

Supplementary Appendix

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

Supplement to: The PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med* 2011;364:1305-14. DOI: 10.1056/NEJMoa1014475.

Dalteparin versus Unfractionated Heparin in

Critically Ill Patients

Supplementary Appendix

The PROTECT Investigators

for the Canadian Critical Care Trials Group

& the Australian and New Zealand Intensive Care Society Clinical Trials Group

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Trial Management and Oversight

To ensure protocol adherence and data quality, initial training sessions were held for research personnel. Methods Center resources included manuals, standard operating procedures, slide sets and a website. Research coordinators submitted data using an internet-based or direct fax-to-computer system (Datafax, Hamilton, Canada). Methods Center personnel validated data and the trial biostatistician assessed data integrity throughout recruitment by central statistical monitoring [1,2]. Site-specific and general audit and feedback were provided using quality control documents, site visits, conference calls, electronic communication, newsletters, and study meetings and research consortium updates.

Research Ethics Boards approved the protocol at participating centers. A modified DAMOCLES Charter [3] guided the independent Data Monitoring Committee of a biostatistician and 2 clinician scientists. The trial biostatistician provided blinded reports to the committee regarding protocol adherence, trial management indicators, effectiveness and safety reports, and the 2 interim and final analyses.

References

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- 2) Heels-Ansdell D, Walter S, Guyatt G, Warkentin T, Crowther Mark, Geerts W, Berwanger O, Rocha M, Freitag A, Cooper J, Qushmaq I, Zytaruk N, Cook DJ for the PROTECT Investigators, Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Central statistical monitoring in an international thromboprophylaxis trial. *Am J Respir Crit Care Med* 2010;181:A6041.
- 3) DAMOCLES Study Group. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet* 2005;365:712-722.

Diagnosis of Pulmonary Embolism

We classified pulmonary embolism (PE) as definite PE, probable PE, possible PE, or no PE. Definite PE was defined by a clearly positive test (such as characteristic intraluminal filling defect on chest computed tomography or high probability ventilation-perfusion scan). Probable PE was defined by a high clinical suspicion (moderate or high pretest probability) and either a non-diagnostic test for PE or no test for PE. Possible PE was defined as low clinical suspicion (low pre-test probability) and a non-diagnostic test for PE. 'No test for PE' is not part of the definition of a possible PE because the clinical concern had to be sufficient to order a test unless the patient was moribund or pre-terminal. No PE was defined as either no test for PE or a clearly negative test for PE. Examples follow:

Definite PE

A 46 year old male was admitted to ICU with severe acute alcoholic pancreatitis and hypovolemic shock. For 5 days, he required mechanical ventilation with FiO_2 of 0.35, and inotrope infusion. On day 6, he became more hypoxic requiring FiO_2 of 0.60. The chest x-ray showed bilateral effusions, unchanged from admission. Chest computed tomography showed an intraluminal filling defect in segmental branches of the left lower lobe and right upper lobe. Study drug was discontinued and intravenous heparin was started.

Probable PE

A 71 year old female was admitted to ICU with septic shock and acute respiratory distress syndrome due to pseudomonas pneumonia. For 8 days, she was treated with lung protective mechanical ventilation, inotropes, and intermittent hemodialysis. On day 9, she developed a swollen left upper arm. Ultrasound revealed a non-compressible left internal jugular vein thrombus at the site of a central venous dialysis catheter inserted 4 days previously. The catheter was removed and study drug continued. On day 10, twice weekly screening ultrasound showed a non-compressible right femoral vein thrombus. No catheter had been inserted at that site previously. Study drug was discontinued and intravenous heparin was started. However, within 4 hours, refractory hypotension and hypoxia developed. Chest x-ray showed no

pneumothorax or other interval change. Transesophageal echocardiography showed a markedly dilated right ventricle and a suspicion of a mobile echodense structure in the right pulmonary artery. The patient died before any other tests could be performed.

Possible PE

A 52 year old female with severe chronic obstructive airways disease and recently resected bowel cancer was admitted to ICU post-operatively with a severe wound infection, dehiscence and septic shock. For 5 days following re-operation, she required mechanical ventilation with FiO_2 of 0.4 and inotrope infusion. On day 6 in the ICU, she developed hypoxia requiring FiO_2 0.7, and required a second inotrope.

