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Full Length Article

# Enoxaparin for symptomatic COVID-19 managed in the ambulatory setting: An individual patient level analysis of the OVID and ETHIC trials

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ABSTRACT

*Background:* Antithrombotic treatment may improve the disease course in non-critically ill, symptomatic COVID-19 outpatients.

*Methods:* We performed an individual patient-level analysis of the OVID and ETHIC randomized controlled trials, which compared enoxaparin thromboprophylaxis for either 14 (OVID) or 21 days (ETHIC) vs. no thromboprophylaxis for outpatients with symptomatic COVID-19 and at least one additional risk factor. The primary efficacy outcome included all-cause hospitalization and all-cause death within 30 days from randomization. Both studies were prematurely stopped for futility. Secondary efficacy outcomes were major symptomatic venous thromboembolic events, arterial cardiovascular events, or their composite occurring within 30 days from randomization. The same outcomes were assessed over a 90-day follow-up. The primary safety outcome was major bleeding (ISTH criteria).

*Results:* A total of 691 patients were randomized: 339 to receive enoxaparin and 352 to the control group. Over 30-day follow-up, the primary efficacy outcome occurred in 6.0 % of patients in the enoxaparin group vs. 5.8 % of controls for a risk ratio (RR) of 1.05 (95%CI 0.57–1.92). The incidence of major symptomatic venous thromboembolic events and arterial cardiovascular events was 0.9 % vs. 1.8 %, respectively (RR 0.52; 95%CI 0.13–2.06). Most cardiovascular thromboembolic events were represented by symptomatic venous thromboembolic events, occurring in 0.6 % vs. 1.5 % of patients, respectively. A similar distribution of outcomes between the treatment groups was observed over 90 days. No major bleeding occurred in the enoxaparin group vs. one (0.3 %) in the control group.

*Conclusions:* We found no evidence for the clinical benefit of early administration of enoxaparin thromboprophylaxis in outpatients with symptomatic COVID-19. These results should be interpreted taking into consideration the relatively low occurrence of events.

## 1. Background

COVID-19 is a viral respiratory infection that led to at least 6 million deaths around the globe [1]. The pro-thrombotic nature of COVID-19 causes arterial but mostly venous thromboembolic events [2]. Randomized trials have confirmed that therapeutic-dose heparin, compared with prophylactic-dose heparin, is beneficial in hospitalized patients with moderately severe COVID-19, but probably not in those who require intensive care or invasive ventilation [3].

Low-molecular-weight heparin (LMWH) is effective and safe in preventing venous thromboembolic disease in medical and surgical patients at high risk of venous thromboembolism, both in an in-hospital and post-discharge settings [4]. It has been postulated that enoxaparin, in addition to its antithrombotic effect, exerts an antiviral and anti-inflammatory effect [5]. On this basis, adding antithrombotic treatment may improve the early course of COVID-19 in ambulatory symptomatic patients [6,7]. Its use has been advocated as part of routine care for patients with COVID-19 in the community during the early phases of the pandemic [8].

In this report, we performed a systematic review and individual patient-level pooled analysis of randomized trials investigating the efficacy and safety of primary thromboprophylaxis with enoxaparin for symptomatic COVID-19 patients treated in the ambulatory setting.

## 2. Patients and methods

A structured systematic review of the literature encompassing published (PubMed/Medline) and terminated/ongoing (clinicaltrials.org, EudraCT) randomized trials was performed by the investigators of the OVID [9–11] and ETHIC [12] trials on April 1st 2023 to confirm that no additional study fulfilled the inclusion criteria. Randomized controlled trials were considered eligible without time restrictions if they included patients with acute symptomatic COVID-19 initially managed in the outpatient setting. Patients had to be randomized to receive either thromboprophylaxis with LMWH or a standard-of-care treatment not including any type of anticoagulation, with the aim of reducing hospitalization, cardiovascular events, and death (or a composite of these clinical events). No specific protocol was developed for this meta-analysis.

