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Assessing differential application of thromboprophylaxis regimes related to risk of pulmonary embolism and mortality in COVID-19 patients through instrumental variable analysis

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Thrombotic complications are common in Coronavirus disease 2019 (COVID-19) patients, with pulmonary embolism (PE) being the most frequent. Randomised trials have provided inconclusive results on the optimal dosage of thromboprophylaxis in critically ill COVID-19 patients. We utilized data from the multicentre CAPACITY-COVID patient registry to assess the effect of differential application of Low Molecular Weight Heparin (LMWH) dose protocols on PE and in-hospital mortality risk in critically ill COVID-19 patients. An instrumental variable analysis was performed to estimate the intention-to-treat effect, utilizing differences in thromboprophylaxis prescribing behaviour between hospitals. We included 939 patients with PCR confirmed SARS-CoV-2 infection from 34 hospitals. Two-hundred-and-one patients (21%) developed a PE. The adjusted cause-specific HR of PE was 0.92 (95% CI: 0.73–1.16) per doubling of LMWH dose. The adjusted cause-specific HR for in-hospital mortality was 0.82 (95% CI: 0.65–1.02) per doubling of LMWH dose. This dose–response relationship was shown to be non-linear. To conclude, this study did not find evidence for an effect of LMWH dose on the risk of PE, but suggested a non-linear decreased risk of in-hospital mortality for higher doses of LMWH. However, uncertainty remains, and the dose–response relationship between LMWH dose and in-hospital mortality needs further investigation in well-designed studies.

Keywords COVID-19, Heparin, Low-molecular-weight, Pulmonary embolism, Hospital mortality, Dose–response relationship, Drug

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Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In its severe form, COVID-19 is associated with lung failure, procoagulant status and high incidence of micro- and macro thrombotic complications[1–8]. The occurrence of thromboembolic events despite standard-dose pharmacological thromboprophylaxis prompted modified thromboprophylaxis dosage regimens to treat COVID-19 patients and escalated dose thromboprophylaxis for COVID-19 patients has been the subject of several observational studies and clinical trials[9–18].

The optimal dose of thromboprophylaxis in critically ill COVID-19 patients is still uncertain, even though several randomised controlled trials (RCTs) have recently been published[12–18]. These RCTs have varied in their primary hypotheses, patient populations, definitions of anticoagulant regimes and primary outcomes. For example, interpretation of the largest trial to date, the integrated trial of the platforms REMAP-CAP, ACTIV-4a and ATTACC, is hampered by its control arm, which includes both standard and intermediate dosed thromboprophylaxis[12]. Moreover, most smaller trials have used composite endpoints, combining all-cause mortality and thrombotic complications, as their primary outcomes[13,14,16,17]. The use of these composite endpoints might have diluted the efficacy of escalated dose thromboprophylaxis. For instance, the escalated dose prophylaxis might have increased all-cause mortality due to major bleeding events but decreased the number of thrombotic complications. In addition, most trials were not adequately powered to test the superiority of escalated thromboprophylaxis for relevant separate clinical outcome measures, such as thrombotic complications and mortality[13,14,16,17]. Finally, a substantial proportion of critically ill COVID-19 patients were found ineligible for randomization, which limits the external generalizability of the results to daily clinical practice[12–14,16]. Taken these limitations together, further evidence is required to determine the effect of escalated thromboprophylaxis on the development of thrombotic complications and mortality in critically ill COVID-19 patients.

Well-designed observational studies that use causal inference methods, such as instrumental variable analysis, can offer valuable evidence for therapeutic questions, such as in this case, to estimate the effect of escalated dose thromboprophylaxis on the risk of thrombotic complications and mortality. The methods allow for the control of confounding by severity and the patient's condition, a considerable problem in standard observational research, while at the same time avoid problems of an RCT, such as selected patient populations that limits generalisability[19,20]. A potential instrumental variable to estimate the effect of escalated dose thromboprophylaxis could be created due to a unique setting in the first COVID-19 wave in the Netherlands. Specifically, the uncertainty of escalated thromboprophylaxis on patient prognosis and a modification of the Dutch thromboprophylaxis guideline for COVID-19 patients[21] resulted in variations of the protocolised dose of thromboprophylaxis between Dutch hospitals, which were most pronounced in the ICU population. The present study utilizes these variations in protocolised thromboprophylaxis to examine the relationship between Low Molecular Weight Heparin (LMWH) dose and pulmonary embolism (PE) risk, as well as in-hospital mortality, in critically ill COVID-19 patients.

Methods

Study design

In this multicentre cohort study, we used data from COVID-19 patients admitted in the first pandemic wave between 27 February 2020 and 1 August 2020 who were included in the CAPACITY-COVID patient registry[22,22]. All included patients were followed from the date of ICU admission until the occurrence of any of the following: PE diagnosis, death, hospital transfer or hospital discharge.

Data collection

The CAPACITY-COVID patient registry has been described in detail previously[22,23]. In short, all adult patients (≥ 18 years) hospitalized with confirmed or highly suspected SARS-CoV-2 infection were eligible for inclusion in the registry. The University Medical Centre Utrecht's ethics committee (MREC, NedMec) approved this study and granted a waiver for informed consent. Local ethics approval was obtained in all participating hospitals[22,22].

For the current analysis, we used baseline data including sex, age, weight, and body mass index (BMI). Additionally, data were obtained on comorbidities, clinical features, laboratory parameters at hospital admission and medical treatments. We enriched the CAPACITY-COVID patient registry with information of the hospitals' thromboprophylaxis protocols for the current analysis.

Inclusion and exclusion criteria

Patients were included if they were admitted to one of the study sites participating in the CAPACITY-COVID registry in the Netherlands during the first COVID-19 wave (between 27 February 2020 and 1 August 2020), had a PCR-confirmed SARS-CoV-2 infection and were admitted to a high dependency unit (HDU) or intensive care unit (ICU), of which thromboprophylaxis protocols were known. Exclusion criteria were a documented venous thromboembolism history, therapeutic anticoagulation before hospital admission and occurrence of venous thromboembolism before HDU/ICU admission.

