Bleeding and thrombosis outcomes in hospitalised COVID-19 patients on low-molecular-weight heparin and antiplatelet therapy

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Background. An increased incidence of thromboembolic events in hospitalised COVID-19 patients has been demonstrated despite the use of low-molecular-weight heparin (LMWH). Antiplatelet therapy prior to admission and early in the disease course has been hypothesised to be protective against thrombosis.
Objectives. To describe the bleeding and thrombosis outcomes in hospitalised patients with confirmed COVID-19 receiving LMWH, with and without concomitant antiplatelet therapy. Secondary objectives were to explore predictors of bleeding and thrombosis outcomes, and dosing practices of antiplatelet therapy and LMWH.
Methods. We conducted a descriptive, cross-sectional study of bleeding and thrombosis outcomes at Tygerberg Academic Hospital, Cape Town, South Africa, during the first COVID-19 wave, in 808 hospitalised patients with confirmed COVID-19 receiving LMWH with and without concomitant antiplatelet therapy. Multivariate logistic regression analysis was performed if predictors were deemed statistically and clinically significant.
Results. Patients receiving both LMWH and antiplatelet therapy had similar bleeding outcomes compared with patients only receiving LMWH (odds ratio (OR) 1.5; 95% confidence interval (CI) 0.6 - 4.0). Patients receiving both LMWH and antiplatelet therapy had increased odds of developing thrombosis compared with patients only receiving LMWH (OR 4.8; 95% CI 2.1 - 10.7).
Conclusion. The bleeding risk in COVID-19 patients receiving both LMWH and antiplatelet therapy was not significantly increased. A potentially higher risk of thrombosis in patients receiving LMWH and antiplatelet therapy was observed. However, this could reflect confounding by indication. Randomised studies are required to further evaluate the use of antiplatelet therapy to treat hospitalised patients with COVID-19.

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In March 2020, the World Health Organization declared COVID-19 a pandemic.[1] After millions of cases and deaths worldwide, effective curative treatment modalities are still lacking. As of 17 March 2022, South Africa (SA) had registered 3 698 803 COVID-19 cases and 99 767 deaths.[2] Worldwide the total number of recorded cases was 464 593 286, with 6 082 147 deaths.[2] Autopsies and clinical studies have described a COVID-associated coagulopathy, affecting all three aspects of Virchow's triad and leading to thrombosis.[3,4] Low-molecular-weight heparin (LMWH) is an anticoagulant used in the treatment of thromboses, and acts by binding to and activating antithrombin III, thereby inhibiting factor Xa.[5] An increase in the incidence of thromboembolic events in COVID-19 patients despite the use of LMWH has been demonstrated in numerous studies.[6-9] Arterial events including stroke, myocardial infarction and limb ischaemia have also been reported.[10-12] Currently, studies are evaluating the use of higher doses of LMWH in hospitalised COVID-19 patients.[13,14]

Platelet activation has also been described in a thrombo-inflammation model of COVID-19,[15] and platelet hyperactivity has been demonstrated in COVID-associated coagulopathy.[16] Antiplatelet therapy prior to admission and early in the disease course has previously been hypothesised to be beneficial in preventing early intravascular thrombosis formation and disease sequelae.[17,18] A small proof-of-concept study[19] of five patients found that triple antiplatelet therapy (aspirin, clopidogrel, tirofiban) in combination with the LMWH fondaparinux significantly improved the level of respiratory support needed in patients with severe COVID-19-related respiratory failure and features of hypercoagulability. No major bleeds were noted over the 30-day follow-up period. Combination therapy with LMWH and antiplatelet medication could therefore potentially mitigate the incidence of both venous and arterial thrombotic events. Robust evidence supporting the effectiveness of combination therapy with LMWH and antiplatelet therapy to treat COVID-19-associated coagulopathy is lacking. However, previous autopsy findings have also reported that diffuse lung haemorrhage and haemorrhagic inflammation have been common findings in COVID-19 patients.[20] The bleeding risk associated with antiplatelet therapy could further compound these pathological findings. This

risk increases with increasing doses and with the use of dual or triple antiplatelet therapy.[21,22] Currently, there are no universal guideline recommendations for the use of antiplatelets in COVID-19 patients outside of standard non-COVID-19 indications such as primary and secondary prevention of ischaemic heart disease and strokes, inflammation, and analgesia. The bleeding risk in the setting of COVID-19 and antiplatelet therapy could paradoxically be either decreased, due to the purported prothrombotic nature of the disease, or increased, due to the concomitant use of LMWH.

