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Enoxaparin for primary thromboprophylaxis in symptomatic outpatients with COVID-19 (OVID): a randomised, open-label, parallel-group, multicentre, phase 3 trial

*Stefano Barco, Davide Voci, Ulrike Held, Tim Sebastian, Roland Bingisser, Giuseppe Colucci, Daniel Duerschmied, André Frenk, Bernhard Gerber, Andrea Götschi, Stavros V Konstantinides, François Mach, Helia Robert-Ebadi, Thomas Rosemann, Noemi R Simon, Hervé Spechbach, David Spirk, Stefan Stortecky, Lukas Vaisnora, Marc Righini, Nils Kucher, on behalf of the OVID investigators**

Summary

Background COVID-19 is a viral prothrombotic respiratory infection. Heparins exert antithrombotic and anti-inflammatory effects, and might have antiviral properties. We aimed to investigate whether thromboprophylaxis with enoxaparin would prevent untoward hospitalisation and death in symptomatic, but clinically stable outpatients with COVID-19.

Methods OVID was a randomised, open-label, parallel-group, investigator-initiated, phase 3 trial and was done at eight centres in Switzerland and Germany. Outpatients aged 50 years or older with acute COVID-19 were eligible if they presented with respiratory symptoms or body temperature higher than 37·5°C. Eligible participants underwent block-stratified randomisation (by age group 50–70 *vs* >70 years and by study centre) in a 1:1 ratio to receive either subcutaneous enoxaparin 40 mg once daily for 14 days versus standard of care (no thromboprophylaxis). The primary outcome was a composite of any untoward hospitalisation and all-cause death within 30 days of randomisation. Analysis of the efficacy outcomes was done in the intention-to-treat population. The primary safety outcome was major bleeding. The study was registered in ClinicalTrials.gov (NCT04400799) and has been completed.

Findings At the predefined formal interim analysis for efficacy (50% of total study population), the independent Data Safety Monitoring Board recommended early termination of the trial on the basis of predefined statistical criteria having considered the very low probability of showing superiority of thromboprophylaxis with enoxaparin for the primary outcome under the initial study design assumptions. Between Aug 15, 2020, and Jan 14, 2022, from 3319 participants prescreened, 472 were included in the intention-to-treat population and randomly assigned to receive enoxaparin (n=234) or standard of care (n=238). The median age was 57 years (IQR 53–62) and 217 (46%) were women. The 30-day risk of the primary outcome was similar in participants allocated to receive enoxaparin and in controls (8 [3%] of 234 *vs* 8 [3%] of 238; adjusted relative risk 0·98; 95% CI 0·37–2·56; p=0·96). All hospitalisations were related to COVID-19. No deaths were reported during the study. No major bleeding events were recorded. Eight serious adverse events were recorded in the enoxaparin group versus nine in the control group.

Interpretation These findings suggest thromboprophylaxis with enoxaparin does not reduce early hospitalisations and deaths among outpatients with symptomatic COVID-19. Futility of the treatment under the initial study design assumptions could not be conclusively assessed owing to under-representation of older patients and consequent low event rates.

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*Investigators are listed at end of article

Department of Angiology, University Hospital Zurich, Zurich, Switzerland (S Barco MD, D Voci MD, T Sebastian MD, Prof N Kucher MD); **Center for Thrombosis and Hemostasis, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany** (S Barco, Prof S V Konstantinides MD); **Department of Biostatistics at Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland** (Prof U Held PhD, A Götschi); **Emergency Department, University Hospital Basel, Basel, Switzerland** (Prof R Bingisser MD, N R Simon MD); **Service of Hematology, Clinica Luganese Moncucco, Lugano, Switzerland** (G Colucci MD); **Department of Hematology, University of Basel, Basel, Switzerland** (G Colucci); **Clinica Sant'Anna, Sorengo, Switzerland** (G Colucci); **Department of Cardiology, Angiology, Haemostaseology and Medical Intensive Care, University Medical Centre Mannheim, Medical Faculty Mannheim, Heidelberg University, Germany** (Prof D Duerschmied MD); **European Center for AngioScience (ECAS) and German Center for Cardiovascular Research (DZHK) partner site Heidelberg–Mannheim, Mannheim, Germany**

Introduction

In December 2019, a first patient tested positive for SARS-CoV-2. In March, 2020, the WHO declared the coronavirus disease-2019 (COVID-19) a pandemic. As of May 9, 2022, about 510 000 000 COVID-19 cases leading to at least 6 million deaths have been reported to the WHO globally.[1]

In the majority of patients, the disease is characterised by a mild course. In others, it manifests as a severe form of interstitial pneumonia leading to a severe acute respiratory syndrome.[2] Since the beginning of the pandemic, COVID-19 has emerged as a highly prothrombotic viral disease, causing arterial and venous thromboembolic events.[3] Randomised trials confirmed that therapeutic-dose (versus prophylactic-dose) heparin is beneficial in hospitalised patients with moderately severe COVID-19, but not in those who require intensive care or invasive ventilation.[4]

Heparins exert antithrombotic and anti-inflammatory effects.[5] It is even possible that they might have antiviral properties against SARS-CoV-2 and other Coronaviridae, and thus could be beneficial in the early phase of the

