

# Efficacy and Safety of D-dimer, Weight, and Renal Function-Adjusted Thromboprophylaxis in Patients with Coronavirus Disease 2019 (COVID-19)

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The activation of inflammatory and coagulation pathways, leading to hypercoagulability with reduced fibrinolysis, has emerged as pivotal mechanism in development of acute respiratory failure and thrombosis in patients with severe coronavirus disease 2019 (COVID-19).<sup>1</sup> Although thrombosis is a major complication in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the optimal thromboprophylaxis regimen in these patients is unknown. High rates of thrombosis, especially in those admitted to intensive care, are usually reported despite standard or even intensified thromboprophylaxis with low molecular weight heparin (LMWH). The uncertainty has been reflected in the diverse recommendations in local, national, and international guidelines.<sup>2–4</sup> Early studies reported that elevated D-dimer values were associated with magnified risk of thrombosis,<sup>5</sup> and this has been confirmed in subsequent studies,<sup>6</sup> even in those in which the thrombosis rate was found to be low.<sup>7</sup> D-dimer has also been a reliable predictor of a poor outcome, and although it is not established that these two observations are linked, large and small vessel thrombosis is

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prominent in the pulmonary circulation both ante- and post-mortem.<sup>8</sup> The prominence of large and small vessel thrombosis in the pathophysiology of COVID-19 and its high frequency despite standard or sometimes increased intensity LMWH suggests that intensified prophylaxis may be beneficial. However, any benefit from this approach would need to be balanced against a possible increase in bleeding complications. The use of intensified versus standard dose LMWH is being investigated in several clinical trials, although only recently initiated in the United Kingdom. Pending the results of such studies, individual National Health Service (NHS) Trusts have developed local thromboprophylaxis guidelines for COVID-19.

This retrospective study assesses the safety and efficacy of D-dimer-, weight-, and renal function-adjusted thromboprophylaxis in patients admitted to a major tertiary NHS Trust in London, U.K. We hypothesized that body mass, renal function, and D-dimer may be important determinants in patients with COVID-19 who may benefit from increased heparin dosage.

The study was undertaken as a service evaluation project, approved by Imperial College Healthcare NHS Trust Clinical Effectiveness Unit and consent was not required. ► **Table 1** summarizes the recommended thromboprophylaxis regimen.

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**Table 1** Weight-, D-dimer-, and renal function-adjusted thromboprophylaxis for patients with COVID-19 admitted to hospitals as per local National Health Service

D-dimer (ng/mL) FEU	Weight	LMWH CrCl > 30 mL/min	LMWH CrCl 20–30 mL/min	UFH CrCl < 20 mL/min
< 1000	< 50 kg	Enoxaparin 20 mg OD	Enoxaparin 20 mg OD	2,500 units BD
	50–100 kg	Enoxaparin 40 mg OD	Enoxaparin 20 mg OD	5,000 units BD
	100–150 kg	Enoxaparin 40 mg BD	Enoxaparin 40 mg OD	7,500 units BD
	> 150 kg	Enoxaparin 60 mg BD	Enoxaparin 40 mg OD	10,000 units BD
1,000–3,000	< 50 kg	Enoxaparin 40 mg OD	Enoxaparin 20 mg OD	5,000 units BD
	50–100 kg	Enoxaparin 40 mg BD	Enoxaparin 40 mg OD	7,500 units BD
	100–150 kg	Enoxaparin 80 mg BD	Enoxaparin 40 mg BD	10,000 units BD
	> 150 kg	Enoxaparin 120 mg BD	Enoxaparin 60 mg BD	15,000 units BD
> 3000	< 35 kg	D/W hem	D/W hem	D/W hem
	35–160 kg	Tinzaparin 175 units/kg OD	Tinzaparin 175 units/kg OD	
	> 160 kg	D/W hem	D/W hem	

Abbreviations: BD, twice daily; CrCl, creatinine clearance; D/W hem, discuss with hematologist on call; FEU, fibrinogen equivalent; LMWH, low molecular weight heparin; OD, once daily; UFH, unfractionated heparin.

