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ORIGINAL

A multicentre controlled pre–post trial of an implementation science intervention to improve venous thromboembolism prophylaxis in critically ill patients

Henry T. Stelfox[1,2,3*], Rebecca Brundin-Mather[4], Andrea Soo[1,3], Jeanna Parsons Leigh[1,2], Daniel J. Niven[1,2], Kirsten M. Fiest[1,2], Christopher James Doig[1,2,3], Danny J. Zuege[1,3], Barry Kushner[1,3], Fiona Clement[2], Sharon E. Straus[5], Deborah J. Cook[6], Sean M. Bagshaw[7] and Khara M. Sauro[1,2]

Abstract

Purpose: To test whether a multicomponent intervention would increase the use of low molecular weight heparin (LMWH) over unfractionated heparin (UFH) for venous thromboembolism (VTE) prophylaxis in critically ill patients and change patient outcomes and healthcare utilization.

Methods: Controlled pre–post trial of 12,342 adults admitted to 11 ICUs (five intervention, six control) May 1, 2015 to April 30, 2017 with no contraindication to pharmacological prophylaxis and an ICU stay longer than 24 h. Models were developed to examine temporal changes in ICU VTE prophylaxis (primary outcome), VTE, major bleeding, heparin-induced thrombocytopenia (HIT), death and hospital costs.

Results: The use of LMWH increased from 45.9% to 78.3% of patient days in the intervention group and from 37.9% to 53.3% in the control group, an absolute increase difference of 17.0% (32.4% vs. 15.4%, $p = 0.001$). Changes in the administration of UFH were inversely related to those of LMWH. There were no significant differences in the adjusted odds of VTE (ratio of odds ratios [rOR] 1.13, 95% CI 0.51–2.46) or major bleeding (rOR 1.22, 95% CI 0.97–1.54) post-implementation of the intervention (compared to pre-implementation) between the intervention group and the control group. HIT was uncommon in both groups ($n = 20$ patients). There were no significant changes for ICU and hospital mortality, length of stay and costs. Results were similar when stratified according to reason for ICU admission, patient weight and kidney function.

Conclusions: A multicomponent intervention changed practice, but not clinical and economic outcomes. The benefit of implementing LMWH for VTE prophylaxis under real-world conditions is uncertain.

Keywords: Intensive care units, Critical care, Venous thromboembolism, Heparin, Implementation science, Effectiveness

*Correspondence: tstelfox@ucalgary.ca
[1] Department of Critical Care Medicine, University of Calgary, 3280 Hospital Drive NW, Calgary T2N 4Z6, Canada
Full author information is available at the end of the article

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Introduction

Venous thromboembolism (VTE) is common in critically ill patients and a leading cause of preventable death [1]. Randomized controlled trials and economic analyses of VTE prophylaxis have reported low molecular weight heparin (LMWH) to be more efficacious in preventing pulmonary embolism (PE) than unfractionated heparin (UFH), and to have similar or better outcomes for deep vein thrombosis (DVT), heparin-induced thrombocytopenia (HIT), bleeding and mortality, with similar or lower hospital costs [2–4]. Recent guidelines recommend LMWH over UFH [5, 6], but audits suggest that clinical practice may not match recommendations [7–10]. Multiple barriers have been identified to the use of LMWH for VTE prophylaxis, including clinician knowledge gaps, absence of local clinical guidelines, and workplace cultures resistant to change [7, 8].

Implementing evidence-informed practices into clinical care is challenging and a large deficiency of modern healthcare [11]. Passive diffusion of new knowledge is slow [11, 12]. Limited efforts are dedicated to evaluate how new practices are implemented into clinical practice and how they perform [13]. As a result, high value (effective) practices are underused (e.g. lung protective ventilation in ARDS) and low value (ineffective or harmful) practices are overused (e.g. routine chest x-rays) [14–17].

We sought to test whether a multicomponent intervention would increase the use of LMWH (and decrease use of UFH) for VTE prophylaxis in critically ill patients and whether this change would influence patient outcomes and healthcare utilization.

Take-home message

Randomized controlled trials have shown low molecular weight heparin to be more efficacious than unfractionated heparin for venous thromboembolism prophylaxis. Implementation science initiatives can increase the use of low molecular weight heparin, but the clinical and economic benefits under real-world conditions are uncertain.

Methods

We used a controlled pre–post clinical trial to evaluate the implementation of an intervention designed to encourage the use of LMWH for VTE prophylaxis in critically ill patients. Study methods were conducted and reported in accordance with recommendations for reporting of intervention evaluation studies using non-randomized designs [18], standards for reporting implementation studies and the template for intervention description [19] and replication [20]. The health research ethics boards at the University of Calgary (16-0541) and University of Alberta (Pro000065343) approved this study.

Intervention

A multicomponent intervention to encourage the use of LMWH for VTE prophylaxis was developed using the theoretical domains framework, MRC framework for complex interventions, data from previous studies and in consultation with local clinicians and managers [7, 8, 21, 22]. The intervention (Supplementary File, Table 1) comprised four components made up of multiple elements tailored to each ICU: (1) education (in-person teaching sessions, web materials, newsletters, pocket cards, posters), (2) clinical decision support tools (updated local practice guideline, updated computerized order set, local champions), (3) reminders (pharmacist reminders on rounds, text messages to residents, computer tags) and (4) audit and feedback (VTE prophylaxis data disseminated via email, website and posters). The intervention was implemented May 2016 and sustained through April 2017 using strategies tailored to each ICU. The goal was to encourage the use of LMWH for VTE prophylaxis for patients without a contraindication to pharmacological prophylaxis. The intervention was targeted to physicians (including trainees), nurse practitioners, pharmacists and bedside nurses. A process evaluation (survey and semi-structured interviews) identified good fidelity of intervention implementation with clinicians demonstrating knowledge of the evidence underpinning VTE prophylaxis and reporting local champions, on-site education and computerized decision support systems to be the most useful components of the intervention. A detailed description of the intervention, its implementation and process evaluation are separately reported [23].

