Intensive Care Med
https://doi.org/10.1007/s00134-019-05899-1

ORIGINAL

Surveillance or no surveillance ultrasonography for deep vein thrombosis and outcomes of critically ill patients: a pre-planned sub-study of the PREVENT trial

Yaseen M. Arabi[1,2,3*], Karen E. A. Burns[4], Sami J. Alsolamy[1,2,3], Mohammed S. Alshahrani[5], Fahad M. Al-Hameed[6,7,8], Zia Arshad[9], Mohammed Almaani[10], Hassan Hawa[11], Yasser Mandourah[12], Ghaleb A. Almekhlafi[13], Abdulsalam Al Aithan[14,15,16], Imran Khalid[17], Jalal Rifai[6,7,8], Gulam Rasool[6,7,8], Sheryl Ann I. Abdukahil[1,2,3], Jesna Jose[3,18], Lara Y. Afesh[3,19], Abdulaziz Al-Dawood[1,2,3] and the Saudi Critical Care Trials Group

Abstract

Purpose: We examined the association between surveillance for deep vein thrombosis (DVT) among medical-surgical critically ill patients by twice-weekly ultrasonography and 90-day all-cause mortality.

Methods: This was a pre-planned sub-study of the Pneumatic Compression for Preventing Venous Thromboembolism (PREVENT) trial (Clinicaltrials.gov: NCT02040103) that compared addition of intermittent pneumatic compression (IPC) to pharmacologic prophylaxis versus pharmacologic prophylaxis alone. The surveillance group included enrolled patients in the trial, while the non-surveillance group included eligible non-enrolled patients. Using logistic regression and Cox proportional hazards models, we examined the association of surveillance with the primary outcome of 90-day mortality. Secondary outcomes were DVT and pulmonary embolism (PE).

Results: The surveillance group consisted of 1682 patients and the non-surveillance group included 383 patients. Using Cox proportional hazards model with bootstrapping, surveillance was associated with a decrease in 90-day mortality (adjusted HR 0.75; 95% CI 0.57, 0.98). Surveillance was associated with earlier diagnosis of DVT [(median 4 days (IQR 2, 10) vs. 20 days (IQR 16, 22)] and PE [median 4 days (IQR 2.5, 5) vs. 7.5 days (IQR 6.1, 28.9)]. There was an increase in diagnosis of DVT (adjusted HR 5.49; 95% CI 2.92, 13.02) with no change in frequency in diagnosis of PE (adjusted HR 0.56; 95% CI 0.19, 1.91).

Conclusions: Twice-weekly surveillance ultrasonography was associated with an increase in DVT detection, reduction in diagnostic testing for non-lower limb DVT and PE, earlier diagnosis of DVT and PE, and lower 90-day mortality.

Trial registration: The PREVENT trial is registered at ClinicalTrials.gov, ID: NCT02040103. Registered on 3 November 2013; Current controlled trials, ID: ISRCTN44653506. Registered on 30 October 2013.

*Correspondence: arabi@ngha.med.sa
[1] Intensive Care Department, Ministry of National Guard Health Affairs, ICU 1425, PO Box 22490, Riyadh 11426, Kingdom of Saudi Arabia
Full author information is available at the end of the article

Tweet Surveillance ultrasonography was associated with an increase in DVT detection, earlier DVT and PE diagnosis, and lower mortality.

Springer

Keywords: Surveillance ultrasonography, Deep vein thrombosis, Pulmonary embolism, Intermittent pneumatic compression, Thromboprophylaxis, Critical care

Introduction

Deep vein thrombosis (DVT) is often undetected in critically ill patients and could lead to pulmonary embolism (PE) with associated morbidity and mortality [1, 2]. A systematic review demonstrated that PE is a leading cause of autopsy-confirmed potentially fatal misdiagnoses in intensive care unit (ICU) patients [3, 4]. Studies have confirmed the poor performance of history and physical examination for detecting DVT in ICU patients [4]. A retrospective study in hospitalized trauma patients who underwent once-weekly surveillance ultrasonography found that 86% of identified DVTs were not clinically suspected [5]. As such, surveillance using lower limb ultrasonography has been proposed to detect silent DVT. Data from randomized controlled trials in critically ill patients that conducted surveillance for DVT reported much higher DVT incidence than what has been traditionally reported in non-surveillance studies [6–8].

With earlier identification of silent DVT, surveillance ultrasonography may reduce the incidence of PE and consequently reduce morbidity and mortality in critically ill patients. However, the evidence supporting this premise in ICU patients is limited. Studies that examined the effect of surveillance on mortality were conducted mainly in neurosurgical and trauma ICU populations and generally showed that surveillance for DVT was associated with increase in the rate of DVT diagnosis, with inconsistent effects on the rate of PE diagnosis and on mortality [9–14]. These studies were mostly single-center studies and often had historical control groups. In addition, the baseline mortality in neurosurgical and trauma ICU populations is generally low and therefore, these studies had limited power to detect a difference in mortality and had limited generalizability to general ICU patients with higher risk of death.

The objective of this pre-planned sub-study was to examine the association between surveillance for DVT by twice-weekly ultrasonography and 90-day all-cause mortality among critically ill medical-surgical patients. Compared to no surveillance, we hypothesized that surveillance for DVT by twice-weekly ultrasonography in this population would be associated with lower mortality by facilitating earlier diagnosis and treatment of venous thromboembolism (VTE) [15].

Methods

The PREVENT trial

The PREVENT trial (the Pneumatic Compression for Preventing Venous Thromboembolism trial, Clinicaltrials.gov: NCT02040103 and Current controlled trials: ISRCTN44653506) [16, 17] evaluated whether adjunctive intermittent pneumatic compression (IPC) combined with pharmacologic thromboprophylaxis with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) compared to pharmacologic thromboprophylaxis reduced incident proximal lower limb DVT. Adult medical, surgical, or trauma ICU patients were enrolled if they weighed at least 45 kg, were expected to stay in the ICU for at least 72 h, and were eligible for pharmacologic thromboprophylaxis with either UFH or LMWH. Exclusion criteria are listed in Table S2 in the Supplementary Appendix. Trial results demonstrated that adjunctive IPC did not result in reducing incident proximal leg DVT [18]. Patients in the PREVENT trial underwent twice-weekly surveillance ultrasonography as part of the study procedures.

