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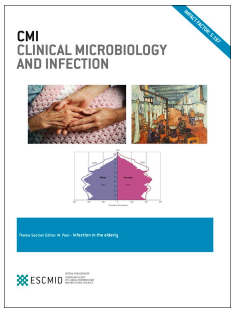

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RESEARCH NOTE

Prophylactic anticoagulation with low molecular weight heparin in COVID-19: cohort studies in Denmark and Sweden

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Abstract

Objectives. To evaluate safety and effectiveness of prophylactic anticoagulation with low molecular weight heparin (LMWH) in individuals hospitalised for COVID-19.

Methods. Using healthcare records from the capital region of Denmark (March 2020-February 2021) and Karolinska University Hospital in Sweden (February 2020-September 2021), we conducted an observational cohort study comparing clinical outcomes 30 days after admission among individuals hospitalised for COVID-19 starting prophylactic LMWH during the first 48 hours of hospitalisation with outcomes among those not receiving prophylactic anticoagulation. We used inverse probability weighting to adjust for confounders and bias due to missing information. Risk ratios, risk differences and robust 95% confidence intervals (CI) were estimated using binomial regression. Country-specific risk ratios were pooled using random-effects meta-analysis.

Results. We included 1692 and 1868 individuals in the Danish and Swedish cohorts. Of these, 771 (46%) and 1167 (62%) received prophylactic LMWH up to 48 hours after admission. The combined mortality in Denmark and Sweden was 12% (N=432) and the pooled risk ratio was 0.89 (CI 0.61-1.29) comparing individuals who received LMWH to those who did not. The relative risk of ICU admission was 1.12 (CI 0.85-1.48), while we observed no increased risk of bleeding (RR 0.60, 0.14-2.59). The relative risk of venous thromboembolism was 0.68 (CI: 0.33-1.38) in Sweden. Less than 5 VTE events were observed among individuals receiving LMWH in Denmark, preventing a meaningful analysis.

Conclusion. We found no benefit on mortality with prophylactic LMWH and no increased risk of bleeding among COVID-19 patients receiving prophylactic LMWH.

Introduction

High rates of venous thromboembolism (VTE) were initially reported in individuals hospitalised for coronavirus disease 2019 (COVID-19) [1] and guidelines for prophylactic anticoagulation in COVID-19 were quickly established [2,3]. Newer and population-based studies, however, reported lower rates of VTE [4]. Randomized trials on prophylactic anticoagulation in COVID-19 are ongoing [5], with available results suggesting no benefit on mortality when comparing intermediate- to full dose anticoagulation in critically ill patients [6,7]. While full-dose anticoagulation may be superior to prophylactic dose in non-critically ill patients [8,9], conflicting results have been reported [10]. An observational study comparing prophylactic anticoagulation to no anticoagulation also indicated a beneficial effect on mortality [11]. We aimed to provide additional evidence by analysing clinical outcomes among COVID-19 patients receiving prophylactic low-molecular weight heparin (LMWH) compared to individuals receiving no anticoagulation.

Methods

We conducted a cohort study using the electronic health records systems from the Capital Region of Denmark and from Karolinska University Hospital, an academic two-site tertiary hospital with 1100 beds, in the Stockholm region in Sweden. Patients were included until 06 February 2021 in Denmark and 31 August 2021 in Sweden. We included all individuals with a positive reverse transcriptase polymerase chain reaction test (RT-PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between 14 days before and 24 hours after admission for COVID-19. Individuals were excluded if they were

below 18 years of age, were current users of anticoagulants, had major bleeding during the previous year, were hospitalised for less than 24 hours, or if they within 48 hours of hospitalisation experienced an outcome of interest or received multiple types of anticoagulation. Individuals were classified as receiving prophylactic LMWH (<=5000 IU dalteparin, 4500 IU tinzaparin or 40 mg enoxaparin) or not during the first 48 hours of hospitalisation. In the main analysis, individuals were followed from 48 hours until 30 days after admission, regardless of changes in exposure status (**web-only supplementary figure S1**). Outcomes were death, intensive care unit admission, receiving a discharge diagnosis of VTE and bleeding. For covariate adjustment, we obtained information on selected hospital diagnoses during the 10 years prior to admission, prescription drug use during the prior year, clinical measurements, and results of blood tests at admission (**supplementary table S1)**.

