The Early Thromboprophylaxis In COVID-19 (ETHIC) trial

Study ID: NCT04492254

Sponsor: Thrombosis Research Institute, London, UK

Study commencement: 27th October 2020

Last Patient Enrolled: 8th November 2021

Final Database Lock: 18th January 2022

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SUMMARY OF STUDY

The Early Thromboprophylaxis In COVID-19 (ETHIC) trial is an open label, multi-centre, randomized controlled phase IIIb trial of community-based symptomatic COVID-19 patients, recruited between October 2020 and November 2021. The trial investigated prophylactic low molecular weight heparin treatment verses standard of care upon the composite rate of hospitalization and mortality. ETHIC is an independent research initiative sponsored by Sanofi and the Thrombosis Research Institute (TRI; London, UK).

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is associated with excessive inflammation and coagulation, a substantial prothrombotic state, and extensive intravascular thrombosis[1-3]. Meta-analyses have recently indicated that venous thromboembolism (VTE) is detected in an overall estimated 17% of patients, although thrombosis rates are considerably higher for hospitalized patients with severe COVID-19[4-6]. Indeed, widespread VTE and small pulmonary artery thrombosis are most frequently detected in critically ill patients and are thought to be intrinsically linked to clinical acute respiratory distress syndrome (ARDS), observed in severe and fatal cases[3, 4, 7, 8]. The pathophysiology of disease progression, however, remains unclear. Elevation in D-dimer and other coagulation factors, such as factor VIII and fibrinogen, have been reported in patients with COVID-19 and may be linked to the profound inflammation, hypoxia, organ failure, and immunothrombosis associated with ARDS[3, 9-11].

Emerging literature has indicated the beneficial potential of anticoagulation (AC) therapy. Heparin behaves both as an anticoagulant and possesses various pleiotropic effects including anti-inflammatory and anti-viral properties. Indeed, it has recently been shown to cause a conformational change to the SARS-CoV-2 surface protein S1 receptor binding domain. Results from the ATTACC, ACTIV-4a, and REMAP-CAP multi-platform trial have indicated that therapeutic-dose heparin increases the probability of survival when administered to hospitalized patients with moderate COVID-1912. In contrast, no impact upon outcomes was observed in severe cases (i.e., patients requiring ICU care at enrolment)[12, 13]. A number of guideline statements have been released either advocating for or discouraging the use of elevated AC therapy for critically ill COVID-19 patients, despite the known associated bleeding risks.

Standard prophylactic-dose low molecular weight heparin (LMWH), however, has been shown to reduce mortality in specific hospitalized patients with severe COVID-19, when administered upon admission for a minimum of 7 days[14]. There is, however, insufficient evidence from randomized controlled trials (RCTS) supporting the use of thromboprophylactic heparin in non-critically ill outpatients. Given the recognised efficacy of LMWH in primary thromboprophylaxis in general medical and surgical patients, and the need to prevent COVID-19 progression to severe stages, evaluating the role of early LMWH in community-based patients at an early disease stage is essential[15].

The Early Thromboprophylaxis In COVID-19 (ETHIC) trial is a multicentre, randomized controlled trial of symptomatic community-based COVID-19 patients. The study was designed to investigate the comparative impact of standard-dose enoxaparin treatment, prescribed at diagnosis, compared with the current standard of care (SOC) in community patients with COVID-19 upon the composite rate of hospitalization and mortality, as well as VTE, bleeding (major, non major clinically relevant, minor), and adverse events. This report describes the captured outcomes data at 21 days, with additional follow up at 50 days and 90 days post treatment initiation. The study aimed to recruit 1,370 numbers of patients, however due to early termination of the study, 219 total patients were analysed using an ITT approach. Recruitment was consecutive and was carried out using random allocation to treatment arm.

METHODS AND STUDY DESIGN

Managing committees

Steering Committee

Walter Ageno, Department of Medicine, University of Insubria, Varese Italy

Juan Arcelus, University of Granada, Celle madrid 119A, Monachil, Spain

Frank Cools, AZ Klina, General Hospital Klina, Brasschaat, Belgium

Harry Gibbs, The Alfred Hospital, Melbourne, Australia

Sylvia Haas, Vascular Center Munich, Munich, Germany

Richard Hobbs, Harris Manchester College, Oxford, UK

Barry Jacobson, Charlotte Maxeke Johannesburg Academic Hopsital, Haematology Department, Johannesburg, South Africa

Ajay K. Kakkar, Thrombosis Research Institute, University College London, London, UK

Renato Lopes, Duke University Medical Center, Durham, Brazilian Clinical Research Institute (BCRI) Sao Paolo, Brazil

Peter MacCallum, Thrombosis Research Institute, Queen Mary University of London, London, UK

Ana Theresa Rocha, Escola de Medicina e Saude Publica, Brazil

Sebastian Schellong, Stadtiches Klinikum Dresden, Dresde, Germany

Alexander G.G. Turpie, Faculty of Health Sciences, McMaster University, Toronto, Canada

Safety Review Committee

Jelle Himmelreich, Amsterdam UMC, University of Amsterdam, department of General Practice, Amsterdam Public Health, Meibergdreef 9, Amsterdam, Netherlands

Gloria Petralia, Thrombosis Research Institute, London, United Kingdom

Peter MacCallum, Thrombosis Research Institute, Queen Mary University of London, London, United Kingdom

Data Safety Monitoring Board

John Camm, St. George's University of London, London, United Kingdom

Keith A.A. Fox, Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK

Alfredo Farjat, Formerly Thrombosis Research Institute, London, United Kingdom

Clinical Events Classification Committee

Harry Gibbs, The Alfred Hospital, Melbourne, Australia

Renato Lopes, Duke University Medical Center, Durham, Brazilian Clinical Research Institute (BCRI) Sao Paolo, Brazil

Sylvia Haas, Vascular Center Munich, Munich, Germany

TRI Project Leadership

Project Leadership: Alice Fernandez, Katerina Brachou, Mary Jane Attenburrow; Data Management: Lewis Castro, Madhusudana Rao; Safety Assessment Coordinator: Lewis Castro

ETHIC Site Investigators

Belgium:

Frank Cools

Brazil:

Ana Thereza Rocha, Adrian Paulo, Morales Kornann, Murillo Antunes;

India:

Pradeep Kumar, Upendra Kaul, Atul Abhyankar, Rajesh Mahajan, Ajit Avhad;

South Africa:

Barry Jacobson, Louis Van Zyl;

Spain:

Jesus Gonzalez Lama;

United Kingdom:

Frances Adams, Andrew Moriarty, Ivan Aloysius, Matthew Capehorn.