(Prof D Duerschmied); **Department of Cardiology and Angiology I, Heart CenterFreiburg University, Faculty of Medicine, University of Freiburg, Freiburg, Germany** (Prof D Duerschmied); **Department of Cardiology, University Hospital of Bern** (A Frenk PhD, S Stortecky MD, L Vaisnora MD), **Institute of Pharmacology** (Prof D Spirk MD), **University of Bern, Bern, Switzerland; Clinic of Hematology, Oncology Institute of Southern Switzerland, Ente Ospedaliero Cantonale, Bellinzona, Switzerland** (B Gerber MD); **Institute of Primary Care** (Prof T Rosemann MD), **University of Zurich** (B Gerber, Prof N Kucher), **Zurich, Switzerland; Department of Cardiology, Democritus University of Thrace, Komotini, Greece** (Prof S V Konstantinides); **Cardiology Division** (Prof F Mach MD), **Division of Angiology and Hemostasis, Department of Medicine** (H Robert-Ebadi MD, Prof M Righini MD), **Division of Primary Care Medicine** (H Spechbach MD), **Geneva University Hospitals, Geneva, Switzerland; Faculty of Medicine, University of Geneva, Switzerland** (H Robert-Ebadi, Prof M Righini)

Correspondence to:
Dr Stefano Barco, Department of Angiology, University Hospital Zurich, 8091 Zurich, Switzerland
stefano.barco@usz.ch

Research in context

Evidence before this study

During the preparation of the study protocol in April 25, 2020, we did a structured, non-systematic review of the literature published in Medline to gather available evidence on thromboembolic complications in patients with COVID-19 and the use of anticoagulation. We used the following keywords for the search: "COVID-19", "SARS-CoV2", "thrombosis", "venous thromboembolism", "anticoagulation", and "heparin". Furthermore, we searched meta-analysis papers investigating the role of thromboprophylaxis in hospitalised and ambulatory patients with medical illnesses. Finally, we accessed national registries and public epidemiological data to obtain information on hospitalisation and mortality rates in the general population across age groups. Before the drafting of the manuscript, we consulted a well-conducted systematic review of ongoing or published, phase 3, randomised, controlled trials investigating the efficacy and safety of anticoagulant treatment in patients with COVID-19. It identified nine phase 3 trials of prophylactic or therapeutic anticoagulation in outpatients. We integrated this information with the results of a structured, non-systematic search of Medline on Jan 10, 2022 that did not lead to the identification of additional studies. Of nine trials, only one, the ACTIV-4B, has been published thus far. The study was stopped for futility as it was found that apixaban or aspirin *vs* placebo did not reduce COVID-19-associated complications. Aside from OVID, only one unpublished study, the ETHIC trial, investigated the efficacy of low-molecular-weight heparin in outpatients with COVID-19. The remaining six, ongoing trials are studying the efficacy and safety of the direct oral anticoagulants rivaroxaban, apixaban, and edoxaban.

Added value of this study

To our knowledge, this is the first and largest randomised controlled trial designed to investigate the efficacy and safety of primary venous thromboembolism prevention with heparin in symptomatic outpatients with COVID-19. We compared enoxaparin given at a standard prophylactic dosage with the standard of care at the time of study design, which included neither specific COVID-19 treatments nor anticoagulation. The results suggest that thromboprophylaxis with enoxaparin did not reduce the risk of early hospitalisation for any cause under the initial assumption of a higher overall risk. The overall risk of COVID-19-related hospitalisation was lower than expected, but still substantial, approximately 3·4% in each group. This lower rate can be explained by the fact that, although our study targeted a population of patients aged 50 years or older, we were unable to effectively enrol highest-risk patients, notably participants aged 70 years or older. As a consequence, the results of OVID must be carefully translated to elderly patients, for whom more evidence from randomised controlled trials is needed.

Implications of all the available evidence

These findings from an individual multinational, randomised, controlled, phase 3 trial on low-molecular-weight heparin, together with those from a published trial on the direct oral anticoagulant apixaban, do not support the routine use of anticoagulants in outpatients with COVID-19, as it might not prevent clinical deterioration in terms of hospitalisations related to COVID-19. Further pooled analyses of published and ongoing trials should confirm these findings, also in relation to venous thromboembolic events.

infection.[6,7] Most individuals with COVID-19 do not require hospitalisation and are managed in primary care. In this context, the OVID trial aimed to investigate whether thromboprophylaxis with low-molecular-weight heparin improves the course of symptomatic, but clinically stable, outpatients with COVID-19.

Methods

Study design and participants

The study design and rationale of the OVID trial together with the third version of the study protocol (version 3.0, May 18, 2020) have been published previously.[8] In brief, OVID was a randomised, open-label, parallel-group, multicentre, investigator-initiated, phase 3 trial done at eight centres in Switzerland and Germany (appendix, pp 10–11). The study was approved by appropriate national regulatory authorities, applicable local COVID-19 scientific boards, and ethical committees. The trial was done in accordance with the Declaration of Helsinki and principles of Good Clinical Practice.

OVID enrolled outpatients aged 50 years or older who presented with acute respiratory symptoms or body temperature higher than 37·5°C, with a positive test for SARS-CoV-2 in the previous 5 days done at recognised COVID-19 test centres and subjected to reporting to the Federal Office of Public Health in Switzerland and Germany, and who were eligible for ambulatory treatment. Additionally, participants were considered eligible if they were able to travel to the study centre for a baseline visit and did not have any condition posing an indication for anticoagulation treatment. Patients were excluded if they had contraindications to anticoagulant treatment, including severe renal or hepatic dysfunction, severe anaemia, recent major bleeding, or were on dual antiplatelet treatment. A complete list of inclusion and exclusion criteria is reported in appendix (pp 2–3). All participants provided written informed consent for participation in the study before enrolment. Study information was available in four languages. A separate informed consent for screening was collected if the patient underwent SARS-CoV-2 testing outside the OVID study centres. Patient screening took place following three main strategies: patients were screened at the study site on the day of SARS-CoV-2 testing, referred from external test

See Online for appendix

centres or general practitioners, or patients or their treating physicians contacted the OVID telephone hotline, which ensured a single contact to receive initial information about the study, verify the eligibility criteria, and plan an in-hospital visit for screening and recruitment at one of the study sites.

