Venous thromboembolism in the critically ill: A prospective observational study of occurrence, risk factors and outcome

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Title

Venous thromboembolism in the critically ill: A prospective observational study of occurrence, risk factors and outcome

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Conflict of interest

The authors declare that they have no conflict of interest in relation to this manuscript.

Abstract

Background The aim of the study was to explore occurrence, risk factors and outcome of venous thromboembolism (VTE) in intensive care unit (ICU) patients.

Methods Prospective observational study of ICU patients receiving thromboprophylaxis at Oslo University Hospital in Norway. Adult medical and surgical patients with ICU length of stay (LOS) longer than 48 hours were included. For detection of VTE, Doppler ultrasound screening of neck, upper and lower extremity veins was used, and computed tomography angiography when clinically indicated for any medical reason.

Results Among 70 included patients, 79 % were males and mean age was 62 ($\pm$ 12.1) years. All received thromboprophylaxis with dalteparin, and 44 (63 %) used graduated compression stockings. VTE was found in 19 (27 %) patients; deep vein thrombosis in 15 (21 %) and pulmonary embolism in four (6 %). Among the VTEs, 11 (58 %) presented within the first 48 hours after admission, nine (47 %) were related to central vein catheters, and five (26 %) were symptomatic. Risk factors for VTE in multivariable analyses were malignancy, abdominal surgery and SAPS II score < 41 with an AuROC (95 % CI) of 0.72 (0.58-0.85, $p=0.01$). Patients with and without VTE had comparable ICU LOS (13 vs. 11 days, $p=0.27$) and mortality (16 vs. 20 %, $p=0.72$).

Conclusion VTE was observed in 27 % of ICU patients receiving thromboprophylaxis. Factors associated with increased risk of VTE were malignancy, abdominal surgery and SAPS II score < 41 . Presence of VTE did not impact on patient outcome.

Introduction

Patients in the intensive care unit (ICU) may suffer from venous thromboembolism (VTE) being deep vein thrombosis (DVT) and/or pulmonary embolism (PE) [1]. Such VTE may be present at admission, or develop during the later ICU stay. VTE occurrence depends on the study population, use of thromboprophylaxis, and diagnostic method utilised to detect DVT and PE. Among known risk factors are genetic disposition, advanced age, immobilisation and surgery [2]. Presence of VTE is associated with adverse outcome, especially PE is considered to be an important cause of preventable morbidity and mortality among ICU patients [3-6]. Recent guidelines therefore recommend initiation of combined pharmacological and mechanical thromboprophylaxis as soon as considered safe [7-8].

Limited data from ICU patients suggest that DVTs often occur in other locations than the lower extremities [9, 10], and/or related to central venous catheters (CVCs) [11, 12]. Many VTEs in ICU patients are not clinically suspected, since clinical features may be absent or difficult to distinguish from other conditions. Such asymptomatic VTE may include DVTs found during Doppler ultrasound (DUS) screening of veins [13, 14], unsuspected PEs observed during autopsy [15], in addition to VTEs found during computed tomography (CT) angiography examinations. An unsettled issue is treatment of VTEs in the ICU, as anticoagulant therapy is challenging due to increased risk of bleeding among critically ill patients already exposed to bleeding complications. It is also uncertain whether catheter-related DVTs should be treated with removal of the catheter.

The purpose of the present study was to assess VTE in medical and surgical high-risk ICU patients receiving thromboprophylaxis. The primary aim was to explore occurrence, risk factors and outcome of VTE. Secondary aims were to describe the observed VTE in terms of location, catheter-relation, symptomatology and treatment.

Methods

Study design and setting

The study was a prospective observational study entitled Norwegian Intensive Care Unit Dalteparin Effect Study (NORIDES study) and the patients were enrolled consecutively. Oslo University Hospital is a community hospital for Oslo, and a regional hospital for 2.7 million people in South-Eastern Norway. The Regional Committee for Medical and Health Research Ethics approved the study (approval number 2012/924). The study was registered at ClinicalTrials.gov (NCT01721928).

Study population

Inclusion criteria were medical and surgical ICU patients at Oslo University Hospital receiving pharmacological thromboprophylaxis with dalteparin (Fragmin, Pfizer, NJ, USA) between December 2, 2012, and March 2, 2016. Exclusion criteria were age < 18 years, intraocular or intracranial bleeding, acute spinal cord lesion, inherited coagulopathy, uncontrolled bleeding, therapeutic anticoagulation, uncorrected coagulopathy, pregnancy or postpartum (< 6 weeks), participation in an interventional study, chronic kidney disease and anticipated ICU length of stay (LOS) < 48 hours. All included patients received pharmacological thromboprophylaxis with dalteparin. Standard dose was subcutaneous dalteparin 5000 IU/day, but this could be altered based on individual risk assessment. Mechanical prophylaxis consisted of bilateral graduated compression stockings (GCS); this was routinely used in the surgical ICU, but not in the medical ICU. The initial goal of the study was to compare patients with acute kidney injury (AKI) treated with continuous renal replacement therapy (CRRT) with a control group of patients having normal kidney function. Enrolment of patients was therefore performed in order to obtain equal number of patients with and without severe AKI treated with CRRT, but enrolment was much lower than