Study Design and Participants

The ETHIC registry (ClinicalTrials.gov identifier: NCT04492254) was an open label, multicentre, randomized controlled trial of symptomatic, high risk, COVID-19 patients of ≥55 years with at least two of the following pre-defined risk factors: age (≥ 70 years), BMI of >25 kg/m^2, chronic lung disease, diabetes, cardiovascular disease, or corticosteroid use. Associated COVID-19 symptoms considered are displayed in Table 1, below. Eligible men and women were enrolled consecutively and were randomized in a 1:1 ratio within 9 days of symptom onset, to received either enoxaparin (40 mg once daily if <100 kg, and 40 mg twice daily if ≥ 100 kg) or no enoxaparin, called the current standard of care (SOC), for 21 days. Patients with contraindications to unfractionated heparin (UFH) or LMWH, previous COVID-19 vaccination, recent (<48 hours)/planned spinal/epidural anaesthesia/puncture, PCI or thrombolytic therapy within preceding 24 hours, increased risk of bleeding complications, pregnancy, severe renal impairment (GFR <30 mL/min), current AC or antiplatelet therapy (excepting low dose aspirin), and current participation within other interventional study outside the purview of TRI sponsored studies, were excluded from the study.

Participants were enrolled into the study between October 2020 and November 2021, from 15 sites across 6 separate countries (Belgium, Brazil, India, South Africa, Spain and the United Kingdom). Participants received their assigned treatment for 21 days and outcomes were assessed at 21 days, 50 days, and 90 days. Feasibility discussions and site selection visits were performed by remote phone or video conference. Feasibility analyses were conducted on our network to identify countries and sites that could deliver the protocol. National coordinating investigator (NCIs) were assigned to each country and assisted with mapping the impact of covid in their respective country, the treatment pathway for eligible patients, and appropriate sites and care settings. A confirmation letter was sent to selected sites to confirm site participation and to arrange a site initiation visit (SIV). During the SIV, the sponsor was responsible for providing appropriate training materials to ensure that all personnel involved in the conduct of the trial were adequately qualified and trained. Regular monitoring calls were scheduled for each participating site. A close out visit was performed remotely for each site at the end of the study.

Table 1. COVID-19 associated symptoms

Symptom	Details
Fever	38^{o}C
Subjective fever	Felt feverish
Cough	New onset or worsening chronic cough
Fatigue/tiredness	-
Shortness of breath	Dyspnoea
Chills	-
Muscle aches	Myalgia
Runny nose	Rhinorrea
Sore throat	-
Loss of smell and/or taste	Anosmia/ ageusia
Nausea or vomiting	-
Diarrhoea	≥3 loose/looser stools/24 hour period
Desaturations	Defined as oxygen levels below what is considered
Heart rate >100 bpm	Tachycardia
Headache	-
Sinus congestion	-
Hoarse voice	-
Abdominal pain	-
Chest pain	-
Laboratory or imaging findings indicating	-

Changes to the Study Protocol

On 13th January 2021, the steering committee voted to update the ETHIC study protocol due to the slower than expected enrollment rate, having reviewed published literature for event rates in this lower risk cohort[16-20]. Protocol amendments included altering the inclusion criteria to include patients who were ≥30 years of age and to reduce the required number of baseline associated risk factors to one. Additionally, the following further associated risk factors were incorporated into the eligibility criteria; previous VTE, liver disease, anemia of chronic disease or sickle cell disease, or an immunocompromised state (other than corticosteroid use). Furthermore, it was decided to exclude patients who had received any COVID-19 vaccination and to allow concomitant clopidogrel <75 mg monotherapy.

Data Collection, Quality Control, and Auditing

ETHIC data were collected using an electronic case report form (eCRF) designed by TRI. Routine monitoring of safety information for adverse events (AE)/ serious AEs (SAE) reports and the eCRF were conducted by the Safety Review Committee. An independent safety review committee adjudicated MEDRA codes used as well as the safety classification of all AEs entered into the system, AE relation to study treatment, and whether an SAE was expected or unexpected. The clinical events classification (CEC) committee was responsible for adjudicating death, reason for hospital admission, and classification of bleeding. The Data and Safety Monitoring Board (DSMB) was responsible for reviewing trial data at pre-specified time points and providing recommendations for study protocols and progress.

All events were managed and reported in accordance with the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting, Topic E2.

Ethics Statement

The ETHIC study was conducted in accordance with the Declaration of Helsinki and guidelines from the International Conference on Harmonisation on Good Clinical Practice (GCP) and the Medicines for Human Use (Clinical Trials) Regulations 2004, and adheres to all applicable national laws and regulations. Clinical Trial Authorisation (CTA) was obtained from each regulatory authority. The study was evaluated and approved by the local/central IEC/IRBs and regulatory authorities according to requirements for each participating country.

All eligible participants were provided with a patient information sheet and consent form. Signed informed consent (paper or electronic) was obtained for all participating individuals, according to local requirements at each participating site. Enrolled patients could withdraw consent at any time by notifying the investigator. If lost to follow up, the investigator attempted to obtain the cause of withdrawal. All events were managed and reported in accordance with the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting, Topic E2.

Procedure and Outcome Measures

Baseline characteristics and clinical data were collected at enrollment: demographic characteristics, care settings, COVID-19 testing methods, time to randomization, COVID-19 symptoms at enrollment, and medical history. ETHIC aimed to evaluate the impact of standard-dose prophylactic enoxaparin treatment upon outcomes compared with the SOC in community patients with COVID-19. Outcomes were first assessed at 21 days, the primary timepoint for this study. Additional follow up data was recorded at 50 and 90 days. The primary efficacy outcome measured was the composite rate of hospitalization and mortality. Secondary efficacy outcomes included hospitalization, VTE, and all-cause mortality (including cardiovascular, non-cardiovascular, specific cause, and major bleed related death).