Electrocardiogram showed sinus tachycardia, a new right bundle branch block and new right axis deviation. The chest x-ray was unremarkable. Urgent bedside transthoracic echocardiography was technically difficult but showed a markedly dilated right ventricle. She suffered a cardiopulmonary arrest and died within 3 hours.

Bleeding Definitions

Bleeding was classified as “major” if it was

- a) Life threatening bleeding due to hypovolemic shock (e.g., from ruptured abdominal aortic aneurysm or upper or lower gastrointestinal hemorrhage)
- b) Life threatening bleeding at a critical site (e.g., intracranial, retroperitoneal, pericardial)
- c) Overt, clinically important bleeding associated with one of the following within 24 hours of the bleed: decrease in hemoglobin >20 g/L, transfusion ≥ 2 packed red blood cells, or decrease in systolic blood pressure > 20 mmHg or increase in heart rate > 20 bpm *in the absence of other causes*
- d) Bleeding at other critical sites (e.g., epidural, intraocular or intraarticular)
- e) Bleeding requiring an invasive intervention (e.g., re-operation)

Bleeding was considered “minor” if it was

- a) overt, but did not meet criteria for major bleeding (e.g., epistaxis, wound-related bleeding, etc)
- b) minor bleeding could be temporally associated with ≥ 2 units packed red blood cells

Serious Adverse Events

Serious adverse events were reported for 7 (0.4%) patients in the dalteparin group and 6 (0.3%) patients in the unfractionated heparin group, respectively, $p=0.76$. Patients in the dalteparin group had a major bleed (6 patients) and HIT with an arterial thrombus (1 patient). Patients in the unfractionated heparin group had major bleeds (5 patients) and HIT with a venous and intracardiac thrombus (1 patient).

Our approach to serious adverse event reporting in this academic trial testing two widely available drugs follows recommendations from the Sensible Conduct of Clinical Trials Symposium held in Washington, DC in 2007 [1]. These methods were approved by the Canadian Critical Care Trials Group, the Australian and New Zealand Intensive Care Society, the PROTECT Data Monitoring Committee and Health Canada.

Reference

1. Cook DJ, Lauzier F, Rocha MG, Sayles MJ, Finfer S. Serious adverse events in academic trials of common drugs in critical care. *Can Med Assoc J* 2008; 178(9):1181-1184.

Meaningful Reporting of Serious Adverse Events in Academic Trials of Established Drugs in ICU

1. We recommend that before commencing academic critical care trials of common drugs, investigators should clearly describe the serious adverse events (SAEs) they plan to identify and report in their protocol, for review by local Research Ethics Boards and Data Monitoring Committees. Investigators should consider labeling the most concerning SAEs as primary, secondary or tertiary outcomes. Adverse events already defined and reported as study outcomes should not routinely also be labeled and reported as SAEs.
2. We recommend that in academic critical care trials of common drugs, SAEs should be largely limited to serious events that are known to result from the study drug, or which might reasonably occur as a consequence of the study drug.
3. We recommend that in academic critical care trials of common drugs, caution is warranted to avoid definitively attributing adverse events to the study drugs; this attribution is more sensible when SAEs are reported in the 2 arms of the trial, examined at an interim analysis or when the trial is complete.
4. We recommend that in academic critical care trials of common drugs, caution is warranted to avoid attributing deaths as SAEs related to the study drug.
5. We recommend that a key role for Research Ethics Boards receiving real-time single-center SAE reports is to identify problems requiring remediation of the protocol or its implementation. Independent Data Monitoring Committees should monitor and interpret individual SAEs in the context of emerging literature, the number of events and patients in each arm enrolled locally and across all centers, and in the context of other trial outcomes. Periodic Data Monitoring Committee reports should be sent to each local Research Ethics Board according to the trial protocol.

