ORIGINAL ARTICLE

Oral Rivaroxaban in the Prophylaxis of COVID-19 Induced Coagulopathy

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Abstract

Background: Preliminary data highlights the importance of anticoagulation therapy in the prevention and treatment of thromboembolism in SARS CoV-2 infection. There is insufficient data comparing the safety and efficacy of direct oral anticoagulants (DOACs) and subcutaneous enoxaparin in the prophylactic management of COVID-19 associated thromboembolic disease, particularly in mild to moderate cases of COVID-19 infection.

Objectives: The study was designed to investigate the efficacy of oral rivaroxaban as a prophylactic anticoagulant in mild to moderate SARS CoV-2 infection.

Methods: In this randomized, open-label, prospective superiority trial involving hospitalized patients with confirmed mild or moderate COVID-19 disease without known thromboembolism, we assigned 230 patients to receive either once-daily oral rivaroxaban (10mg or 15mg) or once-daily subcutaneous enoxaparin (40mg or 60mg) for a median duration of 8 days. The primary outcome was a composite of all major, clinically relevant haemorrhagic and thrombotic events.

Results: The primary efficacy outcome occurred in 4 of 115 patients in the rivaroxaban group (3.5%) versus 16 of 113 patients in the enoxaparin group (14.2%) (hazard ratio 0.207, 95% confidence interval [CI], 0.069 to 0.621, P=0.005). Adverse events developed in 4.3% of patients in the study group and 12.4% in the enoxaparin group (hazard ratio 0.328; 95% CI, 0.118 to 0.910; P=0.032). Major bleeding was seen in 1 patient (0.9%) in the rivaroxaban group and 3 patients (2.7%) in the enoxaparin group.

Conclusions: Rivaroxaban alone was superior to enoxaparin for the prophylactic management of coagulopathy associated with mild to moderate SARS CoV-2 infection.

Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a global, rapidly emerging virus that causes the coronavirus disease 2019 (COVID-19).[1] The disease has impacted nations and resulted in considerable morbidity and mortality, as well as economic and infrastructural collapse. As of 30th March 2021, there are 128,540,982 confirmed cases and over 2,500,000 deaths.[2]

Recent observations suggest that respiratory failure in COVID-19 is not driven by the development of acute respiratory distress syndrome (ARDS) alone. Even though infection is a well-known trigger for venous thromboembolism (VTE),[3-5] microvascular thrombotic processes may play an important role in progression of disease in COVID-19.[6]

Heparin has been the treatment of choice in the management of thromboembolism in numerous disease states.[7] Enoxaparin was the first low molecular weight heparin to be approved by the U.S Food and Drug Administration in 1993 for the management of venous thromboembolism.[8] Studies conducted over the last ten years have shown consistent efficacy and safety of DOACs (direct oral anticoagulants) in prophylaxis and treatment of DVT (deep vein thrombosis),[9] non-valvular atrial fibrillation[10] and cancer-associated venous thromboembolism.[11] The ROXANE trial (Oral Riva**rox**aban versus subcutaneous enoxaparin [Clex**ane**™] in the prophylaxis of COVID-19 induced coagulopathy) was designed to investigate the utility of rivaroxaban alone for management of coagulopathy in mild to moderate COVID-19 infection, as compared to enoxaparin.

Methods

Study Design and Oversight

We conducted a single-centre, randomized, open-label, prospective trial comparing the efficacy and safety of rivaroxaban with that of subcutaneous enoxaparin for the management of venous thromboembolism for those diagnosed with mild or moderate COVID-19 infection at Sevenhills Hospital Dedicated COVID Hospital, Mumbai. The protocol (available within the Supplementary Material) was approved by the institutional ethics committee at the participating institution. Informed consent was obtained and documented from all the patients. Trial was registered with Clinical Trials Registry – India.

The first two authors wrote the first draft of the manuscript and contributed to subsequent versions, made the decision to submit the manuscript for publication, and hereby vouch for the accuracy and completeness of the data and for the fidelity of the study to protocol.