Statistical analyses

Bias due to missing information was handled by inverse probability (IP) weighting of complete cases [12], while measured confounders were adjusted for by IP of treatment weighting [13] (**table S2)**. Covariate balance was assessed using standardised mean differences [14]. IP-weights greater than 4 were truncated. Using binomial regression, we obtained crude and IP-weighted risk differences (RD) and -ratios (RR), with robust 95% confidence intervals, comparing individuals who received LMWH in prophylactic doses to individuals not receiving anticoagulation. Country-specific RRs were pooled using a random effects meta-analysis model.

In sensitivity analyses, we (i) shortened the exposure assessment window to 24 hours, (ii) adjusted for body mass index (omitted from the main analysis due to a high prevalence of missing information in Sweden), (iii) restricted inclusion in Sweden to February 2021 (matching data availability in Denmark), (iv) considered initiation of therapeutic dose LMWH an outcome as a proxy for VTE, and (v) obtained risk estimates among patients who received in-hospital corticosteroid treatment. Statistical analyses were performed using R. The source code is available from https://gitlab.sdu.dk/lclund/lmwh-covid19/.

Ethics

The study was approved by the Danish Patient Safety Authority and the Danish Data Protection Agency. Ethics committee approval and informed consent were not required by Danish law. In Sweden, the study was approved by the Regional Ethical Review Board in Stockholm.

Results

We identified 3483 individuals hospitalised for COVID-19 in Denmark and 3919 individuals in Sweden, of whom 1692 (49%) and 1868 (48%) were included in the final study cohorts (**figure S2**). The median age was 72 and 58 years in the Danish and Swedish cohort. Overall, 1938 individuals (54%) received prophylactic LMWH and 1622 individuals (46%) received no anticoagulation. The proportion of individuals who received prophylactic LMWH in Denmark increased from <10% in March 2020 to about 60% and in Sweden over 80% at the end of the study period (**figure S3**). Individuals receiving

prophylactic LMWH more often received oxygen therapy and in-hospital glucocorticoid treatment for COVID-19 (**table 1**). Individuals with missing information were generally younger, more often female, and more healthy than complete cases (**table S3**). After IP-weighting, the abovementioned characteristics were balanced, except for a slight imbalance in in-hospital corticosteroid treatment (**figure S4**, **table S4**). In the combined population, we observed 432 deaths within 30 days of hospitalisation for COVID-19 (mortality: 12%) and 60 patients had a discharge diagnosis of VTE (1.7%) (**table S5**). We observed 211 deaths (risk 11%) among individuals who received prophylactic LMWH compared to 221 deaths among those who did not (14%; pooled IP-weighted risk ratio [RR] 0.89, 95% CI 0.61-1.29). The relative risk of being admitted to the ICU was 1.12 (0.85-1.48). In the Swedish cohort, the risk of receiving a VTE diagnosis was non-significantly lowered among individuals who received prophylactic LMWH (RR 0.68, 0.33-1.38). We observed too few VTE diagnoses among individuals receiving LMWH in the Danish cohort (n<5) to obtain stable risk estimates. Finally, we observed no increased risk of receiving a discharge diagnosis related to bleeding (RR 0.60, 0.14-2.59) (**figure 1**).

In sensitivity analyses, we observed comparable risk estimates when shortening the exposure assessment window to 24 hours, restricting the inclusion period in Sweden, when adjusting for body mass index or stratifying on in-hospital corticosteroid treatment (**table S6**). In accordance with the other outcomes, the RR for initiating therapeutic LMWH was not increased ($RR_{Denmark}$ 0.99, 0.63-1.57; RR_{Sweden} 1.52, 0.87-2.67).

Discussion

We report no beneficial effect on mortality and the risk of ICU admission with use of LMWH thromboprophylaxis in patients admitted for COVID-19. The risk of receiving a VTE diagnosis was lower when receiving LMWH, albeit with imprecise risk estimates, and the risk of bleeding was not increased.

The main strength of our study is the ability to include rich information on clinical and biochemical measurements using electronic health records based data sources from multiple hospitals, spanning two countries. The major limitation of our study is its non-randomised nature. Even though Danish and Swedish guidelines recommend prophylactic anticoagulation for almost all patients admitted for COVID-19, physicians target treatment to patients at particular risk of VTE. This introduces confounding, as the higher risk patients will be treated, while the lower risk patients remain untreated. Although this potential bias was addressed in our statistical analysis, we cannot rule out some residual confounding, e.g., by suboptimal model specification and measurement of covariates. Finally, we included as reference not only individuals not receiving anticoagulation, but also late initiators (>48 hours post-admission). We made this choice, as censoring unexposed individuals upon initiation of LMWH would introduce informative censoring, as late initiation may be a sign of adverse clinical outcomes.