We conducted a retrospective study with the primary objective of describing the bleeding and thrombosis outcomes in patients with COVID-19 admitted to a tertiary academic hospital (Tygerberg Hospital, Cape Town, SA) and on LMWH, with and without antiplatelet therapy. Secondary objectives were to identify predictors of bleeding and thrombosis outcomes and to explore the dosing practices of antiplatelet and LMWH therapies.

Methods

We conducted a cross-sectional, descriptive study during the first COVID-19 wave in SA. We performed a retrospective file review of patients with COVID-19 admitted to Tygerberg Hospital from 25 March 2020, the date of the first admission, to 31 July 2020, who received the LMWH enoxaparin, the preferred anticoagulant for inpatients in our facility for the prevention and treatment of venous thromboembolism. To reduce selection bias, a pragmatic sample size was used whereby all patients admitted to Tygerberg Hospital with COVID-19 on LMWH were evaluated within the study period. Patients were included if they were ≥18 years of age, had a nasopharyngeal swab confirming COVID-19 by reverse transcriptase polymerase chain reaction, and were prescribed LMWH in prophylactic or therapeutic doses (Fig. 1). Patients were excluded if they had missing or incomplete records. Data were collected using various databases at Tygerberg Hospital. Demographic data and clinical notes were accessed using Enterprise Content Management, an electronic data repository system that scans and uploads medical records of patients seen at Tygerberg Hospital. The JAC system is a database used in Western Cape Province to manage pharmacy stock control and dispensing of medication in the various medical facilities in the province. The JAC system was used to assess antiplatelet exposure by identifying whether antiplatelet therapy had been dispensed within the month prior to admission and/or during admission. Other medication history, including other anticoagulant use, was also captured. The outcome of bleeding or thrombosis was identified as an event if stated in the clinical notes, based on high clinical suspicion by the attending team or radiological evidence. Bleeding was defined as any bleeding event reported by the attending team, and included major and minor bleeds. A thrombotic event was recorded by the attending team if clinical features, biochemical markers and/or radiological evidence indicated thrombosis. A variety of other online data systems were used to capture and corroborate additional information. These included the Electronic Continuity of Care Record, a system used to generate discharge summaries at Tygerberg Hospital; the Picture Archiving and Communication System, an online system recording all radiological interventions during hospital admission of a patient; and the National Health Laboratory Service's national database of laboratory investigations performed. Data collected from the medical records included sex, age, smoking status, comorbidities, organ impairment, level of oxygen therapy required and disease progression. Weight was not reliably captured as it could not routinely be accurately measured. Single, double or triple antiplatelet exposures were recorded, with the doses of each antiplatelet therapy. The dose of LMWH was recorded as prophylactic if it was prescribed as a once-daily dose and therapeutic if prescribed as a twice-daily dose. As per the institutional protocol, patients with mild or moderate disease admitted to the general ward and requiring no oxygen supplementation, nasal prong oxygen, 40% face-mask oxygen or oxygenation via a non-breather mask were prescribed prophylactic LMWH. Patients with severe disease admitted to a high-care unit or intensive care unit (ICU) requiring supplemental oxygen via a non-rebreather mask, high-flow oxygen or intubation were administered therapeutic LMWH. Antiplatelet therapy was not administered as directed therapy for COVID-19 according to the institutional protocols at the time of the study. Laboratory parameters captured included haemoglobin, haematocrit, alanine transaminase, the international normalised ratio, lactate dehydrogenase, platelet count, C-reactive protein, highest D-dimers and troponin. All data collected were deidentified and collated using REDCap (Research Electronic Data Capture) electronic data managing tools hosted at Stellenbosch University. The study received ethics approval from the Stellenbosch University Human Research Ethics Committee (ref. no. #N20/07/043_COVID-19) and Tygerberg Hospital management.

Statistical analysis

Baseline characteristics and normality testing were analysed using GraphPad Prism version 9.0.0 (GraphPad Software Inc., USA). Data were imported from REDCap to Stata version 16 (StataCorp, USA) for analysis. Baseline characteristics were described using percentages and frequencies for binary data or categorical data. Continuous data that were non-normally distributed were reported as medians and interquartile ranges (IQRs). If continuous data were normally distributed, they were reported as means and standard deviations. Proportions of exposure and outcomes were described in 2 × 2 tables. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using χ^2 or logistic regression analysis, where appropriate. A bivariate analysis was conducted, and significant covariates were carried over into a multivariate analysis. Multivariate logistic regression analysis was performed if predictors were deemed statistically and clinically significant. Statistical significance was set at $p<0.05$.