Patients

All consenting, in-hospital patients were eligible if they were between 25 to 75 years of age with objectively

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confirmed evidence (RTPCR) of mild or moderate COVID-19 disease.[12] Dosing regimens for rivaroxaban and enoxaparin were as per local protocols and emerging evidence.[13,14] This included prophylactic to intermediate dosing strategies – enoxaparin 40 mg or 60 mg SC and rivaroxaban 10 mg or 15 mg PO OD - for both treatment arms, given the patients had symptomatic mild or moderate disease. The CHA_2DS_2VASc scoring system was utilised to objectively stratify risk profile of patients.[15-17] Patients with a mild CT-severity index were given anticoagulation (10mg rivaroxaban or 40mg enoxaparin) if CHA_2DS_2VASc score was ≥2 if female, ≥1 if male, D-dimer levels >500 nanograms per millilitre or had previous history of malignancy, deep vein thrombosis (DVT), systemic embolism or ischemic events. All patients with a moderate CT-severity index were treated with anticoagulants (15 mg rivaroxaban or 60mg enoxaparin) considering the increased risk of coagulopathy and progression of disease in accordance with local guidelines.[18-20] A full list of inclusion and exclusion criteria is provided in the Supplementary Material.[21,22]

Randomisation

Patients were allocated in a 1:1 ratio using computer-generated randomization to receive oral rivaroxaban and subcutaneous enoxaparin. Recruitment of participants was continued until 1st November 2020. The intended duration of administration of the drug was for the duration of hospital stay, as decided by the investigating team.

Outcome Measures

The primary outcome was a composite of all major, clinically relevant haemorrhagic and thrombotic events. The primary efficacy endpoints were progression of disease requiring treatment escalation, including need for (i) supplemental oxygen, (ii) need for high-flow oxygen devices or non-invasive ventilation, (iii) invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO); transfer to intensive care; the incidence of radiologically confirmed new or recurrent DVT or PE in the patients during their period of stay in the hospital; stroke and systemic embolism; myocardial infarction; death from vascular causes; and all-cause death. The definitions of the efficacy outcomes are provided in the Supplementary Material.

The primary safety endpoint was bleeding, including major and clinically relevant non-major bleeding. Major bleeding was defined as overt bleeding in a critical site (e.g. intracranial, intraspinal, intraarticular, intrapericardial), associated with a fall in haemoglobin of 2 grams per decilitre or more, leading to transfusion of 2 or more units of packed red blood cells or whole blood. Clinically relevant non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study treatment, or associated with any other discomfort such as pain, or impairment of activities of daily life. (Further details regarding the criteria are provided in the Supplementary Material). As a part of monitoring anticoagulant therapy, bleeding risk was stratified using the HAS-BLED scoring system; ≤3 was considered as having low bleeding risk.[23]

Surveillance and Follow-Up

During the study, one patient was lost to follow-up (discharged against medical advice). As an unconnected and independent treatment strategy, patients in both intervention groups who showed disease progression and/or eligible as per local and institutional treatment guidelines were discharged on prophylactic rivaroxaban (10mg once daily) for 15 days. All patients who were discharged with prophylactic oral anticoagulation were instructed to report to the centre if they had any symptoms of haemorrhagic or thrombotic events. These results are reported separately and have not been included in the primary analysis. (Refer to Supplementary Material)

Statistical Analysis

The study was aimed to test the hypothesis that rivaroxaban would be superior to subcutaneous enoxaparin in the primary efficacy outcome in mild to moderate COVID-19 infection. Assuming a 30% incidence of composite outcome in the enoxaparin group[24] and an effect size (absolute risk reduction) of 15% in the primary composite outcome, we expected to enrol at least 300 participants for the study to provide a power of 80% (two-sided alpha level [α], 0.05). A total of 230 patients were enrolled by the end of the target study period, given the ethical commendations dictated by the IEC and limited participation during the peak of the pandemic. (Refer to Supplementary Material)