Appendix Table 1. Venous Thromboembolic Outcomes (Per-Protocol Analysis)

	Dalteparin (N=1566)	Unfractionated Heparin (N=1561)	Hazard Ratio (95% CI)	P-value
Proximal leg DVT	91 (5.8)	99 (6.3)	0.95 (0.70, 1.29)	0.75
Any DVT	131 (8.4)	150 (9.6)	0.95 (0.73, 1.22)	0.67
Pulmonary embolism				
Definite	17 (1.1)	27 (1.7)		
Probable	4 (0.3)	7 (0.4)		
Possible	1 (0.06)	3 (0.2)		
Definite or Probable	21 (1.3)	34 (2.2)	0.54 (0.30, 0.98)	0.04
Any pulmonary embolism	22 (1.4)	37 (2.4)	0.54 (0.30, 0.95)	0.03
Any VTE	146 (9.3)	170 (10.9)	0.91 (0.72, 1.16)	0.44
VTE or hospital death	439 (28.0)	474 (30.4)	0.95 (0.83, 1.09)	0.44
Heparin-induced thrombocytopenia, N (%)	3 (0.2)	12 (0.8)	0.27 (0.08, 0.98)	0.046

(CI= confidence interval, DVT=deep-vein thrombosis, VTE=venous thromboembolism)

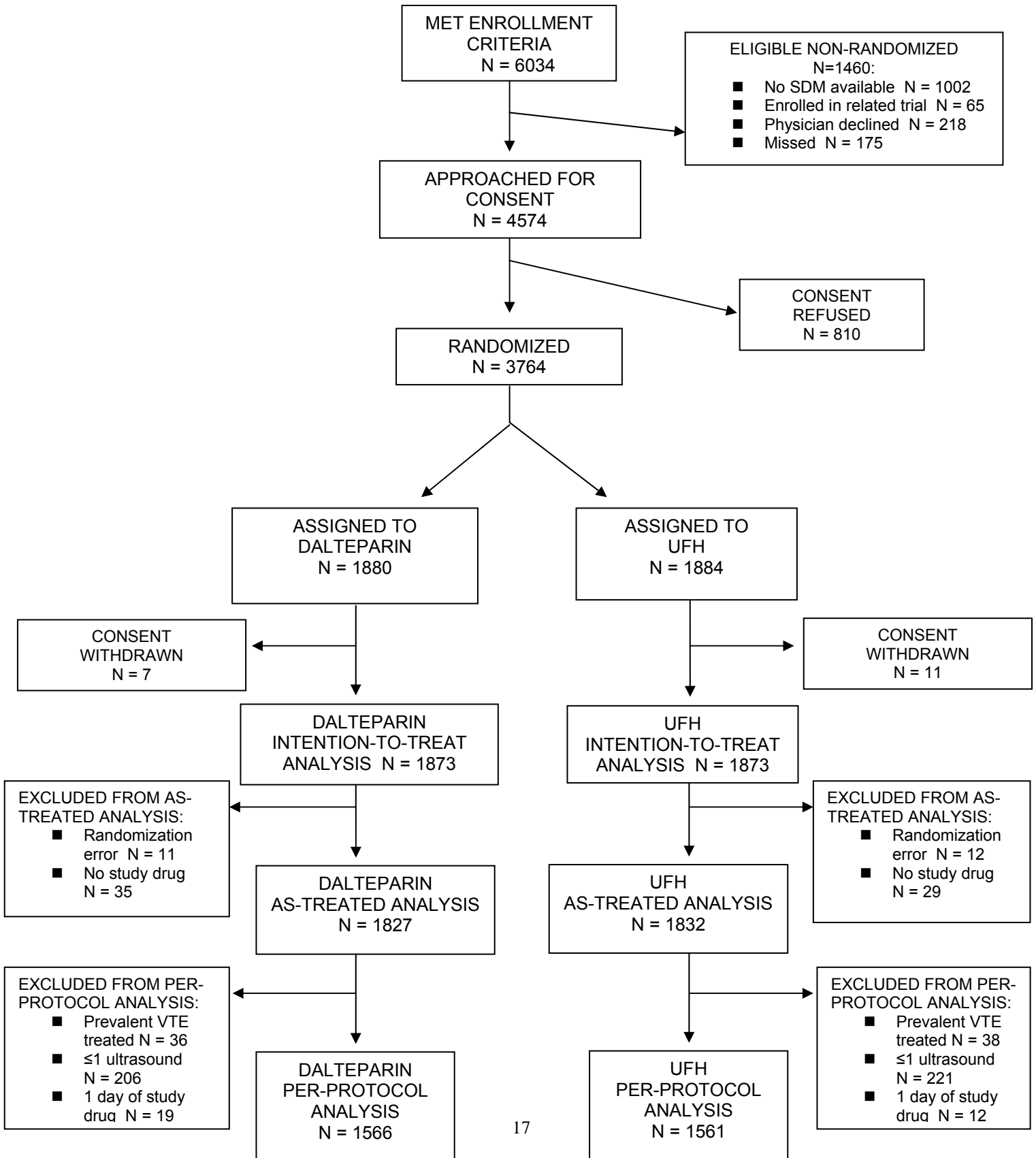
Appendix Table 2. Subgroup Analyses: Proximal Leg DVT (Intention-to-Treat Analysis)