Results

We included 808 patients in our analysis (Fig. 1). Baseline characteristics of the study cohort are described in Table 1. Apart from the concomitant use of LMWH and antiplatelet therapy, there were no other significant drug interactions that could have influenced either the bleeding or the thrombosis outcomes at baseline. Antiplatelet therapy was initiated for non-COVID-19-related medical conditions during hospitalisation in 62.6% of patients (n=112/179), prior to admission in 19.0% (n=34/179), and both prior to and during admission in 18.4% (n=33/179). Of the initiations of antiplatelet therapy during hospitalisation, 6.3% were for secondary prevention due to myocardial infarction and stroke.

Fifteen patients were on therapeutic LMWH and antiplatelet therapy at baseline owing to severe COVID-19 and medical comorbidities, respectively. One patient was on warfarin and antiplatelet therapy at baseline and three patients were on warfarin without antiplatelet therapy, for medical indications.

Bleeding outcomes

The bleeding risk in patients receiving additional antiplatelet therapy compared with those who did not receive antiplatelet therapy was not statistically significant (p=0.41) (Table 2). Of the 19 patients in whom a bleeding episode was recorded, 26.3% (n=5/19) received

single antiplatelet therapy (aspirin 150 mg daily) and 5.3% (*n*=1/19) received dual antiplatelet therapy (aspirin 150 mg and clopidogrel 75 mg daily). Of the patients who did not bleed, 20.9% (*n*=165/789) were on single antiplatelet therapy and 1% (*n*=8/789) received dual antiplatelet therapy. Fifty-three percent (*n*=10/19) of patients who bled received either high-flow oxygen or intubation and ventilation compared with 28.8% (*n*=27/789) who did not bleed. A greater percentage of patients who had a bleeding episode were in the ICU at the time of bleeding compared with patients who did not have a bleeding episode: 52.6% (*n*=10/19) v. 27.1% (*n*=214/789). No thrombolytics were administered prior to the bleeding episode in those who bled. The majority of bleeds were in the gastrointestinal system (31.6%; *n*=6/19), followed by epistaxis (15.8%; *n*=4/19). The prescribing patterns of LMWH and antiplatelet therapy in patients who bled v. those who did not are summarised in Table 3.

Thrombosis outcomes

Patients on concomitant LMWH and antiplatelet therapy were at a significantly higher risk of having thrombosis compared with those who were not on antiplatelet therapy (OR 4.8; 95% CI 2.1 - 10.7) (*p*=0.002) (Table 2). In a subgroup analysis, patients with thrombosis on radiological confirmation receiving LMWH and antiplatelet therapy were not at a higher risk of developing thrombosis compared with patients receiving LMWH without antiplatelet therapy (OR 1.5; 95% CI 0.42 - 5.55) (*p*=0.55). Forty-six percent (*n*=11/24) of patients who developed thrombosis received single antiplatelet therapy, compared with 20.3% (*n*=159/784) of patients who did not develop thrombosis. Dual antiplatelet therapy was given in 8.3% (*n*=2/24) patients in the thrombosis group v. 0.9% (*n*=7/784) patients in the group without thrombosis. Patients who developed thrombosis required more intensive oxygen support than the group without thrombosis (54.17%; *n*=13/24 v. 28.57%; *n*=224/784, respectively) and had higher D-dimer values (median (IQR) 6.9 (2.0 - 13.66) µg/mL v. 2.71 (0.8 - 9.6) µg/mL). Fifty-four percent (*n*=13/24) of patients in the thrombosis group required ICU admission compared with 26.9% (*n*=211/784) without thrombosis. Only one patient received antiplatelet therapy before admission, 37.5% (*n*=9/24) received antiplatelets only during admission, and 12.5% (*n*=3/24) received antiplatelets before and during admission. Table 3 summarises the proportion of patients receiving therapeutic v. prophylactic doses of LMWH. The thrombi were mainly located in the lungs (*n*=10/24; 41.7%), brain (*n*=7/24; 29.2%) and limbs (*n*=3/24; 12.5%). Fifty-eight percent (*n*=14/24) of thrombi were diagnosed based on clinical symptoms and signs and 41.7% (*n*=10/24) on radiological findings.