Take-home message

In general ICU patients, twice weekly surveillance ultrasonography was associated with an increase in deep vein thrombosis detection, earlier deep-vein thrombosis and pulmonary embolism diagnosis, and lower 90-day mortality.

Patients

In this sub-study, we included data from ten participating sites that had ethics approval to collect minimal data on eligible non-enrolled patients and included at least five eligible non-enrolled patients. The surveillance group included patients who were enrolled in the PREVENT trial and included in the modified intention-to-treat cohort [18]. The non-surveillance group included eligible non-enrolled patients, except those who declined informed consent and did not give permission for data collection (Fig. 1). Patients in the non-surveillance group included patients who were unable to give consent and had no available substitute decision maker, unable to provide consent within the randomization window of 48 h from ICU admission, co-enrolled in trials with biologic interaction, not enrolled because either the ICU physician or another treating clinician refused enrollment, and those in whom informed consent was declined but with agreement to collect minimal observational data.

Ultrasonography procedures

In the surveillance group, lower limb ultrasonography was performed within 48 h of enrollment then twice

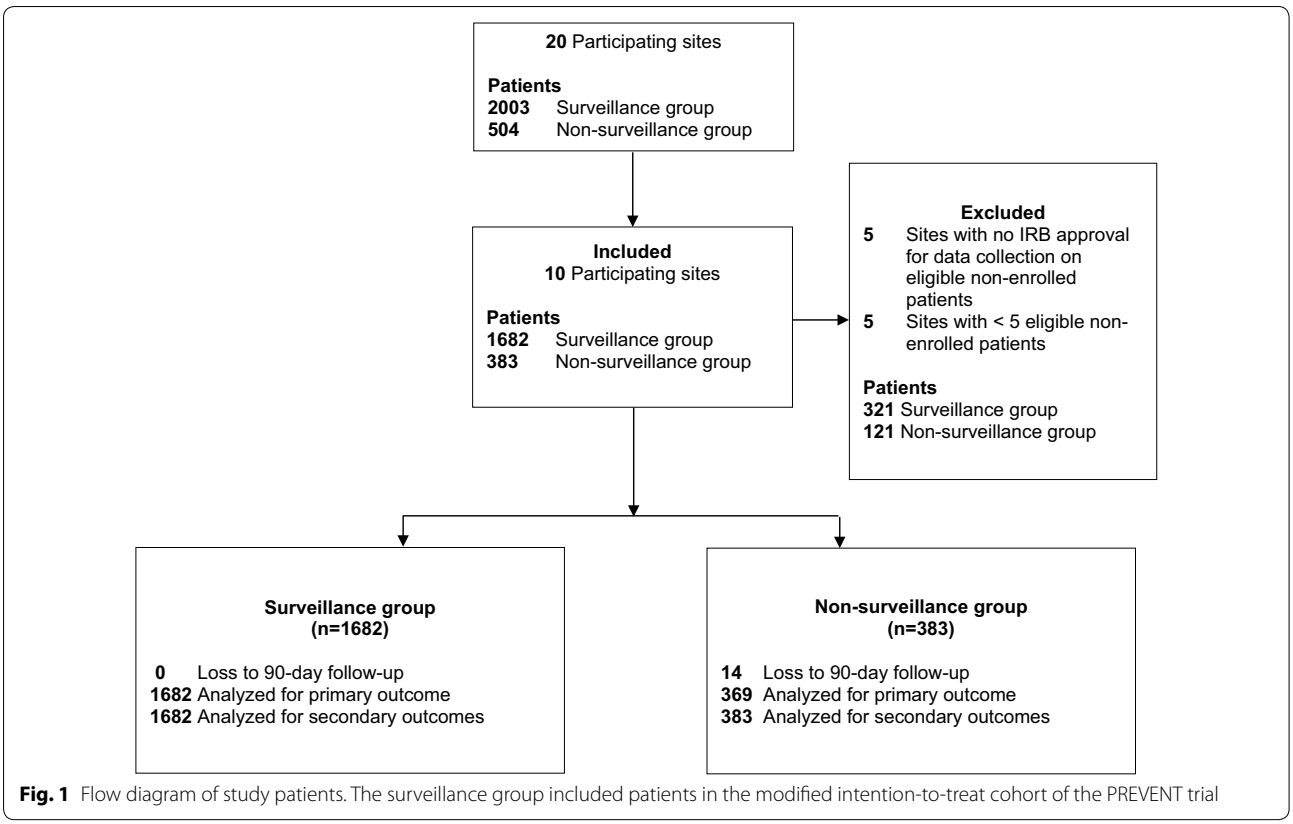

Fig. 1 Flow diagram of study patients. The surveillance group included patients in the modified intention-to-treat cohort of the PREVENT trial

weekly afterwards up to 28 days, diagnosis of DVT, diagnosis of PE, death, or discharge from ICU whichever came first. In the non-surveillance group, ultrasonography was requested by the treating team based on clinical suspicion. In both groups, ultrasonography was performed by certified ultrasonographers and interpreted by local or radiologists at participating sites.

Data

We collected baseline data including demographics, severity of illness and pre-ICU VTE risk factors [15]. We documented data on the main exposure, lower limb ultrasonography and the number of tests performed per patient. We documented the following co-interventions: the type of pharmacologic thromboprophylaxis (UFH or LMWH) and the presence of femoral central venous catheter (CVC) at baseline. We recorded IPC use (for at least 1 day), graduated compression stockings (GCS) application (for at least 1 day), and therapeutic anticoagulation during ICU stay. We recorded the number of all other radiologic tests performed for VTE detection during ICU stay including upper limb and neck ultrasonography, spiral computed tomography (CT) to evaluate for PE, ventilation–perfusion (V/Q) scan of the lungs, CT scan of the abdomen to evaluate thrombosis, transthoracic echocardiogram and transesophageal echocardiogram. The primary outcome was 90-day all-cause mortality. Secondary outcomes included lower limb DVT, PE, ICU and hospital length of stay, and ICU and hospital mortality. Because mortality is a competing risk for VTE, we also evaluated ICU-free days (in the first 28 study days) and ICU and hospital length of stay among survivors.