The primary efficacy analysis was conducted by the investigating team on an intention-to-treat basis with the use of a Cox proportional-hazards model to analyse the time until the first event of the primary trial outcome during the treatment period. The evaluation of the primary outcome was done by considering the time from randomization until the first episode of thrombotic or haemorrhagic event or progression of disease (primary trial outcome); the total duration of hospital stay was used if neither a thrombotic nor haemorrhagic event occurred within the study period (censored time). The primary efficacy data set (intention-to-treat population) and safety data set consisted of all the patients who had undergone randomization and received at least one dose of a trial drug. Bleeding events were included in the analysis if they occurred during treatment or within 48 hours after the last dose of a study drug. All patients who were event-free at the end of the hospital stay were censored. Kaplan–Meier curves were generated to display the distribution of events over time (Figure 2). All data were handled solely by the principal investigators of the trial and analysed by the investigating team with the use of IBM SPSS software (Build 1.0.0 1447).

Results

Patients

Through 1st August 2020 to 1st November 2020, 230 patients were enrolled - 115 received rivaroxaban and 113 received subcutaneous enoxaparin at a dedicated COVID-19 Hospital in Mumbai, India (Figure 1). The characteristics of enrolled participants were similar at baseline (Table 1).

In the rivaroxaban treatment arm, a total of 65 patients received 10mg once daily and 50 patients received a dose of 15mg once daily. Among those receiving subcutaneous enoxaparin, 62 patients received a dose of 40mg daily, and 51 patients received a dose

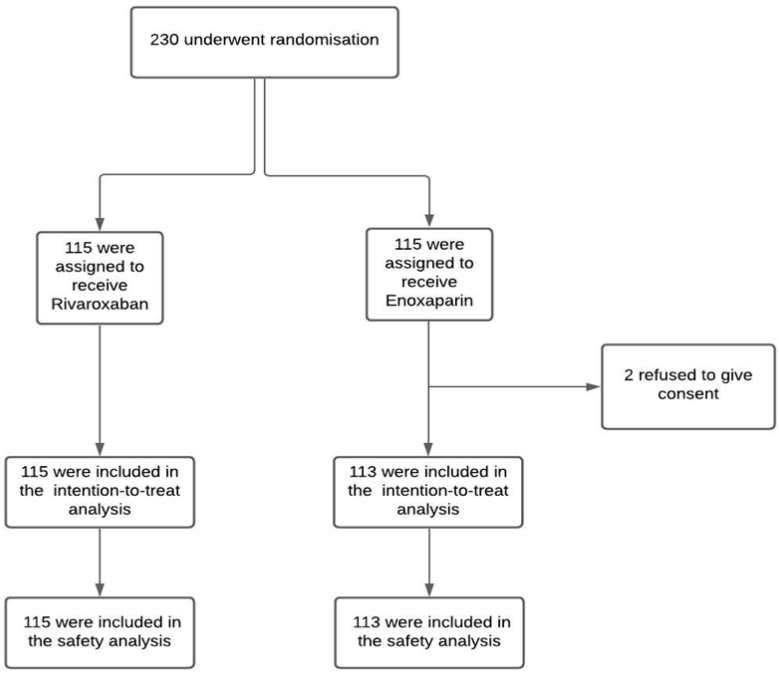

Fig. 1: Enrolment and outcomes

of 60mg daily.

Treatment and Follow-Up

In the enoxaparin group, the median duration of enoxaparin treatment was 8 days (interquartile range [IQR], 6 to 10 days). Compliance was measured systematically by recording the actual number of doses taken (as monitored by investigators on individual case record forms) and total doses that were to be administered as part of treatment regimen. Average adherence to therapy was above 90% in the rivaroxaban group and above 85% of patients in the enoxaparin group. Patients on rivaroxaban received the drug for a median duration of 8 days (IQR, 6 to 10 days).

Clinical Outcomes

The clinical outcomes and treatment characteristics are shown in (Table 2). The intention-to-treat analysis indicated the primary efficacy outcome occurred in 4 patients (3.5%) in the rivaroxaban group as compared to 16 patients (14.2%) in the enoxaparin group, for a hazard ratio of 0.207 (95% confidence interval [CI], 0.069 to 0.621; P = 0.005).