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2
3 expected. Since the study was underpowered in order to compare VTE occurrence in patients
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5 with and without severe AKI, we here present descriptive data on VTE in the ICU. In patients
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7 undergoing CRRT, the haemodialysis circuit was regionally anticoagulated with citrate
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9 (Multifiltrate, Fresenius Medical Care, Bad Homburg, Germany).
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14 **Study definitions**
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16 Comorbidities were classified according to the Charlson comorbidity index [16]. Severity of
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18 illness was assessed using the Simplified Acute Physiology Score (SAPS II) [17] and
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20 Sequential Organ Failure Assessment (SOFA) score [18]. Risk factors for VTE included most
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22 mentioned in the American College of Chest Physicians (ACCP) guidelines [2], and
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24 additional ICU risk factors such as the use of intravenous catheters, low-dose dalteparin
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26 (mean dose < 5000 IU/day) and low-dose GCS (mean duration of GCS use < 20 hours/day).
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28 AKI was defined according to the Kidney Disease - Improving Global Outcome (KDIGO)
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30 criteria [19]. Data on DVT and PE occurrence were collected as outlined in the data collection
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32 section. VTE present at admission was defined as DVT and/or PE diagnosed within 48 hours
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34 after ICU admission. DVT was classified as catheter-associated if an intravenous catheter was
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36 or had been placed in the same vein as the detected thrombus during the ICU stay. VTEs were
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38 considered symptomatic when clinicians ordered a radiological examination with the intention
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40 to detect DVT or PE.
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47 **Data collection**
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49 The main outcomes were DVTs and PEs diagnosed by DUS or CT angiography [20, 21].
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51 Screening of veins for DVT was performed within 48 hours after ICU admission and
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53 thereafter twice a week until discharge from ICU or up to 30 days. We used a GE Healthcare
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55 Logic 8 (GE Medical Systems, Wisconsin, USA) DUS scanner with 4.0-10.0 MHz probes.
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Signs of DVT included non-compressible or partly compressible vein, presence of luminal echo, and/or loss of colour Doppler. Both internal jugular, subclavian, axillary, brachial, common femoral, superficial femoral, greater saphenous and popliteal veins were examined. Additional VTEs were found during CT angiography ordered when clinically indicated for any medical reason, and no screening method for PE was used. All VTE events were confirmed by the radiologists on call, of whom none were part of the study group.

Statistical methods

Data are presented as number (percentage), median (interquartile range (IQR)) or mean (standard deviation (SD)). Continuous variables were compared using the Mann-Whitney U test for skewed data, or independent sample t-test for normally distributed data. Univariate analyses of categorical data were performed using the Pearson's Chi square test, and Fisher's exact test when appropriate. The association between potential risk factors and the VTE were quantified by odds ratio (OR) with 95 % confidence interval (CI). Variables with $p < 0.25$ in the univariate analyses were considered candidates for the multivariate model. Independent risk factors were identified using a multivariate logistic regression model and a manual backward stepwise elimination procedure. Multivariate analyses were preceded by estimation of correlation between risk factors. Evaluation of the predictive accuracy of the models was assessed by calibration and discrimination. Calibration was evaluated by the Hosmer and Lemeshow goodness-of-fit test. A statistically non-significant Hosmer and Lemeshow result ($p > 0.05$) suggests that the model predicts accurately on average. Discrimination was evaluated by analysis of the area under the receiver operating characteristics curve (AuROC), acceptable discriminatory capability was defined as an AuROC above 0.7. Statistical analyses were performed using SPSS 23 for Windows (Armonk, NY, USA: IBM Corp), two-sided p-values less than 0.05 were considered statistically significant.

Results

Patient characteristics

A total of 2419 patients were admitted to the medical or surgical ICU during the study period. Among these, 2140 were excluded due to age < 18 years (n=4), intracranial bleeding (n=179), acute spinal cord lesion (n=25), inherited coagulopathy (n=8), uncontrolled bleeding (n=34), therapeutic anticoagulation (n=148), uncorrected coagulopathy (n=7), pregnancy or postpartum (< 6 weeks) (n=12), participation in an interventional study (n=1), chronic kidney disease (n=77) or anticipated ICU LOS < 48 hours (n=1645). Additional five patients were excluded from further analysis due to ICU LOS < 48 hours. Among the 70 studied ICU patients (Figure 1), 79 % were males, mean age was 62 ($\pm$ 12.1) years, and 50 (71 %) had a surgical reason for admission. All patients received VTE thromboprophylaxis with dalteparin, and 44 (63 %) used GCS. CVCs were present in all patients, and additionally 35 (50 %) had a haemodialysis catheter for renal replacement therapy (RRT). Low-dose dalteparin was used in 15 out of 59 (25 %), whereas low-dose GCS was used in 22 out of 59 (37 %) (Table 1). There was no loss to follow-up.