Randomisation and masking

Eligible participants underwent block-stratified randomisation (by age group 50–70 *vs* >70 years and by study centre) in a 1:1 ratio to receive either enoxaparin or standard of care (no thromboprophylaxis). The randomisation sequence was computer-generated and integrated into the electronic data capture software RedCAP (Vanderbild University, version 9.1.24). This task was done by personnel of the Clinical Trial Unit of the University Hospital Zurich. The study was done as an open-label randomised trial as no enoxaparin-placebo was available during the early phases of the COVID-19 pandemic. Participants and study personnel were aware of treatment allocation, but not of the allocation sequence.

Procedures

The general population was made aware of the OVID trial and of a telephone hotline via social media, television programmes, and advertising material distributed in hospitals, test centres, and general physicians' ambulatories. Participants were instructed by telephone and per email on how to reach the study site alone or with a person from the same household by private car or by dedicated so-called COVID-19 taxis approved by the Federal Office of Public Health. A detailed protocol concerning room usage, shared spaces, protection measures, and storing of medical documents was developed at each centre in collaboration with their Departments of Hygiene and Infectious Diseases. On written consent, the eligibility criteria were verified, including the laboratory assessment of blood count and renal or hepatic function parameters and a routine evaluation of vital parameters, and participants were then randomised by study physicians at each centre. Participants received a study card with the 24/7 contact data of the study team and information on the study drug allocation.

Patients randomly assigned to the enoxaparin group received the first injection of enoxaparin during the baseline visit on the same day. Enoxaparin was given at the recommended dose of 4000 international unit (IU), anti-Xa activity (40 mg)/0·4 mL, once daily by subcutaneous injection of prefilled syringes for a total of 14 days. The subsequent doses of enoxaparin were administered or self-administered at home. All prefilled syringes were provided by study personnel during the baseline visit. Patients received instructions, as well as paper and electronic illustrative materials on how to administer enoxaparin. The study team assessed drug compliance during the scheduled follow-up visits using a standardised questionnaire to monitor study drug compliance and collecting information on suspected adverse events. In addition, participants completed a dedicated form with the syringe stickers reporting their allocated lot number and shipped it back after the completion of the treatment period. Compliance to the study treatment was calculated on the basis of the number of enoxaparin injections administered out of the total prescribed.

Telephone follow-up visits were done by trained personnel 3, 7, 14, 30, and 90 days following randomisation. Study outcomes, suspected serious adverse events, drug compliance (if applicable), disease signs and symptoms, and the vital status of the participant were assessed following a structured protocol. We collected only serious adverse events. In-person medical evaluation was organised or recommended in the presence of signs or symptoms indicating a progression of COVID-19 or any other complication. Information on serious adverse events was also collected during phone follow-up and included the occurrence of the primary outcome, bleeding, or symptoms that might have reflected the new onset of a potentially severe condition. No laboratory monitoring was planned. The investigators and the sponsor had the responsibility for identification, documentation, grading, reporting of outcome, and assessment of the causal relationship for serious adverse events.

At the beginning of the study, the sponsor planned independent monitoring of the trial in collaboration with the deputed division of the Clinical Trial Centre of the University Hospital Zurich. Monitoring was done remotely during the lockdown periods, or by visiting study sites thereafter, and consisted of a site initiation visit followed by regular visits based on the number of patients enrolled.

Outcomes

The primary outcome was a composite of any untoward hospitalisation and all-cause death within the 30 days following randomisation. A reason for hospitalisation had to fulfil the criteria of a serious adverse event to be considered for the primary outcome. The decision to admit a patient was taken by medical personnel not involved in the study.

Secondary efficacy outcomes were a composite of cardiovascular events (deep vein thrombosis, pulmonary embolism, myocardial infarction or myocarditis, peripheral arterial ischaemic events, acute splanchnic vein thrombosis, and ischaemic stroke); each component of the primary outcome assessed independently; disseminated intravascular coagulation (as per International Society on Thrombosis and Haemostasis [ISTH] criteria,[9] in-hospital diagnosis); and net clinical benefit (accounting for the primary efficacy outcome, composite cardiovascular events, and major bleeding) all assessed within 14, 30, and 90 days following randomisation. In the final version of the protocol (amended on Nov 29, 2022), a secondary