One patient receiving 15mg rivaroxaban daily and three patients in the enoxaparin group (1 on 40mg subcutaneous LMWH and 2 patients on 60mg subcutaneous LMWH) required admission to intensive care during course of treatment. The rate of patients requiring transfer to intensive care due to suspected or confirmed pulmonary embolism or cardiorespiratory failure were 0.9% (1 of 115 patients) in the rivaroxaban group and 2.7% (3 of 113 patients) in the enoxaparin therapy group (P = 0.304).

The safety outcome occurred in 5 patients (4.3%) in the study group and 14 patients (12.4%) in the enoxaparin therapy group (P = 0.032) (hazard ratio 0.328; 95% CI, 0.118 to 0.910). Out of this, major bleeding, including systemic bleeding, non-fatal bleeding leading to fall in haemoglobin more than 2 grams per decilitre, requiring interruption or discontinuation of therapy was observed in 1 patient (0.9%) in the rivaroxaban group and 3 patients (2.7%) (P = 0.304) in the enoxaparin group2. The clinically relevant non-major bleeding primarily included large subcutaneous haematomas, intramuscular haematomas, rectal blood loss and epistaxis.

Discussion

A total of 230 consenting patients were enrolled at Sevenhills Dedicated COVID Hospital, Mumbai in this study during the period of pandemic between August 2020 and November 2020. Due to the rapidly evolving and poorly understood nature of the disease itself, the inclusion criteria were designed to ensure the study population was representative of patients with COVID-19 in the real-world setting.

Table 1: Demographic and Clinical Characteristics of the Patients

Characteristics of patients	Rivaroxaban (N=115)	Standard therapy (N=113)
Mean age – yr.	51.5	54
Male sex – no. (%)	71 (58.2)	68 (60.2)
Weight – no.		
<50kg	10	5
50-100kg	92	103
>100kg	13	5
Liver function within normal limits at time of randomisation – no.	114	113
Creatinine levels within normal limits at time of randomisation – no.	115	111
CHADSVASc2 Score ≥2 – no. (%)	51 (49.0)	53 (51.0)
HAS-BLED score		
≤3	112	111
>3	3	2
Pre-existing conditions		
≤1	88	80
≥2	27	33
Diabetes Mellitus	35	34
Hypertension	32	29
Clinical condition on admission		
Sinus tachycardia	39	39
SpO2		
90%< x ≤94%	20	22
≥95%	95	91
Diagnostic methods		
Spiral computed tomography		
Mild	43	36
Moderate	41	48
Pulmonary angiography	5	9
D-dimer		
Raised (>500ng/ml)	36	37
Normal (<499ng/ml)	79	76
Inflammatory markers (inc. CRP, IL-6, Ferritin, LDH)		
Raised	87	100
Normal	28	13
Characteristics of treatment	Rivaroxaban (N=115)	Standard therapy (N=113)
Pre-randomisation treatment with antiplatelet or anticoagulant – no. (%)	3 (2.6)	2 (1.8)
At least one dose of study drug received – no.	115	113
Dosing regimen:		
40mg SC QD LMWH	-	62
60mg SC QD LMWH		51
10mg PO OD Rivaroxaban	65	-
15mg PO OD Rivaroxaban	50	