Presence of VTE

VTE was observed in 19 (27 %) patients; DVT in 15 (21 %) and PE in four (6 %), respectively. VTE was present within 48 hours after ICU admission in 11 (16 %) patients, and developed later during the ICU stay in another eight (11 %) (Table 1). Time from ICU admission to detection of VTE was median two days, ranging from zero to 20 days. The method used to detect VTE was DUS in 11 (16 %) and CT angiography in eight (11 %).

Risk factors for VTE

Many potential risk factors for VTE were identified in the univariate analysis (Table 1). Patients with and without severe AKI treated with CRRT and had similar rate of VTE, although they received comparable pharmacological and mechanical prophylaxis (data not presented). Parameters excluded from the multivariate analysis were trauma, previous VTE and intravenous catheters placed in the internal jugular vein due to zero observations in some of the groups. In multiple logistic regression analysis, malignancy (OR 4.1, 95 % CI 0.9-18.1, $p=0.06$), abdominal surgery (OR 2.0, 95 % CI 0.6-6.5, $p=0.26$) and SAPS II score > 41 (OR 0.4, 95 % CI 0.1-1.2, $p=0.09$) were independent risk factors for VTE (Model II, Table 2). Abdominal surgery was included in the final model although not statistically significant because of a large effect (OR 2.0) and few patients in the study. The Hosmer and Lemeshow goodness-of-fit test was not significant, indicating a satisfactory fit of the model ($\chi^2=3.3$, $p=0.51$). In the best predictive model, AuROC (95 % CI) was 0.72 (0.58-0.85, $p=0.01$) indicating an acceptable discriminative ability between patients with and without VTE (Model II, Figure 2).

Effects of VTE on patient outcome

Patients with and without VTE had comparable ICU LOS (13 versus (vs.) 11 days, $p=0.27$) and mortality (16 vs. 20 %, $p=0.72$) (Table 1). Among the 13 patients that died during their ICU stay, one died due to PE without associated DVT, but none due to bleeding.

Secondary outcomes

The location of VTE events are presented in Figure 3, two PEs were lobar and two were segmental. Nine DVTs were related to intravenous catheters placed in the right internal jugular vein. When comparing DVTs related to intravenous catheters and not, the catheter-

related VTEs developed later during ICU stay (5 vs. 1 days, $p=0.03$), was more often located in the internal jugular vein (100 vs. 0 %, $p<0.01$), detected by DUS screening (89 vs. 30 %, $p=0.02$), asymptomatic (100 vs. 50 %, $p=0.03$) and treated with removal of the catheter (78 vs. 0 %, $p<0.01$) (Appendix S1).

VTE was symptomatic in five (26 %) of the patients with VTE; three with PE and two with DVT. Symptomatic compared to asymptomatic VTE was more often PE (60 vs. 7 %, $p=0.04$), and more seldom located in the internal jugular vein (0 vs. 64 %, $p=0.03$) and catheter-related (0 vs. 64 %, $p=0.03$) (Appendix S2).

Therapeutic anticoagulation was used in 15 (79 %) diagnosed with VTE, including all with PE. In seven out of nine (78 %) patients with catheter-related DVT, the catheters were removed. VTE events present within 48 hours after admission was more often treated with removal of the catheter compared to VTEs developing during the later ICU stay (9 vs. 75 %, $p=0.01$) (Appendix S3).

Discussion

In this study VTE was found in 27 % (21 % DVT, 6 % PE) of high-risk ICU patients despite thromboprophylaxis. Further, VTE was already present within 48 hours after ICU admission in more than half of the patients with VTE. Factors associated with increased risk of VTE were malignancy, abdominal surgery and SAPS II score < 41 , but not severe AKI treated with CRRT. There were no differences in mortality or LOS in patients with and without VTE, although one patient died from the PE. Many of the VTEs were catheter-related, located in the neck and upper extremity veins, and asymptomatic.

Previous findings indicate that approximately 5 % of ICU patients have DVT already at admission [22, 23], and additionally 5-15 % of those receiving thromboprophylaxis develop DVT during the later ICU stay [23]. PE is more infrequent, and reported to be present in approximately 2 % of ICU patients [24]. However, many PEs may be overlooked as shown in a post-mortem study where 6 % had undiagnosed PE [25]. We found comparable VTE occurrence in our study, but we might assume that the frequency of PE was underestimated since we did not use screening methods to detect PE.

