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Competing Risk Analysis for Evaluation of Dalteparin Versus Unfractionated Heparin for Venous Thromboembolism in Medical-Surgical Critically Ill Patients

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Abstract: Failure to recognize the presence of competing risk or to account for it may result in misleading conclusions. We aimed to perform a competing risk analysis to assess the efficacy of the low molecular weight heparin dalteparin versus unfractionated heparin (UFH) in venous thromboembolism (VTE) in medical-surgical critically ill patients, taking death as a competing risk.

This was a secondary analysis of a prospective randomized study of the Prophylaxis for Thromboembolism in Critical Care Trial (PROTECT) database. A total of 3746 medical-surgical critically ill patients from 67 intensive care units (ICUs) in 6 countries receiving either subcutaneous UFH 5000 IU twice daily (n = 1873) or dalteparin 5000 IU once daily plus once-daily placebo (n = 1873) were included for analysis.

A total of 205 incident proximal leg deep vein thromboses (PLDVT) were reported during follow-up, among which 96 were in the dalteparin group and 109 were in the UFH group. No significant treatment effect of dalteparin on PLDVT compared with UFH was observed in either the competing risk analysis or standard survival analysis (also known as cause-specific analysis) using multivariable models adjusted for APACHE II score, history of VTE, need for vasopressors, and end-stage renal disease: sub-hazard ratio (SHR) = 0.92, 95% confidence interval (CI): 0.70–1.21, *P*-value = 0.56 for the competing risk analysis; hazard ratio (HR) = 0.92, 95% CI: 0.68–1.23, *P*-value = 0.57 for cause-specific analysis. Dalteparin was associated with a significant reduction in risk of pulmonary embolism (PE): SHR = 0.54, 95% CI: 0.31–0.94, *P*-value = 0.02 for the competing risk analysis; HR = 0.51, 95% CI: 0.30–0.88, *P*-value = 0.01 for the cause-specific analysis. Two additional sensitivity analyses using the treatment variable as a time-dependent covariate and using as-treated and per-protocol approaches demonstrated similar findings.

This competing risk analysis yields no significant treatment effect on PLDVT but a superior effect of dalteparin on PE compared with UFH in medical-surgical critically ill patients. The findings from the competing risk method are in accordance with results from the cause-specific analysis.

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Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation, CI = confidence interval, CIF = cumulative incidence function, DVT = deep vein thrombosis, HR = hazard ratio, ICU = intensive care unit, IQR = interquartile range, PE = pulmonary embolism, PLDVT = proximal leg deep vein thromboses, PROTECT = Prophylaxis for Thromboembolism in Critical Care Trial, RCT = randomized controlled trial, SD = standard deviation, SHR = sub-hazard ratio, UFH = unfractionated heparin, VTE = venous thromboembolism.

INTRODUCTION

A competing risk is defined as an event that either precludes another event under investigation or fundamentally alters

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the probability of the outcome of interest.[1,2] In health research, it is not uncommon for participants to experience a competing risk event such as death, which prevents observing the event of interest. Failure to recognize the presence of competing risk or to account for it may result in misleading conclusions in clinical trials or epidemiological research.[3]

Critically ill patients in intensive care units (ICUs) are at high risk of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), because of their complex acute and chronic illnesses, analgesia and paralysis, immobility, and other interventions they may receive.[4–6] Until recently, there were insufficient data to adequately compare the efficacy of low-molecular-weight heparin and unfractionated heparin (UFH) in preventing VTE in medical-surgical critically ill patients.[7] The multicenter international randomized controlled trial, PROTECT (Prophylaxis for Thromboembolism in Critical Care Trial), evaluated the efficacy of dalteparin (a low-molecular-weight heparin) versus UFH in proximal leg deep vein thromboses (PLDVT), and other VTEs.[8] The trial reported no significant effect of dalteparin versus UFH on PLDVT, but a significantly superior treatment effect of dalteparin on PE using standard survival analysis (also known as cause-specific analysis).[8] However, the mortality rate (23.3%) was much higher than the rate of PLDVT (5.5%) and PE (1.8%) during follow-up.