Study population and setting

We included consecutive adult medical, surgical and cardiovascular surgical patients admitted to 11 ICUs (nine medical-surgical, two cardiovascular surgical) in nine hospitals in two cities in Alberta, Canada from May 1, 2015 to April 30, 2017. The study period was purposefully selected to encompass twelve 1-month data collection periods pre- and post-intervention implementation as recommended for interrupted time series analyses to account for seasonal variability and time trends [24]. We excluded patients with primary diagnoses of bleeding, neurological disorder (limited evidence to guide prophylaxis) and injury (long-standing guidelines recommending LMWH) [25, 26]. The five ICUs in one city implemented the intervention (intervention group). The six ICUs in the other city did not implement the intervention (control group). The two cities have similar metropolitan populations (ca. 1.2 million) and the same

ministry of health manages the hospitals controlling for temporal trends and unmeasured confounders within the healthcare system. The ICUs are closed units staffed by multi-professional healthcare teams that include accredited ICU physicians, nurse practitioners, medical trainees (fellows/residents), nurses and pharmacists.

Study measures

The primary study measure was daily administration of LMWH for VTE prophylaxis in the ICU. An ICU patient day was defined as any portion of a day between 07:00 and 06:59. We excluded the first day in the ICU from analysis but included the last day in the ICU because for most patients these two days represented less than 24-h periods and VTE prophylaxis was most commonly administered at the start of each day. Days when patients were documented to have a platelet count $< 50 \times 10^9$/L, INR ≥ 2, PTT ≥ 55 s or to have received therapeutic anticoagulation were excluded from analysis. We measured daily administration of UFH (LMWH was intended to replace UFH) and mechanical devices (internal control because the intervention did not provide new guidance for their use).

Secondary study measures included clinical outcomes (DVT, PE, bleeding, HIT, death) and healthcare utilization (ICU and hospital length of stay and costs). We defined DVT and PE using International Statistical Classification of Diseases, 10th Revision, Canada (ICD-10CA) codes available from the Discharge Abstract Database [27]. Restricting the ICD-10CA codes for DVT (I80.1, I80.2, I80.3, I80.9, I82.0, I82.8, I82.9, O22.3, O22.9, O87.1) and PE (I26, I26.9) to type 2 (post-admission diagnosis) and type 3 (secondary diagnosis) diagnostic codes resulted in respective sensitivities of 79.4% and 86.7% and specificities of 94.6% and 93.1% in a validation cohort [28]. Major bleeding was defined by a new diagnosis of cerebral haemorrhage (ICD-10CA codes I60, I61, or I62 restricted to type 2 or type 3 diagnoses) [28], a drop in haemoglobin ≥ 2 g/dL within an ICU day or between two consecutive measurements within 24 h, or transfusion of ≥ 600 ml packed red blood cells (PRBC) within an ICU day [29]. We defined HIT as a positive functional serotonin release assay or lumi-aggregometry.

Healthcare costing measures were defined using two approaches: (1) provincial health system administration micro-costing reports, and (2) average unit cost estimates by utilization [3, 30, 31]. Provincial activity and costing data included patient-specific drug costs, patient-specific supply costs, net direct costs, net drug costs, medical staff costs (excluding physician), patient care administration total costs and indirect total costs. The average unit costs estimates were based on variables outlined in the ePROTECT trial and included medications, laboratory tests, diagnostic tests, transfusions, personnel costs and fixed institutional costs [3].

Data sources

We used a registry trial approach where all data were retrospectively abstracted from existing clinical, administrative, laboratory, diagnostic and finance databases that prospectively capture routine data [32, 33]. The ICU database prospectively captures demographic, clinical and outcome data for all patients admitted to and discharged from the ICU [34]. The Discharge Abstract Database captures data on all hospitalized patients, including vital status, dates of admission and discharge, and up to 25 ICD-10CA diagnostic codes. We obtained all hospital laboratory and transfusion data through Calgary Laboratory Services which extracts data from independent provincial information systems. Diagnostic imaging performed in-hospital was extracted from diagnostic imaging services database, and patient-specific consumption costs for individual services and by functional unit were captured from finance activity and costing services. Average costs per drug, laboratory, radiology and transfusion unit were collected from hospital pharmacy, laboratory services, diagnostic imaging and Canadian Blood Services.

Statistical analyses

We examined temporal changes in use of VTE prophylaxis (data aggregated by month) using interrupted time series analysis. Segmented linear regression models were used to obtain estimates of the changes in the level and slope in the post-implementation period compared to the pre-implementation period.