Statistical analysis

We conducted analyses as per the previously published study protocol and statistical analysis plan [15]. All analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, NC, USA). We compared surveillance group with non-surveillance group using Student's *t* test or the Mann–Whitney *U* test for continuous variables based on normality assumption and the Chi-square test (alternatively Fisher's exact test for expected values < 5) for categorical variables. We compared the outcomes between the surveillance and non-surveillance groups and reported the results as odds ratio (OR) with 95% confidence interval (CI).

Because the assignment to surveillance and non-surveillance group was not random, we assessed the association of surveillance with mortality, DVT and PE

using generalized linear mixed model with the following pre-defined co-variables: type of pharmacologic thromboprophylaxis received (UFH/LMWH), IPC use, GCS use, acute physiology and chronic health evaluation (APACHE) II score, and the presence of femoral CVC at baseline. We also included the presence or absence of chronic health illness (as defined in APACHE II system) as a co-variable, because it had a significant association with exposure on univariable analysis ($p < 0.1$) as indicated in the published statistical analysis plan and because of its possible association with outcomes [15]. In these models, we accounted for clustering by trial site incorporated as random effect using RANDOM statement. To account for time to event, we evaluated the association of surveillance with mortality, DVT and PE using Cox proportional hazards model, adjusting for the same co-variables mentioned earlier. For the mortality outcome, we accounted for clustering by trial site incorporated as random effect. For DVT and PE, we accounted for mortality as a competing outcome using Fine–Gray competing risk regression model. To test the stability of these Cox proportional hazards models, we performed bootstrap techniques using 1000 resamples and we reported the 95% CI using the percentile bootstrap method.

We tested the association of surveillance with continuous outcomes (ICU LOS, ICU-free days, hospital LOS) using negative binomial mixed-effects regression models, adjusting for the same co-variables and for clustering by trial site incorporated as random effect.

Pre-defined subgroup analyses for the primary outcome of 90-day mortality were performed for the following subgroups: patients receiving UFH or LMWH, presence of femoral CVC at baseline, medical admission or surgical trauma admission, body mass index (< 30 or ≥ 30), APACHE II score (< 20 and ≥ 20), presence or absence of chronic respiratory/cardiovascular illness, and participating countries (Table 4). For these analyses, we used generalized linear mixed model and Cox proportional hazards model using the same approach outlined above for the whole cohort. We included interaction terms to assess effect modification of the subgroups on the association between the exposure and outcome. We did not impute for missing values. We considered p values < 0.05 to be statistically significant.

Results

Baseline characteristics

The surveillance group consisted of 1682 patients, while the non-surveillance group had 383 patients (Fig. 1). Table 1 shows the characteristics of patients at baseline. Patients in the surveillance group were older (58.6 ± 20.6 vs. 54.1 ± 19.6 years, $p < 0.0001$), more likely to be males (57.1% vs. 56.9%, p 0.94), and had lower APACHE II scores (20.7 ± 7.2 vs. 22.0 ± 7.7, p 0.0005) compared to non-surveillance patients. They were also less likely to have chronic health illnesses (47.1% vs. 53%, p 0.04) and pre-ICU VTE risk factors (43.6% vs. 53.8%, p 0.0003) and were more likely to have lower creatinine levels [90 µmol/L (IQR 62, 171) vs. 106.5 µmol/L (IQR 71, 172) p 0.004] and a femoral CVC at baseline (15.3% vs. 9.4%, p 0.003) compared to non-surveillance patients.

Co-interventions

The use of UFH and LMWH thromboprophylaxis was not different between the two groups (Table 2). IPC use in the surveillance group was 54.6% compared to 30% in the non-surveillance group ($p < 0.0001$) while GCS were infrequently used in both groups (1% vs. 0.8%, $p > 0.99$, respectively), At least one lower limb ultrasonography was performed in 98.2% of patients in the surveillance group compared to 27.7% in the non-surveillance group ($p < 0.0001$). The median number of lower limb ultrasonography performed per patient in the surveillance group was 2 (IQR 1, 4) compared with 0 (IQR 0, 1) in the non-surveillance group ($p < 0.0001$).

Primary outcome: 90-day mortality

At 90 days, 424/1682 patients (25.2%) in the surveillance group and 83/369 patients (22.5%) in the non-surveillance group had died (crude OR 1.16; 95% CI 0.89, 1.52; p 0.27). Using generalized linear mixed modeling, surveillance ultrasonography was not associated with lower 90-day mortality (adjusted OR 0.87; 95% CI 0.63, 1.20; p 0.39). However, using time-to-event analysis with Cox proportional hazards model, surveillance ultrasound was associated with lower 90-day mortality (adjusted HR 0.75; 95% CI 0.57, 0.99; p 0.04). When bootstrapping techniques were used for Cox proportional hazards model, surveillance ultrasonography was associated with lower 90-day mortality (adjusted HR 0.75; 95% CI 0.57–0.98, Tables 3 and S4).

Deep vein thrombosis and pulmonary embolism

In the surveillance group, DVT was diagnosed earlier compared to the non-surveillance group [median 4 days (IQR 2, 10) vs. 20 days (IQR 16, 22), $p < 0.0001$)] and more frequently [162 of 1682 patients (9.6%) vs. 10 of 382 (2.6%), crude OR 3.96; 95% CI 2.07, 7.58; $p < 0.0001$]. The three statistical approaches with adjustment (generalized linear mixed model, Cox proportional hazards model, and Cox proportional hazards model with bootstrapping) all were consistent in showing an increase in DVT detection with surveillance

Table 1 Baseline characteristics of patients who had twice-weekly surveillance ultrasonography and those who did not