Death prior to a VTE precludes the occurrence of subsequent PLDVT and PE, and therefore it can potentially affect the estimation of thromboprophylaxis efficacy. Evidence has shown that cause-specific analyses that fail to take competing risks into account could report biased findings about the effect of treatments or prognostic factors on outcomes.[3,9,10] Cox regression used for cause-specific analyses may not be appropriate since its assumptions of noninformative censoring and independence of time distributions between PLDVT and death may have been violated because of the existence of competing risks.[2,11] Although in the original trial report, a composite outcome of VTE or death was used to examine the efficacy of dalteparin versus UFH,[8,12] death as a competing event for VTE was not directly accounted for in the analysis.

In this study, we reanalyzed data from PROTECT to explicitly account for death as a competing risk. We used the Fine and Gray proportional subdistribution hazards model that, emerging evidence suggests, is appropriate to use in the presence of competing risk[13,14] to evaluate the efficacy of dalteparin versus UFH in preventing VTE in medical-surgical critically ill patients. Our goal was to perform the competing risk analysis as a sensitivity analysis,[15] and thus assess the robustness of the main findings based on the cause-specific analysis.[8] We performed additional sensitivity analyses: using the treatment variable as a time-dependent covariate in both cause-specific analysis and the Fine and Gray model; and using as-treated and per-protocol approaches. Our primary outcome was PLDVT, and the secondary outcome was PE.

METHODS

Patients and Settings

Details about the design, conduct, and main results of PROTECT (ClinicalTrials.gov Identifier: NCT00182143) have been published elsewhere.[8,12] Briefly, PROTECT was a multicenter randomized controlled trial (RCT) conducted in 67 ICUs from 2006 to 2010 in Canada, the United States, Australia, Brazil, Saudi Arabia, and the United Kingdom, aiming to evaluate the efficacy of subcutaneous UFH 5000 IU twice daily versus dalteparin 5000 IU once daily plus once-daily placebo in VTE in 3746 medical-surgical critically ill patients. Patients were enrolled in this trial if they were $\geq$18-years old, weighed $\geq$45 kg, and were expected to stay in the ICU for $\geq$3 days. Exclusion criteria were an admission diagnosis of trauma, orthopedic surgery, uncontrolled hypertension, or neurosurgery; major hemorrhage within the previous week; stroke, coagulopathy, or thrombocytopenia; pregnancy; or limitation of life-support. Patients with a need for anticoagulant therapy, with a contraindication to heparin or blood products, or who were already enrolled in a related trial, were also excluded. All patients or their surrogates provided written informed consent. Research ethics committees at each center approved the trial (e-Table 1, http://links.lww.com/MD/A398).

Outcomes

The primary outcome was incident PLDVT detected $\geq$3 days postrandomization using bilateral proximal leg venous ultrasounds.[8,12] The screening ultrasonography was performed twice-weekly and if PLDVT was clinically suspected. The secondary outcome was incident PE. Pulmonary emboli were diagnosed when intraluminal filling defects appeared on computed tomography, or when an unmatched perfusion defect on ventilation–perfusion (V/Q) scans existed, or if there were both a pretest probability (clinical suspicion) and a nondiagnostic result on noninvasive testing.[8,12]

Two adjudicators were randomly assigned to independently assess the PLDVT events; 4 adjudicators evaluated each PE event. All adjudicators were blinded to treatment allocation, center, and each other's assessments.[8,12] All enrolled patients were followed up to hospital discharge to record their vital status. Data were censored at 100 days for VTE outcomes.[8,12]

Statistical Analyses

Descriptive statistics for baseline characteristics of the patients were presented as means and standard deviations (SDs) or median and interquartile range (IQR) for data on continuous variables, and frequencies (percentages) for categorical variables. Because the percentage of missing data was small (<5%),[8] we imputed the missing data using the mean or median of the variable in its group when survival analysis was performed. All tests were 2-sided at a significance level of 0.05.