Differences in clinical outcomes and healthcare utilization pre-implementation compared to post-implementation for the intervention group and control group were evaluated for ICU (VTE prophylaxis, bleeding, costs) and overall hospital (DVT, PE, HIT, death, costs) stays and reported as a frequency with percentage or median. Ratios of odds ratios (OR) and ratios of mean ratios (log-transformed length of stay and costs) were calculated using marginal logistic or linear regression with modified generalized estimating equations (GEE) and an exchangeable correlation structure and bias-corrected covariance estimator to account for the small number of ICU sites (clusters) [35, 36]. Models were adjusted for age, gender, ICU admission reason, Charlson score and admission APACHE II score based on perceived clinical relevance and experience with previous analyses using the study registry [30, 33, 37].

Stratified analyses according to reason for ICU admission (medical, surgical, cardiovascular surgical), weight (< 120 kg vs. ≥ 120 kg) and kidney function (over

entire ICU stay: < 30 mL/min/1.73 m^2 vs. ≥ 30 mL/min/1.73 m^2) were also done for temporal changes in use of VTE prophylaxis using segmented linear regression. As stratification resulted in a smaller number of clusters and smaller cluster size, clinical outcomes and healthcare utilization for subgroups were analysed using standard logistic or linear regression with adjustment for age, gender, reason for ICU admission (weight and kidney function models only), Charlson score and admission APACHE II score.

Complete case analyses were used to manage missing data. A two-sided p value of less than 0.05 was considered statistically significant. Analyses were done using R (geepack and geesmv packages for GEE models) [36, 38, 39].

Results

Study population

During the study period 17,242 patients were admitted to the study ICUs. Among these, 12,342 patients satisfied the inclusion criteria and were potentially eligible for pharmacological VTE prophylaxis for a total of 76,782 ICU days (Fig. 1). The median age was 62 years (IQR 51–71 years), 38% were female, 69% had one or more comorbidities and 46% were admitted to the ICU post-operatively. The median APACHE II score within 24 h of ICU admission

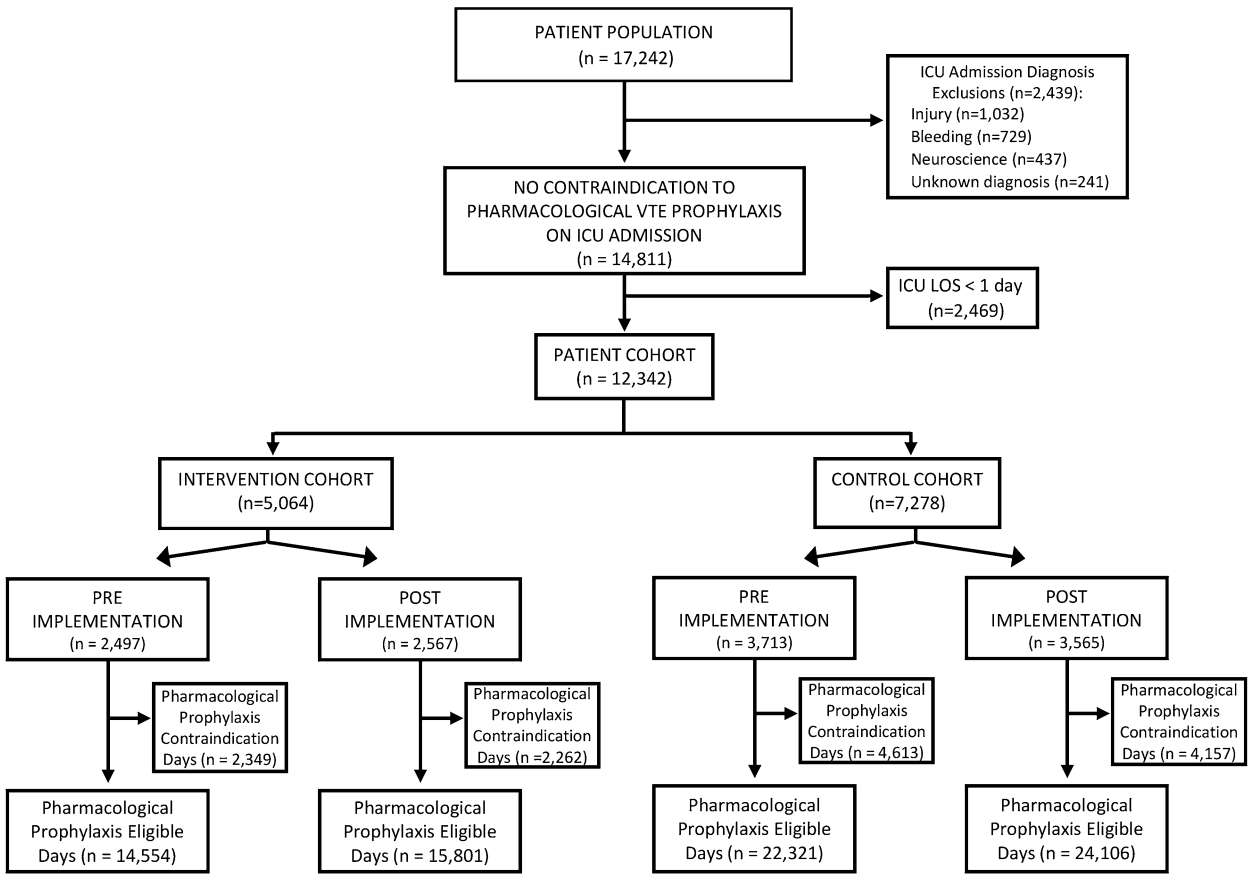

Fig. 1 Flow of patients in the study. Study patients fulfilled all inclusion criteria (≥ 18 years, admitted to a medical-surgical or cardiovascular ICU between May 1, 2015 and April 30, 2017) and had no exclusion criteria. ICU admission diagnoses flagged as possible contraindication to VTE chemoprophylaxis and therefore excluded were categorized as follows: 1032 patients had a primary diagnosis of traumatic injury; 729 patients had a primary admission diagnosis of bleeding; 437 patients had a primary neurological diagnosis; 241 patients had missing data for their primary admission diagnosis. Pharmacological prophylaxis contraindication days were defined by at least one of the following patient criteria: platelet count < 50; prothrombin time INR ≥ 2; activated partial thromboplastin time ≥ 55 or documented receipt of intravenous anticoagulation