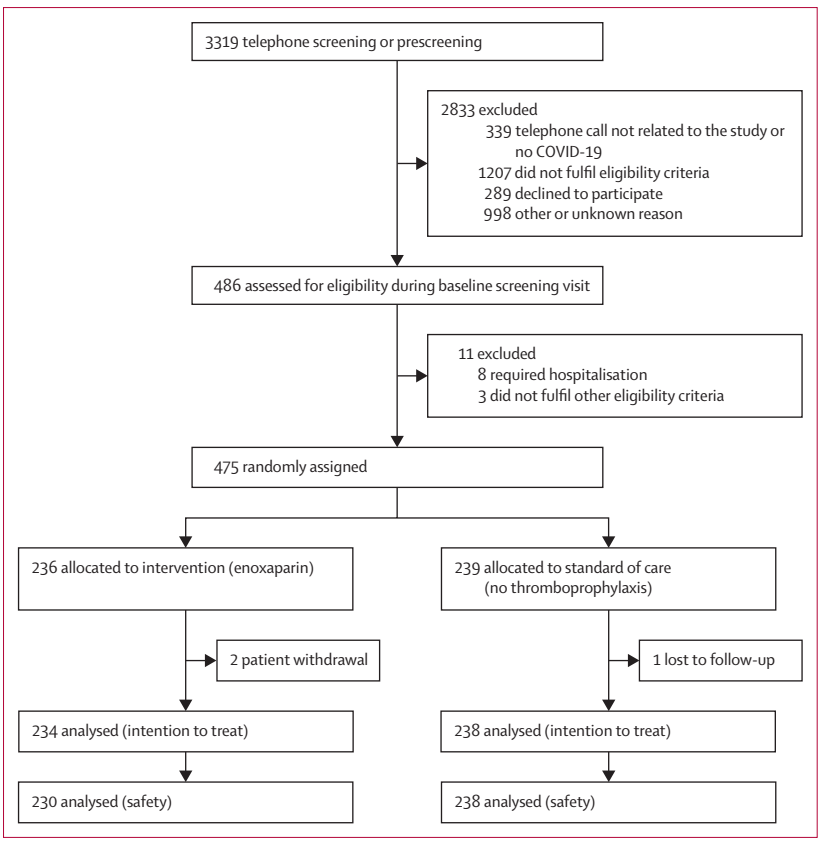

Figure 1: **Trial profile**

composite outcome (hospitalisation for cardiovascular, pulmonary, or COVID-19-related events) was added on the basis of the results of the ACTIV-4b trial.[10]

Safety outcomes were major bleeding and non-major clinically relevant bleeding and serious adverse events (see appendix pp 4–5 for the definitions).

Since all serious adverse events, including hospitalisations, were adjudicated locally and by the sponsor, who had full access to the source medical documentation, no independent adjudication of untoward hospitalisations and deaths was done. The investigators and the sponsor were allowed to contact the patient, the contact person, or the treating physicians to obtain clinical information from discharge letters in case of any hospitalisation or medical treatment. Of note, the study was not designed on the basis of the expected risk reduction in venous thromboembolic events, encompassing deep vein thrombosis and pulmonary embolism. During the preparation of the study protocol in April 2020, we anticipated that appropriate imaging tests for venous thromboembolism, particularly contrast-enhanced computed tomography, would have been underused in this patient population,[3,11] making an objective assessment of events ultimately impossible. Moreover, validated diagnostic algorithms for suspected venous thromboembolism in patients with COVID-19 were lacking. Since the results of the OVID trial were foreseen to be applied on a large population scale, we decided to primarily focus on hard clinical outcomes: any-cause unplanned hospitalisation and death. We expected that many of the outcomes were caused by thrombotic complications of COVID-19, encompassing venous thromboembolism and microthrombosis leading to organ damage, and other pathological mechanisms that low-molecular-weight heparin might have blocked in light of the postulated anti-inflammatory and antiviral properties. Finally, as COVID-19 emerged as a multi-organ disease, we anticipated potential difficulties in outcome assessment and included any unplanned hospitalisations and death in a composite primary outcome without limiting the analysis to respiratory or cardiovascular complications.

Statistical analysis

For the sample size calculation, it was assumed that the rate of the primary outcome would be 15% under standard of care conditions (no thromboprophylaxis). This number was based on assessments of fatality and hospitalisation data in Switzerland between March and May, 2020. We estimated that enoxaparin would decrease the primary outcome to 9% by assuming a substantial reduction in terms of thromboembolic complications at least similar to that observed in thromboprophylaxis studies.[12–14] With a two-sided significance level of 5%, we calculated that 920 patients (allocated in a 1:1 ratio) would be required for 80% power to show superiority of enoxaparin versus standard of care (no thromboprophylaxis). Drop-outs were initially estimated to represent 8% of the study population, therefore requiring a total of up to 1000 patients.

An independent data and safety monitoring board (DSMB) composed of a vascular medicine specialist, a respiratory physician, and a clinical biostatistician monitored the trial. The DSMB advised the sponsor and principal investigators (SB, NK) regarding the continuing safety of participants. When 50% of the overall study population needed to complete the trial had completed follow-up, on Feb 11, 2022, a prespecified interim analysis was done to evaluate whether prespecified stopping criteria for efficacy (superiority) or futility were met. With the conditional power approach, the probability of a significant final result was calculated conditional on the interim results. The underlying design of the two-stage approach was an O'Brien-Fleming group-sequential design. Details and the conditional power matrix displaying specific combinations of event rates in the two groups can be found in the appendix (p 6). The DSMB was authorised to obtain serial additional safety data, including but not limited to major and clinically relevant non-major bleeding events and serious adverse events, and the results of ad hoc risk–benefit analyses. As the foreseen risk of major bleeding complications related to enoxaparin thromboprophylaxis was very low, no statistical stopping

criterion for safety has been prespecified and this decision was left at the discretion of the DSMB members on the basis of the results of risk–benefit analysis.