Table 2: Clinical Outcomes

Outcome	Rivaroxaban (N=115)	Standard therapy (N=113)
Duration of treatment – days		
Median	8	8
Interquartile range	4	4
Mean study treatment duration — days	8.4	8.7
Average compliance (%)	90.1	87.3
Loss to follow-up	0	1
Efficacy		
Intention-to-treat population — no. of patients	115	113
Progression of disease (requiring treatment escalation, worsening of oxygen saturation ≤90% on room air, ICU transfer, cardiorespiratory failure) – no. (%)	4 (3.8)	16 (14.2)
Venous thromboembolism		
Type of first recurrent venous thromboembolism — no. (%)		
Fatal pulmonary embolism	0	0
Death in which pulmonary embolism could not be ruled out	0	0
Nonfatal pulmonary embolism	0	1 (0.9)
Safety		
Adverse event — no. (%) (Major and Clinically relevant Non-Major Bleeding)		
Any event emerging during treatment	5 (4.3)	14 (12.4)
Any serious event emerging during treatment	0	5 (4.4)
Any event resulting in permanent discontinuation of study drug	0	1 (0.9)
Any event leading to or prolonging hospitalization	0	1 (0.9)
Fatal (retroperitoneal, intracranial, gastrointestinal)	0	0
Other nonfatal episode in a critical site	1 (0.9)	1 (0.9)
Associated with a fall in haemoglobin of ≥2 g/dl, transfusion of ≥2 units, or both	1 (0.9)	3 (2.7)
Death or ICU transfer needed during intended treatment period — no. (%)		
Pulmonary embolism or pulmonary embolism not ruled out	0	1 (0.9)
Bleeding	0	1 (0.9)
Myocardial infarction	0	0
Ischemic stroke	0	0
Other cardiac disorder or respiratory failure	1 (0.9)	2 (1.8)
Progression of disease plus major bleeding events – no. (%)	9 (7.8)	30 (26.5)

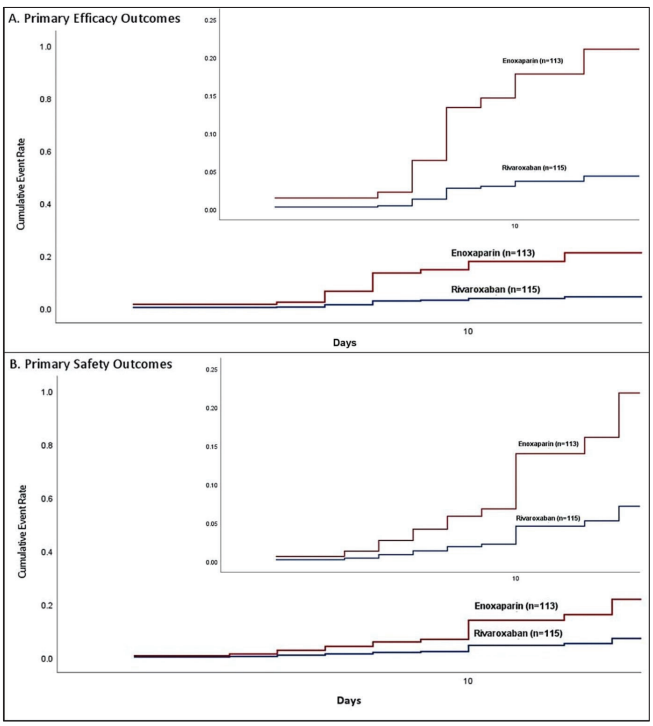

Fig. 2: Kaplan Meier Curves

Appendix Table S1: Events in Post-discharge Prophylaxis

Total no. of patients	117
Mean duration of therapy – days	39
Average Compliance (%)	70
Adverse Events – no. (%)	
Any event during course of treatment	7 (6.0)
Any serious event emerging during treatment	3 (2.6)
Any event leading to permanent discontinuation of drug	3 (2.6)
Any event leading to hospitalization	1 (0.9)
Acute Coronary Events	1 (0.9)
Systemic Embolism	0
Cerebrovascular Event	0
Death due to Vascular Cause	0
Death due to Non-Vascular Cause	1 (0.9)

In patients diagnosed with mild and moderate SARS CoV-2 infection, anticoagulation with oral rivaroxaban alone had improved efficacy as compared to subcutaneous enoxaparin in the prevention of COVID-19 associated coagulopathy. During the period of treatment in-hospital, the intention-to-treat analysis indicated that 7.8% of patients in the rivaroxaban group and 26.5% of patients in the enoxaparin therapy group had a composite outcome of thrombotic or haemorrhagic event. Safety outcome (as described previously) occurred in 4.3% patients in the rivaroxaban group and 12.4% in the enoxaparin group. Out of this, major bleeding occurred in 0.9% of patients in the rivaroxaban group and 2.7% of patients in the enoxaparin group. The drug offered a relative risk reduction of over 70% in the rivaroxaban group and reduced the absolute risk of reaching trial endpoint by 18%. Prophylactic therapy with rivaroxaban prevented an adverse outcome for every 5 patients treated over a median duration of 8 days.