was 18 (IQR 14–24) and the majority of patients received

invasive mechanical ventilation (76%) and vasopressors (64%). Patient characteristics for both the intervention group ($n=5064$) and the control group ($n=7278$) and the pre-implementation ($n=6210$) and post-implementation ($n=6132$) periods are summarized in Table 1.

Table 1 Patient and hospital characteristics

Characteristic	Intervention group		Control group	
	Pre-implementation ($n=2497$)	Post-implementation ($n=2567$)	Pre-implementation ($n=3713$)	Post-implementation ($n=3565$)
Patient characteristics on admission				
Age, median (IQR)	62 (51–71)	62 (50–72)	62 (51–71)	61 (50–71)
Female	959 (38)	941 (37)	1442 (39)	1385 (39)
Comorbidities[a]				
Diabetes	731 (29)	692 (27)	1123 (30)	1072 (30)
Chronic lung disease	308 (12)	295 (12)	699 (19)	530 (15)
Chronic kidney disease	109 (4)	104 (4)	267 (7)	206 (6)
Liver disease	137 (5)	156 (6)	298 (8)	289 (8)
Malignancy	200 (8)	211 (8)	460 (12)	350 (10)
Chronic heart or peripheral vascular disease[b]	749 (30)	751 (30)	1101 (30)	958 (27)
Neurological disease[c]	147 (6)	139 (6)	208 (6)	164 (5)
Charlson score[a]				
0	823 (33)	861 (34)	1001 (27)	1114 (31)
1	588 (24)	592 (23)	821 (22)	775 (22)
2 or more	1081 (43)	1072 (43)	1890 (51)	1650 (47)
Reason for admission				
Medical	1370 (55)	1363 (53)	1988 (54)	1906 (53)
Surgical	327 (13)	318 (12)	689 (19)	646 (18)
Cardiovascular surgical	800 (32)	886 (35)	1036 (28)	1013 (28)
Surgery				
Elective surgery	701 (28)	718 (28)	1172 (32)	1156 (32)
Emergent surgery	413 (17)	476 (19)	531 (14)	488 (14)
No surgery	1383 (55)	1373 (53)	2010 (54)	1921 (54)
APACHE II score, median (IQR)[d]	17 (13–23)	17 (13–24)	19 (15–26)	19 (14–25)
Glasgow coma scale score, median (IQR)[e]	15 (14–15)	15 (13–15)	15 (13–15)	15 (13–15)
SOFA score, median (IQR)	7 (5–9)	7 (5–9)	7 (5–10)	7 (5–9)
Organ support received				
Invasive ventilation	2012 (81)	1965 (77)	2793 (75)	2587 (73)
Non-invasive ventilation	306 (12)	329 (13)	548 (15)	475 (13)
Vasopressors	1670 (67)	1775 (69)	2286 (62)	2152 (60)
Renal replacement therapy	190 (8)	176 (7)	431 (12)	348 (10)
Hospital characteristics				
Teaching hospital	1425 (57)	1436 (56)	2381 (64)	2251 (63)
≥ 600 hospital beds	1728 (69)	1786 (70)	1814 (49)	1660 (47)
≥ 20 ICU beds	574 (23)	573 (22)	2928 (79)	2756 (77)

Data presented as number (per cent) unless otherwise indicated

Patient and hospital characteristics reported for first ICU admission that satisfied inclusion criteria for patients with ICU admissions during the study period

IQR interquartile range, *APACHE* Acute Physiology and Chronic Health Evaluation, *SOFA* sequential organ failure assessment

[a] Data missing for 74 patients

[b] Congestive heart failure, myocardial infarction or peripheral vascular disease

[c] Cerebrovascular disease, hemiplegia or paraplegia or dementia

[d] Data missing for six patients

[e] Data missing for 24 patients

Venous thromboembolism prophylaxis

The use of LMWH increased from 45.9% to 78.3% of patient days in the intervention group and from 37.9% to 53.3% in the control group, an absolute increase difference of 17% (32.4% vs. 15.4%, $p = 0.001$). After intervention implementation, there was an immediate increase in the absolute proportion of days patients received LMWH in the intervention group (11.6%, 95% CI 4.5–18.6%) (Fig. 2, Supplementary File Table 2). Subsequently there were significant changes over time in the absolute proportion of days patients received LMWH in the intervention group (+1.9% per month, 95% CI 0.9–2.9%), but not in the control group (−0.9% per month, 95% CI −1.9 to 0.2%). Changes in the