In agreement with previous studies, we found that patients with malignancy had increased risk of VTE [2]. Abdominal surgery may be associated with VTE in the present study because most such operations were performed due to abdominal malignancy. In contrast to a previous study, we observed that low severity of illness was related to an increased risk of VTE [26]. We also found that patients with and without severe AKI treated with CRRT had similar rates of VTE. This is interesting, since it remains uncertain to what extent presence of severe AKI may alter bleeding and thrombosis risk in ICU patients [27, 28].

DVTs are considered important since emboli are believed to arise from veins, follow the bloodstream, and result in PEs causing haemodynamic compromise and hypoxemia. In previous studies, presence of VTE in ICU patients has been associated with protracted

duration of mechanical ventilation and prolonged ICU and hospital LOS [3, 29, 30]. A large study of thromboprophylaxis in the ICU also revealed that PE was associated with increased mortality [29]. However, in the present relatively small study, patients with and without VTE had comparable outcome, both related to LOS and mortality.

Most VTEs in our study were located in neck and upper extremity veins, and many were related to intravenous catheters. Such catheter-related thrombosis has been observed in 2-69 % of CVCs placed in ICU patients [1, 29], with the risk of associated PE being 7-17 % [31, 32]. The femoral vein seems to be a high-risk location for catheter-associated DVTs in the ICU [33, 34]. As in a recently published study [11], we observed that the internal jugular vein had most catheter-related DVTs. This finding might be important since internal jugular vein thrombosis previously has been associated with high mortality and morbidity rates in ICU patients [10, 35].

Asymptomatic VTEs are common in ICU patients, with a reported variation from 10-100 % for DVT [13, 36] and 19-24 % for PE [37, 38]. Concordantly, we observed that most VTE events in the present study were asymptomatic; especially the DVTs were infrequently clinically suspected. The importance of such asymptomatic VTE is uncertain, with lack of treatment guidelines. Indeed, we need future clinical studies evaluating the efficacy and safety of anticoagulant therapy for asymptomatic VTE in the ICU.

Treatment of VTE in ICU patients is challenging, since major bleeding affects approximately 6 % of those receiving pharmacological thromboprophylaxis [24]. The risk of thrombosis propagation, embolization and acute right ventricular failure must be balanced against the risk of bleeding. PE has a high mortality rate, especially when associated with acute heart failure or circulatory shock [39]. There is evidence showing that anticoagulant therapy reduces mortality in acute PE [40], but treatment of sub-segmental PE is controversial

[41]. Among our patients, therapeutic anticoagulation was prescribed in all patients diagnosed with PE, but not in everyone with DVT.

This study has limitations. First, our thromboprophylaxis management was not fully standardised, including differences between the medical and surgical ICU. Additionally, some VTE events may have been missed since we did not use screening methods to detect PE. The observed association between risk factors and outcome does not necessarily imply a causal relationship. Further, we were unable to include some relevant risk factors in the multivariate analysis due to zero observations in some of the groups. The study also has a limited sample size, and probably restricted external validity. Finally, our study population is not representative for average ICU patients, since we selected patients with prolonged LOS including many with severe AKI. Strengths of the study are that compared patients came from the same cohort and time period, with no loss to follow-up. Both patient-related and ICU-related risk factors were assessed, and DVT screening was performed frequently examining many veins.

In conclusion, VTE was observed in 27 % of high-risk ICU patients receiving thromboprophylaxis. Most of the VTE events were DVTs in other locations than the lower extremities, being present early after ICU admission. Factors associated with increased risk of VTE were malignancy, abdominal surgery and SAPS II score < 41 . Patients with and without VTE had similar mortality and LOS. Many of the VTEs were catheter-related and asymptomatic; their clinical importance and treatment warrant future studies.

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Appendices

Appendix S1

Table with comparison of VTE related to intravenous catheters and not. The file consists of baseline data, risk factors, VTE characteristics and patient outcome.

Appendix S2

Table with comparison of symptomatic and asymptomatic VTE. The file consists of baseline data, risk factors, VTE characteristics and patient outcome.

Appendix S3

Table with comparison of VTE present at admission and developing during ICU stay. The file consists of baseline data, risk factors, VTE characteristics and patient outcome.