The independence assumption of the time distribution between VTE and death may not be satisfied in survival analysis due to the competing risk of death, therefore the Kaplan–Meier method was not appropriate to estimate survival curves for VTE.[2,16] We used the cumulative incidence function (CIF, also known as the subdistribution), which was derived from the cause-specific hazard function and did not require the independence assumption, to estimate the marginal probability of VTE in the presence of competing risk.[13] Specifically, given a time point t, the CIF denoted the probability of experiencing a VTE by the time t when the patients could also die before they developed a VTE. We used the Pepe and Mori method to test whether the CIFs of VTE between the treatment groups (dalteparin versus UFH) were significantly different.[17] The Kaplan–Meier method was used to evaluate the CIF of death, and the log-rank test was performed to compare the CIFs between the treatment groups.[16]

All the analyses were conducted based on the intention-to-treat principle. We first performed univariate analyses for PLDVT and PE in the Fine and Gray model, and Cox regression for cause-specific analysis, respectively. Multivariable analyses

TABLE 1. Baseline Characteristics of the Dalteparin and UFH Group

Characteristics	Dalteparin Group*(n = 1873)	UFH Group† (n = 1873)
Age (year): mean (SD)	61.1 (16.5)	61.7 (16.4)
Gender: n, %		
Male	1052 (56.4)	1061 (57.0)
Female	813 (43.6)	801 (43.0)
APACHE II score: mean (SD)	21.4 (7.8)	21.7 (7.8)
History of personal or family VTE: n, %	86 (4.6)	87 (4.7)
Need for vasopressors: n, %	805 (43.2)	872 (46.8)
End-stage renal failure: n, %	60 (3.2)	58 (3.1)

APACHE = Acute Physiology and Chronic Health Evaluation; SD = standard deviation; UFH = unfractionated heparin; VTE = venous thromboembolism.
* Median follow-up: 18 days; interquartile range: 10–32 days.
† Median follow-up: 17 days; interquartile range: 10–35 days.

were then employed, in which the analyses were adjusted for the Acute Physiology and Chronic Health Evaluation (APACHE) II score, history of personal or family VTE, need for vasopressors, and end-stage renal disease.[8,18] Sub-hazard ratios (SHRs) and corresponding 95% confidence intervals (CIs) were reported for the Fine and Gray model, while hazard ratios (HRs) were presented for cause-specific analysis. Both a statistical test and a graphical examination based on the Schoenfeld residuals were used to assess the proportional hazards assumption.[13,19]

Two additional sensitivity analyses were conducted. Since there may be gaps in the treatment of participants during follow-up, we included the treatment as a time-dependent covariate in both cause-specific analysis and the Fine and Gray model, to investigate whether the estimated treatment effect was robust.[20] Another sensitivity analysis was performed by using as-treated and per-protocol analyses in PLDVT and PE. The as-treated analysis excluded the patients (n = 87) who withdrew consent, never received any study drug, or who were incorrectly randomized.[8,12] The per-protocol analysis excluded the patients (n = 619) who were treated for baseline VTE diagnosed on the first screening ultrasonography, had <2 ultrasound tests, or who received study treatment for <2 days.[8,12]

All analyses were performed using STATA Version 12 (Stata Corp., College Station, TX) and SAS version 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Baseline Characteristics

The selection process of patients in the PROTECT has been published elsewhere.[8] Briefly, in the intension-to-treat analysis, 3746 patients (43.3% females) were included. Their mean age was 61.4 (SD: 16.5) years, and their mean APACHE II score was 21.5 (SD: 7.76) at baseline. The 4.6% of the patients (n = 173) had a history of personal or family VTE, and the percentage of participants diagnosed as end-stage renal disease was 3.2% (n = 118). There were 1677 (44.8%) patients requiring vasopressors at baseline.

The baseline characteristics of the dalteparin and UFH groups are shown in Table 1. There were 1873 participants assigned to dalteparin group and 1873 patients to UFH, respectively. The age, sex composition, APACHE II scores, the percentages having a history of VTE or a diagnosis of end-stage renal disease, and the numbers of patients requiring vasopressors were similar in the 2 groups. The median follow-up for the dalteparin group was 18 days (IQR: 10–32), while the median follow-up for the UFH group was 17 days (IQR: 10–35) (Table 1).

During follow-up, 205 incident PLDVTs were reported, among which 96 were in the dalteparin group and 109 were in the UFH group. The 96 patients with PLDVT in the dalteparin group had similar age (60.2 versus 61.8), female composition (51.04% versus 43.12%), APACHE II scores (22.6 versus 22.4), percentage of history of VTE (6.25% versus 8.26%), diagnosis of end-stage renal disease (5.21% versus 2.75%), and patients requiring vasopressors (47.92% versus 55.96%) to the 109 patients in the UFH group (all *P*-values > 0.20). There were 812 patients (386 and 426 in the dalteparin and UFH group, respectively) who died before they developed a PLDVT during their ICU and hospital stay. The 30-, 60-, and 90-day cumulative incidence of PLDVT for dalteparin compared with UFH group was 11.8% versus 12.2%, 16.2% versus 15.7%, and 17.7% versus 15.7%, respectively. The cumulative incidence curves of PLDVT for these 2 groups are displayed in Figure 1 with considerable overlap. No significant difference of the CIFs for PLDVT between the 2 groups was observed using the Pepe