Safety outcomes included major bleeding, any bleeding (including major, clinically relevant non-major, or minor), and adverse events (AEs). Bleeding severity was defined according to the ISTH criteria; Major bleeding: clinically overt bleeding associated with death, within a critical area or organ, or caused by a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more or leading to transfusion of 2 or more units of whole blood or red cells; Clinically relevant non-major bleeding: requiring medical intervention by a healthcare professional, leading to hospitalization/increasing level of care, promoting face-to-face evaluation; minor bleeding: any overt bleeding that did not meet the criteria for major or clinically relevant non-major bleeding. AEs were defined as any unfavorable and unintended sign, symptom, or disease which was temporally associated with the use of a medicinal project whether related to the study project or not, any new or worsening disease, and any deterioration in laboratory levels/clinical tests associated with symptoms or leading to change/discontinuation of treatment. SAEs must have met one of the following criteria: fatality, life threatening, new/prolonged hospitalization, disability/incapacity, congenital anomaly/birth defect in infant born to mother exposed to the drug, significant medical event that may require medical or surgical intervention to prevent one of the above outcomes.

Populations

Three population sets were analysed during this study. Firstly, the key efficacy population for this study was the intention-to-treat (ITT) group. This consisted of all patients who provided signed informed consent and were randomized. Second, the per-protocol (PP) population was a subset of the ITT population, which excluded patients who complied with <50% of the randomized treatment or had major protocol deviations. Third, the safety population for this study was the as-treated (AT) group, in which the participants were assigned to the treatment they received, irrespective of assigned randomization group. If a participant randomized to enoxaparin did not receive the initial randomized drug, then the participant was assigned to the SOC arm. If a participant randomized to SOC initiated enoxaparin up to 2 days after randomization, the participant was assigned to the enoxaparin arm.

Statistical Analysis

Sample size calculations were based on an alpha of 0.05 and an event rate of 25% in the standard arm. Assuming a relative risk of 0.75 (i.e., an event rate of 18.75% with enoxaparin) and 80% power, the study required a total of 1,370 study participants. As enoxaparin use was well understood, a formal interim analysis by the DSMB was not planned. The DSMB was to review after approximately one third and two thirds of the patients had been enrolled for safety only. However, as the landscape for COVID patients and events evolved, the DSMB was also tasked to evaluate the possible need for a change in sample size after two thirds of the patients were enrolled.

In September 2021, due to concerns that the overall event rate and rate of enrolment was lower than expected, the steering committee requested that the DSMB review unblinded data to provide guidance for trial continuation. The DSMB reviewed the evaluated data: the probability of experiencing the noted control event rate, or less than the noted control rate if the actual event rate was 25% assuming a binomial distribution. Conditional power calculations were conducted to determine either the number of patients required assuming the event rate seen to date, or the change in relative risk required to detect a significant difference at the end of the study[21, 22].
Continuous variables are expressed as median (Q1; Q3) and categorical variables are expressed as frequency and percentage. Due to the very low numbers of events and the early termination of the

study, only the primary outcome was tested for statistical significance with a log-rank test. These data are illustrated using a Kaplan-Meier curve. The unadjusted hazard ratio of enoxaparin versus SOC was estimated by means of Cox regression.

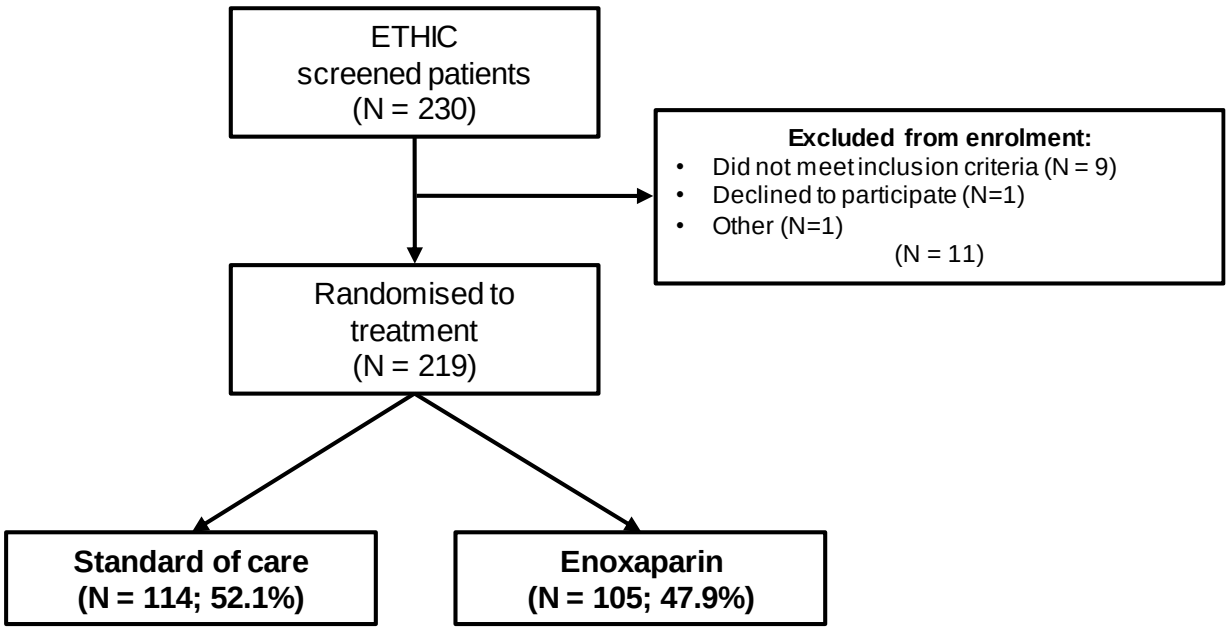
Data were extracted from the study database on 18th January 2022. All analyses were performed using SAS Enterprise Guide 7.1.