Exposure

We used an instrumental variable analysis[20] to estimate the effect of LMWH on PE risk and in-hospital mortality [Online Resource 1]. In this analysis, not the effect of the *actual* received dose but the *protocolised* dose on PE risk and mortality is estimated. The advantage of using the protocolised dose (instrumental variable) instead of the actual dose received is that the actual dose is confounded by the patient's conditions. In contrast, the protocolised dose is independent of these conditions. This approach is similar to the intention-to-treat analysis used in randomized controlled trials.

For this, we used local LMWH prophylaxis protocols as a patient's individual exposure. At the beginning of the COIVD-19 pandemic, the efficacy of the different strategies on patient prognosis was unknown, causing Dutch hospitals to choose different thromboprophylaxis strategies for their COVID-19 patients based on the physicians' local preferences. Differences in LMWH prophylaxis protocols ranging from standard to therapeutic dosages of LMWH, existed across hospitals and changed over time, especially after the publication of the national prophylaxis guidance document on 16 April 2020[21]. Based on this guidance document, most hospitals changed their thromboprophylaxis strategy to a higher dose, but variations in protocols between hospitals remained, due to differences in local opinions and beliefs regarding the optimal strategy. We assumed that the hospital's thromboprophylaxis protocols did not depend on the patient case-mix of the hospital and no other significant differences in treatment policies were in place across hospitals that could affect the outcome. These assumptions were regarded as reasonable as the ICU admissions during the first wave of COVID-19 in the Netherlands were predominantly driven by capacity rather than the severity of illness or patient characteristics[24,25] and treatment options such as dexamethasone or antiviral drugs were not routinely applied to treat COVID-19 in the first wave of the COVID-19 pandemic[26].

Hence, the LMWH prophylaxis dose, according to the hospital's prophylaxis protocol at the date of admission to HDU/ICU, was used as a patient's individual exposure. For hospitals that adjusted doses to the weight or BMI of the patient, the protocolised dose was calculated according to the patients' weight or BMI; when weight or BMI was missing, we used the mean LMWH dose given in the hospital during the patient's admission. For patients transferred to another hospital after HDU/ICU admission, the protocolised LMWH dose of the initial hospital was used. To ascertain that the two types of LMWH (dalteparin/nadroparin) were equally interpreted, nadroparin and dalteparin doses were expressed in IE anti-Xa units. The correspondence between protocolised LMWH dose and the actual received dose was evaluated in two academic hospitals by checking the ICU patients' electronic health records for the actual LMWH starting dose and recording the reason in case of deviation.

Outcome

The primary outcome was time from HDU/ICU admission to PE. A PE was defined as a diagnosis of PE indicated in the patient's electronic health record since there was no central adjudication of a PE in the CAPACITY-COVID registry[22]. The secondary outcome was time from HDU/ICU admission to in-hospital mortality.

Statistical analysis

Descriptive results are presented using descriptive statistics. Tertiles of protocolised LMWH were created for which the demographic characteristics, comorbidities, clinical features and laboratory parameters were described. Two-sided tests were used to assess differences. The cumulative incidences of PE and in-hospital mortality were estimated in a competing risk analysis treating in-hospital mortality and transfer to another hospital as competing risks. Patients discharged from the hospital had their data censored at the date of observing the last event in the data (13 July 2020).

Univariable Cox proportional hazard models were used to study the association between covariates and PE occurrence. The studied covariates were calendar time (days) starting at 27 February 2020, age, sex, weight and whether a patient was transferred from another hospital before ICU admission. Calendar time was used because of the increased awareness of PE over time, and hospital transfer was seen as a proxy for disease severity. In particular, patients transferred from another hospital compose a specific group of patients; on the one hand, patients at low risk of transportation-related complications might be more likely to be transported, on the other hand, patients with severe disease might be more likely to be transported to academic hospitals for third-line therapy.

The relation between protocolised dose and outcomes was studied in multivariate cox proportional hazard models. The protocolised LMWH dose was log-transformed to account for the skewness in the distribution of protocolised LMWH dose. Four models were explored: (1) a crude model; (2) model 1 with calendar time added; (3) model 2 with age, sex and hospital transfer added; (4) model 3 with weight (kg) added. The shape of the relationship between LMWH dose and the outcomes was examined with restricted cubic spline functions.

Again, the end of follow-up of discharged patients was censored at the date of observing the last event (13 July 2020).

In the abovementioned models, transfer to another hospital and, in the case of PE, in-hospital mortality and in the case of in-hospital mortality, PE, were treated as competing risks. We did not adjust for other baseline characteristics as we assumed that the hospital's LMWH dose protocols did not depend on the patient case-mix of the hospital. Statistical analyses were performed in the software R version 4.0.5[27].

Sensitivity analysis

In the main analysis, no distinction between nadroparin and dalteparin doses was made. In a sensitivity analysis, nadroparin levels were converted to the equivalent dalteparin levels by multiplying nadroparin levels with a factor 2500/2850. In addition, the impact of the outliers in protocolised LMWH dose on our analysis was checked in a sensitivity analysis. Finally, the baseline characteristics of dyslipidaemia, baseline blood pressure and sex were added in a multivariable Cox model to assess their impact on our analysis.

Results

Data selection

In total, 1107 patients fulfilled our inclusion criteria, and 168 were subsequently excluded from the analysis (Fig. 1).