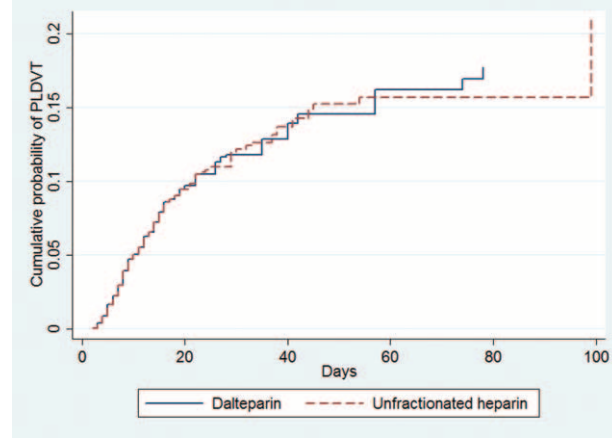

FIGURE 1. Cumulative incidence curves of PLDVT in dalteparin and UFH group. PLDVT = proximal leg deep vein thrombosis, UFH = unfractionated heparin.

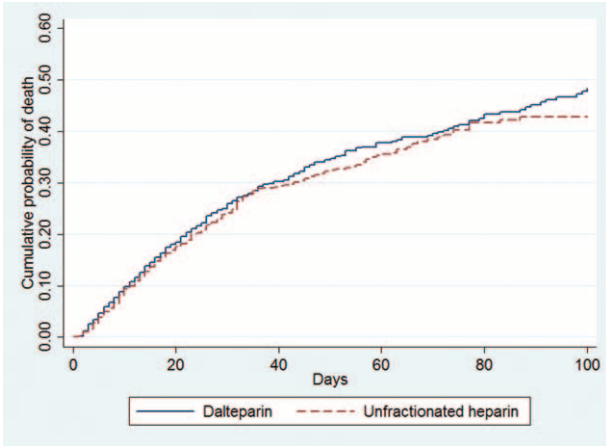

FIGURE 2. Cumulative incidence curves of death in dalteparin and unfractionated heparin (UFH) group using the Kaplan–Meier method.

and Mori test (P-value = 0.66). The cumulative incidence curves of mortality using the Kaplan–Meier method between the dalteparin group and UFH group are shown in Figure 2. Similarly no significant difference of these 2 CIFs for death was found (P-value = 0.23 for log-rank test).

Comparison Between Competing Risk Analysis and Cause-Specific Analysis

Results from the Fine and Gray model and the cause-specific method to evaluate the efficacy of dalteparin versus UFH in PLDVT are presented in Table 2. No significant treatment effect of dalteparin on PLDVT was observed in either the competing risk analysis or the cause-specific analysis using univariate analyses: SHR = 0.92, 95% CI: 0.71–1.21, P-value = 0.56 for the Fine and Gray model; HR = 0.92, 95% CI: 0.70–1.21, P-value = 0.54 for the cause-specific method. Similar findings were also identified in multivariable models adjusted for APACHE II score, history of VTE, need for vasopressors, and end-stage renal disease: SHR = 0.92, 95% CI: 0.70–1.21, P-value = 0.56 for the Fine and Gray model; HR = 0.92, 95% CI: 0.68–1.23, P-value = 0.57 for the cause-specific analysis (Table 2). Moreover, we performed another multivariable analysis in both competing risk analysis and cause-specific analysis adjusted for age, female gender, APACHE II score, history of VTE, need for vasopressors, and end-stage renal disease. Findings remained consistent: SHR = 0.92, 95% CI: 0.70–1.22, P-value = 0.55 for the Fine and Gray model; HR = 0.92, 95% CI: 0.69–1.21, P-value = 0.54 for the cause-specific analysis.