	Surveillance group (*N* = 1682)	Non-surveillance group (*N* = 383)	*p* value
Age (years)—mean (SD)	58.6 ± 20.6	54.1 ± 19.6	< 0.0001
Male sex—*n* (%)	961 (57.1)	218 (56.9)	0.94
BMI (kg/m^2)—mean (SD)	28.9 ± 8.4	28.2 ± 9.2	0.02
Location prior to ICU admission—*n* (%)			
Emergency room	852 (50.7)	250 (65.3)	< 0.0001
Hospital ward	549 (32.6)	86 (22.5)	
Operating room	151 (9.0)	24 (6.3)	
Other hospital (ICU or ward)	124 (7.4)	14 (3.7)	
Other	6 (0.4)	9 (2.3)	
Admission category—*n* (%)			
Medical	1310 (77.9)	307/380 (80.8)	0.45
Surgical	229 (13.6)	46/380 (12.1)	
Trauma	143 (8.5)	27/380 (7.1)	
APACHE II—mean (SD)	20.7 ± 7.2	22.0 ± 7.7	0.0005
Chronic health illnesses—*n* (%)			
None	792 (47.1)	203 (53.0)	0.04
Chronic respiratory disease	347 (20.6)	70 (18.3)	
Chronic cardiovascular disease	318 (18.9)	77 (20.1)	
Chronic renal disease	236 (14.0)	33 (8.6)	
Immunosuppression	174 (10.3)	26 (6.8)	
Chronic liver disease	43 (2.6)	21 (5.5)	
Pre-ICU VTE risk factors—*n* (%)			
None	734 (43.6)	206 (53.8)	0.0003
Hospitalization in the past 3 months for any reason (excluding this hospital admission)	414 (24.6)	60 (15.7)	
Paralysis or immobilization of a lower or upper extremity related to stroke or injury prior to this hospital admission	200 (11.9)	22 (5.7)	
Active malignancy (treatment within past 6 months or palliation)	158 (9.4)	14 (3.7)	
Recent surgery (in the last 48 h)	152 (9.0)	27 (7.0)	
Acute stroke (this hospital admission)	78 (4.6)	6 (1.6)	
Trauma	50 (3.0)	6 (1.6)	
History of malignancy (past 5 years; other than non-melanoma skin cancer)	31 (1.8)	7 (1.8)	
Personal history of VTE	19 (1.1)	7 (1.8)	
Family history of VTE	2 (0.1)	0	
Known thrombophilic state	2 (0.1)	1 (0.3)	
Post-partum (within 3 months)	2 (0.1)	0	
Estrogen therapy	1 (0.1)	1 (0.3)	
Others	46 (2.7)	55 (14.4)	
Laboratory results prior to randomization—mean (SD)			
INR	1.2 ± 0.4	1.2 ± 0.5	0.01
Creatinine (μmol/L)—median (IQR)	90.0 (62.0, 171.0)	106.5 (71.0, 172.0)	0.004
Platelets (10^9/L)	252.9 ± 128.7	230.9 ± 118.5	0.004
PTT	33.1 ± 10.2	31.4 ± 13.8	0.0007
Hemoglobin (g/L)	106.6 ± 95.7	113.2 ± 27.4	< 0.0001
Central femoral venous catheter—*n* (%)	258 (15.3)	36 (9.4)	0.003

To convert the values for creatinine to micromoles per liter, multiply by 88.4

For continuous variables, the following have missing values: BMI ($n = 2$); APACHE II score ($n = 1$); INR ($n = 205$); creatinine ($n = 150$); platelets ($n = 155$); PTT ($n = 212$); hemoglobin ($n = 154$)

For categorical variables that have missing values, we reported data as numerators and denominators. Other variables do not have no missing values

Continuous variables were compared using Mann–Whitney *U* test

Categorical variables were compared using Chi-square test

SD standard deviation, *BMI* body mass index, *APACHE* acute physiology and chronic health evaluation, *INR* international normalized ratio, *PTT* partial thromboplastin time, *VTE* venous thromboembolism

Table 2 Summary of interventions and co-interventions among patients who had twice-weekly surveillance ultrasonography and those who did not

	Surveillance group (*N* = 1682)	Non-surveillance group (*N* = 383)	*p* value
Use of IPC at least for 1 day—no. (%)	919 (54.6)	115 (30.0)	< 0.0001
Use of graduated compression stockings—no. (%)	16 (1.0)	3 (0.8)	> 0.99[a]
Pharmacologic thromboprophylaxis			
Prophylactic UFH	1025 (60.9)	243 (63.4)	0.36
Prophylactic LMWH	657 (39.1)	140 (36.6)	
Diagnostic testing, *n* (%)			
Patients with at least one ultrasonography—*n* (%)	1652 (98.2)	106 (27.7)	< 0.0001
Median number of lower limb ultrasound per patient—median (IQR)	2 (1, 4)	0 (0, 1)	< 0.0001
Ultrasonography for upper extremities and neck to evaluate for thrombosis—*n* (%)	31(1.8)	26 (6.8)	< 0.0001
Patients with spiral CT of chest to evaluate for PE—*n* (%)	68 (4.0)	47 (12.3)	< 0.0001
Patients with V/Q scan of the lungs—*n* (%)	1 (0.1)	0 (0)	> 0.99[a]
Patients with CT scan of the abdomen to evaluate thrombosis—*n* (%)	70 (4.2)	21 (5.5)	0.26
Patients with transthoracic echocardiograms—*n* (%)	224 (13.3)	114 (29.8)	< 0.0001
Patients with transesophageal echograms—*n* (%)	10 (0.6)	8 (2.1)	0.005

Continuous variables were compared using Mann–Whitney *U* test

Categorical variables were compared using Chi-square test except for the *p* value labeled with [a] indicating the use of Fisher's exact test

There are no missing values in this table

IPC intermittent pneumatic compression, *UFH* unfractionated heparin, *LMWH* low-molecular-weight heparin, *PE* pulmonary embolism

ultrasonography (for Cox proportional hazards models with bootstrapping: aHR 5.49; 95% CI 2.92, 13.02, Table 3).

In the surveillance group compared to the non-surveillance group, PE was diagnosed earlier [median 4 days (IQR 2.5, 5) compared with 7.5 days (IQR 6.1, 28.9), *p* 0.045], although the number of PE events did not differ statistically [16 of 1682 patients (1%) compared to 6 of 382 (1.6%), crude OR 0.60; 95% CI 0.23, 1.55; *p* 0.29]. The three statistical approaches for adjustment showed no difference in the frequency of PE diagnosis between groups.

Diagnostic tests for venous thromboembolism

The surveillance group compared to non-surveillance had fewer ultrasonography tests of the upper extremities and neck to evaluate for thrombosis (1.8% vs. 6.8%, $p < 0.0001$), spiral CTs of the chest (4% vs. 12.3%, $p < 0.0001$), transthoracic echocardiograms (13.3% vs. 29.8%, $p < 0.0001$), and transesophageal echocardiograms (0.6% vs. 2.1%, *p* 0.005), respectively (Table 2).