Thromboprophylaxis as per guidelines was started on admission in all cases and the standard thromboprophylaxis was 40 mg of enoxaparin except in patients with creatinine clearance < 30 mL/min, for whom it was 20 mg of enoxaparin. Data were collected from the electronic records of consecutive patients admitted from April 10 to 23, 2020. Statistical analyses were performed using GraphPad Prism v8.4.2. Results are reported as mean and standard deviation (SD) or median (range) as appropriate. Comparisons for normally distributed or log-transformed data were done using the two-sample independent *t*-test, while Wilcoxon rank-sum test was used for non-normal data. Cox proportional hazards models were used to determine the said predictors first using univariate models and then where possible a multivariable model when the variables in the univariate model were significant at  $p < 0.05$ . Fisher's exact test was used to compare differences between groups where appropriate. A two-sided  $p < 0.05$  was considered statistically significant.

Of the 261 patients admitted with suspected COVID-19 during the study period, this analysis is restricted to the 171

with COVID-19 confirmed by reverse transcription polymerase chain reaction from throat swabs and not on anticoagulant on admission. Mean age was 65 (SD = 16.2) years and 59.6% were male. Out of 171 patients included in this study, 82 patients had computed tomography pulmonary angiography (CTPA), and of these, 21 patients had confirmed pulmonary embolism (PE) making an overall PE rate of 12.3% (21/171) in the study population. Out of the 82 patients who had CTPA, 48 patients had the imaging based on clinical suspicion of PE of which 10/48 (20.8%) had confirmed PE, and 34 patients had CTPA prompted by D-dimer levels > 3,000 ng/mL (normal range < 500 ng/mL fibrinogen equivalent) of which 34/82 patient (32.3%) had confirmed PE. Two patients had deep vein thrombosis (one with PE in the CTPA group) confirmed by Doppler scan, one patient had cerebral infarction confirmed by CT brain, and another had portal vein thrombosis confirmed by CT abdomen. Therefore, the overall venous thrombosis and arterial thrombosis rates were 13.4% (23/171) and 0.6% (1/171), respectively. ► **Table 2** compares first the characteristics of patients who did or did not develop thrombosis. There

**Table 2** Comparison of demographic and clinical features and outcomes of patients with COVID-19 who develop thrombosis versus no thrombosis

Variable	Category	Thrombosis Mean (%) (24/171; %)	No thrombosis Mean (%) (147/171; %)	<i>p</i> -Value
Age (y) (mean [SD])		67.3 (14.7)	65.0 (18.0)	0.66
Gender	Male	16 (66.6)	86 (58.5)	0.50
	Female	8 (33.4)	61 (41.5)	
Body mass index (kg/m <sup>2</sup> ) (mean [SD])		29.37 (7.1)	27.2 (8.2)	0.62
Ethnicity	Arab	2 (8.3)	1 (0.7)	
	Asian/other Asian	2 (8.3)	8 (5.4)	

(Continued)

**Table 2** (Continued)

Variable	Category	Thrombosis Mean (%) (24/171; %)	No thrombosis Mean (%) (147/171; %)	p-Value
	Black	3 (12.5)	19 (12.9)	
	Chinese	0 (0.0)	2 (1.4)	
	Indian	1 (4.2)	11 (7.5)	
	Mixed	0 (0.0)	2 (1.4)	
	Other	8 (33.3)	29 (19.7)	
	White	8 (33.3)	71 (48.3)	
	Unknown	0 (0.0)	4 (2.7)	0.37
Smoking	Current	2 (8.3)	13 (9.0)	
	No	15 (65.4)	72 (49.7)	
	Ex-smoker	5 (19.2)	26 (18.9)	
	Unknown	2 (8.3)	34 (23.5)	0.35
Diabetes mellitus	Yes	6 (25.0)	49 (33.3)	
	No	18 (75.0)	98 (66.7)	0.46
Cardiac history	Yes	5 (20.8)	18 (12.2)	
	No	19 (79.2)	129 (87.8)	0.32
Malignancy – Active or treated in last 6 mo	Yes	3 (12.5)	16 (10.8)	
	No	21 (87.5)	131 (89.2)	0.67
Autoimmune disease	Yes	3 (12.5)	11 (7.4)	
	No	21 (87.5)	136 (92.6)	0.42
Family history of VTE	Yes	4 (16.7)	17 (11.5)	
	No	20(83.3)	130 (88.5)	0.50
Presence of renal or hepatic dysfunction	Yes	4 (16.7)	6 (4.0)	
	No	20 (83.3)	141 (96.0)	<b>0.035</b>
Renal replacement therapy	Yes	4 (16.7)	6 (4.1)	
	No	20 (83.3)	141 (95.9)	<b>0.045</b>
On admission correct dose of enoxaparin was prescribed	Yes	9 (37.5)	101 (68.7)	
	No	15 (62.5)	46 (31.3)	<b>0.005</b>
TEDS prescribed on admission	Yes	2 (8.3)	20 (13.6)	
	No	22 (91.7)	127 (86.4)	0.74
ITU admission	Yes	10 (41.7)	19 (12.9)	
	No	14 (58.3)	128 (87.1)	<b>0.001</b>
Major bleeding	Yes	2 (8.3)	9 (6.1)	
	No	22 (91.7)	138 (93.9)	0.65
Minor bleeding	Yes	4 (16.7)	17 (11.6)	
	No	20 (83.3)	130 (88.4)	0.20
MOF	Yes	4 (15.4)	16 (11.0)	
	No	20 (80.8)	131 (89.0)	0.48
Death	Yes	4 (16.7)	21 (14.3)	
	No	20 (83.3)	126 (85.7)	0.75