Subgroup	Dalteparin	Unfractionated Heparin	Hazard Ratio (95% CI) ¹	P Value for Interaction
	Events / patients (%)	Events / patients (%)		
Admission Type				
Medical	78/1409 (5.5)	81/1422 (5.7)	1.04 (0.75, 1.44)	0.11
Surgical	18/464 (3.9)	28/451 (6.2)	0.57 (0.29, 1.10)	
Vasopressors				
No	50/1057 (4.7)	48/990 (4.8)	0.96 (0.62, 1.49)	0.99
Yes	46/805 (5.7)	61/872 (7.0)	0.97 (0.63, 1.49)	
End Stage Dialysis Dependent Renal Disease				
No	91/1805 (5.0)	106/1804 (5.9)	0.92 (0.68, 1.24)	0.65
Yes	5/60 (8.3)	3/58 (5.2)	1.40 (0.23, 8.56)	

¹ Hazard ratios were obtained from Cox Regression stratified by center and medical versus surgical admission status.

Appendix Figure 1.*

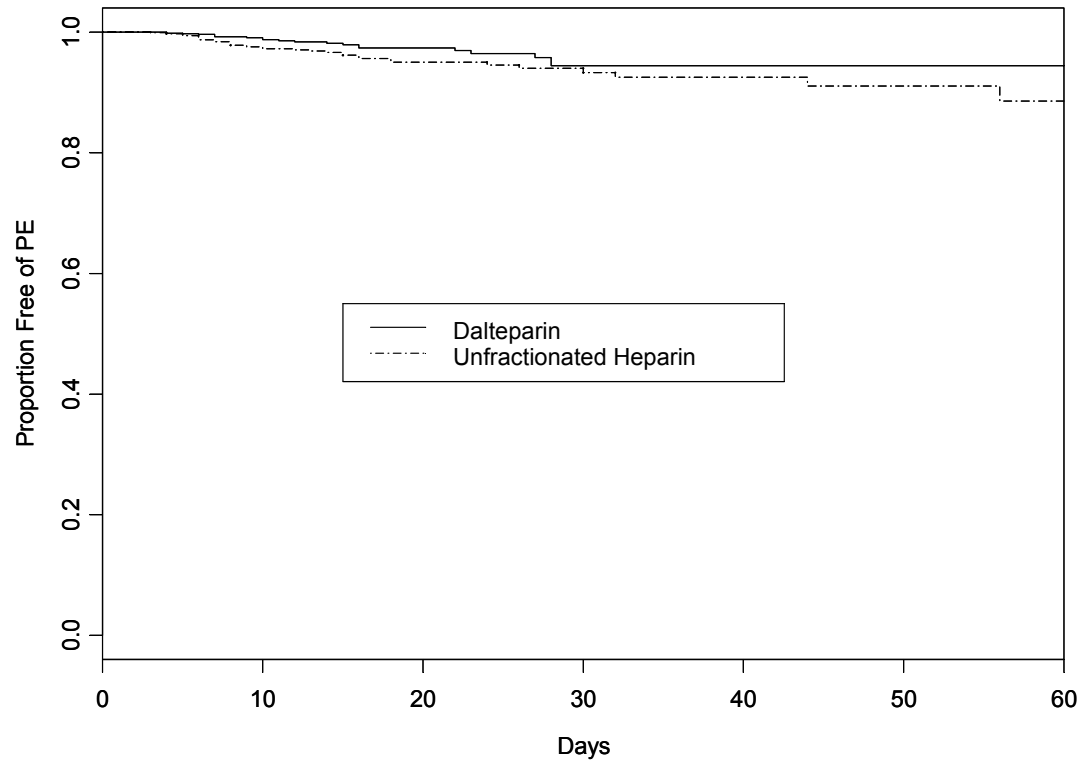
This figure shows the flow of patients in the trial. See the footnote below for details.