In the multivariate logistic regression analysis, prophylactic LMWH dosing was found to be independently associated with bleeding (OR 0.39; 95% CI 0.15 - 0.99) (*p*=0.049). The other variables carried over from the bivariate analysis were not found to be statistically significant in the multivariate analysis: cardiovascular disease, prophylactic LMWH, D-dimers and platelet counts for bleeding; and antiplatelet therapy, prophylactic LMWH, use of thrombolytics, renal impairment, mechanical ventilation, D-dimers and platelet counts for thrombosis.

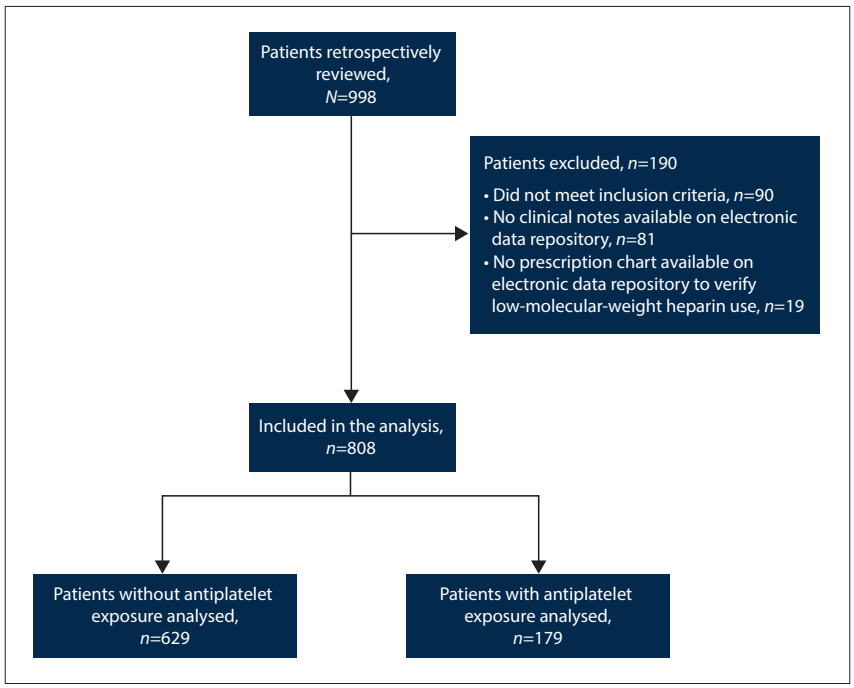

Fig. 1. Flow diagram of the study.

Discussion

We found that hospitalised COVID-19 patients treated with LMWH and antiplatelet therapy had similar bleeding outcomes compared with patients who were only treated with LMWH. Conversely, patients treated with LMWH and antiplatelet therapy were more likely to develop thrombosis compared with patients who were only treated with LMWH.

Our study findings are similar to those in a retrospective cohort of 42 critically ill patients admitted to an ICU with COVID-19 and prescribed intermediate (4 000 IU or 6 000 IU 12-hourly) or higher doses (100 IU/kg 12-hourly) of LMWH and aspirin (100 mg).[23] The investigators found a 65% incidence of venous thromboembolism in patients receiving high-dose LMWH and aspirin but similar bleeding outcomes to patients receiving only LMWH.[23] Some retrospective studies reported no significant benefit in improving COVID-19 outcomes in patients administered antiplatelet therapy for non-COVID-19 indications.[24-27] Conversely, Chow *et al.*[28] found improved mechanical ventilation outcomes in COVID-19 patients who were given aspirin up to seven days prior to or within 24 hours of hospital admission. However, the sample size was small and the comparator group more ill.

The incidence of thrombotic events in our cohort on LMWH and antiplatelet therapy could be explained by a number of reasons. First, the paradoxical observation of a higher incidence of thrombosis in those receiving antiplatelet therapy may be related to the initiation of antiplatelet therapy in patients who had more severe disease at baseline, rather than a consequence of it. In our study, patients on antiplatelet therapy had more comorbidities as risk factors for developing severe COVID-19 disease, as well as higher oxygen requirements at baseline.[29] Second, timing of antiplatelet therapy could be an important factor, and the possible benefit of prior or earlier antiplatelet therapy in the disease course cannot be excluded. Antiplatelet therapy was initiated during hospitalisation in the majority of our cohort (62.6%). Third, the dose of aspirin may have been too low for an antithrombotic effect. It has been reported previously that