While devising the inclusion criteria for the study, we used the CHA_2DS_2VASc scoring system to triage patients at risk of progression of disease. This scoring system had the advantage of having components that were found to increase risk of severe COVID-19 disease, including age, comorbidities such as hypertension, diabetes mellitus, stroke, and vascular disease. In the recent months, this scoring system has been modified and validated as a useful tool in stratifying patients with COVID-19 pneumonia (Gunduz R et al; Quisi A et al, Cetinkal G et al).

Our data suggests that rivaroxaban has a statistically superior benefit-risk

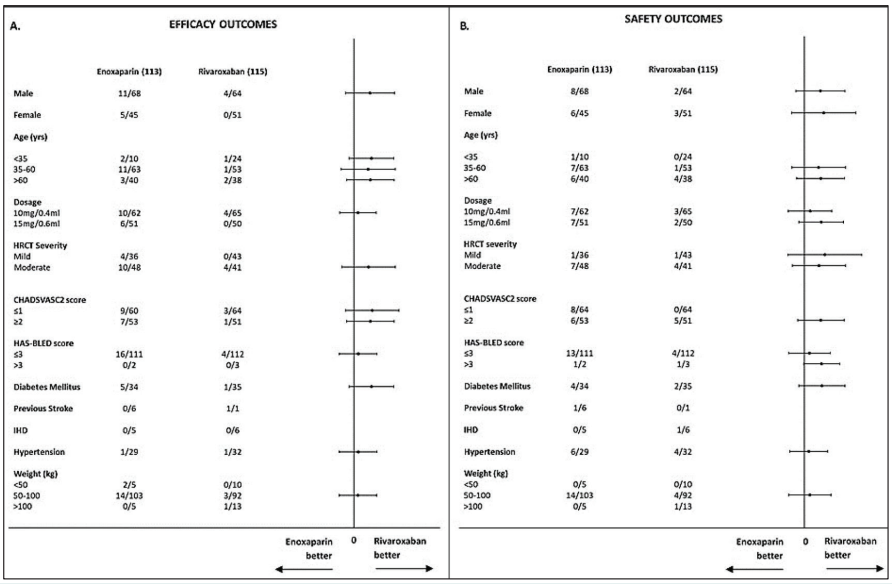

Fig. 3: Efficacy and Safety Outcomes in Subgroups

profile in the prophylaxis of COVID-19 associated coagulopathy in mild and moderate COVID-19 infection. The incidence of thromboembolic episodes and progression of disease were lower, as was the development of clinically relevant adverse effects. Treatment with rivaroxaban resulted in fewer patients requiring intensive care and supplemental oxygen. Within the sample population investigated, there were fewer rates of development of thromboembolic episodes. Prophylactic to intermediate dosing strategies presented in this study were of comparable utility in management of disease, as shown in emerging evidence around the world.

Given the difficulty of administering a parenteral agent such as enoxaparin, including patient discomfort, reduced levels of compliance (Haykal T, Zayed T, Deliwala S), and increased exposure of healthcare workers to infectious patients, the oral anticoagulant rivaroxaban is a promising alternative as evidence by our study. The trial indicates that rivaroxaban is safe, effective, and practical in the management of patients with mild to moderate COVID-19 infection. Additionally, direct oral anticoagulants can be seamlessly continued post-discharge,[25] unlike their counterpart low molecular weight heparin that requires bridging over a period of several days.[26] The findings of this trial are promising, and increased adherence, ease of use, and improved benefit-risk profile[27] make this drug a clinically viable alternative for prevention of coagulopathy associated with SARS CoV-2 infection.