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Model I
Parameters included
Malignancy
SAPS II score > 41

Model II
Parameters included
Malignancy
Abdominal surgery
SAPS II score > 41

Observed venous thromboembolism (n=19)

Located as internal jugular vein thrombosis (n=9), pulmonary embolism (n=4) or thrombosis of the brachial (n=2), inferior mesenteric (n=1), external iliacal (n=1), femoral (n=1) or bilateral popliteal (n=1) veins

Table 1 Univariate analyses of risk factors for venous thromboembolism

	Patients with VTE (n=19)	Patients without VTE (n=51)	Risk factor for VTE	Crude OR (95 % CI) for VTE	p- value
Baseline data					
Age, years	63.0 ± 12.2	60.9 ± 12.2	Age > 63 years	0.94 (0.33-2.69)	0.902
Male sex	16 (84.2)	39 (76.5)	Male sex	1.64 (0.41-6.61)	0.744
Weight, kilogram	84.0 (78.0-90.0)	80.0 (70.0-90.0)	Weight > 82 kg	1.47 (0.51-4.22)	0.478
BMI, kilogram/meter ²	24.5 (22.6-26.0)	24.8 (22.6-26.7)	BMI > 25 kg/m ²	0.61 (0.20-1.86)	0.380
Surgical admission	12 (63.2)	38 (74.5)	Surgical admission	0.59 (0.19-1.81)	0.350
Any comorbidity	12 (63.2)	36 (70.6)	Comorbidity	0.71 (0.24-2.17)	0.552
Patient risk factors					
Neurosurgery last 6 weeks	0 (0.0)	5 (9.8)	Neurosurgery	0.71 (0.61-0.83)	0.313
Thoracic surgery last 6 weeks	2 (10.5)	4 (7.8)	Thoracic surgery	1.38 (0.23-8.24)	0.660
Abdominal surgery last 6 weeks	10 (52.6)	14 (27.5)	Abdominal surgery	2.94 (0.99-8.74)	0.048
Orthopaedic surgery last 6 weeks	1 (5.3)	4 (7.8)	Orthopaedic surgery	0.65 (0.07-6.24)	1.000
Trauma last 6 weeks	0 (0.0)	7 (13.7)	Trauma	0.70 (0.59-0.82)	0.177
Immobilisation	19 (100.0)	50 (98.0)	Immobilisation	1.38 (1.19-1.60)	1.000
Paresis of lower extremities	1 (5.3)	2 (3.9)	Paresis	1.36 (0.12-15.9)	1.000
Malignancy, any type	6 (31.6)	5 (9.8)	Malignancy	4.25 (1.12-16.2)	0.058
Venous compression	1 (5.3)	3 (5.9)	Venous compression	0.89 (0.09-9.11)	1.000
Previous VTE	2 (10.5)	0 (0.0)	Previous VTE	4.00 (2.65-6.04)	0.071
First degree relative with VTE	0 (0.0)	0 (0.0)	Relative with VTE	n.a.	n.a.
Other risk factor ^a	0 (0.0)	0 (0.0)	Other risk factor ^a	n.a.	n.a.
ICU risk factors					
Catheter femoral vein (n=59) ^b	2 (25.0)	15 (29.4)	Femoral catheter ^b	0.80 (0.15-4.42)	1.000
Catheter subclavian vein (n=59) ^b	5 (62.5)	33 (64.7)	Subclavian catheter ^b	0.91 (0.19-4.25)	1.000
Catheter IJV (n=59) ^b	8 (100.0)	33 (67.4)	IVJ catheter ^b	1.24 (1.07-1.45)	0.092
SOFA score admission day	8.5 (3.8-16.8)	8.0 (6.0-11.0)	SOFA score > 8	0.60 (0.19-1.94)	0.391
SAPS II, score	36.4 ± 14.4	41.9 ± 16.6	SAPS II score > 41	0.38 (0.13-1.15)	0.083
Presence of severe AKI	9 (47.4)	26 (51.0)	Severe AKI	0.87 (0.30-2.49)	0.788
Low-dose dalteparin (n=59) ^{b,c}	2 (25.0)	13 (25.5)	Low-dose dalteparin ^{b,c}	0.97 (0.18-5.44)	1.000
Low-dose GCS (n=59) ^{b,d}	3 (37.5)	19 (37.3)	Low-dose GCS ^{b,d}	1.01 (0.22-4.71)	1.000
Number of DUS examinations	3.5 (2.0-4.8)	2.0 (2.0-5.0)	DUS examinations > 3	0.58 (0.17-2.04)	0.395
Outcome					
ICU LOS	13.0 (5.0-21.0)	11.0 (7.0-16.0)	ICU LOS >16 days	1.90 (0.61-5.90)	0.265
Hospital LOS	19.0 (13.0-30.0)	18.0 (10.0-30.0)	Hospital LOS >23 days	1.07 (0.36-3.20)	0.904
ICU mortality	3 (15.8)	10 (19.6)	Dead in ICU	0.77 (0.19-3.16)	0.715
Hospital mortality	3 (15.8)	12 (23.5)	Dead in hospital	0.61 (0.15-2.45)	0.744
Mortality 1 year	5 (26.3)	19 (37.3)	Dead within 1 year	0.60 (0.19-1.94)	0.391

Categorical data are presented as number (%) and compared using two-sided Pearson's Chi square test, and Fisher's exact test when appropriate. Continuous data with skewed distribution are presented as median (interquartile range), and continuous data with normal distribution are presented as mean (± standard deviation). *VTE* venous thromboembolism, *OR* odds ratio, *CI* confidence interval, *BMI* body mass index, *ICU* intensive care unit, *IVJ* internal jugular vein, *SOFA* sequential organ failure assessment, *SAPS* simplified acute physiology score, *AKI* acute kidney injury, *GCS* graduated compression stockings, *DUS* Doppler ultrasound, *LOS* length of stay, *n.a.* not applicable.