Secondary outcomes

Surveillance ultrasonography was associated with lower ICU mortality (Table 3). Hospital mortality, ICU-free days, ICU length of stay among survivors, and hospital length of stay among survivors were not different between the two groups (Table 3).

Subgroup analyses

Subgroup analyses demonstrated no heterogeneity in the association between surveillance and 90-day mortality with the exception to subgroups by APACHE II (Table 4). Surveillance was associated with a significant reduction in 90-day mortality among patients with APACHE II ≥ 20 but not among those with APACHE II < 20 (*p* value for interaction 0.01).

Discussion

Our study showed that twice-weekly surveillance ultrasonography was associated with an increase in DVT detection, earlier DVT and PE diagnosis, reduced diagnostic testing for PE and non-lower limb DVT, and lower 90-day mortality.

Compression ultrasonography is noninvasive and highly sensitive and specific for the diagnosis of lower limb DVT in symptomatic patients [19–21], although it may be less sensitive in patients who do not have symptoms [22]. However, it is still debated as to whether or not critically ill patients should be systematically screened for DVT using compression ultrasonography [4, 23–25]. Studies have demonstrated that surveillance ultrasonography in trauma and neurologic ICU patients is associated with increased detection of DVT. The effect of surveillance ultrasonography on PE was not consistent across studies with some studies showing a reduction in PE, while others showed no change and some suggesting

Table 3 Association of surveillance ultrasonography with outcomes

	Surveillance group (*N* = 1682)	Non-surveillance group (*N* = 383)	Generalized linear mixed model, aOR (95% CI)[a]	*p* value	Cox proportional hazards model, aHR (95% CI)[b]	*p* value	Cox proportional hazards model with bootstrapping, aHR (95% CI)
90-day mortality—*n* (%)	424/1682 (25.2)	83/369[A] (22.5)	0.87 (0.63, 1.20)	0.39	0.75 (0.57, 0.99)	0.04	0.75 (0.57, 0.98)
All proximal DVT (all proximal and distal)—*n*/*N* (%)	162/1682 (9.6)	10/382[B] (2.6)	3.64 (1.82, 7.28)	0.0003	5.22 (2.56, 10.63)	< 0.0001	5.49 (2.92, 13.02)
Time to DVT (days)—median (IQR)	4 (2, 10)	20 (16, 22)	–	–	–	–	–
Pulmonary embolism—*n*/*N* (%)	16/1682 (1.0)	6/382 (1.6)	0.28 (0.08, 1.00)	0.051	0.53 (0.20, 1.36)	0.19	0.56 (0.19, 1.91)
Time to PE (days)—median (IQR)	4 (2.5, 5)	7.5 (6.1, 28.9)	–	–	–	–	–
ICU mortality—*n* (%)	245/1682 (14.6)	61/383 (15.9)	0.64 (0.44, 0.92)	0.02	0.71 (0.51, 0.99)	0.04	0.69 (0.51, 0.97)
Hospital mortality—*n* (%)	439/1682 (26.1)	83/383 (21.7)	0.95 (0.69, 1.32)	0.78	0.78 (0.59, 1.02)	0.07	0.77 (0.58, 1.04)
Negative binomial mixed-effects regression model, estimate (standard error)[c]							
ICU LOS (days)—median (IQR)	8 (5, 16)	10 (6, 17)	− 0.07 (0.06)	0.27	–	–	–
ICU LOS among survivors	8 (4, 14)	10 (6, 16)	− 0.10 (0.07)	0.15	–	–	–
ICU-free days	18 (0, 23)	16 (0, 21)	0.12 (0.08)	0.14	–	–	–
Hospital LOS (days)—median (IQR)	20 (11, 45)	16 (10, 31)	0.17 (0.07)	0.01	–	–	–
Hospital LOS among survivors	20 (11, 48)	17 (10, 31)	0.14 (0.08)	0.06	–	–	–

aOR adjusted odds ratio, *aHR* adjusted hazards ratio, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *LOS* length of stay

[A] 90-day mortality was not available for 14 patients in the non-surveillance group as they were lost to follow-up

[B] DVT data were not available for one patient in the non-surveillance group

[a] Generalized linear mixed model was used to evaluate the association of surveillance with mortality, DVT and PE adjusting for the following co-variables: type of heparin (UFH/LMWH), IPC use, GCS use, APACHE II score, presence of femoral central venous catheter at baseline and the presence chronic health illness and accounting for clustering by trial site incorporated as random effect

[b] Cox proportional hazards model was used to evaluate the association of surveillance with time to mortality, DVT and PE adjusting for the same co-variables listed above. For the mortality outcome, we accounted for clustering by trial site incorporated as random effect. For deep vein thrombosis and pulmonary embolism, we accounted for mortality as a competing outcome using Fine–Gray competing risk model

[c] The association of surveillance with continuous outcomes (ICU LOS, ICU-free days, hospital LOS) was assessed using negative binomial mixed-effects regression model, adjusting for the same co-variables, and for clustering by trial site incorporated as random effect

an increase in PE detection [9–13]. Conversely, data on the association of surveillance ultrasonography with mortality are limited with some studies showing no difference and others not reporting mortality at all [9–13].

Surveillance ultrasonography was associated with earlier diagnosis of DVT and PE. The observed reduction in testing for PE might be a surrogate for fewer cases of clinically suspected PE. One potential explanation for our findings is that earlier DVT and PE detection and treatment translated into a reduction in mortality. However, the number of PE detected cases does not necessarily reflect PE incidence in the ICU, since testing for PE was based on clinician suspicion and there is no widely accepted and standardized approach for screening critically ill patients for PE. In addition, the low incidence in our study may reflect the fact that all patients were receiving pharmacologic thromboprophylaxis. Finally, another potential explanation is that earlier diagnosis and treatment of DVT might have reduced the need to conduct further investigations to detect PE.