Abbreviations: ITU, intensive treatment unit; MOF, multiorgan failure; SD, standard deviation; TEDS, Treatment Episode Data Set; VTE, venous thromboembolism.

Note: Results are reported as mean and standard deviation (SD) or median (range) or number with % as appropriate. p-Values in bold indicate that the difference between the patients with thrombosis vs no thrombosis is significant.

were no differences in the age, sex, and body mass index (BMI) between patients with or without thrombosis. No differences were observed in complete blood cell count, fibrinogen, or activated partial thromboplastin time, or PaO<sub>2</sub>/FiO<sub>2</sub> ratio (Supplementary Table S1) between groups at presentation. A trend toward higher D-dimer levels was noted in patients who developed thrombosis (median [range] 2,500 ng/mL [500–> 20,000] vs. 2,300 [450–19,730],  $p = 0.08$ ). However, mean platelet volume (MPV) (reference range 7.4–11.5 fL) and prothrombin time values (reference range 12.2–17.4 seconds) were significantly higher in thrombosis patients at presentation (11.8 [range 7.4–12.9] vs. 10.1 [range 7.3–11.6] fL,  $p = 0.01$  and 19.3 [range 12.8–24.7] vs. 17.3 [range 12.1–20.1] seconds,  $p = 0.04$ , respectively). Presence of renal or hepatic dysfunction and requirement for renal replacement were significantly higher in patients who developed thrombosis. As previously

reported,<sup>9</sup> patients treated in intensive therapy unit (ITU) had significantly higher rate of thrombosis (10/29, 34.5%), than those treated in general medical wards (14/142, 9.8%),  $p = 0.001$ .

Although weight-, D-dimer-, and renal function-adjusted thromboprophylaxis was recommended, only 110/171 patients were treated according to the guidelines, while all others (61/171) received standard LMWH thromboprophylaxis. The reason for nonadherence was not documented and was most likely attributable to the lack of awareness of recently introduced guidelines. In univariate analysis, no differences were found in age, sex, and laboratory tests (including D-dimer or C-reactive protein) or PaO<sub>2</sub>/FiO<sub>2</sub> ratio at presentation between patients who received intensified versus standard dose of LMWH (► **Table 3**). Therefore, multivariate analysis was not performed.