* Eligible patients fulfilled all inclusion criteria and had no exclusion criteria. Eligible non-randomized patients are categorized as follows: 1002 patients had no substitute decision maker available (e.g., had no family members or no family members reachable, etc.); 65 patients were enrolled in a related trial (e.g., a trial testing a drug or device that influenced thrombotic or bleeding risk, industry trial precluding co-enrolment, etc.); 218 patients had a physician who declined to permit their patients to be approached (e.g., concern about patient's clinical status, family's psychosocial situation, etc.); 175 patients were missed (e.g., research coordinator, study pharmacist, or ultrasonographer unavailable, administrative error, workload due to H1N1 epidemic, etc.). UFH = unfractionated heparin, SDM = substitute decision maker.

Appendix Figure 2.

This figure shows the Kaplan-Meier time-to-event curves for pulmonary embolism.

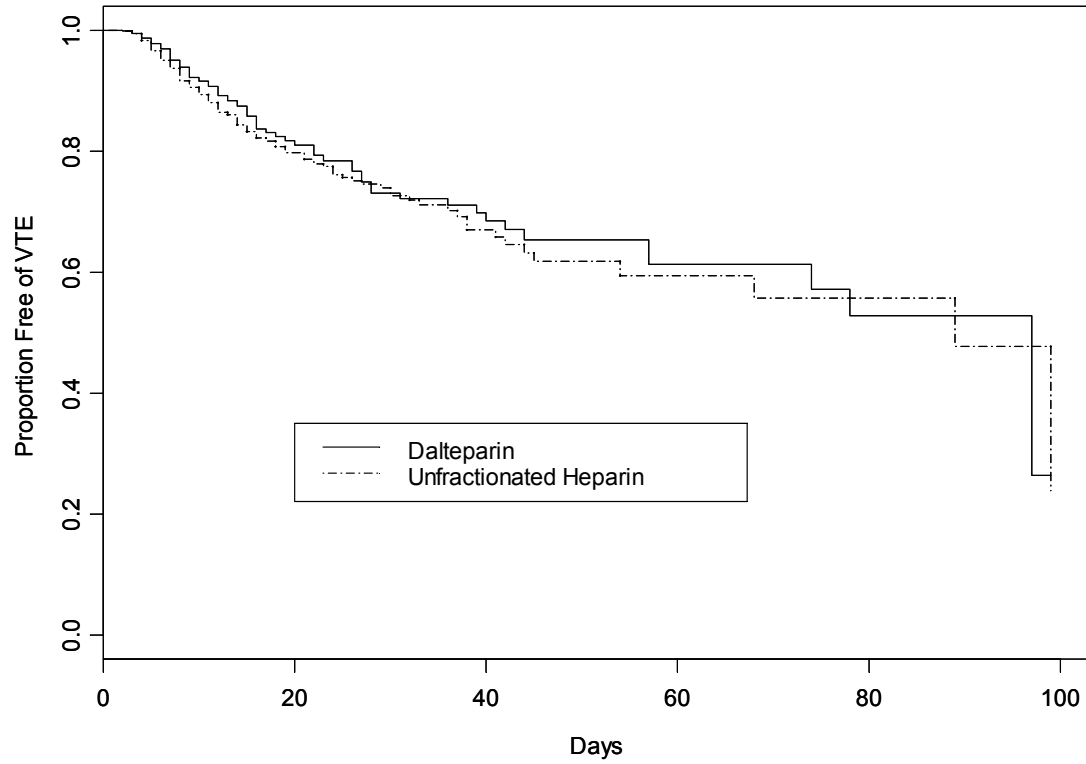


No. at risk

Dalteparin	1873	638	261	135	74	44	30
Unfractionated Heparin	1873	620	252	108	66	40	21

Appendix Figure 3.

This figure shows the Kaplan-Meier time-to-event curves for any venous thromboembolism.