It is unclear whether equipoise exists regarding the role for surveillance ultrasonography in critically ill patients. On one hand, surveillance ultrasonography may reduce mortality that results from undiagnosed DVT and subsequent PE. On the other hand, surveillance ultrasonography may detect asymptomatic DVTs of unknown clinical significance, leading to "overtreatment" with therapeutic

Table 4 Association of surveillance ultrasonography with 90-day mortality among subgroups, using generalized linear mixed model and Cox proportional hazards model

	Surveillance group (*N* = 1682)	Non-surveillance group (*N* = 383)	Generalized linear mixed model, aOR (95% CI)	*p* value	*p* value for interaction	Cox proportional hazards model, aHR (95% CI)	*p* value	*p* value for interaction
UFH	301/1025 (29.4)	60/229 (26.2)	0.95 (0.65, 1.39)	0.79	0.31	0.80 (0.58, 1.10)	0.17	0.50
LMWH	123/657 (18.7)	23/140 (16.4)	0.69 (0.37, 1.28)	0.24		0.66 (0.39, 1.11)	0.12	
Femoral CVC at baseline	81/258 (31.4)	13/36 (36.1)	0.73 (0.31, 1.69)	0.45	0.64	0.52 (0.27, 1.03)	0.06	0.38
No femoral CVC at baseline	343/1424 (24.1)	70/333 (21.0)	0.93 (0.66, 1.32)	0.69		0.81 (0.61, 1.09)	0.17	
Trauma/surgical	42/372 (11.3)	7/72 (9.7)	1.06 (0.41, 2.71)	0.90	0.87	0.77 (0.33, 1.80)	0.55	0.90
Medical	382/1310 (29.2)	76/295 (25.8)	0.87 (0.62, 1.23)	0.43		0.78 (0.58, 1.03)	0.08	
BMI < 30	279/1070 (26.1)	52/246 (21.1)	0.89 (0.58, 1.35)	0.58	0.70	0.75 (0.53, 1.07)	0.11	0.96
BMI ≥ 30	145/611 (23.7)	30/122 (24.6)	0.93 (0.56, 1.55)	0.79		0.81 (0.53, 1.24)	0.33	
APACHEII ≥ 20	242/868 (27.9)	69/225 (30.7)	0.68 (0.46, 1.00)	0.05	0.01	0.61 (0.44, 0.83)	0.002	0.003
APACHE II < 20	182/814 (22.4)	14/144 (9.7)	1.62 (0.85, 3.08)	0.14		1.36 (0.75, 2.47)	0.31	
With chronic respiratory or cardiovascular illnesses	156/583 (26.8)	27/127 (21.3)	1.08 (0.63, 1.86)	0.77	0.31	0.86 (0.55, 1.36)	0.52	0.42
Without chronic respiratory or cardiovascular illnesses	268/1099 (24.4)	56/242 (23.1)	0.75 (0.50, 1.13)	0.17		0.67 (0.48, 0.94)	0.02	
Saudi Arabia	409/1485 (27.5)	49/203 (24.1)	1.03 (0.71, 1.48)	0.9	0.28	0.77 (0.56, 1.05)	0.09	0.92
Canada	15/69 (21.7)	32/112 (28.6)	0.32 (0.13, 0.80)	0.01		0.52 (0.26, 1.06)	0.07	
India	0/128 (0.0)	2/54 (3.7)	–	–		–	–	

Generalized linear mixed model was used to evaluate the association of surveillance with 90-day mortality adjusting for the following co-variables: type of heparin (UFH/LMWH), IPC use, GCS use, APACHE II score, presence of femoral central venous catheter at baseline and the presence of chronic health illness and accounting for clustering by trial site incorporated as random effect

Cox proportional hazards model was used to evaluate the association of surveillance with time to 90-day mortality adjusting for the same co-variables listed above

90-day mortality was not available for 14 patients in the non-surveillance group as they were lost to follow up. BMI data were not available for two patients and admission diagnosis category (trauma, surgical/medical) was not available for three patients

p value for interaction is the test of interaction between exposure (surveillance and non-surveillance) and each subgroup

Please refer to Methods section and footnote of Table 3 for details of the model

aHR adjusted hazards ratio, *aOR* adjusted odds ratio, *BMI* body mass index, *CVC* central venous catheter, *LMWH* low-molecular-weight heparin, *PE* pulmonary embolism, *UFH* unfractionated heparin

anticoagulation, and exposing critically ill patients to treatment complications and added cost. Previous studies in trauma and neurosurgical patients did not show mortality reduction. However, the baseline mortality in these studies was low ranging from 3 to 9% [9–14]. In contrast, our study, which included medical-surgical ICU patients with a higher baseline mortality rate, showed that surveillance ultrasonography was associated with lower mortality. This finding was further supported by a subgroup analysis that showed that patients with high APACHE II and not those with low APACHE II had mortality reduction.

We used different statistical models to assess the associations of the surveillance and different outcomes (90-day mortality, DVT and PE) namely a generalized linear mixed model and a Cox proportional hazards model and assessed the robustness of the latter analysis using bootstrapping techniques. In these models, we accounted for pre-defined confounders. We also accounted for the competing effect of mortality on DVT and PE and for clustering by study sites. The point estimates across the three models were relatively comparable and the differences in confidence intervals may reflect the number of events. The Cox proportional model with bootstrapping probably provides the best estimate as it accounts for potential confounding, time to event, and utilizes a resampling technique. Nevertheless, all of these estimates should be considered hypothesis generating and require validation in a prospective randomized controlled trial.

Our study has several strengths. First, this sub-study was pre-specified. Second, our study was not limited to trauma and neurosurgical patients but rather is generalizable to patients found in general mixed medical-surgical ICUs. Third, it includes multicenter and multinational

data which further enhances the generalizability of our findings. Fourth, the protocol participants in the PREVENT trial received twice-weekly ultrasonography and we documented high protocol adherence [18]. Fifth, data on surveillance and non-surveillance patients were obtained in the context of a contemporaneous, prospective parallel design RCT, as opposed to a historical control study, reducing the potential confounding effects related to changes in treatment and standard of care over time.