^aOther risk factors assessed were presence of oestrogen hormone treatment, inflammatory bowel disease, nephrotic syndrome, myeloproliferative disorders and paroxysmal nocturnal haemoglobinuria. ^bOnly assessed in patients without VTE at admission. ^cLow-dose dalteparin was defined as mean dalteparin <5000 IE/day. ^dLow-dose GCS was defined as use of bilateral graduated compression stockings <20 hours/day.

Table 2 Multivariate analyses of risk factors for venous thromboembolism

	Variables	OR	Univariate 95 % CI	p-value	OR	Multivariate 95 % CI	p-value
Model I	Malignancy	4.25	1.12-16.2	0.058	5.13	1.24-21.27	0.024
	SAPS II score > 41	0.38	0.13-1.15	0.083	0.32	0.01-1.05	0.061
Model II	Malignancy	4.25	1.12-16.2	0.058	4.12	0.94-18.08	0.061
	Abdominal surgery	2.94	0.99-8.74	0.048	1.98	0.61-6.47	0.256
	SAPS II score > 41	0.38	0.13-1.15	0.083	0.36	0.11-1.19	0.094

OR odds ratio, *CI* confidence interval, *SAPS* simplified acute physiology score.

Figure legends

Figure 1

Title: Flow chart of the study.

Legend: *ICU* intensive care unit, *LOS* length of stay, *AKI* acute kidney injury, *kg* kilogram.

Figure 2

Title: Predictive models for venous thromboembolism.

Legend: Data presented as area under receiver operating characteristics curve (*AuROC*) with odds ratio (*OR*) and 95 % confidence interval (*CI*), *SAPS* simplified acute physiology score.

Figure 3

Title: Venous thromboembolism events observed in the study.

Legend: *VTE* venous thromboembolism, *ICU* intensive care unit. ^aVTE present at admission was defined as DVT and PE diagnosed within 48 hours after ICU admission.

Appendix S1 Comparison of VTE related to intravenous catheters and not

	All VTE (n=19)	Catheter- related VTE (n=9)	Not catheter- related VTE (n=10)	p- value
Baseline data				
Age, years	63.0 ± 12.2	61.0 ± 12.8	64.0 ± 12.2	0.717
Male sex	16 (84.2)	8 (88.9)	8 (80.0)	1.000
Surgical admission	12 (63.2)	6 (66.7)	6 (60.0)	1.000
Any comorbidity	12 (63.2)	6 (66.7)	6 (60.0)	1.000
SAPS II, score	36.4 ± 14.4	36.4 ± 17.4	36.3 ± 12.1	0.983
Patient risk factors				
Surgery or trauma last 6 weeks	11 (57.9)	5 (55.6)	6 (60.0)	1.000
Immobilisation	19 (100.0)	9 (100.0)	10 (100.0)	n.a.
Paresis of lower extremities	1 (5.3)	0 (0)	1 (10.0)	1.000
Cancer, any type	6 (31.6)	3 (33.3)	3 (30.0)	1.000
Venous compression	1 (5.3)	0 (0.0)	1 (10.0)	1.000
Previous VTE	2 (10.5)	1 (11.1)	1 (10.0)	1.000
ICU risk factors^a (n=8)				
CVC catheter femoral vein	1 (12.5)	1 (16.7)	0 (0.0)	1.000
CVC catheter subclavian vein	4 (50.0)	3 (50.0)	1 (50.0)	1.000
CVC catheter internal jugular vein	8 (100.0)	6 (100.0)	2 (100.0)	n.a.
Dialysis catheter femoral vein	2 (25.0)	2 (33.0)	0 (0.0)	1.000
Dialysis catheter subclavian vein	2 (25.0)	2 (33.0)	0 (0.0)	1.000
Dialysis catheter internal jugular vein	2 (25.0)	1 (16.7)	1 (50.0)	0.464
Low-dose dalteparin ^b	2 (25.0)	2 (33.0)	0 (0.0)	1.000
Low-dose GCS ^c	3 (37.5)	3 (50.0)	0 (0.0)	0.464
VTE characteristics				
Time to VTE, days	2.0 (1.0-9.0)	5.0 (1.5-14.0)	1.0 (1.0-3.5)	0.034
DVT in femoral vein	1 (5.3)	0 (0.0)	1 (10.0)	1.000
DVT in subclavian vein	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
DVT in internal jugular vein	9 (47.4)	9 (100.0)	0 (0.0)	< 0.001
DVT in other vein	5 (26.3)	0 (0.0)	5 (50.0)	0.033
PE	4 (21.1)	0 (0)	4 (40.0)	0.087
Diagnosed by DUS screening	11 (57.9)	8 (88.9)	3 (30.0)	0.020
Symptomatic	5 (26.3)	0 (0.0)	5 (50.0)	0.033
Treated with anticoagulation	15 (78.9)	6 (66.7)	9 (90.0)	0.303
Treated with removal of the catheter	7 (36.8)	7 (77.8)	0 (0.0)	0.001
Outcome				
ICU LOS	13.0 (5.0-21.0)	13.0 (8.0-38.5)	8.5 (4.5-19.0)	0.182
Hospital LOS	19.0 (13.0-30.0)	26.0 (13.0-54.0)	18.0 (7.3-21.3)	0.053
ICU and hospital mortality	3 (15.8)	0 (0)	3 (30.0)	0.211
Mortality 1 year	5 (26.3)	1 (11.1)	4 (40.0)	0.303