Table 2 also shows results for evaluation of dalteparin versus UFH for the outcome of PE. There were 24 patients with incident PE reported in the dalteparin group, while 43 patients were diagnosed with PE in the UFH group. Dalteparin was associated with significantly fewer PE compared with UFH in the univariate analysis, with a SHR of 0.58 (P-value = 0.03) for the competing risk analysis and a HR of 0.58 (P-value = 0.03) for the cause-specific method. The significant treatment effect of dalteparin remained unchanged in the multivariable analysis in both the Fine and Gray model (SHR = 0.54, 95% CI: 0.31–0.94, P-value = 0.02) and the cause-specific analysis (HR = 0.51, 95% CI: 0.30–0.88, P-value = 0.01), compared with UFH (Table 2).

Additional Sensitivity Analyses

Table 3 shows results of additional sensitivity analyses including the treatment as a time-dependent covariate in both cause-specific analysis and the Fine and Gray model. Similar findings to the analyses using dalteparin and UFH as time-invariant covariates (Table 2) were reported: no significant treatment effect of dalteparin on PLDVT compared with UFH was found (P-values $\geq$ 0.50), while a significantly protective effect on PE was observed (P-values $<$ 0.05) in both the competing risk analysis and the cause-specific method (Table 3).

Another sensitivity analysis was conducted by using as-treated and per-protocol multivariable analyses in PLDVT and

TABLE 2. Univariate and Multivariable Analyses in PLDVT and PE in the Fine and Gray Model and the Cause-Specific Method

	PLDVT				PE			
Method	**Dalteparin (n = 1873)**	**UFH (n = 1873)**	**Statistics* (95% CI)**	***P*-Value**	**Dalteparin (n = 1873)**	**UFH (n = 1873)**	**Statistics* (95% CI)**	***P*-Value**
Univariate analysis								
Fine and Gray model	96 (5.13)†	109 (5.82)†	0.92 (0.71–1.21)	0.56	24 (1.28)†	43 (2.30)†	0.58 (0.35–0.95)	0.03
Cause-specific analysis			0.92 (0.70–1.21)	0.54			0.58 (0.34–0.96)	0.03
Multivariable analysis‡								
Fine and Gray model	96 (5.13)†	109 (5.82) †	0.92 (0.70–1.21)	0.56	24 (1.28)†	43 (2.30)†	0.54 (0.31–0.94)	0.02
Cause-specific analysis			0.92 (0.68–1.23)	0.57			0.51 (0.30–0.88)	0.01

PE = pulmonary embolism, PLDVT = proximal leg deep vein thrombosis, UFH = unfractionated heparin.
* Sub-hazard ratio (SHR) for the Fine and Gray model; hazard ratio (HR) for the cause-specific analysis.
† Expressed as the number and percentage (%) of the venous thromboembolism event.
‡ Adjusted for the Acute Physiology and Chronic Health Evaluation II score, history of personal or family venous thromboembolism, need for vasopressors, and end-stage renal failure.

TABLE 3. Additional Sensitivity Analyses Using Treatment as a Time-Dependent Covariate in the Cause-Specific Analysis and the Fine and Gray Model

	PLDVT (n = 205)		PE (n = 67)	
Method	**Statistics* (95% CI)**	***P*-Value**	**Statistics*(95% CI)**	***P*-Value**
Univariate analysis				
Fine and Gray model	0.86 (0.53–1.40)	0.54	0.47 (0.25–0.90)	0.02
Cause-specific analysis	0.85 (0.52–1.37)	0.50	0.48 (0.25–0.91)	0.02
Multivariable analysis†				
Fine and Gray model	0.87 (0.53–1.42)	0.58	0.48 (0.26–0.91)	0.02
Cause-specific analysis	0.87 (0.54–1.42)	0.58	0.48 (0.24–0.91)	0.03

CI = confidence interval, PE = pulmonary embolism, PLDVT = proximal leg deep vein thrombosis.
* Sub-hazard ratio (SHR) for the Fine and Gray model; hazard ratio (HR) for the cause-specific analysis.
† Adjusted for the Acute Physiology and Chronic Health Evaluation II score, history of personal or family venous thromboembolism, need for vasopressors, and end-stage renal failure.