RESULTS

Study Population

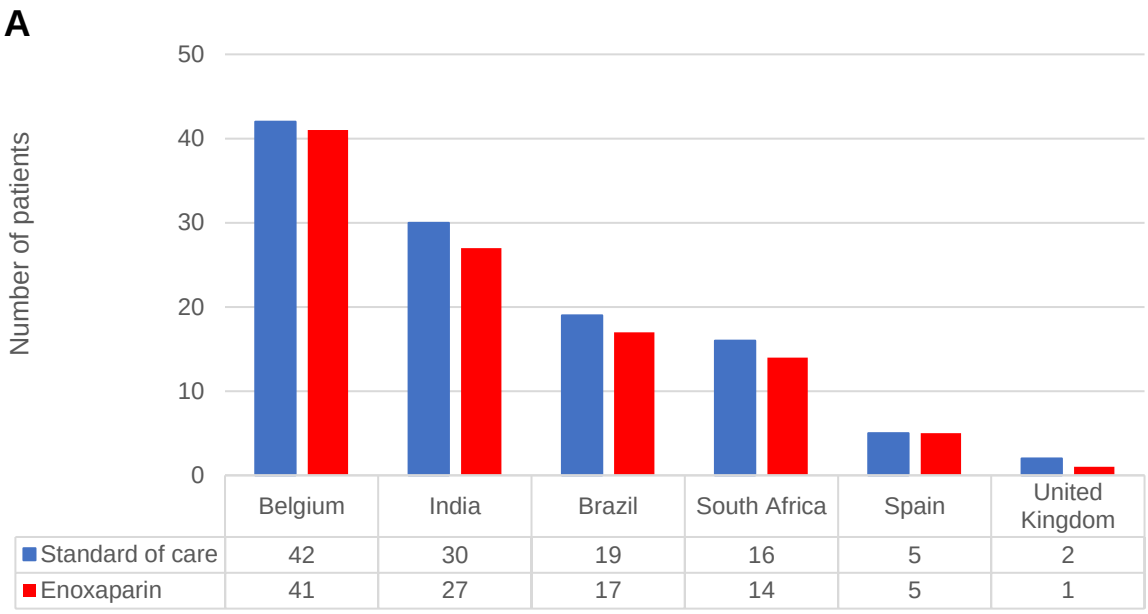
Enrolment into the ETHIC study commenced on 27th October 2020. On 8th November 2021, due a low overall event rate, slower than anticipated rate of enrolment, and the perceived futility of results obtained, enrolment was terminated following evaluation and recommendation from the DSMB. Of 230 screened patients, a total of 219 eligible symptomatic COVID-19 outpatients were enrolled into the ETHIC study (Figure 1). The enoxaparin treatment group was comprised of 105 patients (47.9%) and the SOC treatment group comprised of 114 patients (52.1%).

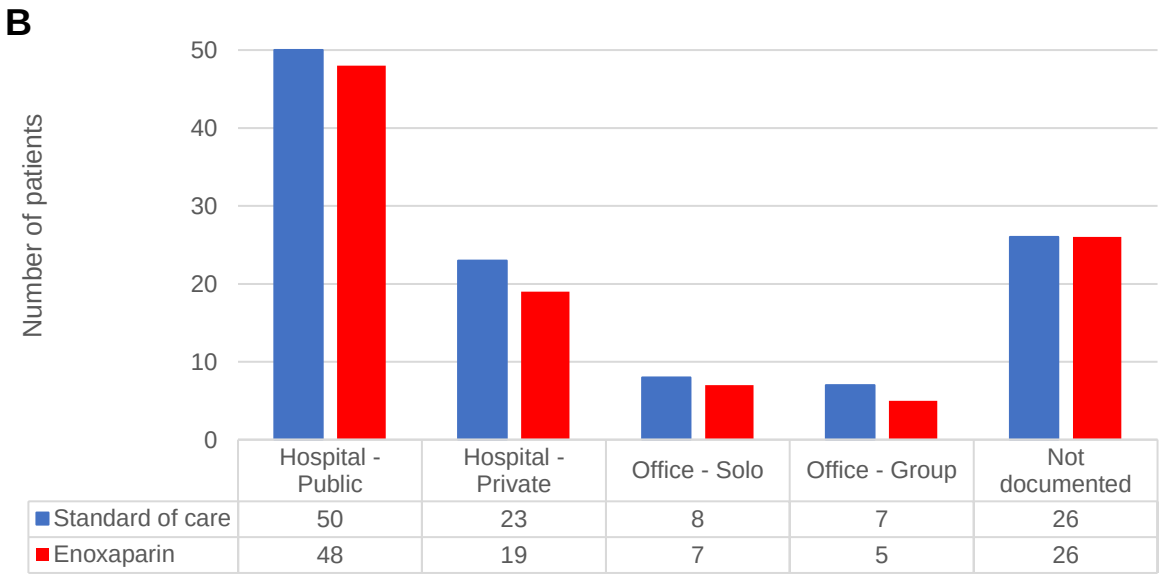
Figure 1. Flow chart of the study population of the ETHIC trial.



The greatest proportion of patients in both the enoxaparin group and the SOC group was enrolled from Belgium and India (Figure 2A) and the majority of patients were enrolled from public hospitals (Figure 2B).

Figure 2. Distribution of a) country and b) care setting information by treatment group





Baseline Demographic Characteristics

At baseline, the median (IQR) age of the enoxaparin and the SOC treatment arms of ETHIC population was 59 (51-66) and 59 (50-66), the median BMI was 30.1 kg/m^2 (27.5-31.9) and 28.8 kg/m^2 (26.3-32.2), and 57.1% and 54.9% were male, respectively. Caucasian patients comprised the largest proportion of each (57.1% and 61.1%) followed by Asian patients (27.6% and 27.4). Patients were most often diagnosed via a nasopharyngeal swab (77.9% and 76.6%). The median time to randomization following diagnosis, was 2 days for both groups. A full description of baseline characteristics can be found in Table 2 below.

Table 2. Baseline demographics and clinical characteristics.