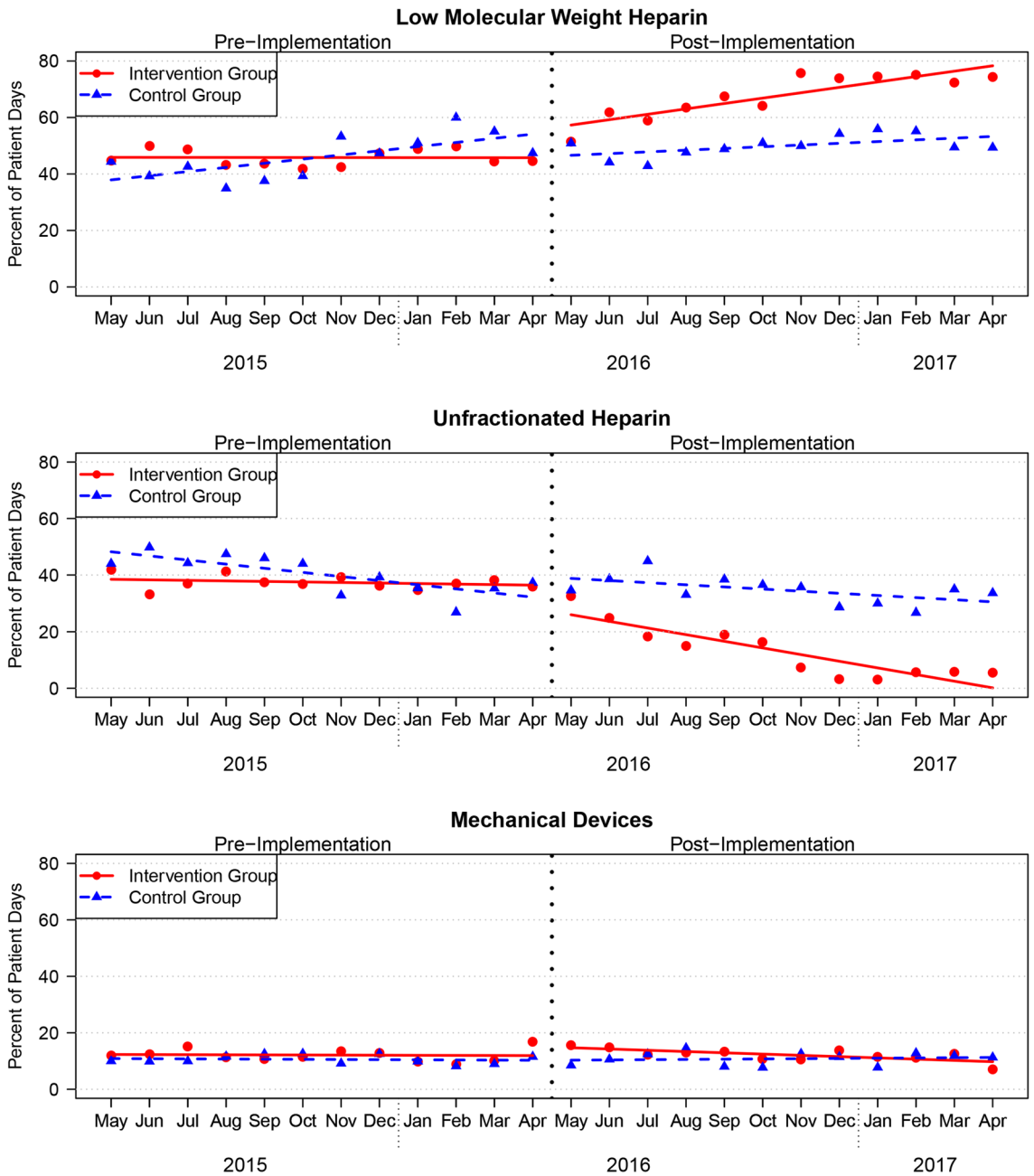

Fig. 2 Trends in use of low molecular weight heparin, unfractionated heparin and mechanical devices for venous thromboembolism prophylaxis over time. Symbols represent the observed proportion of days that a specific type of venous thromboembolism prophylaxis was provided aggregated per month; lines represent the mean estimated from a segmented linear regression model; the dashed vertical line represents the month in which intervention was implemented

administration of UFH were inversely related to those of LMWH. The use of mechanical devices for prophylaxis did not change in either group.

Clinical outcomes and healthcare utilization

Pre-implementation of the intervention, VTE was documented in 3.0% of patients in the intervention group and 2.4% of patients in the control group (Table 2). Post-implementation of the intervention, VTE was documented in 2.4% of patients in the intervention group and 2.1% of patients in the control group. There was no significant difference in the adjusted odds of VTE post-implementation of the intervention (compared to pre-implementation) between the intervention group and the control group (ratio of odds ratios [OR] 1.13, 95% CI 0.51–2.46, $p = 0.77$, Fig. 3). Similarly, there was no significant difference in the adjusted odds of major bleeding between the two groups pre- and post-implementation