Missing data

There were 12 patients with no information on the outcome (death, discharge or hospital transfer). In the analyses, these patients were treated as if discharged alive. The date of occurrence of several reported events was missing, i.e., the date of PE (n = 2), deep venous thrombosis (n = 5), catheter-related thrombosis (n = 1) and other thromboembolism (n = 1), and were imputed as occurring 6 days after hospital admission in accordance with Kaptein et al.[28]. The weight of 65 patients was missing. For these patients, we used the average LMWH dose in the hospital during the time the patient was admitted. They were also excluded from the final Cox proportional hazard model. In our study population, 157 patients were transferred to another hospital and 320 people were transferred from another hospital. These patients were treated as unique patients in our analysis, as we were not able to identify duplicates in our data. We assume the number of duplicates in our data was low as approximately only 30 duplicates existed in the CAPACITY-COVID registry of 6000 people.

Descriptive data

Of the 939 patients, 257 (27%) were female, and the median age was 64 years (IQR: 56–72). The patient characteristics were predominantly balanced across the three equally sized groups of protocolised LMWH dose (tertiles) (Table 1). Patients admitted in the early days of the first wave were more likely to get low protocolised LMWH dose than those admitted later. Patients in the low and high dose category were more often transferred from another hospital than those in the middle dose category. Patients were more often treated with (hydroxy) chloroquine in the low and middle dose compared to the high dose category.

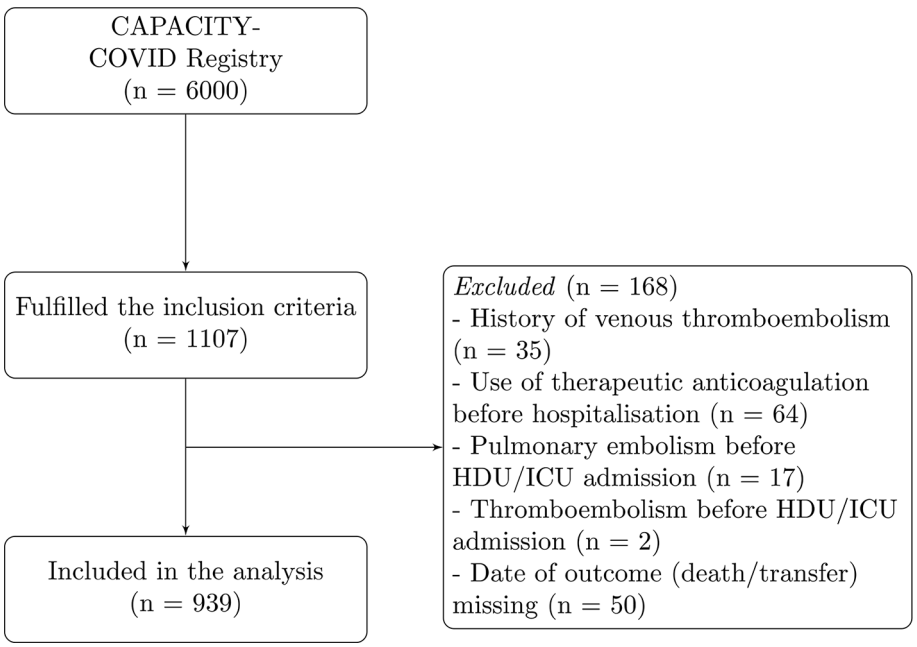

Fig. 1. Flow diagram of patient selection. Flow diagram of patient selection from the CAPACITY-COVID registry (HDU, high dependency unit, ICU, intensive care unit).

	2500–3800	3800–5700	5700–18,000	Missing (%)
Number of patients	312	283	344	
Demographics				
Female (No. (%))	94 (30.1)	83 (29.3)	80 (23.3)	0
BMI (mean (SD))[a]	28.1 (5.0)	28.0 (4.4)	29.2 (5.5)	9.2
Weight (mean (SD))	86.6 (16.9)	85.2 (15.3)	91.0 (18.5)	6.9
Age (median [IQR])	65.0 [57.0, 72.0]	65.0 [57.0, 72.0]	64.0 [54.0, 71.0]	0
Laboratory parameters				
CRP (median [IQR]) (mg/dL)	14.3 [8.3, 22.4]	14.2 [8.2, 21.9]	13.8 [7.4, 17.1]	3.5
Haemoglobin (mean (SD)) (g/dL)	12.9 (1.9)	13.2 (2.1)	13.1 (2.3)	7.5
Platelet count (median [IQR]) (×103/μL)	221.0 [167.8, 280.5]	209.0 [158.0, 254.5]	228.0 [169.0, 305.5]	9.5
White blood cell count (median [IQR]) (cells/μL)	7800 [5200, 10900]	7700 [5400, 10500]	8400 [5900, 11700]	5
Lymphocyte count (median [IQR]) (cells/μL)	700 [400, 1000]	800 [500, 1100]	900 [600, 1200]	26.7
Creatinine (median [IQR]) (mg/dL)	960 [0.77, 1.21]	0.94 [0.75, 1.17]	0.98 [0.79, 1.29]	7.7
D-dimer (median [IQR]) (μg/mL)	1.3 [0.7, 3.1]	1.5 [1.0, 4.0]	1.5 [0.8, 3.8]	72.5
Clinical characteristics				
Temperature (mean (SD)) (degree Celsius)	37.8 (1.1)	38.1 (1.0)	37.9 (1.1)	16.3
Heart rate (mean (SD)) (beats per minute)	88.0 (17.8)	90.7 (16.9)	91.8 (20.0)	13.2
Systolic blood pressure (mean (SD)) (mmHg)	130.0 (22.9)	133.7 (22.8)	134.3 (22.2)	14.8
Diastolic blood pressure (mean (SD)) (mmHg)	71.0 (14.6)	74.6 (15.6)	74.7 (15.5)	14.8
Respiratory rate (median [IQR]) (breaths per minute)	22.0 [18.0, 27.0]	24.0 [20.0, 30.0]	24.0 [19.0, 28.0]	20.8
Comorbidities				
Diabetes mellitus (No. (%))	72 (23.6)	65 (23.0)	80 (23.6)	1.4
Lipidaemia (No. (%))	71 (24.4)	92 (33.8)	78 (25.7)	7.7
Hypertension (No. (%))	118 (38.8)	112 (40.1)	125 (37.5)	2.4
Chronic kidney disease (No. (%))	20 (6.4)	21 (7.4)	19 (5.5)	0
Chronic obstructive pulmonary disease (No. (%))	26 (8.4)	22 (7.8)	28 (8.2)	0.3
Inflammatory immune disease (No. (%))	36 (11.5)	26 (9.2)	32 (9.3)	0.1
Cardiac diagnosis (No. (%))	52 (16.7)	60 (21.3)	84 (24.5)	0.2
Hospital stay				
Number of days between 27 February 2020 and day of HDU/ICU admission (mean (SD))	29.5 (7.4)	30.7 (9.7)	41.1 (18.2)	0
Transferred from another hospital (No. (%))	107 (34.3)	86 (30.4)	127 (36.9)	0
Medical treatment				
(Hydroxy)chloroquine (No. (%))	237 (77.2)	185 (67.0)	171 (50.9)	2.1