Variable	Enoxaparin (n=105)	Standard of Care (n=114)
Age, median years (Q1; Q3)	59 (51 to 66)	59 (50 to 66)
Male, n (%)	60 (57.1)	62 (54.9)
Race, n (%)		
Arab/Middle Eastern	1 (1.0)	1 (0.9)
Asian	29 (27.6)	31 (27.4)
Black	4 (3.8)	1 (0.9)
Mixed	5 (4.8)	4 (3.5)
White	60 (57.1)	69 (61.1)
White (Hispanic)	6 (5.7)	6 (5.3)
Unknown	0 (0)	1 (0.9)
Missing	0	1
BMI, median kg/m^2 (Q1; Q3)	30.1 (27.5 to 31.9)	28.8 (26.3 to 32.2)
Smoking status, n (%)		
Current smoker	13 (11.8)	5 (5.0)
Previous smoker	20 (18.2)	21 (21.0)
Never smoker	77 (70.0)	74 (74.0)
Alcohol consumption		
Abstinent/light consumption	91 (91.9)	81 (90.0)

Moderate consumption	7 (7.1)	9 (10.0)
Heavy consumption	1 (1.0)	0 (0.0)
Covid-19 testing method, n (%)		
Nasal Swab	5 (4.8)	3 (2.7)
Nasopharyngeal Swab (NP)	81 (77.9)	85 (76.6)
Oropharyngeal (OP)	3 (2.9)	2 (1.8)
NP and OP	15 (14.4)	21 (18.9)
Days from Covid-19 diagnosis to randomization, median (Q1; Q3)	2.0 (1.0 to 3.0)	2.0 (1.0 to 3.0)
Symptoms at enrolment, n (%)		
Fever	44 (41.9)	51 (45.1)
Subjective Fever	20 (19)	25 (22.1)
Cough	57 (54.3)	66 (58.4)
Tiredness	47 (44.8)	49 (43.4)
Dyspnoea	10 (9.5)	11 (9.7)
Chills	24 (22.9)	23 (20.4)
Muscle aches	46 (43.8)	53 (46.9)
Runny nose	27 (25.7)	35 (31.0)
Sore throat	34 (32.4)	34 (30.1)
Nausea/vomiting	12 (11.4)	20 (17.7)
Diarrhoea	15 (14.3)	16 (14.2)
Loss of Smell	37 (35.2)	38 (33.6)
Decreased measured oxygen levels	4 (3.8)	1 (0.9)
Heart rate > 100 beats per minute	3 (2.9)	5 (4.4)
Headache	40 (38.1)	66 (58.4)
Sinus congestion	9 (8.6)	10 (8.8)
Hoarse voice	7 (6.7)	5 (4.4)
Stomach ache (abdominal pain)	4 (3.8)	2 (1.8)
Chest pain	2 (1.9)	8 (7.1)
Laboratory or imaging findings indicating Covid-19 infection	10 (9.5)	8 (7.1)

BMI; body mass index

Vaccination status

As described in the protocol, eligible patients could not have been vaccinated prior to enrolment. Two protocol violations regarding prior vaccination status were recorded: one patient in the enoxaparin group had received their first dose COVID-19 vaccination 119 days prior to randomization and one patient in the SOC group had received their first dose vaccination 18 days prior to enrolment (Table 3). After enrolment, 43 (41.0%) in the enoxaparin group and 50 (43.9%) patients in SOC group received at least a first dose vaccination. The median time (25th, 75th percentiles) from enrolment to first dose vaccination was 40 days (Q1:Q3, 31 to 61) in the enoxaparin group and 42 days (Q1:Q3, 36 to 57) in the SOC group.

Table 3. Distribution of COVID-19 vaccination doses before and after enrolment by treatment group

Variable, n (%)	Enoxaparin (n=105)	Standard of Care (n=114)
Before enrolment		
At least one dose	1 (1.0)	1 (0.9)
Two doses	1 (1.0)	0 (0.0)
After enrolment		
At least one dose	43 (41.0)	50 (43.9)
Two doses	29 (27.6)	36 (31.6)

Clinical Characteristics

With the exception of chronic lung disease, which was less prevalent in the enoxaparin group than the SOC group (7.9% versus 16.3%), baseline clinical characteristics were comparable between both treatment arms of the study. Hypertension was the most common clinical characteristic recorded in each group; 73.7% versus 67.4%, respectively, followed by diabetes at 31.6% versus 30.2% and vascular disease at 15.8% versus 16.3%, respectively. A full description of medical history is shown in Table 4 below.

Table 4. Clinical history documented at baseline

Variable, n (%)	Enoxaparin (n=105)	Standard of Care (n=114)
Chronic lung disease[1]	6 (7.9)	14 (16.3)
Diabetes	24 (31.6)	26 (30.2)
Active cancer[2]	0 (0.0)	2 (2.3)
Vascular disease	12 (15.8)	14 (16.3)
Heart valve disease (moderate or severe)	0 (0.0)	1 (1.2)
Treated arrhythmia	1 (1.3)	2 (2.3)
Heart failure	0 (0.0)	1 (1.2)
Hypertension	56 (73.7)	58 (67.4)
Congenital heart disease	1 (1.3)	0 (0.0)
Prior Stroke or transient ischemic attack	2 (2.6)	1 (1.2)
Carotid artery disease	2 (2.6)	0 (0.0)
Prior venous thromboembolism	2 (2.6)	0 (0.0)
Chronic liver disease	1 (1.3)	0 (0.0)
Immunocompromised condition[2]	1 (1.3)	3 (3.5)

[1]Asthma, emphysema, chronic obstructive pulmonary disease, pulmonary fibrosis

[2]immunosuppressive therapy including steroids, HIV

Concomitant medication recorded at baseline for each study arm is provided in Table 5 below. The most common co-medications recorded for the enoxaparin group were statins (26.7%), beta blockers (23.8%), oral antidiabetic agents (22.9%), low dose aspirin (21.0%), and angiotensin receptor blockers (16.2%). The most common medications recorded for the SOC group were beta blockers (27.2%), statins (26.3%), low dose aspirin (21.9%), and oral antidiabetic agents (16.7%), and calcium channel blockers (16.7%). Concomitant use of LMWH, other than enoxaparin, was recorded in 8.6% of the enoxaparin group and 12.3% of the SOC group.