Table 1. Baseline characteristics of the study cohort (*N*=808)

Characteristics	Antiplatelet therapy (*n*=179)	No antiplatelet therapy (*n*=629)
Age (years), mean (SD)	58.0 (12.4)	51 (13.0)
Sex (male), *n* (%)	99 (55.3)	301 (47.9)
Current smoker, *n* (%)	11 (6.2)	28 (4.5)
Comorbidities, *n* (%)		
Hypertension	130 (72.6)	315 (50.1)
Diabetes mellitus	112 (62.6)	249 (39.6)
Obesity	82 (45.8)	323 (51.4)
Cardiac disease	27 (15.1)	28 (4.5)
Chronic pulmonary disease	13 (7.6)	34 (5.4)
Active tuberculosis	3 (1.7)	17 (2.7)
HIV	16 (8.9)	104 (16.5)
Cancer	2 (1.1)	13 (2.1)
LMWH dosing (mg), median (IQR)*	80 (40 - 100)	40 (40 - 80)
Therapeutic, *n* (%)	100 (55.9)	175 (27.8)
Prophylactic, *n* (%)	79 (44.1)	454 (72.2)
Antiplatelet therapy, *n* (%)		
Aspirin	170 (95.0)	-
Aspirin + clopidogrel	9 (5.0)	-
Antiplatelet initiation, *n* (%)		
Within one month of admission	36 (20.0)	-
During admission	114 (63.7)	-
Both	31 (17.3)	-
Pregnant, *n* (%)	2 (2.8)	9 (2.8)
Organ impairment, *n* (%)		
Hepatic	11 (6.2)	6 (1.0)
Renal	62 (34.6)	141 (22.4)
CVS	17 (9.5)	22 (3.5)
Oxygen requirements, *n* (%)		
No oxygen	15 (8.4)	89 (14.2)
Nasal prongs oxygen	12 (6.7)	97 (15.4)
High-flow nasal cannula	38 (21.2)	93 (14.8)
40% oxygen	32 (17.9)	159 (25.3)
Non-rebreather	36 (20.1)	132 (21.0)
Intubation	46 (25.7)	60 (9.5)
Laboratory parameters (baseline), median (IQR)		
Haemoglobin (g/L)	13.3 (11.8 - 14.4)	13.0 (12.0 - 15.0)
Haematocrit (L/L)	0.4 (0.4 - 0.4)	0.4 (0.4 - 0.4)
Lactate dehydrogenase (U/L)	493 (377 - 685)	449 (358 - 590)
C-reactive protein	152 (83 - 227)	133 (67 - 223)
Highest D-dimers (μg/mL)	3.3 (0.8 - 9.6)	2.6 (0.9 - 12.0)
Alanine transferase (U/L)	27 (20 - 44)	30 (20 - 50)
INR	1.2 (1.1 - 1.3)	1.2 (1.1 - 1.3)
Troponin (ng/mL)	22.0 (10.0 - 52.5)	19.0 (9.0 - 50.0)
Platelets (× 109/L)	264 (209 - 334)	261 (206 - 338)
eGFR (mL/min/1.73 m^2), *n* (%)		
<15	8 (4.5)	22 (3.5)
15 - 29	10 (5.6)	27 (4.3)
30 - 44	16 (9.0)	44 (7.0)
45 - 59	32 (18.0)	61 (9.8)
>60	112 (62.9)	471 (75.4)
Disease progression, *n* (%)		
ICU admission	13 (7.3)	8 (1.3)
Discharged home	91 (50.8)	474 (75.4)
Death	75 (41.9)	147 (23.4)

LMWH = low-molecular-weight heparin; IQR = interquartile range; CVS = cardiovascular system; INR = international normalised ratio; eGFR = estimated glomerular filtration rate; ICU = intensive care unit.
*Enoxaparin is the LMWH used in our setting. Therapeutic dosing is regarded as twice-daily dosing, and prophylactic dosing is once-daily dosing.