PE (Table 4). There were 3659 and 3127 patients included for as-treated and per-protocol analysis, respectively. No significant relationship between dalteparin and decreased risk of PLDVT was found (*P*-values > 0.50): SHR = 0.92 and 0.96 in as-treated and per-protocol analysis for the Fine and Gray model; HR = 0.91 and 0.95 in as-treated and per-protocol analysis for the cause-specific method. Nevertheless, compared with UFH, a superior effect of dalteparin on PE was observed (*P*-values < 0.05), with a SHR of 0.54 and 0.61 in as-treated and per-protocol analysis for the competing risk analysis and a HR of 0.48 and 0.54 in as-treated and per-protocol analysis for the cause-specific method, respectively (Table 4).

DISCUSSION

In this study based on data from the international PROTECT trial, we conducted a competing risk analysis to evaluate the effect of dalteparin versus UFH for the VTE prevention in medical-surgical critically ill patients, taking death as a competing risk. The competing risk analysis showed no significant effect of dalteparin compared with UFH on PLDVT, but a lower risk of PE. These findings were in agreement with results from the cause-specific analysis in the main report.[8] Similar results from additional sensitivity analyses supported the robustness of these findings.

In both the competing risk analysis and cause-specific analysis, we observed a significant difference in PE while no difference in PLDVT for dalteparin compared with UFH. One hypothesis may be due to the difference in nonleg DVT.[8] Nevertheless, there was no significant difference in nonleg DVT between the dalteparin and UFH group.[21] Another possible interpretation may rely on the fact that, unlike the PLDVT, the PE outcome was not screened twice-weekly.[8,12] However, little was known whether the difference in the detection would lead to the difference in the PLDVT and PE outcomes in the PROTECT. More evidence is needed to further explore and clarify the difference in PE for dalteparin versus UFH in critically ill patients.[8,21]

Given the presence of competing risk of death, it may not be appropriate in general to simply censor patients who died before they had a chance to experience a VTE using a cause-specific analysis. Theoretically, the distribution of time-to-censorship may provide information about the distribution of time-to-event, and therefore the assumption of noninformative

TABLE 4. Additional Sensitivity Analyses Using As-Treated (n = 3659) and Per-Protocol (n = 3127) Multivariable Analyses* in PLDVT and PE in the Cause-Specific Analysis and the Fine and Gray Model

	As-Treated Analysis				Per-Protocol Analysis			
Outcome	**Dalteparin (n = 1827)**	**UFH (n = 1832)**	**Statistics* (95% CI)**	***P*-Value**	**Dalteparin (n = 1566)**	**UFH (n = 1561)**	**Statistics* (95% CI)**	***P*-Value**
PLDVT								
Fine and Gray model	94 (5.15)†	108 (5.90)†	0.92 (0.70–1.21)	0.56	91 (5.81)†	99 (6.34)†	0.96 (0.72–1.27)	0.76
Cause-specific analysis			0.91 (0.68–1.23)	0.54			0.95 (0.70–1.29)	0.75
PE								
Fine and Gray model	22 (1.20)†	42 (2.29)†	0.54 (0.33–0.91)	0.02	22 (1.40)†	37 (2.37)†	0.61 (0.38–0.97)	0.04
Cause-specific analysis			0.48 (0.27–0.84)	0.01			0.54 (0.30–0.95)	0.03

CI = confidence interval, PE = pulmonary embolism, PLDVT = proximal leg deep vein thrombosis, UFH = unfractionated heparin.
* Adjusted for the Acute Physiology and Chronic Health Evaluation II score, history of personal or family venous thromboembolism, need for vasopressors, and end-stage renal failure.
* Sub-hazard ratio (SHR) for the Fine and Gray model; hazard ratio (HR) for the cause-specific analysis.
† Expressed as the number and percentage (%) of the venous thromboembolism event.

censoring may not be satisfied in standard survival analysis.[2,16,22] Similarly, those patients who died without having developed a VTE may not be representative of the other patients who remained in the risk set, thereby violating the assumption of independence of survival times between VTE and death.[2,16] Ignoring the competing risk could result in incorrect estimation of the actual risk of VTE in the Kaplan–Meier method,[23–25] and bias the benefit of interventions in trials or the associations between risk factors and outcomes in cohort studies using a cause-specific analysis.[26–28] In contrast, the Fine and Gray model modifies the risk sets such that patients experiencing the competing event are retained artificially in the cohort, with decreasing weight to account for the declining observability in the analyses, rather than being simple censored.[13] The Fine and Gray model could directly use the CIFs to calculate the hazards, and subsequently investigate the treatment effect expressed as a SHR.[16] Compared with the standard survival analysis, the Fine and Gray model had been supported by emerging evidence to account for competing risk, and the SHR had been justified as a better way to estimate the treatment effect than a HR in the Cox regression model.[2,3,14]