Table 1. Clinical characteristics of the patients at hospital admission, per tertile of protocolised LMWH dose (IE anti-Xa). Abbreviations: BMI, Body Mass Index; CRP, C-reactive protein; D-dimer, dimerized plasmin fragment D; IQR, interquartile range; SD, standard deviation. SI conversion factors: To covert CRP to milligrams per litre, multiply by 10; To convert Creatinine to micromoles per litre, multiply by 88.4. D-dimer to nanomoles per litre, multiply by 5.476; Haemoglobin to grams per litre, multiply by 10. White blood cell count to 109 per litre, multiply by 0.001; lymphocyte count to 109 per litre, multiply by 0.001; Platelet count to 109 per litre, multiply by 0.001. [a]Body mass index is calculated as weight in kilograms divided by height in meters squared.

The patients included in the analysis originated from 34 hospitals. Twenty-two (65%) hospitals prescribed nadroparin and 12 hospitals (35%) dalteparin [Online Resource 2]. All thromboprophylaxis protocols recommended to prescribe LMWH at hospital admission from the start of the COVID-19 pandemic, but the regimes differed between the hospitals. In total, for 702 patients (75%) the protocolised LMWH dose ranged between 2,500 and 5,700 IE anti-Xa (standard), for 231 patients (25%) between 5,700 and 11,400 IE anti-Xa (intermediate), and for 6 patients (1%) the protocolised dose was 18,000 IE anti-Xa (therapeutic) [Online Resource 2]. In the general ward, minor differences in thromboprophylaxis strategies were detected across hospitals [Online Resource 2].

The exposure of protocolised LMWH was validated in two hospitals. In the first hospital, adherence to the guideline was checked in 58 ICU patients. In this hospital, 45 (78%) patients received the protocolised dose LMWH as thromboprophylaxis. In the second hospital, adherence was checked in 92 patients of whom 58 (63%) patients received the dose that was protocolised on the first day of HDU/ICU admission. Twenty-five (27%) patients did not receive the protocolised dose on the first day of HDU/ICU admission, of whom 2 patients got the protocolised dose on the second day of their HDU/ICU admission. In addition, 9 patients (10%) started with UFH on the first day of HDU/ICU admission. Reasons to deviate from the hospital's protocol included

renal impairment and use of ECMO, insufficient anti-Xa levels, indication for therapeutic anticoagulation and categorisation into a different weight category[29].

Outcomes

In total, 201 (21%) PEs were diagnosed, 522 (56%) patients were discharged alive, 260 (28%) patients died in the hospital, and 157 (17%) were lost to follow-up due to a transfer to another hospital. The median length of ICU stay was 18 days (IQR: 10–32). The median time between hospital and ICU admission was 2 days (IQR: 0–4). The median time between HDU/ICU admission and the diagnosis of PE was 8 days (IQR 4–12).

Figure 2 shows the number of PE diagnoses and the number of patients hospitalised at the HDU/ICU over time. The first PE diagnosis was established approximately 4 weeks after the first COVID-19 case in the Netherlands. The cause-specific univariable hazard ratio (HR) for PE per one day increase in calendar time was 1.04 (95% CI 1.03–1.05). For in-hospital mortality, the cause-specific univariable HR per one day increase in calendar time was 0.99 (95% CI 0.98–1.00).

A PE diagnosis was more likely if a patient was transferred from another hospital: cause-specific univariable HR 2.20 (95% CI 1.67–2.90). This effect did not change when the model was adjusted for calendar time. In-hospital mortality was less likely if a patient was transferred from another hospital, with a cause-specific univariable HR 0.80 (95% CI 0.61–1.04). A PE diagnosis was more likely for older patients, (cause-specific univariable HR 1.02 per increase of 1 year (95% CI 1.00–1.03)), which did not change when the model was adjusted for calendar time. Older patients were also more likely to die, with a cause-specific univariable HR 1.07 per increase of 1 year (95% CI 1.05–1.08). A PE diagnosis was more likely for males: cause-specific univariable HR 1.59 (95% CI 1.14–2.22). Males were also more likely to die in hospital, cause-specific univariable HR 1.47 (95% CI 1.10–2.00).

LMWH dose in relation to PE and mortality risk

Figure 3 shows the cumulative incidence of PE for the tertiles of LMWH dose. The crude cause-specific HR for PE for a doubling of the LMWH dose was 1.03 (95% CI 0.83–1.28). Adjusting the model for calendar time (days between 27 February 2020 and the date of HDU/ICU admission) decreased the HR to 0.92 (95% CI 0.73–1.17), and additionally adjusting the model for age, sex and hospital transfer decreased the HR to 0.90 (95% CI 0.71–1.13). Adjusting the model for weight increased the HR to 0.92 (95% CI 0.73–1.16).

Figure 4 shows the cumulative incidence of in-hospital mortality for the tertiles of LMWH dose. The crude cause-specific HR for in-hospital mortality for a doubling of LMWH dose was 0.78 (95% CI 0.64–0.95). Adjusting the model for calendar time did not affect the HR, 0.79 (95% CI 0.64–0.98), and additionally adjusting the model for age, sex and hospital transfer increased the HR to 0.85 (95% CI 0.68–1.05). Finally, adjusting the model for weight decreased the HR to 0.82 (95% CI 0.65–1.02).