aspirin at low doses of between 75 and 100 mg is ineffective as an antithrombotic in non-COVID-19 patients weighing >70 kg,[30] while aspirin doses >325 mg reduced cardiovascular events at higher body weights.[30,31] It is therefore possible that the median aspirin dose of 150 mg administered to patients in the present study may have been subtherapeutic and that with increasing body weight, higher doses are required to achieve adequate antithrombotic effects. Last, higher doses of LMWH in patients admitted with COVID-19 may paradoxically be associated with an increased risk of thrombotic events.[32,33] Mennuni *et al.*[33] found an increased trend in venous thromboembolism in patients treated with higher doses of LMWH compared with lower doses, with no statistically significant difference in aspirin use between the two groups. A large percentage of patients with thrombotic events in our study received therapeutic doses of LMWH, either with or without antiplatelet therapy. Currently there are numerous trials evaluating the role and adverse effects of a broad range of LMWH doses in COVID-19.[34]

We found no statistically significant difference in bleeding outcomes between the two groups in our cohort. However, in a subgroup analysis, we found that patients were more likely to bleed if therapeutic doses of LMWH were prescribed with antiplatelet therapy, but causality could not be ascertained. Our study findings of a higher tendency to bleed on therapeutic doses of LMWH are in keeping with previous studies.[35,36] Musoke *et al.*[36] found that patients bled more on therapeutic doses of LMWH, and 40% of their cohort was on antiplatelet therapy.

Study limitations

Our study has several limitations. Causality could not be assessed owing to the cross-sectional study design. The higher antiplatelet use in patients with thrombosis probably reflects confounding by indication. This apparent confounding should be further explored in larger, randomised and adequately powered clinical trials. Arguably, patients with a higher risk of thrombosis could have had a higher pre-risk probability of developing severe COVID-19 and COVID-19-associated coagulopathy due to the risk factors present. This could also have been the initial reason for being prescribed antiplatelet therapy as per standard indications. Patients did not have routine weight measurements, which made interpretation of weight-adjusted doses of LMWH and antiplatelet therapy difficult. To limit COVID-19 exposure among staff and patients, not all patients with clinical evidence of COVID-19-associated coagulopathy had radiological imaging done to aid diagnosis of thrombosis or bleeding. Where radiological imaging was not possible, the diagnosis of bleeding or thrombosis was made on high clinical suspicion by the attending team. For this reason, we could not eliminate the possibility of over-diagnosing thrombosis in our cohort.

Conclusion

We found that the bleeding risk in hospitalised COVID-19 patients was not significantly increased in patients treated with antiplatelet therapy in addition to LMWH. We found an increased risk of thrombosis in patients who received both LMWH and antiplatelet therapy. Our finding probably reflects confounding by indication, but underdosing of antiplatelet therapy, especially in patients weighing >70 kg, could not be excluded. Randomised clinical trials are needed to further assess the role of antiplatelet therapy in the management of COVID-19 patients.

Table 2. Bleeding and thrombosis outcomes in patients receiving LMWH with or without antiplatelet therapy

	Outcome, *n* (%)		
Exposure	**Bleeding**	**No bleeding**	**OR (95% CI)**
Antiplatelet therapy	6 (3.4)	173 (96.6)	1.5 (0.6 - 4.0)
No antiplatelet therapy	13 (2.1)	616 (97.9)	
	Thrombosis	**No thrombosis**	
Antiplatelet therapy	13 (7.3)	166 (92.7)	4.8 (2.1 - 10.7)
No antiplatelet therapy	11 (1.8)	618 (98.2)	

LMWH = low-molecular-weight heparin; OR = odds ratio; CI = confidence interval.

Table 3. Representation of antiplatelet and anticoagulation therapy in patients with bleeding v. no bleeding, and thrombosis v. no thrombosis*

	Outcome, *n* (%)			
Group stratification	**Bleeding**	**No bleeding**	**OR (95%CI)**	***p*-value**
Prophylactic LMWH only	7/19 (36.8)	447/789 (56.7)	-	-
Therapeutic LMWH only	6/19 (31.6)	169/789 (21.4)	2.3 (0.8 - 6.8)	0.15
Therapeutic LMWH + antiplatelet therapy	5/19 (26.3)	95/789 (12.0)	3.36 (1.0 - 10.8)	0.04
Prophylactic LMWH + antiplatelet therapy	1/19 (5.3)	78/789 (9.9)	0.8 (0.1 - 6.8)	0.85
	Thrombosis	**No thrombosis**		
Prophylactic LMWH only	4/24 (16.7)	450/784 (57.4)	-	-
Therapeutic LMWH only	7/24 (29.2)	168/784 (21.4)	4.69 (1.4 - 16.2)	0.015
Therapeutic LMWH + antiplatelet therapy	9/24 (37.5)	91/784 (11.6)	11.13 (3.4 - 36.9)	<0.001
Prophylactic LMWH + antiplatelet therapy	4/24 (16.7)	75/784 (9.6)	6.0 (1.5 - 24.5)	0.013

OR = odds ratio; CI = confidence interval; LMWH = low-molecular-weight heparin.
*Interventions compared with prophylactic LMWH therapy only.