Table 5. Concomitant medications at baseline

Variable, n (%)	Enoxaparin (n=105)	Standard of Care (n=114)
Angiotensin receptor blockers	17 (16.2)	17 (14.9)
Angiotension converting enzyme inhibitors	13 (12.4)	12 (10.5)
Anti-arrhythmic medication other than digoxin	0 (0)	1 (0.9)
Antibiotics	11 (10.5)	13 (11.4)
Antihelmintics	0 (0)	1 (0.9)
Antiplatelets	1 (1.0)	1 (0.9)
Benzodiazepines	4 (3.8)	4 (3.5)
Beta blockers	25 (23.8)	31 (27.2)
Bronchodilators	5 (4.8)	4 (3.5)
Calcium channel blockers	16 (15.2)	19 (16.7)
Hydroxychloroquine	1 (1.0)	1 (0.9)
Immunotherapy	0 (0)	1 (0.9)
Insulin	3 (2.9)	2 (1.8)
Low dose aspirin (acetylsalicylic acid) (100mg)	22 (21.0)	25 (21.9)
Low molecular weight heparins[1]	9 (8.6)	14 (12.3)
Nitrates	0 (0)	2 (1.8)
Non-steroidal anti-inflammatory drugs	3 (2.9)	7 (6.1)
Oral antidiabetic agents	24 (22.9)	19 (16.7)
Other anti-inflammatory/ immune modulating agents	5 (4.8)	1 (0.9)
Potassium sparing diuretics/ mineralocorticoid receptor antagonists	0 (0)	2 (1.8)
Proton-pump inhibitors/ H2-receptor antagonist	14 (13.3)	18 (15.8)
Selective serotonin reuptake inhibitors	6 (5.7)	5 (4.4)
Statins	28 (26.7)	30 (26.3)
Steroids, inhaled or nasal	11 (10.5)	12 (10.5)
Steroids, oral	13 (12.4)	10 (8.8)
Antiviral agents (including HIV medication)	1 (1.0)	0 (0)
Other diuretics	1 (1.0)	1 (0.9)
Missing	12	23

[1]**Non study drugs**

Enoxaparin Treatment

Of the 105 patients randomized to the enoxaparin treatment group, 83.8% received a single daily dose of 40 mg, and 16.2% received a twice-daily dose of 40 mg. The median duration of enoxaparin treatment was 21 days, the primary endpoint as dictated by the study protocol. Enoxaparin treatment ceased most often due to reaching end of treatment planned (73.8%), due to adverse event (12.6%), or due to patient choice (12.6%). One patient changed their dose during treatment from 40 mg once daily to 40mg twice daily during this study. A total of 6 patients had their treatment interrupted and restarted. The median time from randomization to interruption was 4 days (Table 6).

Table 6. Administered dosages of enoxaparin

Variable, n (%)	Enoxaparin (n=105)
Daily dose of Enoxaparin	
40 mg once daily	88 (83.8)
40 mg twice daily	17 (16.2)
Reason drug stopped	
Adverse Event	13 (12.6)
End of treatment planned	76 (73.8)
Patient decision	13 (12.6)
Other	1 (1.0)
Missing	2
Enoxaparin dose changed[1]	1 (1.0)
Enoxaparin treatment interrupted and restarted[2]	6 (5.7)

[1]Dose changed from 40 mg once daily to 40 mg twice daily, [2]Median (Q1; Q3) time from randomization to interruption was 4 (2 to 12) days

Clinical Efficacy Outcomes According to the Intention to Treat Population

At 21 days, 213 (97.3%) of the 219 enrolled patients achieved follow up. Of the 6 patients who did not reach 21 days, 5 patients were lost to follow up and 1 patient died. Stratified according to 'intention-to-treat' analysis, the composite of all-cause mortality and hospitalization was observed in 12 patients in both the enoxaparin (11.4%) and SOC (10.5%) groups (Table 6). Cumulative incidence curves for all-cause mortality/hospitalization are provided in Figure 3. No evidence was found of a reduction for the primary outcome in patients randomized to enoxaparin (log-rank test p-value: 0.829, hazard ratio (95% CI) of enoxaparin vs SOC: 1.09 (0.49-2.43)).

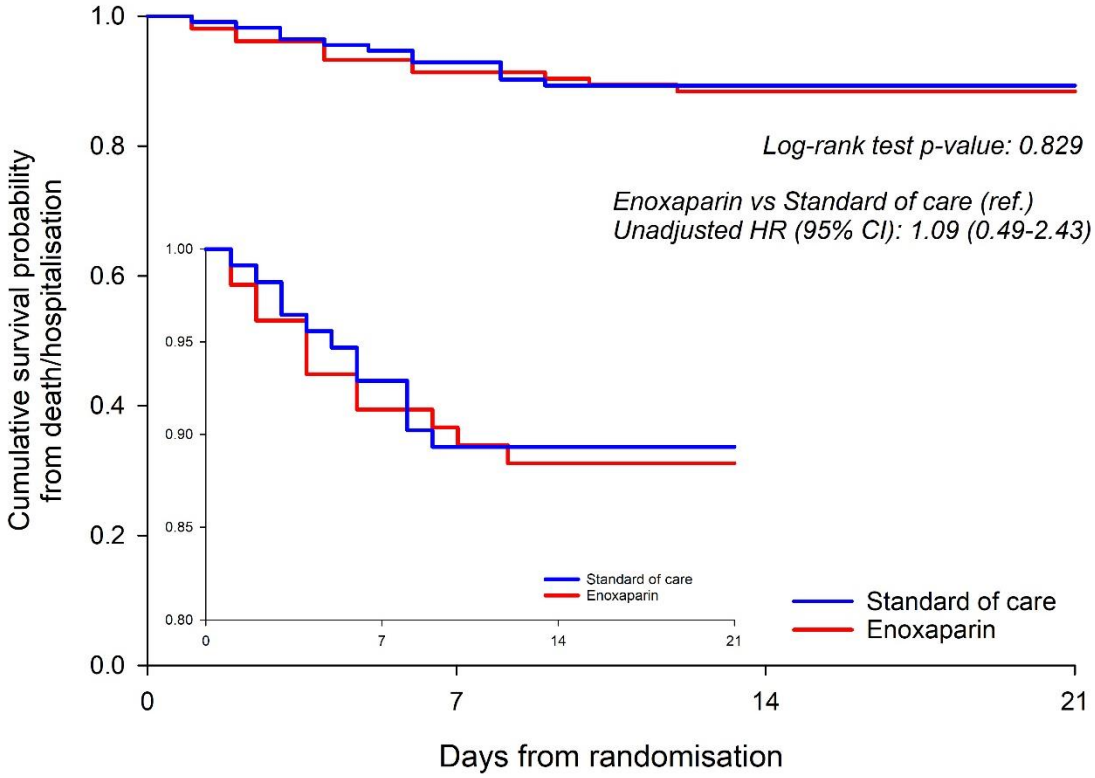
All-cause death was recorded for one patient in the enoxaparin arm and cause of death was unknown. This patient was hospitalized prior to death. A total of 12 patients were hospitalized in each treatment group. Additional information for hospitalization events is provided in Table 7 below. Of hospitalization patients, 33.3% of those in the enoxaparin group and 41.7% of the SOC group required supplemental oxygen. At 21 days, one patient in each group experienced a VTE event: deep vein thrombosis within the enoxaparin group and pulmonary embolism in the SOC group. Neither of these two patients had prior VTE before randomization. At 90 days, the composite of cumulative all-cause death and hospitalization remained at 12 patients in each group (Table 6).