Table 2 Clinical outcome and healthcare utilization

	Intervention group			Control group			Intervention vs. control group
	Pre-implementation ($n = 2497$)	Post-implementation ($n = 2567$)	Odds/mean ratios (95% CI)	Pre-implementation ($n = 3713$)	Post-implementation ($n = 3565$)	Odds/mean ratios (95% CI)	Ratio of odds/mean ratios (95% CI)[a]
Clinical outcomes							
Venous thromboembolism	75 (3.0)	77 (3.0)	1.03 (0.60–1.75)	88 (2.4)	75 (2.1)	0.91 (0.52–1.60)	1.13 (0.51–2.46)
Deep vein thrombosis	48 (1.9)	54 (2.1)	1.12 (0.69–1.84)	51 (1.4)	51 (1.4)	1.08 (0.47–2.48)	1.04 (0.39–2.77)
Pulmonary embolism	32 (1.3)	28 (1.1)	0.88 (0.41–1.89)	44 (1.2)	28 (0.8)	0.68 (0.49–0.94)	1.31 (0.57–3.01)
Major bleeding	477 (19.1)	490 (19.1)	0.98 (0.78–1.23)	743 (20.0)	596 (16.7)	0.80 (0.75–0.86)	1.22 (0.97–1.54)
Heparin-induced thrombocytopenia	2 (0.1)	7 (0.3)	[e]	6 (0.2)	5 (0.1)	[e]	[e]
Death							
Intensive care unit	254 (10.2)	284 (11.1)	1.08 (0.90–1.30)	307 (8.3)	318 (8.9)	1.16 (1.01–1.32)	0.94 (0.75–1.18)
Hospital	333 (13.3)	345 (13.4)	0.99 (0.82–1.20)	483 (13.0)	429 (12.0)	0.97 (0.80–1.19)	1.02 (0.77–1.34)
Healthcare utilization							
Length of stay, days[b]							
Intensive care unit	3.8 (1.9–7.6)	3.9 (2.0–7.7)	1.03 (0.98–1.08)	3.9 (2.1–7.6)	3.8 (2.2–7.1)	0.97 (0.90–1.05)	1.05 (0.96–1.15)
Hospital	12.0 (6.7–22.3)	10.4 (6.2–19.1)	0.89 (0.79–1.01)	11.5 (6.6–22.6)	9.1 (5.4–16.8)	0.81 (0.73–0.90)	1.10 (0.94–1.29)
Actual costs[c]							
Intensive care unit	13,332 (7636–27,708)	13,965 (8323–25,960)	1.01 (0.91–1.11)	12,771 (6868–25,587)	11,937 (7050–23,168)	0.96 (0.84–1.09)	1.05 (0.90–1.23)
Hospital	37,457 (24,005–66,384)	37,331 (24,901–64,324)	1.00 (0.93–1.07)	36,575 (22,950–64,064)	33,579 (20,996–56,929)	0.91 (0.86–0.97)	1.09 (1.00–1.20)
Modelled costs[d]							
Intensive care unit	14,987 (10,286–25,579)	16,387 (10,291–25.637)	1.02 (0.98–1.06)	16,404 (10,397–25,639)	16,398 (10,310–25,568)	0.99 (0.94–1.04)	1.04 (0.97–1.11)
Hospital	25,616 (16,813–43,546)	23,860 (16,220–38,509)	0.92 (0.85–1.00)	26,222 (17,143–43,946)	22,786 (15,743–35,894)	0.87 (0.81–0.94)	1.05 (0.95–1.17)

Data presented as number (per cent) unless otherwise indicated

[a] Ratio of odds ratios and mean ratios (long-transformed measures of length of stay and costs) calculated using marginal logistic or linear regression with modified generalized estimating equations and exchangeable correlation structure and bias-corrected covariance estimator to account for the small number of ICU sites (clusters). Models adjusted for age (categorized as < 30, 30–40, 40–50, 50–60, 60–70, 70–80, 80+), gender, admission reason (medical/surgical vs. cardiovascular), Charlson score category (0, 1, 2+) and APACHE II score

[b] Median (interquartile range)

[c] Direct and indirect healthcare costs in Canadian dollars excluding physician billings. Median (interquartile range)

[d] Direct and indirect healthcare costs in Canadian dollars modelled using ePROTECT. Median (interquartile range)