Analysis of the efficacy outcomes was done in the intention-to-treat (ITT) population. The safety population included patients who received at least one dose of the study medication and were alive 12 h after randomisation. The main analysis of the primary outcome was based on a log-binomial model, including treatment group and stratification variable age group (reference level 50–70 years) as independent variables, aiming to estimate the adjusted relative risk (RR) for the composite primary outcome. The secondary outcomes were analysed by means of a similar log-binomial model, but without adjustment for age group. A relative risk smaller than one favoured the enoxaparin group. All estimates were reported with the corresponding Wald 95% CI. All p values except for the p value of the main analysis of the primary outcome are to be considered exploratory. The cumulative incidence of the primary outcome was displayed graphically by treatment group, taking the event times into account. Sensitivity analyses included the evaluation of the primary outcome in the safety population. Statistical programming was done with R (version 4.1.1) in combination with dynamic reporting via Sweave. The study is registered with ClinicalTrials.gov (NCT04400799).

Role of the funding source

The funder of the study had no role in study design, data collection, management, data analysis, data interpretation, or writing of the report.

Results

Between Aug 15, 2020 and Jan, 14, 2022, from 3319 participants prescreened, 475 with acute symptomatic COVID-19 scheduled for an ambulatory treatment were enrolled in the trial and randomly assigned to receive prophylactic-dose enoxaparin versus standard of care (no anticoagulation). The trial profile is depicted in figure 1. Two participants withdrew their participation in the study, whereas no follow-up data were available for one patient. The final intention-to-treat population consisted of 472 patients: 234 received enoxaparin and 238 no thromboprophylaxis.

Baseline characteristics were similar in the enoxaparin group and in the standard-of-care group (table 1). The median age of participants was 57 years (IQR 53–62; 95th percentile 70), 217 (46%) were women, and 446 (96%) were Caucasian. The median time between diagnosis of COVID-19 and randomisation was three (IQR 1–5) days. Overall, 115 (24%) of 472 participants had arterial hypertension, 38 (8%) diabetes, 22 (5%) a known atherosclerotic disease, and nine (2%) chronic obstructive pulmonary disease.

The most prevalent initial respiratory symptoms were cough (n=367; 78%), rhinorrhea (n=341; 72%), expectoration (n=197; 42%), and sore throat (n=183; 39%).

	Enoxaparin group (n=234)	Standard of care group (n=238)	Missing values
Age, years	56 (53–62)	57 (53–62)	0
Men	120 (51%)	135 (57%)	..
Women	114 (49%)	103 (43%)	0
Body-mass index, kg/m²	25·7 (4·4)	26·3 (4·7)	2
Race and ethnic group	..	..	5
Caucasian	223 (96%)	223 (95%)	..
Black	0	3 (1%)	..
Asian	6 (3%)	5 (2%)	..
Other	3 (1%)	4 (2%)	..
Comorbidities			
Atherosclerotic disease*	8 (3%)	14 (6%)	0
Arterial hypertension	53 (23%)	62 (26%)	0
Diabetes	18 (8%)	20 (8%)	0
Chronic obstructive pulmonary disease	4 (2%)	5 (2%)	0
Chronic heart failure	1 (<1%)	1 (<1%)	0
History of smoking	41 (18%)	40 (17%)	0
Previous malignancy	8 (3%)	14 (6%)	0
Hormonal treatment	13 (6%)	6 (3%)	0
Laboratory tests and vital signs			
Platelet count, n×1000/µL	206 (171–244)	205 (174–247)	1
Lymphocyte count, n×100/µL	1·7 (1·2–23·0)	1·8 (1·3–16·0)	54
Oxygen saturation, %	97·2 (1·4)	97·0 (1·5)	0
Heart rate, n/min	76 (12)	77 (13)	0
Respiratory rate, n/min	16 (3)	16 (3)	1
Baseline medications			
ACE-inhibitors	10 (4%)	14 (6%)	0
Corticosteroids	5 (2%)	3 (1%)	0
Immunosuppressive drugs	1 (<1%)	1 (<1%)	0
Antiplatelet agents	13 (6%)	13 (6%)	0
Statins	27 (12%)	25 (11%)	0

Data are n (% of available data), mean (SD), or median (IQR), unless otherwise specified. *Atherosclerotic diseases include acute coronary syndrome, angina, previous myocardial infarction, previous stroke, peripheral arterial disease.

Table 1: **Baseline characteristics**

Overall, 169 (36%) participants had a body temperature of more than 37·5°C. Dyspnoea at rest was present in 39 (8%) participants, whereas 181 (38%) had exertional dyspnoea. COVID-19 typical symptoms such as anosmia and dysgeusia were present in 261 (55%) and 238 (50%) participants, respectively. 19 (4%) participants reported syncopal or pre-syncopal episodes and 42 (9%) palpitation. A total of 363 participants were enrolled in the trial before the SARS-Cov-2 vaccination campaign with one of the two available vaccines (Pfizer–BioNTech and Moderna) or were not vaccinated. 11 participants received three doses of the vaccine, 25 participants received two doses, and nine participants received only one dose. Vaccination status of 46 participants was not collected or not available.

Compliance to the study treatment of at least 80%, indicating that the percentage of enoxaparin injections administered out of the total prescribed, was recorded in 211 (93%) of 226 participants who did not reach the

	Enoxaparin group (n=234)	Standard-of-care group (n=238)	Adjusted relative risk (95% CI)	p value
Primary outcome				
Any untoward hospitalisation and death	8 (3%)	8 (3%)	0·98 (0·37–2·56)†	0·96
Any untoward hospitalisation	8 (3%)	8 (3%)	1·02 (0·39–2·67)	0·97
Death	0	0	..	..
Secondary efficacy outcomes				
Cardiovascular events	2 (1%)	4 (2%)	0·51 (0·09–2·74)	0·43
Pulmonary embolism	1 (<1%)	4 (2%)	0·25 (0·03–2·26)	0·22
Ischaemic stroke	1 (<1%)	0	..	..
Other events*	0	0	..	..
COVID-19-related hospitalisation	8 (3%)	8 (3%)	1·02 (0·39–2·67)	0·97
Disseminated intravascular coagulation	0	0	..	..
Safety outcomes	n=230	n=238		
Major bleeding	0	0	..	..
Non-major clinically relevant bleeding	0	0	..	..