Table 6. Cumulative efficacy endpoints during follow-up, by treatment (n=219)

Outcomes	21 Days		50 Days		90 Days	
	Enoxaparin Events, n (%)	SOC Events, n (%)	Enoxaparin Events, n (%)	SOC Events, n (%)	Enoxaparin Events, n (%)	SOC Events, n (%)
Primary Outcomes						
All-cause death	1 (1.0)	0 (0)	1 (1.0)	1 (0.9)	1 (1.0)	1 (0.9)
Hospitalization	12 (11.4)	12 (10.5)	12 (11.4)	12 (10.5)	12 (11.4)	12 (10.5)
Composite all-cause death and hospitalization	12 (11.4)	12 (10.5)	12 (11.4)	12 (10.5)	12 (11.4)	12 (10.5)
Secondary outcomes						
VTE	1 (1.0)	1 (0.9)	1 (1.0)	2 (1.8)	1 (1.0)	2 (1.8)

SOC; standard of care, VTE; venous thromboembolism

Figure 3. Cumulative survival probability for death/hospitalization by treatment group



Patients at risk

Standard of care	114	104	100	99
Enoxaparin	105	95	91	91

Table 7. Hospitalization event additional information by treatment among patients hospitalized within 21 Days

Variable, n (%)	Enoxaparin (n=12)	Standard of Care (n=12)
Mechanical ventilation/ ECMO	3 (25.0)	-
Non-invasive ventilation/high flow oxygen	2 (16.7)	1 (8.3)
Hospitalized on supplemental oxygen	4 (33.3)	5 (41.7)
Hospitalized not requiring supplemental oxygen	-	-
Hospitalized not requiring ongoing medical care	-	1 (8.3)
Acute medical care or admission to ICU	4 (33.3)	-

ECMO; extracorporeal membrane oxygenation, ICU; intensive care unit.

Clinical Safety Outcomes According to the Intention to Treat Population

At 21 days, 2 patients within the enoxaparin group (1.9%) and one patient within the SOC group (0.9%) experienced any bleeding event. Major bleeding, specifically abnormal uterine bleeding, was recorded for just one patient within the SOC group only.

Adverse events were experienced by 22 patients (21.0%) of the enoxaparin group and 13 patients (11.4%) of the SOC group (Table 8). Adverse event rates varied by participating country (Table 9). No adverse events were identified in India. To verify, sites and monitors were asked to review. No additional events were found.

Serious AEs were reported less often in the enoxaparin group (59.1%) compared with the SOC group (92.3%) (Table 10). The most common adverse events experienced in both the enoxaparin and SOC groups was COVID-19 related pneumonia (27.3% and 38.5%, respectively).

At 90 days, the cumulative percentage of any bleeding in the enoxaparin group was 2.9% and in the SOC group was 2.6%. The total percentage of adverse events in the enoxaparin and SOC groups increased to 24 patients (22.9%) and 19 patients (16.7%), respectively (Table 8).

Table 8. Cumulative safety endpoints during follow-up, by treatment (n=219)

Outcome	21 Days		50 Days		90 Days	
	Enoxaparin Events, n (%)	SOC Events, n (%)	Enoxaparin Events, n (%)	SOC Events, n (%)	Enoxaparin Events, n (%)	SOC Events, n (%)
Any bleed[1]	2 (1.9)	1 (0.9)	2 (1.9)	2 (1.8)	3 (2.9)	3 (2.6)
Major bleed	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)
Adverse Events	22 (21.0)	13 (11.4)	23 (21.9)	17 (14.9)	24 (22.9)	19 (16.7)

SOC; standard of care

Table 9. Number of patients who experienced at least one adverse event within 90 days of follow-up by country

Country	Overall, n (%) (n=43)
Belgium (n=83)	23 (27.7)
Brazil (n=36)	9 (25.0)
South Africa (n=30)	6 (20.0)
Spain (n=10)	4 (40.0)
United Kingdom (n=3)	1 (33.3)
India (n=57)	0 (0.0)

Table 10. Adverse event details among patients who had an adverse event within 21 days

Adverse Event, n (%)	Enoxaparin (n=22)	Standard of Care (n=13)
Adverse event information, n (%)		
Serious adverse event	13 (59.1)	12 (92.3)
Resulting in persisting or significant disability or incapacity	4 (18.2)	3 (23.1)
Life-threatening adverse event	6 (27.3)	2 (15.4)
Adverse event severity		
Mild	6 (27.3)	3 (23.1)
Moderate	10 (45.5)	8 (61.5)
Severe	6 (27.3)	2 (15.4)
Type of adverse event, n (%)		
COVID-19 pneumonia	6 (27.3)	5 (38.5)
COVID-19 respiratory infection	0	2 (15.4)
Fever	0	1 (7.7)
Fibrin D dimer high	0	1 (7.7)
Hypoxemia	1 (4.5)	2 (15.4)
Oxygen saturation decreased	2 (9.1)	1 (7.7)
Pulmonary embolism	0	1 (7.7)
Chest discomfort	1 (4.5)	0

Chills	1 (4.5)	0
Hypermenorrhea	1 (4.5)	0
Hypotension	1 (4.5)	0
Injection site bruising	1 (4.5)	0
Nausea	1 (4.5)	0
Near fainting	1 (4.5)	0
Oxygen saturation low	1 (4.5)	0
Rash on legs & arms	1 (4.5)	0
Respiratory failure	1 (4.5)	0
Shingles	1 (4.5)	0
Shortness of breath	1 (4.5)	0
Vertigo	1 (4.5)	0

Clinical Outcomes According to the 'As-Treated' Population

Two patients who were randomized to standard of care received enoxaparin. Two patients who were randomized to enoxaparin did not receive the treatment. The sample size according to the "as treated" definition was thus 105 for enoxaparin and 114 for SOC. At 21 days, stratified according to the 'as-treated' analysis, the composite of all-cause mortality and hospitalization was observed in 11 patients (10.5%) in the enoxaparin group and 13 patients (11.4%) in the SOC group (Table 11). All-cause death was recorded for one patient in the enoxaparin arm and cause of death was unknown. At 90 days, the composite of cumulative all-cause death and hospitalization remained at 11 and 13 patients in each group, respectively.