We investigated the dose–response relation between LMWH dose and PE and in-hospital mortality by fitting restricted cubic splines. Figures 5 and 6 show predicted HRs of PE and in-hospital mortality per protocolised LMWH dose using the model's mean LMWH dose as the reference (4784.8 IE anti-Xa).

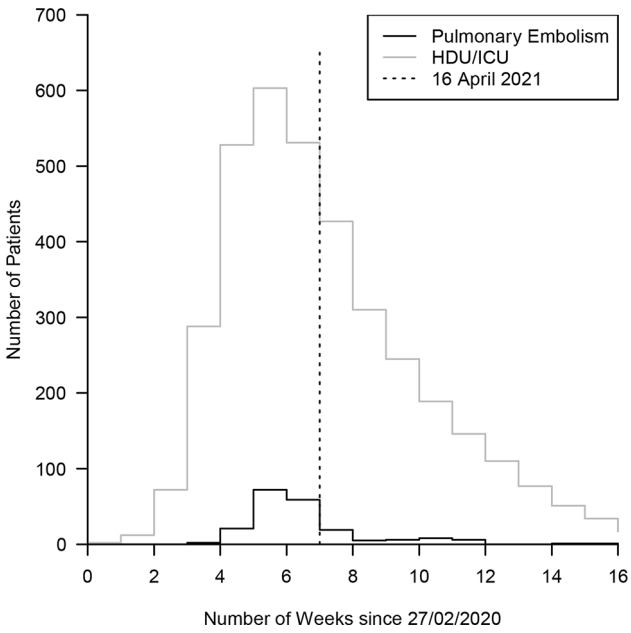

Fig. 2. Number of PE diagnoses and number of hospitalised patients. The number of PE diagnoses (black line) and the number of patients hospitalised at the high dependency unit (HDU) or intensive care unit (ICU) (grey line) per week. A thromboprophylaxis guidance document was published in the Netherlands on 16 April 2020 (week 7, dashed line).

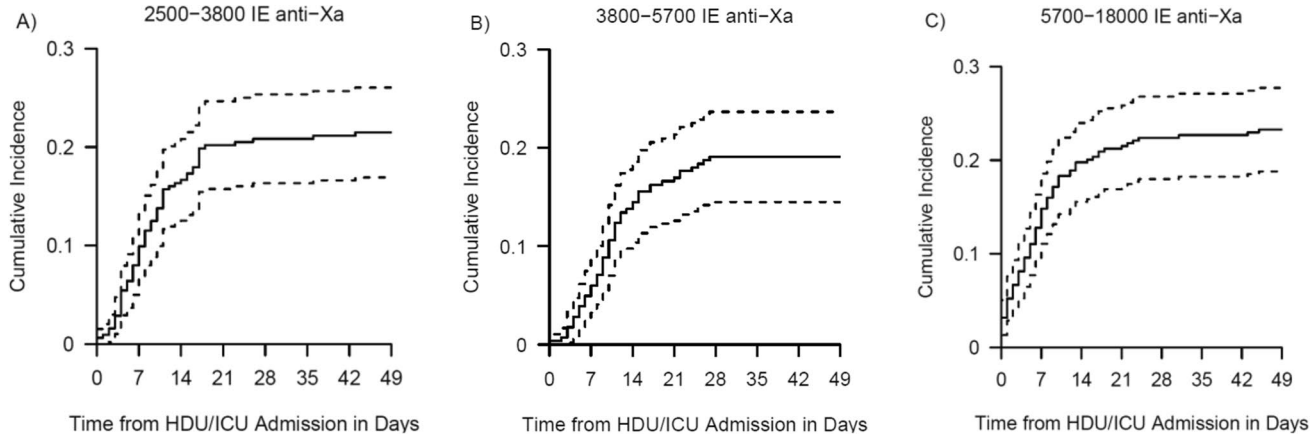

Fig. 3. Cumulative incidence for PE. Cumulative incidence for PE in a competing risk analysis adjusted for the competing risk of in-hospital mortality and transfer to another hospital for the tertiles of LMWH dose (panels **A**–**C**). To account for the competing risk of hospital discharge, end of follow-up of discharged patients was censored at the date of observing the last event in the data (13 July 2020, > 49 days).