[e] Sample size too small for modelling

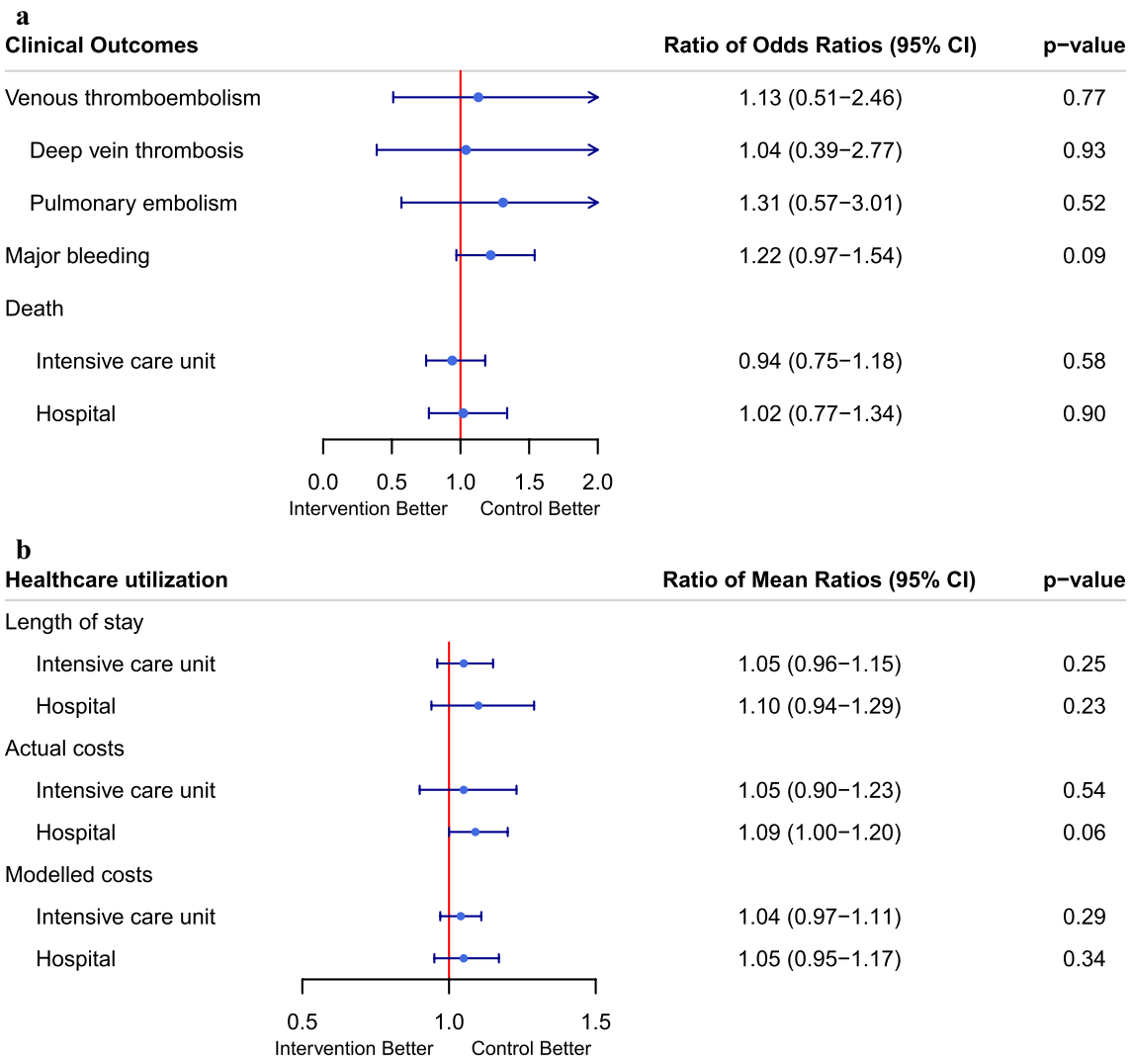

Fig. 3 Forest plots of the **a** Clinical outcomes and **b** Healthcare utilization data

(ratio of ORs 1.22, 95% CI 0.97–1.54, $p=0.095$). HIT was uncommon in both groups ($n=20$ patients). There were no significant changes pre- and post-implementation of the intervention between the intervention and control group for ICU and hospital mortality, length of stay and costs.

Secondary analyses

Sensitivity analyses that included different ICD-10 code case definitions for secondary study measures, data-derived (patient and hospital characteristics) propensity score risk adjusted models and stratification according to reason for ICU admission, weight and kidney function (Supplementary File, Fig. 1, Table 3, Table 4) produced similar results. When clinical outcomes and healthcare utilization were compared across the entire study period, patients who only received LMWH were less likely to experience any bleeding (OR 0.79, 95% CI 0.67–0.94), more likely to stay longer in ICU (ratio of means 1.14, 95% CI 1.12–1.25) and incur higher total ICU costs (ratio of means 1.19, 95% CI 1.12–1.25) compared to patients who only received UFH (Supplementary File, Table 5). When clinical outcomes and healthcare utilization were compared pre- and post-implementation regardless of study group, patients post-implementation were less likely to experience major bleeding (OR 0.87, 95% CI 0.79–0.96), have a shorter hospital stay (ratio of means 0.85, 95% CI 0.82–0.88) and lower total hospital costs (ratio of means 0.95, 95% CI 0.90–0.99) (Supplementary File, Table 6).

Discussion

We found that a multicomponent intervention was associated with a change in VTE prophylaxis. Increasing the use of LMWH relative to UFH for pharmacological VTE prophylaxis was not associated with changes in VTE, major bleeding, HIT, ICU and hospital mortality, length of stay or costs. The results were stable across a number of subgroup and sensitivity analyses.

Passive diffusion of knowledge produces slow changes in clinical practice, as illustrated by gradual increased use of LMWH for VTE prophylaxis in both the intervention and control groups during the pre-implementation period and in the control group during the post-implementation period. Our study illustrates how a comprehensive implementation science initiative can accelerate change practice. We engaged patients, clinicians, managers and researchers in identifying potential quality improvement priorities [40–42], audited care practices to determine opportunities for improvement [7], identified facilitators and barriers to best practice [7], developed a multicomponent intervention by mapping the facilitators and barriers to implementation science tools [23] and implemented and evaluated our intervention in a large patient population using a controlled pre–post trial. The result was an absolute increase of 17% in the use of LMWH in the intervention group compared to the control group. At the end of the study fewer than 1% of patients in the intervention group received UFH for VTE prophylaxis compared to 30% of patients in the control group. These changes in clinical practice were not associated with changes in clinical outcomes or healthcare utilization.