At 21 days, major bleeding was recorded for just one patient within the SOC group only. Adverse events were experienced by 21 patients (20.0%) of the enoxaparin group and 14 patients (12.3%) of the SOC group (Table 12). At 90 days, the cumulative percentage of any bleeding in the enoxaparin group was 2.9% and in the SOC group was 2.6%. The total percentage of adverse events in the enoxaparin and SOC groups increased to 23 patients (21.9%) and 20 patients (17.5%), respectively (Table 12).

Table 11. Efficacy events by treatment group and follow-up period from randomization.

Treatment classified according to the 'as treated' definition

Outcomes	21 Days		50 Days		90 Days	
	Enoxaparin Events, n (%)	SOC Events, n (%)	Enoxaparin Events, n (%)	SOC Events, n (%)	Enoxaparin Events, n (%)	SOC Events, n (%)
Primary Outcomes						
All-cause death	1 (1.0)	0 (0.0)	1 (1.0)	1 (0.9)	1 (1.0)	1 (0.9)
Hospitalization	11 (10.5)	13 (11.4)	11 (10.5)	13 (11.4)	11 (10.5)	13 (11.4)
Composite all-cause death and hospitalization	11 (10.5)	13 (11.4)	11 (10.5)	13 (11.4)	11 (10.5)	13 (11.4)
Secondary Outcomes						
VTE	1 (1.0)	1 (0.9)	1 (1.0)	2 (1.8)	1 (1.0)	2 (1.8)

SOC; standard of care, VTE; venous thromboembolism

Table 12. Safety events by treatment group and follow-up period from randomization.

Treatment classified according to 'as treated' definition

Outcome	21 Days		50 Days		90 Days	
	Enoxaparin Events, n (%)	SOC Events, n (%)	Enoxaparin Events, n (%)	SOC Events, n (%)	Enoxaparin Events, n (%)	SOC Events, n (%)
Any bleed[1]	2 (1.9)	1 (0.9)	2 (1.9)	2 (1.8)	3 (2.9)	3 (2.6)
Major bleed	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)
Adverse Events	21 (20.0)	14 (12.3)	22 (21.0)	18 (15.8)	23 (21.9)	20 (17.5)

SOC; standard of care

Clinical Outcomes According to the Per Protocol Population

A total of 21 patients were excluded from this analysis (5 from the Standard of Care group and 16 from the enoxaparin group). The sample size for the two groups in this analysis is thus 109 for the SOC group and 89 for the enoxaparin group. At 21 days, stratified according to the 'per-protocol' analysis, the composite of all-cause mortality and hospitalization was observed in 10 patients (11.2%) in the enoxaparin group and 12 patients (11.0%) in the SOC group (Table 13). All-cause death was recorded for one patient in the enoxaparin arm and cause of death was unknown. At 90 days, the composite of cumulative all-cause death and hospitalization remained at 10 and 12 patients in each group, respectively.

At 21 days, major bleeding was recorded for just one patient within the SOC group only. Adverse events were experienced by 16 patients (18.0%) of the enoxaparin group and 13 patients (11.9%) of the SOC group (Table 14). At 90 days, the cumulative percentage of any bleeding in the enoxaparin group was 3.4% and in the SOC group was 2.8%. The total percentage of adverse events in the enoxaparin and SOC groups increased to 18 patients (20.2%) and 19 patients (17.4%), respectively (Table 14).

Table 13. Efficacy events by treatment group and follow-up period from randomization. Treatment classified according to the 'per protocol' definition.

Outcomes	21 Days		50 Days		90 Days	
	Enoxaparin Events, n (%)	SOC Events, n (%)	Enoxaparin Events, n (%)	SOC Events, n (%)	Enoxaparin Events, n (%)	SOC Events, n (%)
Primary Outcomes						
All-cause death	1 (1.1)	0 (0.0)	1 (1.1)	1 (0.9)	1 (1.1)	1 (0.9)
Hospitalization	10 (11.2)	12 (11.0)	10 (11.2)	12 (11.0)	10 (11.2)	12 (11.0)
Composite all-cause death and hospitalization	10 (11.2)	12 (11.0)	10 (11.2)	12 (11.0)	10 (11.2)	12 (11.0)
Secondary Outcomes						
VTE	1 (1.1)	1 (0.9)	1 (1.1)	2 (1.8)	1 (1.1)	2 (1.8)

Table 13. Safety events by treatment group and follow-up period from randomization.

Treatment classified according to the 'per protocol' definition.

Outcome	21 Days		50 Days		90 Days	
	Enoxaparin Events, n (%)	SOC Events, n (%)	Enoxaparin Events, n (%)	SOC Events, n (%)	Enoxaparin Events, n (%)	SOC Events, n (%)
Any bleed[1]	2 (2.3)	1 (0.9)	2 (2.3)	2 (1.8)	3 (3.4)	3 (2.8)
Major bleed	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)
Adverse Events	16 (18.0)	13 (11.9)	17 (19.1)	17 (15.6)	18 (20.2)	19 (17.4)

SOC; standard of care

LIMITATIONS OF THE ETHIC TRIAL

The ETHIC Trial has certain limitations. Firstly, the trial was designed as an open-label study, as placebo treatment during the course of this investigate would not have been ethically appropriate for the control treatment arm. Secondly, adjustments to the inclusion and exclusion criteria were made during the course of this study, to account for the low event rate, include an adjustment of age limit from above 55 years to above 30 years old. Finally, difficult with patient enrolment during the pandemic led to low patient numbers and the early termination of the study.

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