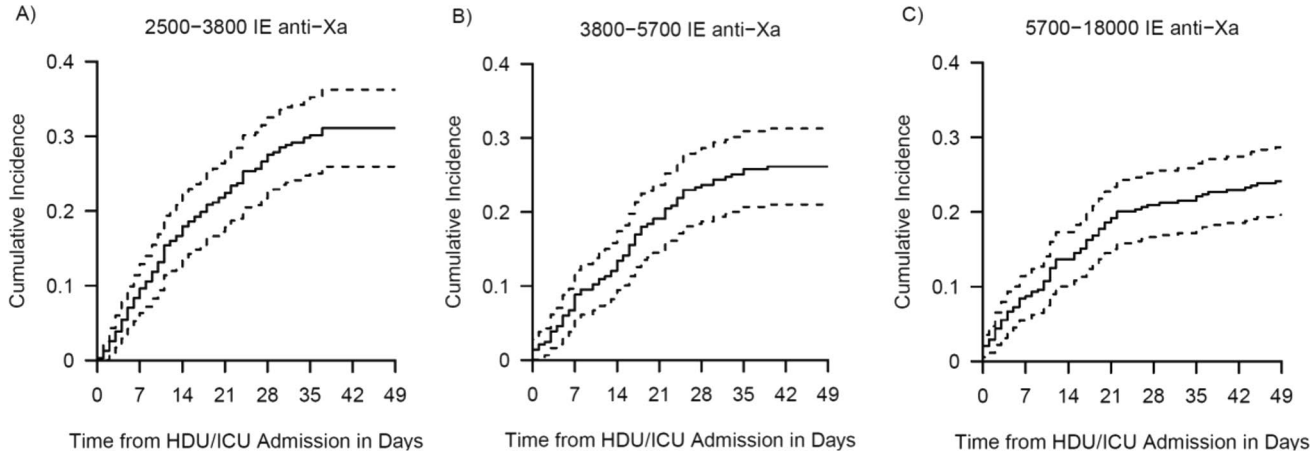

Fig. 4. Cumulative incidence for in-hospital mortality. Cumulative incidence for in-hospital mortality in a competing risk analysis adjusted for the competing risk of transfer to another hospital for the tertiles of LMWH dose (panels **A**-**C**). To account for the competing risk of hospital discharge, end of follow-up of discharged patients was censored at the date of observing the last event in the data (13 July 2020, > 49 days).

Sensitivity analysis

Converting nadroparin levels to dalteparin levels did not quantitatively change the main analysis results [Online Resource 3]. The six patients (1%), who were exposed to a protocolised LMWH dose of 18,000 IE anti-Xa [Online Resource 2], were removed from the analysis to check the sensitivity of the results to the high LMWH dose. Removing these patients did not quantitatively change the main analysis results [Online Resource 3]. In a multivariable Cox model, the covariates sex, dyslipidaemia and baseline blood pressure were added. This addition did not quantitatively change the results for the endpoint pulmonary embolism [Online Research 3]. For the endpoint in-hospital mortality, the cause-specific HR increased to 0.98 (95% CI 0.74–1.29).

Discussion

In our study of Dutch critically ill COVID-19 patients during the first wave of the pandemic, utilizing differences between thromboprophylaxis protocols across hospitals in an instrumental variable analysis, we found no evidence for an effect of increasing LMWH dose on pulmonary embolism (PE) risk. However, our results suggest a non-linear decreased risk of in-hospital mortality for higher doses of LMWH, but uncertainty remains.

Our results are in line with the trial COVID-PACT[17], evaluating the effect of therapeutic dose vs standard dose prophylaxis in critically ill COVID-19 patients. In their intention-to-treat analysis, a slightly larger all cause-mortality was observed in the standard prophylaxis group (32.1%) compared to the therapeutic prophylaxis group (27.9%), with a hazard ratio of 0.80 (0.56, 1.16). Similarly, the all-cause mortality we found was lower in the higher dose group with 25.0% in the high dose category, 26.5% in the middle dose category and 31.7% in the low dose category. Our results are in disagreement with the INSPIRATION trial, which compared intermediate

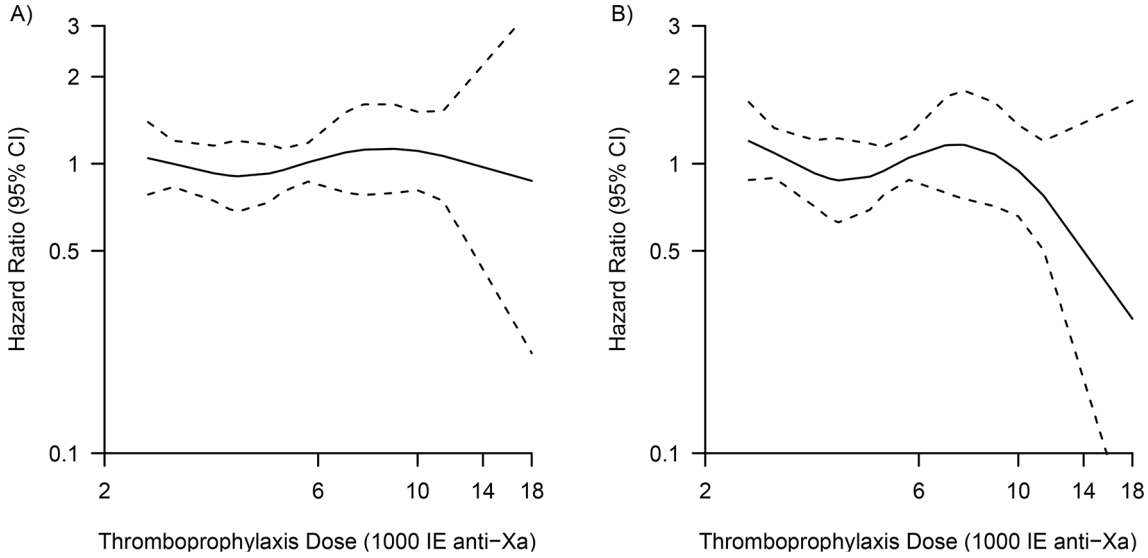

Fig. 5. Relationship between protocolised LMWH dose and PE. Relationship between protocolised LMWH dose and PE analysed with a restricted cubic spline with 4 knots in a cause-specific Cox proportional hazard model. The knots were placed at 2,850, 3,971, 5,700 and 11,400 IE anti-Xa. (**A**) Crude model; (**B**) model adjusted for calendar time (days between 27 February 2020 and HDU/ICU admission), age, hospital transfer and weight. To account for the competing risk of hospital discharge, end of follow-up of discharged patients was censored at the date of observing the last event in the data (13 July 2020, > 49 days).