In this study, we observed a virtually identical treatment effect of dalteparin versus UFH on VTE in the competing risk analysis and the cause-specific method (Table 2). One of the most important reasons was that the cumulative incidences of mortality between the dalteparin group and UFH group were very similar (Figure 2), in which the 2 cumulative incidence curves overlapped substantially (P-value = 0.23 for log-rank test). Therefore, the similar mortality between the 2 groups yielded analogous censoring in the cause-specific analysis that ignored competing risk. All these findings further supported a similar effect of dalteparin versus UFH on the development of PLDVT but a protective effect on PE in medical-surgical critically ill patients.

There were 3 other trials investigating the efficacy of low-molecular-weight heparin in DVT compared with UFH in medical-surgical critically ill patients,[29–31] as summarized in a recent systematic review.[7] No protective effect of low-molecular-weight heparin on DVT was found in these trials. However, none of them took the competing risk such as death into consideration, despite the high mortality during follow-up. Therefore, it is uncertain whether the competing events would influence the treatment effect reported in these trials.

One study compared the efficacy of dalteparin versus oral anticoagulant therapy in the prevention of recurrent VTE in cancer patients using the standard survival analysis and the Fine and Gray model.[32] These investigators reported a similar treatment effect of dalteparin from these 2 analyses, with a HR of 0.48 in the cause-specific method and a SHR of 0.47 in the competing risk analysis, respectively, and concluded that if the time distribution of competing risks was similar between the treatment groups, standard survival analysis and competing risk method would produce similar findings.[32] If, however, the trial intervention had a different effect on the mortality and the censoring of a competing risk exerted a different influence on the probability of outcomes of interest, a cause-specific analysis ignoring competing risk would lead to misleading findings.[28,32]

For instance, in Pintilie example, he modified the data and assessed the effect of radiation versus chemotherapy on cardiac hospitalization in 689 patients with Hodgkin lymphoma.[3] The cause-specific analysis yielded an effect of radiation versus chemotherapy on cardiac hospitalization that was not significant (HR: 1.07, 95% CI: 0.71–1.63), while the Fine and Gray model found that radiation was significantly related with increased risk of cardiac hospitalization (SHR: 1.63, 95% CI: 1.10–2.45). The interpretation relied on the fact that the treatment groups had different effect on the risk of death (HR: 0.38, 95% CI: 0.31–0.47 for radiation versus chemotherapy). In other words, the time distribution of death in the chemotherapy group was different from the radiation group, and more patients died in the chemotherapy group before they could experience cardiac hospitalization than in the radiation group. Even though no clinical conclusion could be drawn due to the modification of the data,[3] this example did show that the cause-specific method ignoring the difference of censoring of the competing risk would result in a biased finding. Therefore, in the presence of competing events, a competing risk analysis or a comparison between a competing risk and standard survival analysis would be recommended to minimize the potential impact of competing risks and avoid incorrect conclusions.

Strengths of this study include a large sample size from a multicenter RCT and the use of optimally available statistical methods to investigate the efficacy of dalterparin versus UFH in VTE, taking into death as a competing risk account. Additional sensitivity analyses were also conducted to further assess and support the robustness of the original findings. However, we did not account for the transfer to a nontrial hospital as another potential competing event for VTE in this study. Given the limited data recorded in the database, no analysis could be performed to assess whether the competing risk of transfer to a non-trial hospital would impact the estimation of treatment effect on VTE. Furthermore, because this study focused on methodological analysis and aimed to assess the impact of competing risk, we did not have the data on serological tests and coagulation states for patients in this RCT. Therefore, for the phenomenon that there was significant difference in PE but no difference in PLDVT in the treatment groups, we could not use the serological or coagulation results to further illuminate the mechanism.

CONCLUSION

In this competing risk analysis using data from an international critical care trial, no significant difference was found between dalteparin and UFH on PLDVT, but dalteparin significantly reduced the risk of PE in medical-surgical critically ill patients. All the findings from the competing risk method were in accordance with results from a cause-specific analysis, increasing the inferences from the original findings.

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