Data are n (%). *Other cardiovascular events include deep vein thrombosis, myocardial infarction, arterial ischaemia, and acute splanchnic vein thrombosis. †Risk ratio was adjusted for age (stratification variable), as prespecified in the study protocol. Net clinical benefit could not be calculated as no major bleeding events occurred.

Table 2: **Study outcomes within the 30 days following randomisation in the intention-to-treat population**

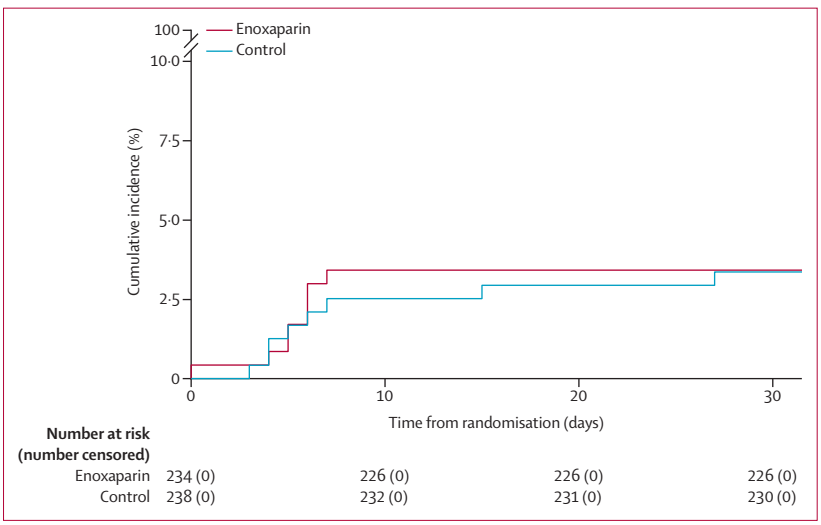

Figure 2: **Cumulative incidence of the primary outcome**
Time 0 corresponds to the baseline visit and the day of enrolment in the trial.

endpoint. No patients required dose reductions or discontinued enoxaparin for drug-related toxicity. The safety population consisted of 468 participants: 230 in the enoxaparin group and 238 in the standard of care group. Patients were followed for a median of 30 (IQR 30–30) days. The number of patients with at least one unplanned ambulatory visit was 48 (21%) in the enoxaparin group and 59 (25%) in the standard-of-care group. Of these, a suspected deep vein thrombosis or unspecific limb symptoms were the reason for assessment in three (1%) patients in the enoxaparin group and in five (2%) patients in the standard-of-care group. Persisting or worsening respiratory symptoms led to an unplanned visit in 14 (6%) and 17 (7%) patients, respectively.

At the predefined formal interim analysis for efficacy (50% of total study population; data cutoff of Feb 11, 2022), the independent DSMB recommended early termination of the trial on the basis of predefined statistical criteria having considered the very low probability of showing superiority of thromboprophylaxis with enoxaparin for the primary outcome under the initial study design assumptions. A primary outcome event occurred in eight patients (3%) who were assigned to receive enoxaparin and eight (3%) in the standard of care group within the 30 days following randomisation (figure 1 and table 2). For the comparison of enoxaparin with standard treatment, the relative risk for the primary outcome was 0·98 (95% CI 0·37–2·56; p=0·96; adjusted for the stratification variable age). All hospitalisations were related to COVID-19 and mostly due to pneumonia and respiratory insufficiency. No deaths were reported within the 30 days following randomisation. Participants in the two treatment groups exhibited the same 30-day cumulative incidence of COVID-19-related hospitalisations (figure 2). A predefined heterogeneity analysis for the primary outcome and the main clinical characteristics of patients with primary outcome are reported in appendix (pp 7–9). A post-hoc analysis of the primary outcome in the safety population was done: six (3%) of 230 participants in the enoxaparin group were hospitalised versus eight (3%) of 238, corresponding to a crude relative risk of 0·78 (95% CI 0·27–2·20).

The main secondary efficacy outcome, which was composed of major arterial and venous cardiovascular events, occurred in two (1%) patients of 234 who received enoxaparin and in four (2%) of 238 controls (table 2), corresponding to a relative risk of 0·51 (95% CI 0·09–2·74). The events consisted of one pulmonary embolism and one ischaemic stroke in the enoxaparin group and of four pulmonary embolism events in the standard-of-care group. The relative risk of pulmonary embolism in patients in the enoxaparin group (*vs* standard of care group) was 0·25 (95% CI 0·03–2·26). All pulmonary embolism events were symptomatic and diagnosed with computed tomography pulmonary angiogram; three of them (one in the enoxaparin group) involved the subsegmental pulmonary arteries only and two involved the segmental branches. The patient who developed ischaemic stroke was diagnosed with a patent foramen ovale; a pulmonary embolism or deep vein thrombosis was excluded by imaging.