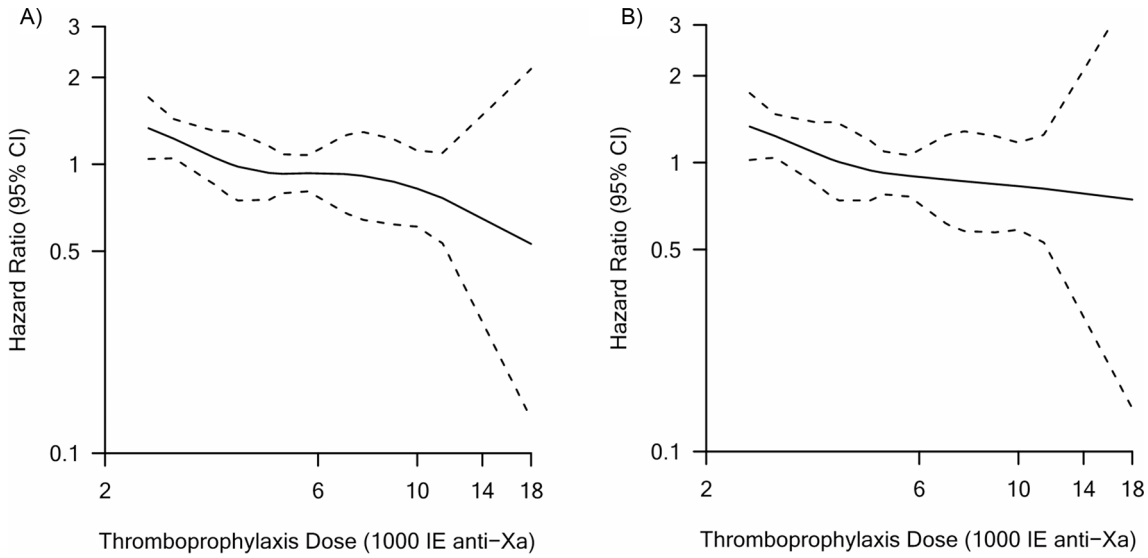

Fig. 6. Relationship between protocolised LMWH dose and in-hospital mortality. Relationship between protocolised LMWH dose and in-hospital mortality analysed with a cubic restricted spline with 4 knots in a cause-specific Cox proportional hazard model. The knots were placed at 2,850, 3,971, 5,700 and 11,400 IE anti-Xa. (**A**) Crude model; (**B**) model adjusted for calendar time (days between 27 February 2020), age, hospital transfer and weight. To account for the competing risk of hospital discharge, end of follow-up of discharged patients was censored at the date of observing the last event in the data (13 July 2020, > 49 days).

dose with low dose LMWH in critically ill COVID-19 patients. The INSPIRATION trial's secondary outcome of all-cause mortality was slightly higher in the intermediate dose group (43.1%) compared to 40.9% in the standard dose group, with an absolute risk difference of 2.2% (95% CI – 5.9–10.3%)[13]. In the other trial evaluating intermediate vs standard thromboprophylaxis[15], the primary outcome of all-cause mortality was higher in the standard dose (21%) compared to the intermediate dose (15%) with an odds ratio of 0.66 (0.30–1.45). Of note, the trial design was based on an expected mortality of up to 40%, while assuming the risk would be reduced to 20% in the intermediate group.

A direct comparison between our results and the results of most RCTs evaluating therapeutic to standard thromboprophylaxis is hampered by the definition of the control arm. In the combined trial of the REMAP-CAP, ACTIV-4a and ATTACC, patients randomised to the control arm received 'usual care thromboprophylaxis', which consisted of a low dose in 40.4%, an intermediate dose in 51.7% and a (sub) therapeutic dose in 7.9% of included patients[12]. In the HEP-COVID trial, which included patients based on high-risk features (D-dimer level > 4 times the upper limit of normal (ULN) or sepsis-induced coagulopathy score > 4), the control group also consisted of a combination of low dose (61.3% of included patients) and intermediate dose (38.7% of included patients)[16]. In the Swiss COVID-HEP trial[14], severe patients, with either D-dimer level > 4 times the ULN or an ICU admission, received either low or intermediate-dose in the control arm depending on the ICU status before randomization. The results of these trials do not allow to conclude on mutual differences between standard, intermediate and therapeutic thromboprophylaxis on hospital survival, even though the all-cause mortality was slightly larger in the therapeutic group (19.4%) compared to standard group (25.0%) in the HEP-COVID trial, with a relative risk of 0.78 (95% CI 0.49–1.23)[12,14,16]. However, the heterogeneity of the control arm might have affected the trials' results, e.g. the intermediate dose prophylaxis may have diluted the effect of therapeutic thromboprophylaxis[30]. Besides, the HEP-COVID and the COVID-HEP trials were not powered to test for the superiority of all-cause mortality[14,16].

Our analysis provides important insights into the effect of escalated thromboprophylaxis on the risk of PE and mortality in admitted ICU COVID-19 patients. It is one of the first studies that investigates the relationship between LMWH and PE risk and in-hospital mortality in COVID-19 patients. RCTs performed on this topic generally compare a therapeutic dose with a control group containing one other (e.g. intermediate or standard) or a mixture of several dosages (e.g. usual care)[12–17]. This approach leads to estimating the relative effect of therapeutic doses, but makes it impossible to compare e.g., intermediate dose to low dose or, in case of a mixture of several dosages, the effect of therapeutic dose vs low dose may be diluted with intermediate dose[30]. In contrast, our approach makes it possible to investigate the dose–response effect of LMWH. A higher dose of thromboprophylaxis may prevent (micro)thrombi but at the same time increase risk of bleeding, suggesting a trade-off between standard and higher dosed thromboprophylaxis. This trade-off is also suggested by our investigations of the dose–response relationship between LMWH dose and in-hospital mortality, adding insights into the potential mechanism of escalated LMWH prophylaxis in ICU COVID-19 patients.

The most important strength of our study is that we made use of a unique setting that caused variation in protocolised LMWH doses as thromboprophylaxis in hospitals in the Netherlands in early 2020. At that time, the efficacy of the different thromboprophylaxis strategies on patient prognosis was unknown. This led to random assignment of strategies across Dutch hospitals based on local physicians' preferences. This setting allowed us to use protocolised LMWH dose as an instrument and, thereby, evaluate the effect of escalated thromboprophylaxis on the risk of PE and in-hospital mortality. This estimated effect is similar to an intention-to-treat effect, which is often a conservative estimate of the true effect. This way, we were able to include a less selected study population and control for confounding, as actual received LMWH dose may be confounded by severity, whereas protocolised LMWH is not[20]. As a result, our study is more applicable to day-to-day care and has increased relevance and external generalizability outside of a trial setting.