Venous thromboembolism prophylaxis is recommended for all critically ill patients [43]. A systematic review published in 2015 identified eight randomized controlled trials (RCTs) (5567 patients) that compared LMWH with UFH [4]. The pooled data demonstrated that for every 100 ICU patients enrolled, there were 9.1 DVTs, 1.3 PEs and 4.2 major bleeds [4]. When LMWH was compared to UFH there was a 10% relative lower risk of DVT, PE, major bleeding or death [4]. An economic analysis of the largest trial (PROTECT, $n = 3764$ medical-surgical patients) reported LMWH to be more effective with similar or lower costs than UFH [3]. On the basis of the available data, LMWH is increasingly recommended as the preferred pharmacological prophylaxis [5, 6] and strategies to implement these recommendations are being explored [7, 8, 23]. A 2018 Cochrane systematic review and meta-analysis identified 11 RCTs ($n = 33,207$) that assessed interventions (e.g. education) to increase VTE prophylaxis in hospitalized medical-surgical adult patients [44]. The authors reported that alerts (computer or human) and multicomponent interventions (e.g. education plus standardized orders) were respectively associated with a 21% and 4% absolute increase in the use of pharmacological or mechanical prophylaxis. Alerts were also associated with a reduction in symptomatic VTE at 3 months. One study in the review was conducted in critically ill patients; a cluster RCT of 118 ICUs randomized to routine care or a rounding checklist that included VTE prophylaxis amongst multiple processes of care [45]. Three-quarters of patients in both groups received some form of prophylaxis and the incidence of VTE was not assessed.

In a controlled pre–post trial with multiple centres and a large sample size we successfully changed practice, but not clinical outcomes and healthcare utilization as reported in RCTs. Why the discrepancy between our observations and those reported in RCTs? The most likely explanation is the difference in the research approaches; RCTs are designed to evaluate efficacy while implementation science studies are designed to change practice and evaluate effectiveness. Studies of efficacy evaluate interventions under ideal conditions that maximize internal validity and the likelihood of detecting an intervention effect, while minimizing the risk of harm [46]. Conversely, studies of effectiveness evaluate the benefits and harms of interventions in 'real-world' clinical practice settings [46]. These settings are characterized by diverse patient characteristics, incomplete intervention adherence, variable provider expertise and limited resources. For example, although pharmacological prophylaxis is recommended for all ICU patients without contraindications, the PROTECT trial enrolled 3764 patients from 67 ICUs over 4 years—less than 5% of all patients admitted to the study units [2]. Our study included all patients potentially eligible for pharmacological prophylaxis—12,342 patients from a population of 17,242 patients (72%). In the PROTECT trial, patients received allocated study drugs on 96.7% of days. At the end of our study, patients in the intervention group received LMWH on 78.3% of days. Finally, the modelled costs in economic analyses of an RCT are likely to be primarily informed by factors related to the intervention and clinical outcomes studied. In the real world there are a multitude of factors that influence costs that may overwhelm those considered in models. Our data highlight the complementary value of sequentially conducting evaluations of efficacy and effectiveness as recently called for in editorials accompanying publication of the 2016 Surviving Sepsis Campaign guidelines [47, 48]. Evaluations of efficacy serve as proof of principle and evaluations of effectiveness serve as tests of implementation into clinical practice.

Our study needs to be interpreted within the context of its strengths and limitations. We used a controlled pre–post trial that was practical for an applied healthcare

system intervention. Although studies suggest that interrupted time series analyses provide similar effect estimates as cluster RCTs, we are not able to evaluate causal relations, only associations, and there is a risk of residual confounding [49]. We used clinical and administrative registries as our sources of data. This was efficient, allowing us to focus our resources on the intervention and include a large number of patients in the study. Registries are contingent on the data entered. Our validation work suggests good concordance between data recorded in the registries and clinician notes [28, 34]. While patients enrolled in RCTs can be prospectively screened for study outcomes (e.g. Doppler ultrasound surveillance for DVT in the PROTECT trial) [2], registry-based trials are dependent on the outcomes being clinically diagnosed and documented in the medical record. Finally, our study illustrates how clinical practice can be changed using implementation science methods. The practice change observed was moderate in size, and consistent with the literature, which limits our ability to interpret the absence of change in clinical outcomes and healthcare utilization. Nevertheless, in subgroup analyses, even the large differences in VTE prophylaxis observed among the 3735 cardiovascular surgical patients (absolute increase in use of LMWH, intervention group 87.1% vs. control group 0.8%) did not translate into differences in clinical outcomes and healthcare utilization.

Conclusions

Our multicomponent intervention was associated with a change in clinical practice. Adoption of LMWH for pharmacological VTE prophylaxis did not reproduce the clinical or economic benefits reported in RCTs. These data highlight the importance of evaluating the implementation of evidence-informed clinical practices in real-world conditions.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05532-1) contains supplementary material, which is available to authorized users.

Author details
[1] Department of Critical Care Medicine, University of Calgary, 3280 Hospital Drive NW, Calgary T2N 4Z6, Canada. [2] Department of Community Health Sciences, University of Calgary, Calgary, AB, Canada. [3] Alberta Health Services, Calgary, Canada. [4] W21C Research and Innovation Centre, University of Calgary, Calgary, AB, Canada. [5] Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada. [6] Deparment of Medicine and Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada. [7] Department of Critical Care Medicine, Faculty of Medicine and Dentistry, and the School of Public Health, University of Alberta, Edmonton, AB, Canada.

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Compliance with ethical standards

Conflicts of interest
Funding sources had no role in the design, conduct, or reporting of this study and we are unaware of any conflicts of interest.

Ethical approval
The health research ethics boards at the University of Calgary (16-0541) and University of Alberta (Pro000065343) approved this study.

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