Categorical data are presented as number (%) and compared using two-sided Pearson's Chi square test, and Fisher's exact test when appropriate. Continuous data had skewed distribution and are presented as median (interquartile range), and compared using two-tailed Mann-Whitney U test. Continuous data with normal distribution are presented as mean (± standard deviation), and compared using two-sided independent sample T test. *VTE* venous thromboembolism, *SAPS* simplified acute physiology score, *ICU* intensive care unit, *CVC* central venous catheter, *GCS* graduated compression stockings, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *DUS* Doppler ultrasound, *LOS* length of stay, *n.a.* not applicable. ^a Treatment risk factors were only assessed in patients without VTE at admission. ^b Low-dose dalteparin was defined as mean dalteparin < 5000 IU/day. ^c Low-dose GCS was defined as use of graduated compression stockings bilateral to knee or hip level < mean 20 hours/day.

Appendix S2 Comparison of symptomatic and asymptomatic VTE

	All VTE (n=19)	Symptomatic VTE (n=5)	Asymptomatic VTE (n=14)	p- value
Baseline data				
Age, years	63.0 ± 12.2	67.0 ± 7.8	61.6 ± 13.4	0.408
Male sex	16 (84.2)	4 (80.0)	12 (85.7)	1.000
Surgical admission	12 (63.2)	3 (60.0)	9 (64.3)	1.000
Any comorbidity	12 (63.2)	3 (60.0)	9 (64.3)	1.000
SAPS II, score	36.4 ± 14.4	29.4 ± 7.5	38.9 ± 15.6	0.216
Patient risk factors				
Surgery or trauma last 6 weeks	11 (57.9)	3 (60.0)	8 (57.1)	1.000
Immobilisation	19 (100.0)	5 (100.0)	14 (100.0)	n.a.
Paresis of lower extremities	1 (5.3)	0 (0.0)	1 (7.1)	1.000
Cancer, any type	6 (31.6)	2 (40.0)	4 (28.6)	1.000
Venous compression	1 (5.3)	1 (20.0)	0 (0.0)	0.263
Previous VTE	2 (10.5)	1 (20.0)	1 (7.1)	0.468
ICU risk factors^a (n=8)				
CVC catheter femoral vein	1 (12.5)	0 (0.0)	1 (14.3)	1.000
CVC catheter subclavian vein	4 (50.0)	0 (0.0)	4 (57.1)	1.000
CVC catheter internal jugular vein	8 (100.0)	1 (100.0)	7 (100.0)	n.a.
Dialysis catheter femoral vein	2 (25.0)	0 (0.0)	2 (28.6)	1.000
Dialysis catheter subclavian vein	2 (25.0)	0 (0.0)	2 (28.6)	1.000
Dialysis catheter internal jugular vein	2 (25.0)	0 (0.0)	2 (28.6)	1.000
Low-dose dalteparin ^b	2 (25.0)	0 (0.0)	2 (28.6)	1.000
Low-dose GCS ^c	3 (37.5)	0 (0.0)	3 (37.5)	1.000
VTE characteristics				
Time to VTE, days	2.0 (1.0-9.0)	1 (1.0-4.5)	2.5 (1.0-12.5)	0.156
DVT in femoral vein	1 (5.3)	0 (0.0)	1 (7.1)	1.000
DVT in subclavian vein	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
DVT in internal jugular vein	9 (47.4)	0 (0.0)	9 (64.3)	0.033
DVT in other vein	5 (26.3)	2 (40.0)	3 (21.4)	0.570
PE	4 (21.1)	3 (60.0)	1 (7.1)	0.037
Diagnosed by DUS screening	11 (57.9)	1 (20.0)	10 (71.4)	0.111
Catheter related VTE	9 (47.4)	0 (0.0)	9 (64.3)	0.033
Treated with anticoagulation	15 (78.9)	4 (80.0)	11 (78.6)	1.000
Treated with removal of the catheter	7 (36.8)	0 (0.0)	7 (50.0)	0.106
Outcome				
ICU LOS	13.0 (5.0-21.0)	16.0 (7.0-19.0)	12.0 (4.5-25.8)	0.889
Hospital LOS	19.0 (13.0-30.0)	19.0 (9.0-20.5)	22.5 (13.0-35.8)	0.285
ICU and hospital mortality	3 (15.8)	2 (40.0)	1 (7.1)	0.155
Mortality 1 year	5 (26.3)	2 (40.0)	3 (21.4)	0.570