The finding that prophylactic anticoagulation with LMWH thromboprophylaxis does not reduce mortality is not in alignment with results from a similar observational study [11]. This could be attributed to lower statistical precision or residual confounding in our study but may also be related to the different populations and baseline risk of VTE. Comparison of our risk estimates with the published randomised controlled trials conducted in non-

critically ill patients is difficult, as these lacked a comparison group not receiving anticoagulants. One of the three trials in non-critically ill patients reported null-findings in accordance with our results [10].

Conclusion

In these cohort studies, we found no beneficial effect of prophylactic LMWH on mortality or the risk of ICU admission in patients hospitalised for COVID-19. The risk of VTE was reduced among individuals receiving prophylactic anticoagulation, albeit with low statistical precision, while patients receiving prophylactic anticoagulation were not at an increased risk of bleeding events.

Author contributions

Conceptualization: LCL and JH.

Methodology: All authors.

Data curation: AHA, PH

Software: AHA, PH, LCL

Formal analysis: PH, LCL

Resources: JP, EJS, JH

Writing – original draft: LCL, JH

Writing – Review & Editing: All authors.

Conflicts of interest

LCL reports participation in research projects funded by Menarini Pharmaceuticals and LEO Pharma, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the current work. AP reports participation in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma, all regulator-mandated phase IV-studies, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this paper. JP and EJS report participation in research projects funded by Eli Lilly, Johnson & Johnson, Amgen AB, Novartis and Vertex Pharmaceuticals all with funds paid to the institution where she/he was employed (no personal fees) and with no relation to the current work. TSP reports participation in research projects funded by Amgen AB with funds paid to the institution where he was employed (no personal fees) and with no relation to the current work. AHA, JH, JB, PN, PH report no conflicts of interest.

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Table 1. Baseline characteristics of individuals receiving prophylactic LMWH and those not receiving prophylactic anticoagulation for the capital regions of Denmark and Sweden

	Denmark			Sweden		
	Prophylactic LMWH (N=771)	**No anticoagulation** (N=921)	**Miss-ing**	**Prophylactic LMWH** (N=1167)	**No anticoagulation** (N=701)	**Miss-ing**
Demographics						
Age, median [IQR]	72.00 [59.00, 82.00]	72.00 [56.00, 81.00]	-	60.00 [47.00, 73.00]	55.00 [36.00, 70.00]	-
Male sex	412 (53)	465 (50)	-	658 (56)	349 (50)	-
Time period			-			-
Before June 2020	94 (12)	525 (57)		414 (36)	363 (52)	
June to October 2020	119 (15)	74 (8)		122 (11)	94 (13)	
November 2020 to February 2021	558 (72)	322 (35)		383 (33)	149 (21)	
March to June 2021	-	-		216 (19)	90 (13)	
July 2021 to August 2021	-	-		32 (3)	5 (1)	
Clinical measurements						
Body mass index			16			50
<18.5	34 (5)	31 (4)		22 (4)	8 (3)	
18.5-24	230 (34)	256 (35)		203 (33)	133 (41)	
25-34	343 (51)	398 (54)		366 (59)	163 (51)	
35+	69 (10)	56 (8)		30 (5)	17 (5)	
Smoking history			29			100
Ex-smoker	287 (53)	299 (45)		-	-	
Current smoker	55 (10)	70 (10)		-	-	
Body temperature, C			<1			9
37.5-38.4	219 (28)	266 (29)		353 (31)	165 (29)	
38.5+	194 (25)	192 (21)		358 (32)	115 (20)	
Respiratory frequency/min > 22	305 (40)	280 (31)	<1	527 (47)	215 (38)	9
Systolic blood pressure < 100 mmHg	26 (3)	42 (5)	<1	41 (4)	22 (4)	9
Reduced peripheral oxygen saturation, %			7			16