No safety outcomes, including major and clinically-relevant-non-major bleeding, occurred within the 30 days following randomisation (table 2). Information on minor bleeding was collected although did not represent a predefined safety outcome: bleeding not fulfilling the criteria for major or clinically-relevant-non-major

bleeding was reported in 26 (11%) patients in the enoxaparin group and in four (2%) patients in the control group. In the enoxaparin group, they mainly consisted of bruising at the injection site (n=14) or a small haematoma (n=8). No episodes of heparin-induced thrombocytopenia were recorded.

A total of 17 serious adverse events were recorded (eight in the enoxaparin group, nine in the control group): 16 consisted of grade 4 adverse events and corresponded to the primary outcome of the study (appendix pp 8–9). One event consisted of a grade 3 adverse event (pulmonary embolism not requiring hospitalisation) and occurred in a patient randomly assigned to receive standard of care (no thromboprophylaxis).

Discussion

OVID is, to our knowledge, the first randomised trial testing the efficacy and safety of thromboprophylaxis with low-molecular-weight heparin in symptomatic outpatients with COVID-19 aged 50 years or older. The trial was prematurely stopped on the basis of predefined rules for futility for the primary outcome. Prophylactic-dose enoxaparin for 2 weeks did not appear to improve the early course of COVID-19. Most events occurred in the first 7–10 days after randomisation when patients were still on active treatment, indicating that a longer duration of enoxaparin treatment was unlikely to provide additional benefit.

The overall risk of hospitalisation was lower than expected. This was partly related to the under-representation of participants aged 70 years or older, possibly owing to the obstacles in planning a screening visit at participating sites and the reluctance of older patients, and the low prevalence of comorbidities. Epidemiological and cohort studies showed that the risk of COVID-19 related complications, hospitalisation, and death increased exponentially with age.[1,3] As a consequence, the results of OVID must be carefully translated to the group of septuagenarians and older, but remain valid and clinically useful for patients aged 50–70 years. In this regard, they parallel the findings from the ACTIV-4B trial, which showed that neither the direct oral anticoagulant apixaban nor aspirin could, compared with placebo, reduce rates of hospitalisation due to cardiopulmonary complications in a cohort of low-risk symptomatic outpatients with COVID-19.[10]

In OVID, the 30-day cumulative incidence of symptomatic pulmonary embolism events was 2% in patients who did not receive enoxaparin versus <1% in the enoxaparin group. We were unable to obtain precise estimates for secondary efficacy outcomes because OVID was not powered to investigate whether thromboprophylaxis reduces venous thromboembolic events. With such low event rates as observed in our study groups, more than 3000 participants would have been required to show superiority of thromboprophylaxis for the reduction of venous thromboembolism. The ACTIV-4B trial included approximately 165 patients per treatment group. Similarly, it did not report any venous thromboembolic events in the apixaban or placebo groups.[10] In post-discharge outpatients at higher risk for venous thromboembolism per the International Medical Prevention Registry on Venous Thromboembolism with D-Dimer (IMPROVEDD) score, the MICHELLE trial showed that thromboprophylaxis with rivaroxaban (*vs* no thromboprophylaxis) reduced cardiovascular events after hospitalisation owing to COVID-19.[15] Future pooled analyses of published,[10] terminated (NCT04492254), and ongoing (NCT04746339, NCT04516941, NCT04508023, NCT04504032, NCT04673214, NCT04542408) trials, should verify whether and in which subgroup of outpatients an early thromboprophylaxis could reduce the risk of venous thromboembolic complications.

Our study has several limitations. First, OVID was designed as an open-label study, given the difficulties in obtaining enoxaparin-placebo in early 2020. Although the number of unplanned outpatient visits was similar in the two treatment groups, we cannot exclude the possibility that the lack of a placebo-controlled group affected the decision to do diagnostic imaging for acute pulmonary embolism. Nonetheless, the clinical severity of patients who required hospitalisation, all with COVID-19-related events, might indicate that the open-label design was less relevant in this perspective. Second, the primary outcome events have not been externally adjudicated and the criteria for hospital admission as well as the overall bed capacity varied over time, implying time-dependent changes in the characteristics of ambulatory patients. Similarly, we faced the surge of different variants of SARS-CoV-2 over time, which might have been characterised by different severity in terms of thrombogenicity and letality.[16] Data on SARS-CoV-2 variants were not routinely collected in the study, but epidemiological data indicates that OVID enrolment was stopped just before the surge of the omicron variants.[17] Thus far, OVID data are only available 30 days after the enrolment of the last patient; however, follow-up at 90 days has just been completed for the last patient enrolled and the results will be integrated in a subsequent report. Third, our patients had a low prevalence of comorbidities, were a mainly Caucasian population from two high-income countries and had, in most cases, a normal body-mass index. Indeed, the sample size calculation of the OVID trial was based on the assumption of a much higher overall event rate of 9% for the primary outcome. As previously discussed, we were unable to enrol many patients older than 70 years of age, possibly owing to low screening capacity and logistical issues, and this led to a lower rate. In this respect, enoxaparin thromboprophylaxis can be considered futile under the aforementioned assumptions and no firm conclusions can be drawn on its efficacy and safety in high-risk patients, including older patients, or in individuals of other ethnic backgrounds.

In conclusion, these findings suggest thromboprophylaxis with enoxaparin does not reduce early

hospitalisations and deaths among outpatients with symptomatic COVID-19. Futility of the treatment under the initial study design assumptions could not be conclusively assessed owing to under-representation of older patients and consequent low event rates.