The rationale for use of anticoagulation in management of the SARS CoV-2 pandemic was discovered early in the pandemic, and has since, significantly changed disease outcomes. In the Tongji hospital in Wuhan, Tang et al. discovered that use of heparin reduced mortality in patients with severe COVID-19 infection.[28]

In April 2020, Paranjape et al. at Mount Sinai Health System in New York City used various forms of anticoagulation in a large cohort of patients.[29] The study concluded that anticoagulation was associated with lower in-hospital mortality, more specifically, prophylactic dose anticoagulation showed improved survival rates. However, our study observed progress of hospitalised patients in the ward which provided clearer association of anticoagulation use and progression of disease requiring intensive care.

The ACTION trial presented in the ACC 21 sessions discussed similar anticoagulation dosing strategies in the management of COVID-19 pneumonia. The study failed to show that therapeutic anticoagulation was beneficial as compared to prophylactic anticoagulation (Lopes et al).

The trial conducted by Albani et al. compared therapeutic versus prophylactic dosing regimens and revealed similar results (Filippo Albani et al).

In contrast to this, therapeutic dose anticoagulation in moderately ill patients with COVID-19 was found to increase probability of survival until discharge and reduced need for organ support. However, it was associated with significantly more major bleeding events as compared to prophylactic doses.[30]

All above trials discuss the importance of clinically appropriate dosing regimens in the anticoagulation strategy employed in the management of COVID-19 infection. However, our study fundamentally differs in exploring the utility of oral anticoagulants as compared to parenteral anticoagulants. There is still insufficient data directly comparing efficacy of oral anticoagulation and parenteral anticoagulation in management of COVID-19 infection.

The main limitations of our study include the relatively small sample size. Lack of blinding and long-term follow up to shed light on continuing post-covid thromboembolic phenomenon create possible restrictions to the overall conclusion of the study. Subgroup analyses of dosing groups were inconclusive. A larger trial with adequate participants can further validate individual endpoints of this study. Given the ethical restrictions of this poorly understood infection and its global burden during the early phase of the pandemic, patients with severe COVID-19 infection could not be included, as dictated by the Institutional Ethics Committee (IEC). Further research on utility of oral anticoagulants in severe cases of COVID-19 infection can explore the efficacy of this class of drugs in varied stages of the infection.

Only 3 of 115 patients in the rivaroxaban group and 2 of 113 patients in the enoxaparin group were on antiplatelet therapy pre-randomization. However, whether this could have had implications on the overall effect of the intervention drug remains to be studied. Other direct oral anticoagulants (DOACs), such as apixaban and dabigatran, were not available to be included as potential interventions in the study. This could have provided a better insight into the efficacy of direct oral anticoagulants as a group in the

prophylactic management of COVID-19 associated coagulopathy. Our results are generally consistent with findings of anticoagulation dosing regimens in COVID-19 but provide additional, important insight into efficacy of DOACs in COVID-19 disease.

Our randomized controlled trial demonstrated that rivaroxaban as a single oral agent was not only as effective but superior, in the prophylactic management of coagulopathy associated with SARS CoV-2 infection. The relative ease of use and efficacy of rivaroxaban, supported by existing literature of its utility in several thromboembolic diseases, introduces a promising alternative in the management of an illness that continues to plague health care systems around the world.

Participating Institution
All authors were affiliated to the participating institution "Seven Hills Dedicated COVID Hospital (DCH)" in Mumbai, Maharashtra, India during the study.

Key Message and Statement

The protocol (available within the Supplementary Material) was approved by the institutional ethics committee at the participating institution. We have received no external funding or support for the work. All monetary support and resources were provided for by the institution which was under the Brihanmumbai Municipal Corporation as part of the group of major hospitals dedicated to managing the COVID-19 pandemic. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors declare that they have no known competing financial interests or personal relationships that could have influenced the study and final publication.

Abbreviations List

ARDS: Acute Respiratory Distress Syndrome; COVID-19: Coronavirus Disease 2019; CT: Computed Tomography; DOACs: Direct oral anticoagulants; DVT: Deep Vein Thrombosis; IBM SPSS: International Business Machines Statistical Package for the Social Sciences; IEC: Institutional Ethics Committee; LMWH: Low molecular weight heparin; mg: milligrams; PE: Pulmonary Embolism; RT-PCR: Reverse transcriptase – polymerase chain reaction.

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