Categorical data are presented as number (%) and compared using two-sided Pearson's Chi square test, and Fisher's exact test when appropriate. Continuous data had skewed distribution and are presented as median (interquartile range), and compared using two-tailed Mann-Whitney U test. Continuous data with normal distribution are presented as mean (± standard deviation), and compared using two-sided independent sample T test. *VTE* venous thromboembolism, *SAPS* simplified acute physiology score, *ICU* intensive care unit, *CVC*: central venous catheter, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *DUS* Doppler ultrasound, *LOS* length of stay, *n.a.* not applicable. ^a Treatment risk factors were only assessed in patients without VTE at admission. ^b Low-dose dalteparin was defined as mean dalteparin < 5000 IU/day. ^c Low-dose GCS was defined as use of graduated compression stockings bilateral to knee or hip level < mean 20 hours/day.

Appendix S3 Comparison of VTE present at admission^a and developing during ICU stay

	All VTE (n=19)	VTE at admission ^a (n=11)	VTE during ICU stay (n=8)	p- value
Baseline data				
Age, years	63.0 ± 12.2	62.7 ± 11.8	63.4 ± 13.5	0.913
Male sex	16 (84.2)	9 (81.8)	7 (87.5)	1.000
Surgical admission	12 (63.2)	6 (54.5)	6 (75.0)	0.633
Any comorbidity	12 (63.2)	7 (63.6)	5 (62.5)	1.000
SAPS II, score	36.4 ± 14.4	33.9 ± 13.2	39.8 ± 16.1	0.398
Patient risk factors				
Surgery or trauma last 6 weeks	11 (57.9)	6 (54.4)	5 (62.5)	1.000
Immobilisation	19 (100.0)	11 (100.0)	8 (100.0)	n.a.
Paresis of lower extremities	1 (5.3)	1 (9.1)	0 (0.0)	1.000
Cancer, any type	6 (31.6)	4 (36.4)	2 (25.0)	1.000
Venous compression	1 (5.3)	1 (9.1)	0 (0.0)	1.000
Previous VTE	2 (10.5)	1 (9.1)	1 (12.5)	1.000
VTE characteristics				
Time to VTE, days	2.0 (1.0-9.0)	1.0 (1.0-1.0)	10.5 (5.8-14.0)	< 0.001
DVT in femoral vein	1 (5.3)	1 (9.1)	0 (0.0)	1.000
DVT in subclavian vein	0 (0.0)	0 (0.0)	0 (0.0)	n.a.
DVT in internal jugular vein	9 (47.4)	3 (27.3)	6 (75.0)	0.070
DVT in other vein	5 (26.3)	4 (36.4)	1 (12.5)	0.338
PE	4 (21.1)	3 (27.3)	1 (12.5)	0.603
Diagnosed by DUS screening	11 (57.9)	5 (45.5)	6 (75.0)	0.352
Symptomatic	5 (26.3)	4 (36.4)	1 (12.5)	0.338
Treated with anticoagulation	15 (78.9)	9 (81.8)	6 (75.0)	1.000
Treated with removal of the catheter	7 (36.8)	1 (9.1)	6 (75.0)	0.006
Outcome				
ICU LOS	13.0 (5.0-21.0)	8.0 (5.0-16.0)	20.0 (11.5-35.5)	0.062
Hospital LOS	19.0 (13.0-30.0)	19.0 (8.0-24.0)	24.5 (13.0-54.8)	0.272
ICU and hospital mortality	3 (15.8)	3 (27.3)	0 (0.0)	0.228
Mortality 1 year	5 (26.3)	4 (36.4)	1 (12.5)	0.338

Categorical data are presented as number (%) and compared using two-sided Pearson's Chi square test, and Fisher's exact test when appropriate. Continuous data had skewed distribution and are presented as median (interquartile range), and compared using two-tailed Mann-Whitney U test. Continuous data with normal distribution are presented as mean (± standard deviation), and compared using two-sided independent sample T test. *VTE* venous thromboembolism, *ICU* intensive care unit, *SAPS* simplified acute physiology score, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *DUS* Doppler ultrasound, *LOS* length of stay, *n.a.* not applicable. ^aVTE present at admission was defined as DVT and PE diagnosed within 48 hours after ICU admission.