Our study also has limitations. First, a main limitation of this observational study is the non-random assignment leading to imbalance between surveillance and non-surveillance groups and raising concerns regarding the potential effect of measured and unmeasured confounders on outcomes. To this end, we identified several potentially important imbalances between the surveillance and non-surveillance groups including lower APACHE score, tendency to have chronic illness, fewer pre-ICU VTE risk factors, and lower creatinine levels. Second, we did not have data regarding complications of therapeutic anticoagulation. Consequently, our study was not designed to assess and compare differences in complications resulting from treatment of DVTs that otherwise would have not been detected. Third, we cannot separate increased DVT detection with scheduled screening from the actions taken by clinicians in response to positive test results and the impact of treatment decisions on outcomes in our study. Fourth, our data come from only 10 of the 20 participating sites in the PREVENT trial. The comparatively small number of non-enrolled patients versus enrolled patients available for analysis likely limited the power of our study. Fifth, due to the nature of limited data in the non-surveillance group, time-dependent co-variables were not available. For example, we had data on femoral central venous catheter insertion on admission, but not throughout the ICU course in the non-surveillance group. We did not have detailed physiologic parameters about chronic health illnesses and their severity. Sixth, the observed differences in the associations across different models highlight the effects of confounding. Therefore, we think that this observational study, like all other prior observational studies addressing this question, cannot be used to establish causality or to inform a change in clinical practice. Nevertheless, the question of using surveillance ultrasonography in high-risk medical-surgical patients is an important one and has not been addressed before. In addition, the findings of benefit from early detection of DVT are biologically plausible. In this light, our findings should be considered as 'hypothesis generating'. It is our hope that these findings will stimulate dialogue about the role for surveillance ultrasound in the ICU and provide the rationale for conducting a large-scale randomized controlled trial on this topic. This research question is particularly relevant today with the wide availability of point-of-care ultrasonography.

In conclusion, twice-weekly surveillance ultrasonography in medical-surgical ICU patients was associated with an increase in DVT detection, earlier diagnosis of DVT and PE, reduction in diagnostic testing for PE and non-lower limb DVT, and lower 90-day mortality. These hypothesis-generating findings should be tested in a prospective randomized controlled trial.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05899-1) contains supplementary material, which is available to authorized users.

Author details
[1] Intensive Care Department, Ministry of National Guard Health Affairs, ICU 1425, PO Box 22490, Riyadh 11426, Kingdom of Saudi Arabia. [2] King Abdullah International Medical Research Center, ICU 1425, PO Box 22490, Riyadh 11426, Kingdom of Saudi Arabia. [3] King Saud Bin Abdulaziz University for Health Sciences, ICU 1425, PO Box 22490, Riyadh 11426, Kingdom of Saudi Arabia. [4] Interdepartmental Division of Critical Care Medicine, Unity Health Toronto-St Michael's Hospital, Li Ka Shing Knowledge Institute, Toronto, Canada. [5] Department of Emergency and Critical Care Medicine, College of Medicine, King Fahd Hospital of the University, Imam Abdulrahman Bin Faisal University, Dammam, Kingdom of Saudi Arabia. [6] Intensive Care Department, Ministry of National Guard Health Affairs, Jeddah, Kingdom of Saudi Arabia. [7] King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Kingdom of Saudi Arabia. [8] King Abdullah International Medical Research Center, Jeddah, Kingdom of Saudi Arabia. [9] Department of Anesthesiology and Critical Care, King George's Medical University, Lucknow, India. [10] Department of Pulmonary and Critical Care Medicine, King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia. [11] Critical Care Medicine Department, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. [12] Military Medical Services, Ministry of Defense, Riyadh, Kingdom of Saudi Arabia. [13] Department of Intensive Care Services, Prince Sultan Military Medical City, Riyadh, Kingdom of Saudi Arabia. [14] Intensive Care Division, Department of Medicine, King Abdulaziz Hospital, Al Ahsa, Saudi Arabia. [15] King Saud Bin Abdulaziz University for Health Sciences, Al Ahsa, Saudi Arabia. [16] King Abdullah International Medical Research Center, Al Ahsa, Kingdom of Saudi Arabia. [17] Critical Care Section, Department of Medicine, King Faisal Specialist Hospital & Research Center, Jeddah, Saudi Arabia. [18] Department of Biostatistics and Bioinformatics, King Abdullah International Medical Research Center, Riyadh, Kingdom of Saudi Arabia. [19] Research Office, Bioinformatics, King Abdullah International Medical Research Center, Riyadh, Kingdom of Saudi Arabia.

Funding
The PREVENT trial was funded by King Abdulaziz City for Science and Technology (Grant AT 34-65) and King Abdullah International Medical Research Center (Grant RC12/045/R), both in Riyadh, Saudi Arabia. The funding agencies had no role in study design or conduct, data collection, statistical analysis, or writing of the manuscript.

Compliance with ethical standards

Conflicts of interest
The authors declare that they have no conflicts of interest.

Publisher's Note

Received: 16 September 2019 Accepted: 11 December 2019
Published online: 24 February 2020