Declaration. None.

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1. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 – 11 March 2020. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 (accessed 25 May 2021).
2. Worldometer. Coronavirus: South Africa. 2,383,490 cases and 70,018 deaths. https://www.worldometers.info/coronavirus/country/south-africa/ (accessed 4 December 2021).
3. Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: A prospective cohort study. Ann Intern Med 2020;173(4):268-277. https://doi.org/10.7326/M20-2003
4. Becker RC. COVID-19 update: COVID-19-associated coagulopathy. J Thromb Thrombolysis 2020;50(1):54-67. https://doi.org/10.1007/s11239-020-02134-3
5. Brunton LL, Hilal-Dandan R, Knollmann BC. In: Shanahan JF, Lebowitz H, eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th ed. New York: McGraw-Hill Education, 2018:588.
6. Menter T, Haslbauer JD, Nienhold R, et al. Post-mortem examination of COVID19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings of lungs and other organs suggesting vascular dysfunction. Histopathology 2020;77(2):198-209. https://doi.org/10.1111/his.14134
7. Bikdeli B, Madhavan MV, Jimenez D, et al. COVID-19 and thrombotic or thromboembolic disease: Implications for prevention, antithrombotic therapy, and follow-up. J Am Coll Cardiol 2020;75(23):2950-2973. https://doi.org/10.1016/j.jacc.2020.04.031

8. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: A multicenter prospective cohort study. Intensive Care Med 2020;46(6):1089-1098. https://doi.org/10.1007/s00134-020-06062-x
9. Llitjos J, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. J Thromb Haemost 2020;18(7):1743-1746. https://doi.org/10.1111/jth.14869
10. Oxley TJ, Mocco J, Majidi S, et al. Large-vessel stroke as a presenting feature of COVID-19 in the young. N Engl J Med 2020;382(20):e60. https://doi.org/10.1056/NEJMc2009787
11. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in hospitalised patients with COVID-19 in a New York City health system. JAMA 2020;324(8):799-801. https://doi.org/10.1001/jama.2020.13372
12. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145-147. https://doi.org/10.1016/j.thromres.2020.04.013
13. Marietta M, Vandelli P, Mighali P, Vicini R, Coluccio V, D'Amico R. Randomised controlled trial comparing efficacy and safety of high versus low low-molecular weight heparin dosages in hospitalised patients with severe COVID-19 pneumonia and coagulopathy not requiring invasive mechanical ventilation (COVID-19 HD): A structured summary of a study protocol. Trials 2020;21(1):574. https://doi.org/10.1186/s13063-020-04475-z
14. ClinicalTrials.gov. https://clinicaltrials.gov/ (accessed December 2021).
15. Connors JM, Levy JH. Thromboinflammation and the hypercoagulability of COVID-19. J Thromb Haemost 2020;18(7):1559-1561. https://doi.org/10.1111/jth.14849
16. Battinelli EM. COVID-19 concerns aggregate around platelets. Blood 2020;136(11):1221-1223. https://doi.org/10.1182/blood.2020007805
17. Zhou X, Li Y, Yang Q. Antiplatelet therapy after percutaneous coronary intervention in patients with COVID-19: Implications from clinical features to pathologic findings. Circulation 2020;141(22):1736-1738. https://doi.org/10.1161/CIRCULATIONAHA.120.046988
18. Godino C, Scotti A, Maugeri N, et al. Antithrombotic therapy in patients with COVID-19? – Rationale and evidence. Int J Cardiol 2021;324:261-266. https://doi.org/10.1016/j.ijcard.2020.09.064
19. Viecca M, Radovanovic D, Forleo GB, Santus P. Enhanced platelet inhibition treatment improves hypoxemia in patients with severe COVID-19 and hypercoagulability. A case control, proof of concept study. Pharmacol Res 2020;158:104950. https://doi.org/10.1016/j.phrs.2020.104950
20. Lang ZW, Zhang LJ, Zhang SJ, et al. A clinicopathological study of three cases of severe acute respiratory syndrome (SARS). Pathology 2003;35(6):526-531. https://doi.org/10.1080/00313020310001619118
21. Peters RJG, Mehta SR, Fox KAA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: Observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. Circulation 2003;108(14):1682-1687. https://doi.org/10.1161/01.CIR.0000091201.39590.CB
22. Van Rein N, Heide-Jørgensen U, Lijfering WM, Dekkers OM, Sørensen HT, Cannegieter SC. Major bleeding rates in atrial fibrillation patients on single, dual, or triple antithrombotic therapy. Circulation 2019;139(6):775-786. https://doi.org/10.1161/CIRCULATIONAHA.118.036248
23. Pavoni V, Gianesello L, Pazzi M, Stera C, Meconi T, Frigieri FC. Venous thromboembolism and bleeding in critically ill COVID-19 patients treated with higher than standard low molecular weight heparin doses and aspirin: A call to action. Thromb Res 2020;196:313-317. https://doi.org/10.1016/j.thromres.2020.09.013
24. Banik J, Mezera V, Köhler C, Schmidtmann M. Antiplatelet therapy in patients with COVID-19: A retrospective observational study. Thromb Update 2021;2:100026. https://doi.org/10.1016/j.tru.2020.100026
25. Sivaloganathan H, Ladikou EE, Chevassut T. COVID-19 mortality in patients on anticoagulants and antiplatelet agents. Br J Haematol 2020;190(4):e192-e195. https://doi.org/10.1111/bjh.16968
26. Tremblay D, van Gerwen M, Alsen M, et al. Impact of anticoagulation prior to COVID-19 infection: A propensity score-matched cohort study. Blood 2020;136(1):144-147. https://doi.org/10.1182/blood.2020006941
27. Russo V, di Maio M, Attena E, et al. Clinical impact of pre-admission antithrombotic therapy in hospitalised patients with COVID-19: A multicenter observational study. Pharmacol Res 2020;159:104965. https://doi.org/10.1016/j.phrs.2020.104965
28. Chow JH, Khanna AK, Kethireddy S, et al. Aspirin use is associated with decreased mechanical ventilation, ICU admission, and in-hospital mortality in hospitalised patients with coronavirus disease 2019. Anesth Analg 2021;132(4):930-941. https://doi.org/10.1213/ANE.0000000000005292
29. Harrison SL, Fazio-Eynullayeva E, Lane DA, Underhill P, Lip GYH. Comorbidities associated with mortality in 31,461 adults with COVID-19 in the United States: A federated electronic medical record analysis. PLoS Med 2020;17(9):e1003321. https://doi.org/https://doi.org/10.1371/journal.pmed.1003321
30. Rothwell PM, Cook NR, Gaziano JM, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: Analysis of individual patient data from randomised trials. Lancet 2018;392(10145):387-399. https://doi.org/10.1016/S0140-6736(18)31133-4
31. Halbur CR, Gulbrandsen TR, West CR, Brown TS, Noiseux NO. Weight-based aspirin dosing may further reduce the incidence of venous thromboembolism following primary total joint arthroplasty. J Arthroplasty 2021;36(12):3986-3992. https://doi.org/10.1016/j.arth.2021.06.008
32. Salmon T, Titley M, Noori Z, Crosby M, Sankaranarayanan R. Anticoagulants and antiplatelets in COVID-19: Impact on survival and thromboembolism development. Heart 2021;107(Suppl 1):A117. https://doi.org/10.1136/heartjnl-2021-BCS.150
33. Mennuni MG, Renda G, Grisafi L, et al. Clinical outcome with different doses of low-molecular-weight heparin in patients hospitalised for COVID-19. J Thromb Thrombolysis 2021;52(3):782-790. https://doi.org/10.1007/s11239-021-02401-x
34. Tritschler T, Mathieu ME, Skeith L, et al. Anticoagulant interventions in hospitalised patients with COVID-19: A scoping review of randomised controlled trials and call for international collaboration. J Thromb Haemost 2020;18(11):2958-2967. https://doi.org/10.1111/jth.15094
35. Jiménez D, García-Sanchez A, Rali P, et al. Incidence of VTE and bleeding among hospitalised patients with coronavirus disease 2019: A systematic review and meta-analysis. Chest 2021;159(3):1182-1196. https://doi.org/10.1016/j.chest.2020.11.005
36. Musoke N, Lo KB, Albano J, et al. Anticoagulation and bleeding risk in patients with COVID-19. Thromb Res 2020;196:227-230. https://doi.org/10.1016/j.thromres.2020.08.035

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