<88	40 (5)	15 (2)		55 (5)	27 (5)	
88-92	122 (17)	100 (12)		199 (19)	65 (13)	
Oxygen therapy, l/min			3			11
1-4	280 (37)	200 (23)		437 (39)	139 (25)	
5+	76 (10)	51 (6)		102 (9)	32 (6)	
Biochemical measurements						
Estimated GFR l/min/1.73m2			3			10
30-59	101 (13)	119 (13)		192 (17)	115 (20)	
15-29	37 (5)	36 (4)		51 (5)	35 (6)	
<15	11 (1)	8 (1)		21 (2)	8 (1)	
Haemoglobin below reference	289 (38)	335 (37)	2	333 (30)	186 (32)	9
Leukocyte levels			3			8
Below reference	183 (24)	226 (25)		81 (7)	51 (9)	
Above reference	49 (6)	52 (6)		214 (19)	174 (29)	
Thrombocyte levels			3			9
Below reference	100 (13)	130 (15)		175 (16)	93 (16)	
Above reference	76 (10)	84 (10)		54 (5)	22 (4)	
Elevated D-dimer*	355 (66)	323 (67)	40	705 (72)	234 (70)	30
Prescription drug use prior to hospitalisation						
Platelet inhibitors	193 (25)	226 (25)	-	125 (11)	71 (10)	-
Antihypertensives	346 (45)	400 (43)	-	312 (27)	175 (25)	-
Loop diuretics	115 (15)	116 (13)	-	89 (8)	69 (10)	-
Glucose lowering therapy	176 (23)	171 (19)	-	206 (18)	111 (16)	-
Lipid lowering therapy	235 (30)	273 (30)	-	189 (16)	84 (12)	-
Glucocorticoids	191 (25)	91 (10)	-	277 (24)	122 (17)	-
In-hospital dexa-/betamethasone treatment	505 (65)	158 (17)	-	381 (33)	108 (15)	-
Medical history						
VTE	6 (1)	11 (1)	-	-	-	-
Atrial fibrillation	15 (2)	31 (3)	-	12 (1)	15 (2)	-
Heart valve disease	34 (4)	39 (4)	-	15 (1)	16 (2)	-
Cardiovascular disease	188 (24)	204 (22)	-	165 (14)	95 (14)	-

Heart failure	57 (7)	55 (6)	-	56 (5)	38 (5)	-
Ischaemic stroke	58 (8)	66 (7)	-	28 (2)	21 (3)	-
Current cancer	76 (10)	81 (9)	-	90 (8)	73 (10)	-
Pulmonary disease	172 (22)	185 (20)	-	140 (12)	71 (10)	-
Liver disease	15 (2)	20 (2)	-	39 (3)	27 (4)	-

LMWH: Low molecular weight heparin; GFR: Glomerular filtration rate; VTE: Venous thromboembolism

*Age-specific cut-offs between 0.5 and 0.8 FEU/l

Figure 1. Inverse probability weighted number of events, risks and risk estimates for effectiveness and safety outcomes in Denmark, Sweden and combined.

LMWH: Low molecular weight heparin; Ref.: Reference cohort not receiving anticoagulation; RR: Risk ratio; RD: Risk difference; ICU: Intensive care unit; VTE: Venous thromboembolism

Capital region of Denmark, Stockholm region of Sweden

		Risk, % (Events)		Comparison		
Outcome		LMWH (N=696/1258)	Ref. (N=823/549)	RR (95% CI)	RD (95% CI)	Pooled RR (95% CI)
Mortality		16 (112)	21 (173)	0.76 (0.58, 1.01)	-5.0 (-10, 0.2)	0.89 (0.61, 1.29)
		7.1 (89)	6.4 (35)	1.12 (0.72, 1.74)	+0.7 (-2.2, 3.7)	
ICU admission		8.0 (56)	7.2 (59)	1.13 (0.70, 1.84)	+0.9 (-2.8, 4.7)	1.12 (0.85, 1.48)
		3.8 (48)	3.5 (19)	1.11 (0.57, 2.13)	+0.4 (-1.9, 2.7)	
VTE diagnosis		n<5	0.7 (6)	NR	NR	-
		2.6 (33)	4.0 (22)	0.68 (0.33, 1.38)	-1.3 (-3.8, 1.3)	
Bleeding		1.0 (7)	0.6 (5)	1.53 (0.32, 7.39)	+0.3 (-1.0, 1.7)	0.60 (0.14, 2.59)
		1.8 (23)	5.6 (31)	0.33 (0.17, 0.63)	-3.8 (-6.6, -0.9)