Our study has some limitations that should be considered when interpreting the results. One major limitation is that we were unable to verify protocol compliance due to the lack of information on the actual received LMWH. However, the compliance rates observed in the two academic hospitals were 78% and 63%, which were similar to those reported in the INSPIRATION trial for both standard (70%) and intermediate-dose LMWH (76%)[13]. Protocol deviations occurred in cases of indication of therapeutic anticoagulation, renal replacement therapy or ECMO. The compliance is expected to be higher in non-academic and smaller hospitals that do not use ECMO or renal replacement therapy. Furthermore, these deviations have likely happened irrespective of the protocolised LMWH and, therefore, will only affect absolute risks.

The second limitation is the inability to check for balance of clinical characteristics at HDU/ICU admission due to unavailability of such data in the CAPACITY database. However, clinical characteristics at hospital admission were comparable across the different dosing groups. To prevent the groups from becoming too small, we grouped them into three categories of equal size, even though intensity might be more clinically relevant. Similarly, analysing the protocolised dose as a continuous log transformed variable is less clinically relevant but was necessary to account for the skewness of the protocolised LMWH dose.

The third limitation is that we assumed there were no significant differences in non-anticoagulant treatment policies across hospitals. We checked this assumption for (hydroxy)chloroquine, which was shown unbalanced. Yet, (hydroxy)chloroquine is not expected to have affected PE risk or in-hospital mortality. This assumption has not been evaluated for other treatment options such as dexamethasone and antiviral and immunosuppressive drugs, but is regarded as reasonable. At the time, these treatments were not routinely applied[26]. Moreover, any effect of these different treatment policies on thromboprophylaxis dosing or risk of thrombosis is unknown[28].

A fourth limitation is that misclassification in PE diagnosis may have occurred. The differences in PE diagnoses over time caused by increased awareness have been accounted for by adjusting our analysis for calendar time. Nonetheless, hospitals might differ in the protocol for testing for PE. Moreover, patients may not have been tested when there was no clinical consequence. Depending on whether the misclassification in PE was dependent on the thromboprophylaxis protocol or not, the misclassification error could have attenuated or amplified the estimated effect[20].

Finally, although our study's setting may increase its external generalisability compared to RCTs, it is uncertain whether our results can be translated to other ICU populations, waves and different SARS-CoV-2 variants as we only included Dutch ICU patients from the first pandemic wave. In the first wave, the variations of the protocolised dose were most pronounced compared to other waves, resulting in a better instrument. However, differences between initial wave and subsequent waves do exist. For instance, during the initial wave, Dutch ICU

patients were younger and had fewer comorbidities than before the pandemic and subsequent waves[31,32], which may affect PE risk and in-hospital mortality. Moreover, current improved treatment, such as dexamethasone, anti-viral and immunosuppressive drugs, the decreased virulence of the different SARS-CoV-2 variants and the availability of COVID-19 vaccines have increased the overall survival of COVID-19 patients[28,33,34]. It is unknown whether these new treatment modalities and vaccine availability affect the observed dose–response relationship between LMWH and in-hospital mortality. Additionally, including only Dutch patients may have limited the generalisability of our results as significant differences have been observed between Dutch, German and Belgian ICU patients regarding comorbidities, disease severity, ICU duration, treatment and mortality[35]. Diagnostic strategies on thrombotic events especially differed between the different regions; in Belgian patients, leg ultrasound was more frequently used and in the Dutch patients, CT pulmonary angiography[35]. Therefore, it could be that PE was more often diagnosed in the Netherlands than in other countries, affecting absolute risks of PE. Finally, only a small number of patients in our data were exposed to a protocolised therapeutic dose of LMWH. While the results of our analysis were not affected by the removal of these six patients, extrapolation of our results to therapeutic dose anticoagulation is uncertain.

In conclusion, our study did not find evidence for an effect of LMWH dose on the risk of PE. Nonetheless, our findings were suggestive for a potential reduction in the risk of in-hospital mortality with higher dose of LMWH as thromboprophylaxis, and for a non-linear relationship between LMWH dose and in-hospital mortality. Further investigation on the dose–response relationship between thromboprophylaxis and in-hospital mortality is necessary, and well-designed studies are needed to explore this relationship in more depth.

Ethics approval

This study complies with the Declaration of Helsinki. This study is not subject of the Dutch Medical Research Involving Human Subjects Act (WMO). Our research received a non-waiver and ethical approval from the ethics committee of the University Medical Centre Utrecht (MREC), as it only uses data from routine care and participants are not subjected to procedures or rules of behavior. Medical ethical approval was obtained for each participating site. During the COVID-19 pandemic, the Dutch National Organization of Academic Hospitals (NFU) and the Committee on Regulation of Health Research (COREON) issued a statement (in Dutch) stating that an opt-out procedure would suffice for COVID-19 research not subjected to the WMO. We followed this guidance and implemented an opt-out procedure. Additionally, we obtained informed consent where necessary, depending on the local procedures at the participating hospitals.

Data availability

Data are unsuitable for public deposition due to ethical restrictions and legal framework of the Netherlands. The data can be made available upon request to the authors with permission of the CAPACITY-COVID collaborative consortium. All inquiries about access to data can be sent to dctc@erasmusmc.nl.

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Author contributions

Linda Nab, Saskia le Cessie and Suzanne C. Cannegieter designed the study protocol. The data was provided and collected by Marijke Linschoten, Folkert W. Asselbergs, Chantal Visser and the Dutch COVID and Thrombosis Coalition & the CAPACITY-COVID collaborative consortium. Linda Nab analyzed the data and created the models. Linda Nab and Chantal Visser wrote the manuscript. All authors reviewed, provided feedback on drafts, and approved the final manuscript for submission.

Competing interests

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Additional information

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