OVID investigators
Stefano Barco, Davide Voci, Ulrike Held, Tim Sebastian, Roland Bingisser, Giuseppe Colucci, Daniel Duerschmied, André Frenk, Bernhard Gerber, Andrea Götschi, Stavros V Konstantinides, François Mach, Helia Robert-Ebadi, Thomas Rosemann, Noemi R Simon, Hervé Spechbach, David Spirk, Stefan Stortecky, Lukas Vaisnora, Marc Righini, Nils Kucher, Stéphanie Roth Zetzsche, Rebecca Spescha, Claudia Leeger, Yulia Butscheid, Eliane Probst, Evy Micieli, Gabor Forgo, Fabian Johner, Alexandru Grigorean, Georgios Vatsakis, Dagmar Keller Lang, Silvana Rampini Speck, Barbara Hasse, Marco Rueegg, Isabelle Arnold, Christian Nickel, Jeannette Busch, Marc Blondon, Frédéric Glauser, Micol G Cittone, Chiara Kessler, Diona Gjermeni, Christoph B Olivier, Nadine Gauchel, Paul Biever, Lukas Hobohm, Dorothea Becker, Marc Schindewolf, Arnaud Kuenzi, Silvia Ulrich.

Contributors
SB, TS, UH, and NK contributed to the conception and design of the study, and to the drafting of the study protocol. SB and NK are the co-principal investigators of the study. SB, RB, GC, AF, BG, UH, FM, MR, TR, TS, SS, NK were part of the steering committee for the study. SB, UH, TS, RB, GC, AF, BG, FM, TR, SS, MR, and NK acquired funding. SB, DV, TS, RB, GC, DD, AF, BG, SVK, HR-E, NRS, SS, LV, MR, and NK were responsible for the collection of clinical data. UH and AG were responsible for the statistical analysis plan and statistical analysis. SB was responsible for writing the first version of the manuscript. SB, UH, and AG accessed and verified the data. All authors interpreted the data, and critically reviewed the manuscript and approved the final version. All authors had full access to the data in the study and had final responsibility for the decision to submit for publication. The complete author list of co-authors, including OVID investigators and committee members, is available in the appendix (pp 10–13).

Declaration of interests
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Data sharing
The current study protocol (version 4.0, Nov 29, 2021), after the inclusion of German study centres, is available on request. The previous version of the study protocol (version 3.0, May 18, 2020) has been published together with the study design paper.[8] Anonymised participant data will be made available when the trial and planned subgroup analyses are complete, on requests directed to the co-principal investigators and corresponding authors (SB and NK). Proposals will be evaluated and approved by the sponsor and steering committee members on the basis of scientific value before sharing of the data. Data sharing will be organised through secure methods after an agreement between sponsor, steering committee members, and investigators has been signed.

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References
1 COVID-19 Excess Mortality Collaborators. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020–21. *Lancet* 2022; **399:** 1513–36.
2 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395:** 497–506.
3 Lodigiani C, Iapichino G, Carenzo L, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res* 2020; **191:** 9–14.
4 Sholzberg M, da Costa BR, Tang GH, et al. Randomized trials of therapeutic heparin for COVID-19: a meta-analysis. *Res Pract Thromb Haemost* 2021; **5:** e12638.
5 Young E. The anti-inflammatory effects of heparin and related compounds. *Thromb Res* 2008; **122:** 743–52.
6 Paiardi G, Richter S, Oreste P, Urbinati C, Rusnati M, Wade RC. The binding of heparin to spike glycoprotein inhibits SARS-CoV-2 infection by three mechanisms. *J Biol Chem* 2022; **298:** 101507.
7 Conzelmann C, Müller JA, Perkhofer L, et al. Inhaled and systemic heparin as a repurposed direct antiviral drug for prevention and treatment of COVID-19. *Clin Med (Lond)* 2020; **20:** e218–21.
8 Barco S, Bingisser R, Colucci G, et al. Enoxaparin for primary thromboprophylaxis in ambulatory patients with coronavirus disease-2019 (the OVID study): a structured summary of a study protocol for a randomized controlled trial. *Trials* 2020; **21:** 770.
9 Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; **3:** 692–94.
10 Connors JM, Brooks MM, Sciurba FC, et al. Effect of Antithrombotic Therapy on Clinical Outcomes in Outpatients With Clinically Stable Symptomatic COVID-19: the ACTIV-4B Randomized Clinical Trial. *JAMA* 2021; **326:** 1703–12.
11 Roncon L, Zuin M, Barco S, et al. Incidence of acute pulmonary embolism in COVID-19 patients: systematic review and meta-analysis. *Eur J Intern Med* 2020; **82:** 29–37.
12 Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. *N Engl J Med* 1999; **341:** 793–800.

13 Kakkar AK, Cimminiello C, Goldhaber SZ, Parakh R, Wang C, Bergmann JF. Low-molecular-weight heparin and mortality in acutely ill medical patients. *N Engl J Med* 2011; **365:** 2463–72.

14 Bajaj NS, Vaduganathan M, Qamar A, et al. Extended prophylaxis for venous thromboembolism after hospitalization for medical illness: a trial sequential and cumulative meta-analysis. *PLoS Med* 2019; **16:** e1002797.

15 Ramacciotti E, Barile Agati L, Calderaro D, et al. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. *Lancet* 2022; **399:** 50–59.

16 Mumoli N, Conte G, Cei M, et al. In-hospital fatality and venous thromboembolism during the first and second COVID-19 waves at a center opting for standard-dose thromboprophylaxis. *Thromb Res* 2021; **203:** 82–84.

17 covSPECTRUM. Enabled by data from GISAID. https://cov-spectrum.org/explore/Switzerland/AllSamples/Past6M (accessed March 29, 2022).