**Table 3** Comparison of demographic and clinical features and outcomes of patients received who intensified regimen versus standard regimen of LMWH

Variable	Category	Intensified regimen, mean (SD)/N (%) 110/171 (%)	Standard regimen, mean (SD)/N (%) 61/171 (%)	p-Value
Age (y) (mean [SD])		64.40 (13.7)	65.3 (16.0)	0.61
Gender	Male	67 (60.9)	35 (57.4)	
	Female	43 (39.1)	26 (42.6)	0.74
Body mass index (kg/m <sup>2</sup> ) (mean [SD])		28.39 (7.1)	27.9 (7.2)	0.60
Ethnicity	Arab	2 (1.8)	1 (1.6)	
	Asian/other Asian	8 (5.4)	2 (3.3)	
	Black	13 (11.8)	9 (14.8)	
	Chinese	2 (1.8)	0 (0.0)	
	Indian	7 (6.4)	5 (8.2)	
	Mixed	2 (1.8)	0 (0.0)	
	Other	20 (18.2)	17 (27.9)	
	White	53 (48.2)	26 (42.6)	
	Unknown	3 (2.7)	1 (1.6)	0.33
Smoking	Current	11 (10.0)	4 (6.6)	
	No	59 (53.6)	28 (45.9)	
	Ex-smoker	20 (18.2)	13 (21.3)	
	Unknown	20 (18.2)	16 (26.2)	0.32
Diabetes mellitus	Yes	32 (29.1)	23 (37.7)	
	No	78 (70.9)	38 (62.3)	0.30
Cardiac history	Yes	16 (14.6)	7 (11.5)	
	No	94 (85.5)	54 (88.5)	0.64
Malignancy – Active or treated in last 6 mo	Yes	12 (10.9)	5 (8.20)	
	No	98 (89.1)	56 (91.8)	0.79
Autoimmune disease	Yes	8 (12.5)	6 (9.8)	
	No	102 (87.5)	55 (91.2)	0.57
Family history of VTE	Yes	14 (12.7)	7 (11.5)	
	No	96 (87.3)	54 (88.5)	1.00

(Continued)

**Table 3** (Continued)

Variable	Category	Intensified regimen, mean (SD)/N (%) 110/171 (%)	Standard regimen, mean (SD)/N (%) 61/171 (%)	p-Value
Presence of renal or hepatic dysfunction	Yes	7 (6.4)	3 (4.9)	
	No	103 (93.6)	58 (95.1)	1.00
Renal replacement therapy	Yes	6 (5.5)	4 (6.6)	
	No	104 (94.6)	57 (93.4)	0.74
ITU admission	Yes	13 (11.8)	16 (28.1)	
	No	97 (88.2)	41 (71.9)	<b>0.016</b>
Major bleeding	Yes	8 (7.3)	3 (5.0)	
	No	102 (92.7)	57 (95.0)	0.74
Minor bleeding	Yes	15 (13.6)	6 (9.8)	
	No	95 (86.4)	55 (90.6)	0.62
MOF	Yes	9 (8.2)	11 (17.7)	
	No	101 (91.8)	50 (82.3)	0.082
Length of stay in hospital (median and range) d		8 (4–36) d	9 (3–39) d	0.51
Thrombosis	Yes	9 (8.2)	15 (24.6)	
	No	101 (91.8)	46 (75.4)	<b>0.005</b>
Death	Yes	12 (10.9)	13 (21.3)	
	No	98 (89.1)	51 (78.7)	0.074

Abbreviations: ITU, intensive treatment unit; LMWH, low molecular weight heparin; MOF, multiorgan failure; SD, standard deviation; VTE, venous thromboembolism.

Note: Results are reported as mean and standard deviation (SD) or median (range) or number with % as appropriate.

p-Values in bold indicate that the difference between the two groups is significant.

As hypothesized, a significantly higher proportion of patients who received standard thromboprophylaxis had CTPA (43/61) compared with those who received intensified thromboprophylaxis (39/110),  $p < 0.0001$ , but there was no difference in the proportion of patients with PE who had CTPA in the two groups (8/39, 20.5% vs. 13/43, 30.2%),  $p = 0.44$ . This indicates a lack of bias resulting from physician knowledge of the thromboprophylaxis regimen. Those who received the recommended adjusted dose of LMWH had significantly lower rate of thrombosis (9/110, 8.2%) compared with those receiving standard thromboprophylaxis (15/61, 24.6%),  $p = 0.005$ . The number of patients admitted to ITU was significantly lower in patients receiving adjusted dose LMWH (13/100, 11.8%) compared with standard dose (16/61, 28.07%,  $p = 0.01$ ). Transfer to ITU was only after several days for both patients receiving intensified thromboprophylaxis (6 days [range 4–12]) and those receiving standard thromboprophylaxis (7 days [range 4–13]). These are not significantly different:  $p = 0.52$ . Although the differences in multiorgan failure (MOF) and mortality between groups were not significant ( $p = 0.08$  and  $0.07$ ), the trends were toward better outcomes with adjusted dose LMWH and may be limited by sample size (– **Table 3**). Importantly, there were no differences in major or clinically significant nonmajor bleeding in patients with thrombosis versus no thrombosis or those receiving adjusted versus standard thromboprophylaxis.