References

1. Cook DJ, Crowther MA (2010) Thromboprophylaxis in the intensive care unit: focus on medical-surgical patients. Crit Care Med 38:S76–S82
2. Attia J, Ray JG, Cook DJ, Douketis J, Ginsberg JS, Geerts WH (2001) Deep vein thrombosis and its prevention in critically ill adults. Arch Intern Med 161:1268–1279
3. Winters B, Custer J, Galvagno SM Jr, Colantuoni E, Kapoor SG, Lee H, Goode V, Robinson K, Nakhasi A, Pronovost P, Newman-Toker D (2012) Diagnostic errors in the intensive care unit: a systematic review of autopsy studies. BMJ Qual Saf 21:894–902
4. Crowther MA, Cook DJ, Griffith LE, Devereaux PJ, Rabbat CC, Clarke FJ, Hoad N, McDonald E, Meade MO, Guyatt GH, Geerts WH, Wells PS (2005) Deep venous thrombosis: clinically silent in the intensive care unit. J Crit Care 20:334–340
5. Adams RC, Hamrick M, Berenguer C, Senkowski C, Ochsner MG (2008) Four years of an aggressive prophylaxis and screening protocol for venous thromboembolism in a large trauma population. J Trauma 65:300–306
6. Skrifvars MB, Bailey M, Presneill J, French C, Nichol A, Little L, Duranteau J, Huet O, Haddad S, Arabi Y, McArthur C, Cooper DJ, Bellomo R, Investigators E-T, The ACTG (2017) Venous thromboembolic events in critically ill traumatic brain injury patients. Intensive Care Med 43:419–428
7. Group PlftCCCT, The A, New Zealand Intensive Care Society Clinical Trials G, Cook D, Meade M, Guyatt G, Walter S, Heels-Ansdell D, Warkentin TE, Zytaruk N, Crowther M, Geerts W, Cooper DJ, Vallance S, Qushmaq I, Rocha M, Berwanger O, Vlahakis NE (2011) Dalteparin versus unfractionated heparin in critically ill patients. N Engl J Med 364:1305–1314
8. De Martino RR, Beck AW, Edwards MS, Corriere MA, Wallaert JB, Stone DH, Cronenwett JL, Goodney PP (2012) Impact of screening versus symptomatic measurement of deep vein thrombosis in a national quality improvement registry. J Vasc Surg 56(1045–1051):e1041
9. Allen CJ, Murray CR, Meizoso JP, Ginzburg E, Schulman CI, Lineen EB, Namias N, Proctor KG (2016) Surveillance and early management of deep vein thrombosis decreases rate of pulmonary embolism in high-risk trauma patients. J Am Coll Surg 222:65–72
10. Haut ER, Noll K, Efron DT, Berenholz SM, Haider A, Cornwell EE III, Pronovost PJ (2007) Can increased incidence of deep vein thrombosis (DVT) be used as a marker of quality of care in the absence of standardized screening? The potential effect of surveillance bias on reported DVT rates after trauma. J Trauma 63:1132–1135
11. Shackford SR, Cipolle MD, Badiee J, Mosby DL, Knudson MM, Lewis PR, McDonald VS, Olson EJ, Thompson KA, Van Gent JM, Zander AL (2016) Determining the magnitude of surveillance bias in the assessment of lower extremity deep venous thrombosis: a prospective observational study of two centers. J Trauma Acute Care Surg 80:734–739
12. Samuel S, Patel N, McGuire MF, Salazar M, Nguyen T (2019) Analysis of venous thromboembolism in neurosurgical patients undergoing standard versus routine ultrasonography. J Thromb Thrombolysis 47:209–215
13. Malhotra AK, Goldberg SR, McLay L, Martin NR, Wolfe LG, Levy MM, Khiatani V, Borchers TC, Duane TM, Aboutanos MB, Ivatury RR (2014) DVT surveillance program in the ICU: analysis of cost-effectiveness. PLoS ONE 9:e106793
14. Dickerson JC, Harriel KL, Dambrino RJ, Taylor LI, Rimes JA, Chapman RW, Desrosiers AS, Tullis JE, Washington CW (2019) Screening duplex ultrasonography in neurosurgery patients does not correlate with a reduction in pulmonary embolism rate or decreased mortality. J Neurosurg 1:1–9
15. Arabi YM, Burns KEA, Al-Hameed F, Alsolamy S, Almaani M, Mandourah Y, Almekhlafi GA, Al Bshabshe A, Alshahrani M, Khalid I, Hawa H, Arshad Z, Lababidi H, Al Aithan A, Jose J, Abdukahil SAI, Afesh LY, Al-Dawood A (2018) Surveillance or no surveillance for deep venous thrombosis and outcomes of critically ill patients: a study protocol and statistical analysis plan. Medicine 97:e12258
16. Arabi Y, Al-Hameed F, Burns KEA, Mehta S, Alsolamy S, Almaani M, Mandourah Y, Almekhlafi GA, Al Bshabshe A, Finfer S, Alshahrani M, Khalid I, Mehta Y, Gaur A, Hawa H, Buscher H, Arshad Z, Lababidi H, Al Aithan A, Jose J, Abdukahil SAI, Afesh LY, Dbsawy M, Al-Dawood A, Group Pt (2018) Statistical analysis plan for the Pneumatic CompREssion for PreVENting Venous Thromboembolism (PREVENT) trial: a study protocol for a randomized controlled trial. Trials 19:182
17. Arabi YM, Alsolamy S, Al-Dawood A, Al-Omari A, Al-Hameed F, Burns KE, Almaani M, Lababidi H, Al Bshabshe A, Mehta S, Al-Aithan AM, Mandourah Y, Mekhlafi G, Finfer S, Abdukahil SA, Afesh LY, Dbsawy M, Sadat M (2016) Thromboprophylaxis using combined intermittent pneumatic compression and pharmacologic prophylaxis versus pharmacologic prophylaxis alone in critically ill patients: study protocol for a randomized controlled trial. Trials 17:390
18. Arabi YM, Al-Hameed F, Burns KEA, Mehta S, Alsolamy SJ, Alshahrani MS, Mandourah Y, Almekhlafi GA, Almaani M, Al Bshabshe A, Finfer S, Arshad Z, Khalid I, Mehta Y, Gaur A, Hawa H, Buscher H, Lababidi H, Al Aithan A, Abdukahil SAI, Jose J, Afesh LY, Al-Dawood A (2019) Adjunctive intermittent pneumatic compression for venous thromboprophylaxis. N Engl J Med 380(14):1305–1315
19. Lensing AW, Prandoni P, Brandjes D, Huisman PM, Vigo M, Tomasella G, Krekt J, Wouter Ten Cate J, Huisman MV, Buller HR (1989) Detection of deep-vein thrombosis by real-time B-mode ultrasonography. N Engl J Med 320:342–345
20. Mattos MA, Londrey GL, Leutz DW, Hodgson KJ, Ramsey DE, Barkmeier LD, Stauffer ES, Spadone DP, Sumner DS (1992) Color-flow duplex scanning for the surveillance and diagnosis of acute deep venous thrombosis. J Vasc Surg 15:366–375
21. Monreal M, Montserrat E, Salvador R, Bechini J, Donoso L, MaCallejas J, Foz M (1989) Real-time ultrasound for diagnosis of symptomatic venous thrombosis and for screening of patients at risk: correlation with ascending conventional venography. Angiology 40:527–533
22. Kearon C, Ginsberg JS, Hirsh J (1998) The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. Ann Intern Med 129:1044–1049
23. Cook D, McMullin J, Hodder R, Heule M, Pinilla J, Dodek P, Stewart T, Canadian ICUDG (2001) Prevention and diagnosis of venous thromboembolism in critically ill patients: a Canadian survey. Crit Care (Lond, Engl) 5:336–342
24. Cook D, Meade M, Guyatt G, Griffith L, Granton J, Geerts W, Crowther M (2004) Clinically important deep vein thrombosis in the intensive care unit: a survey of intensivists. Crit Care 8:R145–R152
25. Harris LM, Curl GR, Booth FV, Hassett JM Jr, Leney G, Ricotta JJ (1997) Screening for asymptomatic deep vein thrombosis in surgical intensive care patients. J Vasc Surg 26:764–769