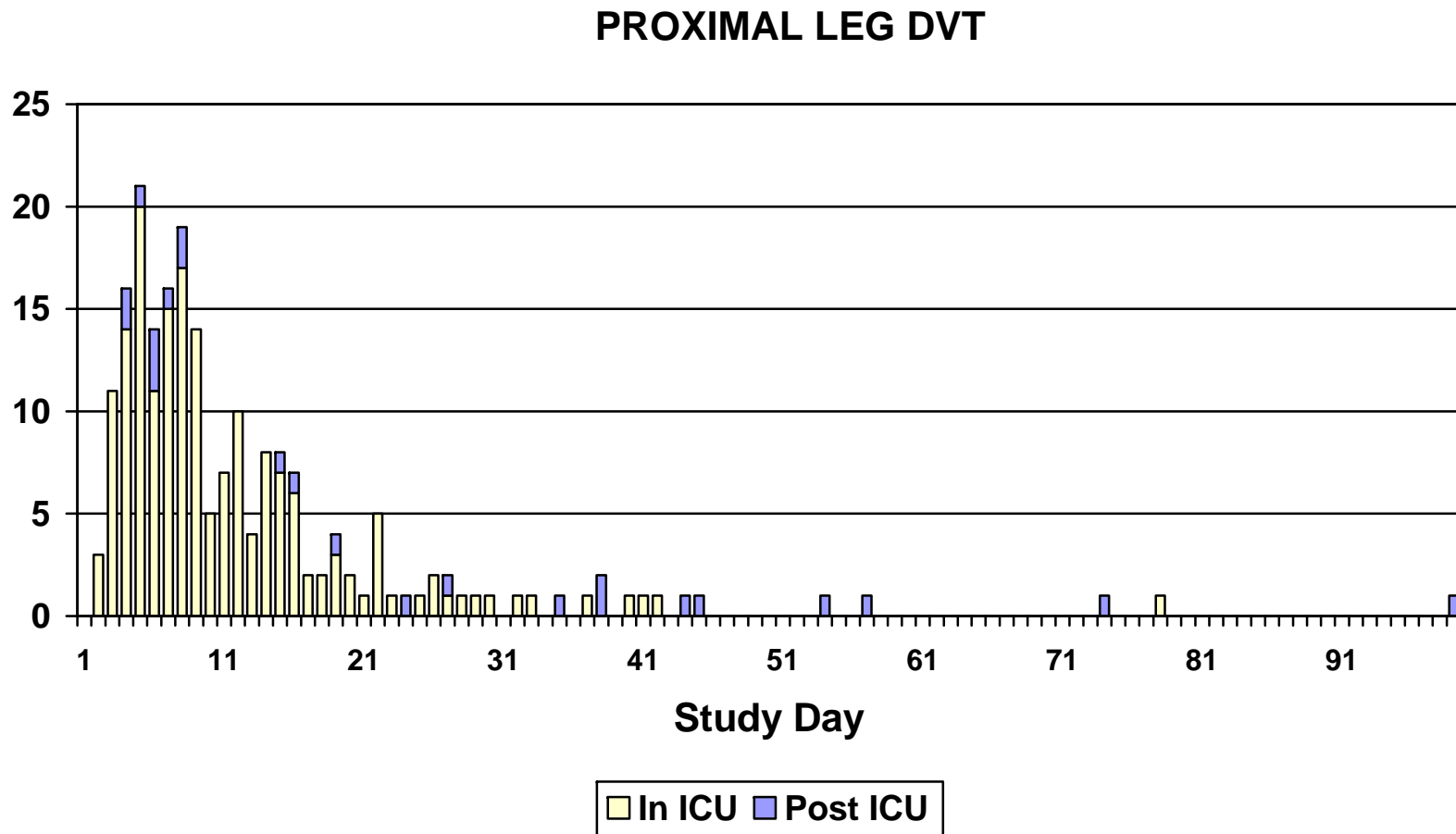


No. at risk

Dalteparin	1873	230	59	21	10	2
Unfractionated Heparin	1873	219	53	15	12	1

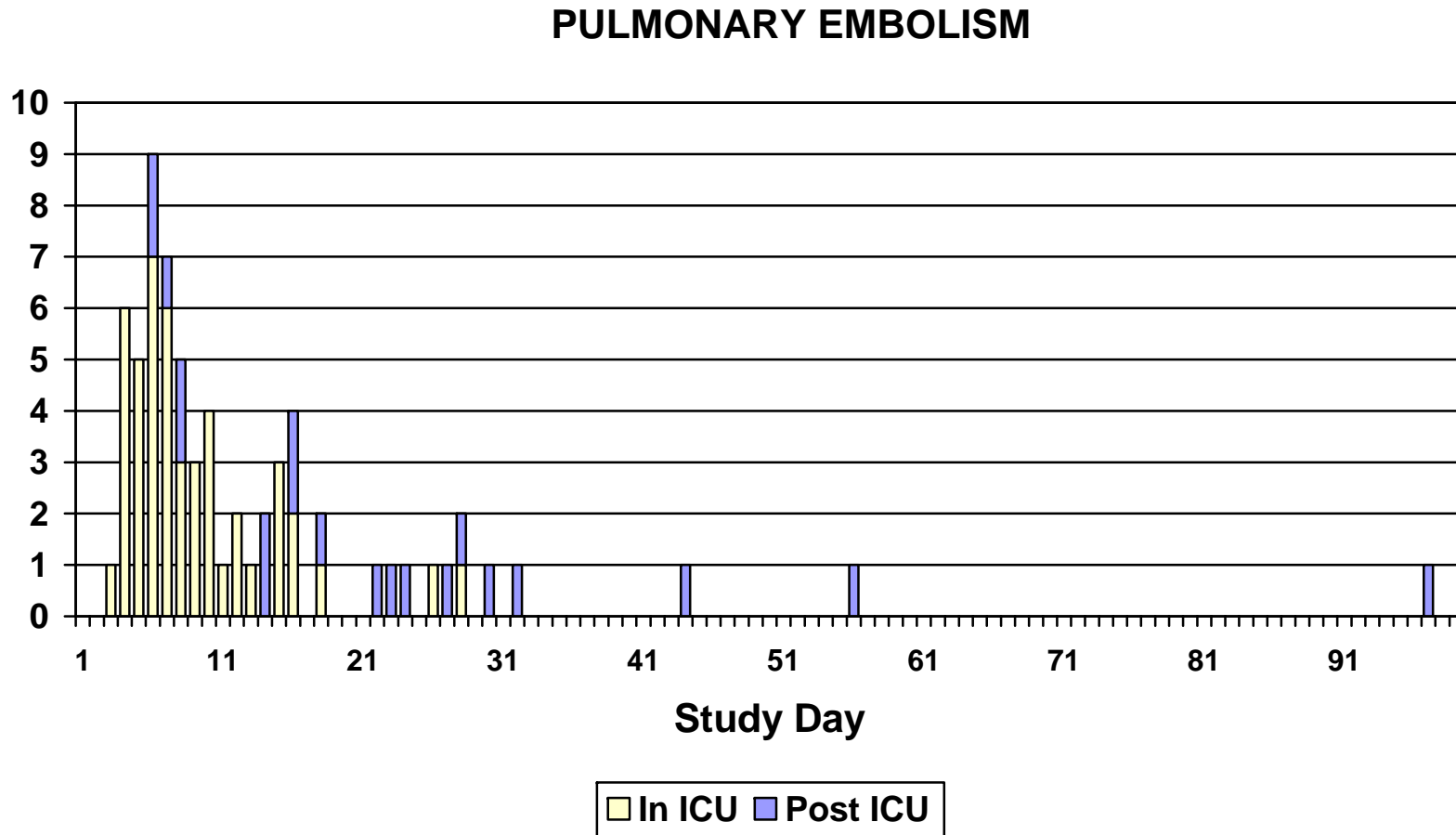
Appendix Figure 4.

This figure shows the numbers of proximal leg deep venous thromboses detected in the trial, by day from randomization.



Appendix Figure 5.

This figure shows the numbers of pulmonary emboli diagnosed in the trial, by day from randomization.



Appendix Figure 6.

This figure shows the numbers of venous thromboembolic events in the trial, by day from randomization.

ANY VENOUS THROMBOEMBOLISM