In this retrospective single-center study, patients who received intensified LMWH dose based on weight, renal function, and D-dimer levels had significantly lower rate of thrombosis and admission to intensive care unit (ICU) compared with those who received standard thromboprophylaxis. There were no differences in the age, gender, BMI, or other preexisting comorbidities between the two groups, which are known to be associated with worse outcome in patients with COVID-19.

The incidence of thrombosis in patients with COVID-19 infection is not fully established and reports of incidence vary widely from 3 to 40%.<sup>7,9–11</sup> Overall, the data indicate that the incidence is higher than in comparable patients, but the figures are likely confounded by differences in severity of infection in the studied groups (thrombosis being more common with increasing severity as observed here), by use and intensity of thromboprophylaxis regimens, by diagnostic criteria (not all studies required objective detection of thrombosis), inclusion of patients requiring extracorporeal membrane oxygenation, and by ethnic differences in thrombotic tendency. The thrombosis incidence of 34% in our patients on ITU is toward the higher end of the reported range (but lower than Middeldorp et al and Helms et al)<sup>9,10</sup> and the non-ITU patients' rate is similarly at the high end of the reported range. Notably, the rate of thrombosis and requirement for ITU admission were significantly lower in patients who received intensified and weight-

adjusted thromboprophylaxis regimen, and there were trends toward lower rate of developing MOF and mortality, which could have reached significance if the sample size was larger.

The higher than expected rate of thrombosis despite standard thromboprophylaxis has prompted several other authors to adopt a policy of intensified thromboprophylaxis.<sup>10</sup> An observational report of 2,773 patients hospitalized for COVID-19 showed a reduction in mortality in ICU patients who received therapeutic anticoagulation.<sup>11</sup> In patients needing mechanical ventilation ( $N = 395$ ), in-hospital mortality was 29.1%, with median survival of 21 days for those anticoagulated compared with 62.7% in patients who were not, with median survival of 9 days. Again, there was no significant increase in major bleeding (1.9% vs. 3%;  $p = 0.2$ ). The impact of anticoagulation preceding admission is not clear and variable results have been reported.<sup>9,12,13</sup>

Apparent benefit from a D-dimer-, weight-, and renal function-adjusted thromboprophylaxis regimen may arise directly from more intense anticoagulation and prevention of large and small vessel thrombosis in patients with intense inflammatory reaction to the infection. High-intensity anticoagulation may also be of benefit because the high concentrations of acute phase reactants produce heparin resistance, with lower than expected anti-Xa levels achieved from standard dosing.<sup>14</sup> In addition, obesity is associated with more severe disease, making weight-adjusted dosing regimen of particular benefit in this group of patients. Finally, noncoagulant effects of heparin on viral entry and potentiation of DNAase degradation of neutrophil extracellular traps may be beneficial.<sup>15</sup>

The association of impaired renal and hepatic function with thrombosis may reflect severity of disease. An increase in MPV suggests increased platelet turnover and shortened platelet survival may reflect sequestration in microvascular occlusions. The low frequency of thrombocytopenia may be because production is increased by the intense inflammatory response.

Like many current reports, the major limitations of this study are its relatively small sample size and retrospective design. While we believe these observational data are useful, there remains a need for randomized studies with selected and stratified treatment groups and several these studies are currently under way.

#### Authors' Contributions

D.R.J.A. was involved in study concept and design, analysis and interpretation of data, review of the literature, and prepared the first draft of the manuscript. C.S., D.S., P.K., E. M., N.B., C.G., and R.L. collected the data, E.K. and S.J.C. provided the radiology data and interpreted them, and R. A. analyzed the data. A.S. and M.L. interpreted the data, review of the literature, and revised the manuscript. All authors approved the final version of the manuscript.

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#### Conflict of Interest

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