatment major bleeding	15 (4.5%)	22 (3.2%)	1.36 (0.71-2.62)	1.24 (0.59-2.58)
Severity of clinical presentation, n (%)**				
Category 1	2 (13.3%)	6 (27.2%)		
Category 2	10 (66.7%)	12 (54.5%)		
Category 3	3 (20%)	3 (13.6%)		
Category 4	0 (0%)	1 (4.5%)		
All-cause mortality	71 (21.5%)	187 (27.5%)	0.75 (0.57-0.98)	0.68 (0.51-0.92)
Progression of cancer	62 (87.3%)	164 (87.7%)		
Death for which PE could not be ruled out	3 (4.2%)	5 (2.7%)		
Fatal bleeding	0 (0%)	2 (1.1%)		
Other	6 (8.5%)	16 (8.6%)		

*Hazard ratio adjusted for age, sex, anticoagulant treatment, performance status (2 vs lower), cancer type (hematological, lung, gastrointestinal, gynecological, other), and tumor stage (metastatic vs non-metastatic and hematological). For recurrent VTE events additionally adjusted for prior VTE, for major bleeding events additionally adjusted for the presence of any bleeding risk factor.

**Classification of the clinical course of major bleeding events: Category 1: Bleeding events for which only measures were applied to treat discomfort, without transfusions of erythrocytes; Category 2: Bleeding events requiring only standard measures such as transfusions of

erythrocytes, and straight forward interventions; Category 3: Life-threatening bleeding events for which immediate and elaborate measures were used to avoid death. These bleedings could still be fatal after all interventions and could lead to persistent disability; Category 4: Bleeding events for which death was unavoidable, so that no lifesaving attempts were made.

Abbreviation: CI, confidence interval; IQR, interquartile range; PE, Pulmonary embolism; VTE, venous thromboembolism.

Supplementary Table 2. Specification of study outcomes in edoxaban and dalteparin treatment groups.

	Incidental VTE			Symptomatic VTE		
	Edoxaban (n=160)	Dalteparin (n=171)	Hazard ratio*	Edoxaban (n=355)	Dalteparin (n=351)	Hazard ratio
Total study period						
Primary outcome						
First recurrent VTE or major bleeding	19 (11.9%)	23 (13.5%)	0.94 (0.51-1.73)	46 (13.5%)	48 (14.2%)	0.95 (0.63-1.42)
Secondary outcomes						
Recurrent VTE	8 (5.0%)	18 (10.5%)	0.50 (0.22-1.16)	33 (9.6%)	41 (12.2%)	0.79 (0.50-1.26)
On-treatment major bleeding	12 (7.5%)	8 (4.7%)	1.63 (0.66-3.99)	18 (5.3%)	8 (2.4%)	2.17 (0.94-5.00)
First 6-month study period						
Primary outcome						
First recurrent VTE or major bleeding	15 (9.4%)	18 (10.5%)	0.93 (0.47-1.85)	38 (11.1%)	38 (11.3%)	0.98 (0.63-1.54)
Secondary outcomes						
Recurrent VTE	8 (5.0%)	13 (7.6%)	0.68 (0.28-1.65)	26 (7.6%)	33 (9.8%)	0.78 (0.46-1.30)
On-treatment major bleeding	8 (5.0%)	7 (4.1%)	1.29 (0.47-3.57)	16 (4.7%)	6 (1.8%)	2.63 (1.03-6.73)

Abbreviations: VTE, venous thromboembolism

* Hazard ratio adjusted for randomization stratification factors of trial, bleeding risk factors and requirement of edoxaban dose reduction (see Raskob, NEJM, 2017). Risk factors for bleeding included the use of antiplatelet therapy, the presence of brain tumor, bevacizumab in the 6 weeks prior randomization, regionally advanced or metastatic disease, gastrointestinal of urothelial cancer. Patients qualified for edoxaban dose reduction in case of a creatinine clearance of 30 to 50 ml per minute, a body weight of 60 kg or less, or if receiving concomitant treatment with potent P-glycoprotein inhibitors.

Supplementary text 1. Calculation of the perfusion score and definition of anatomical extent for patients with pulmonary embolism.

Perfusion score

The range of the perfusion score lies between 0 and 1, and is the sum score of the perfusion score values for all lobes. A value of 1 means no lobe involvement (no perfusion defect), 0 means full lobe involvement.

Values of the perfusion score for each lobe:

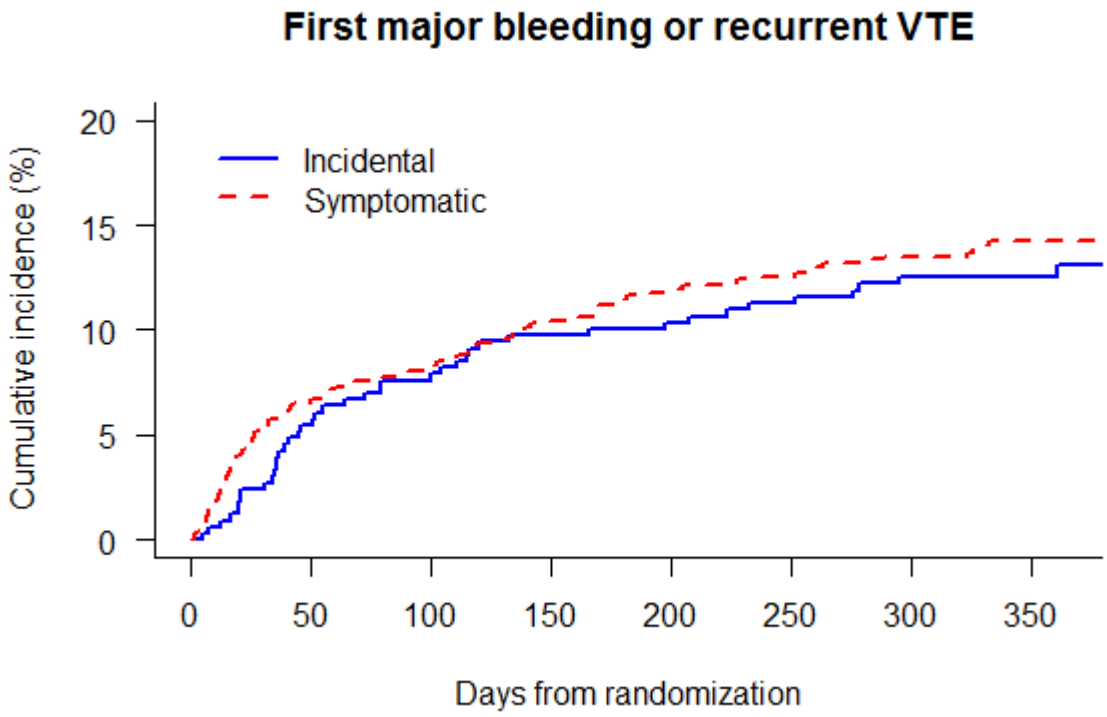
- value = missing, if lobe involvement missing
- value = 1, if 0% lobe involvement ticked
- value = 0.75, if 25% lobe involvement ticked
- value = 0.5, if 50% lobe involvement ticked
- value = 0.25, if 75% lobe involvement ticked
- value = 0, if 100% lobe involvement ticked

Calculation of the total perfusion score = [(Right upper lobe (value) + right middle lobe (value) + right lower lobe (value))/3] x 0.55 + [(Left upper lobe (value) +lingular lobe (value) + left lower lobe (value))/3] x 0.45

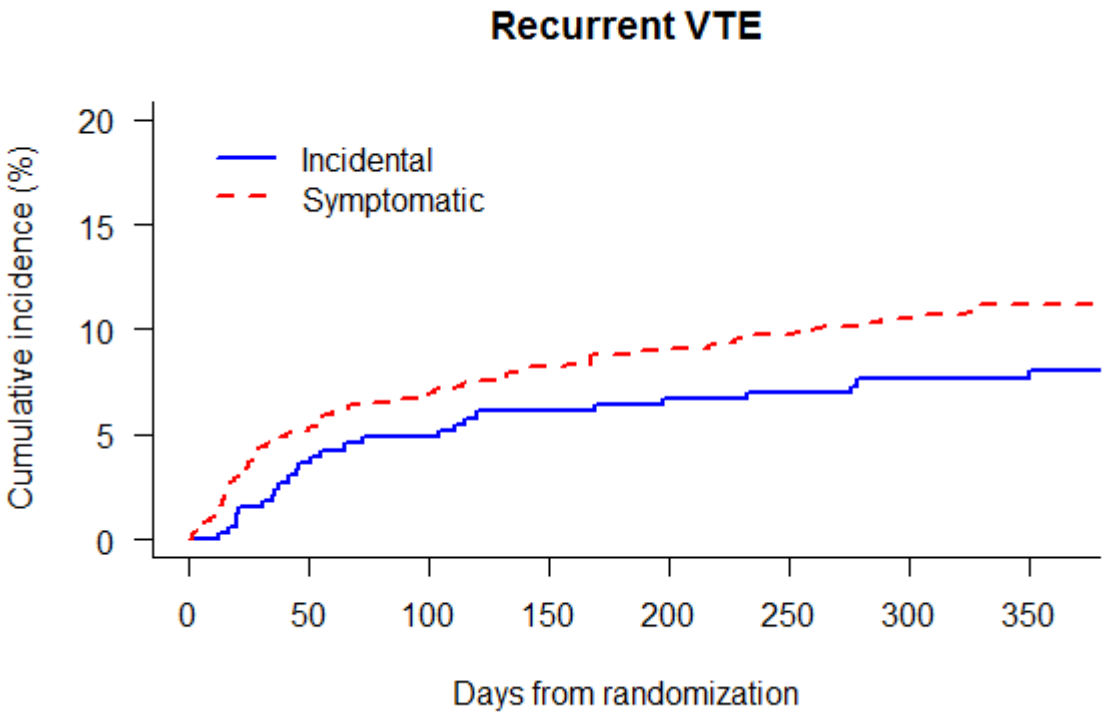
Classification of the anatomical extent:

- Limited: < 25 % or single lobe.
- Extensive: multiple lobes and > 25 % of entire pulmonary vasculature.
- Intermediate: All other cases not mentioned in above categories would fall into the intermediate category.

Supplementary figure 5A. Cumulative incidence of the primary outcome in incidental venous thromboembolism vs symptomatic venous thromboembolism in competing risk analysis.



Supplementary figure 5B. Cumulative incidence of recurrent venous thromboembolism in incidental venous thromboembolism vs symptomatic venous thromboembolism in competing risk analysis.



Supplementary figure 5C. Cumulative incidence of major bleeding in incidental venous thromboembolism vs symptomatic venous thromboembolism in competing risk analysis.