Both the OVID [9–11] and ETHIC [12] trials were open-label, multicenter, randomized phase III trials that compared primary thromboprophylaxis with enoxaparin vs. no treatment in symptomatic but clinically stable outpatients with a new diagnosis of COVID-19. Both studies were prematurely stopped for futility and their individual results have been previously published [9–12]. The presented pooled analysis aimed to obtain more precise risk estimates than those from the individual trials.

The OVID trial (NCT04400799) was conducted at 8 centres in Switzerland and Germany. Outpatients aged 50 years or older with a diagnosis of acute COVID-19 over the prior 5 days were eligible if they presented with respiratory symptoms or body temperature higher than 37.5 °C. Eligible participants underwent block-stratified randomization (by age group 50–70 years versus >70 years and by study centre) in a 1:1 ratio to receive either subcutaneous once-daily enoxaparin 40 mg for 14 days or standard of care (no thromboprophylaxis). The primary outcome was a composite of all-cause hospitalization and all-cause death within 30 days of randomization.

The ETHIC trial (NCT04492254) was done at 15 centres in 6 countries (Belgium, Brazil, India, South Africa, Spain, and the UK). Participants aged at least 30 years who had not received a COVID-19 vaccine and had symptomatic, confirmed COVID-19 in the outpatient setting plus at least one risk factor for severe disease were eligible. In the first version of the study protocol, patients were required to be older than 54 years and have at least two risk predefined risk factors: age ≥ 70 years, a body-mass index of at least 25 kg/m$^2$, chronic lung disease, diabetes mellitus, cardiovascular disease, or corticosteroid use. The complete list of risk factors according to the amended version of the protocol is available as Supplementary Material. Eligible participants were randomized within 9 days of symptom onset in a 1:1 ratio to receive either subcutaneous enoxaparin for 21 days (once-daily 40 mg if they weighed <100 kg and twice-daily 40 mg if they weighed ≥100 kg) or standard of care (no thromboprophylaxis). The primary outcome was the composite of all-cause hospitalization and all-cause mortality at 21 days after randomization.

For the purposes of the present analysis, we defined the primary efficacy outcome as the 30-day occurrence of any unplanned hospitalization or all-cause death. Secondary efficacy outcomes were major symptomatic venous thromboembolic events, arterial cardiovascular events, or their composite occurring within 30 and 90 days from randomization, as well as the primary outcome occurring within 90 days

from randomization. The primary safety outcome was major bleeding, as defined in both studies by the ISTH criteria. [13]

The authors of this study agreed on a statistical analysis plan before data sharing. The individual pseudonymized data were pooled and made uniform with respect to key baseline and outcome variables before the final data analysis, which was performed at the University of Zurich.

For the primary analysis, we chose a one-stage approach for individual patient data meta-analysis, to model the binary primary outcome. Treatment group, coded as daily enoxaparin injection as compared to standard of care, as a fixed effect and study-specific random intercepts and slope effects to account for correlation of data within each study were fitted in a generalized linear mixed model framework with a log link function. The estimand was the risk ratio (RR) for the primary outcome event under enoxaparin as compared to standard of care regime.

For the 30-day analysis, we censored patients for outcome analyses at 33-day follow-up as the study protocols allowed visits being performed within a time window of plus/minus 3 days. We performed secondary analyses again using generalized linear mixed models for the primary endpoint at 90 days from randomization. We analysed the primary outcome events by additionally including the variable age group as fixed effect (>70 years vs. 30–70 years) as an adjustment variable. The same model specification as for the primary outcome was used to estimate the RR of the secondary outcomes. These included cardiovascular events, considered as the composite of venous thromboembolic events (VTE) and arterial events (AE). VTE was defined as a composite of deep vein thrombosis (DVT) and pulmonary embolism (PE), whereas AE as the composite of myocardial infarction, stroke, and arterial ischemia. If event rates were very low, we performed no formal statistical analysis but instead numbers and percentages of total were reported in descriptive tables. Pre-specified subgroup analyses were performed for the variables age (30–50, 51–70, >70 years), sex, BMI (<25, 25–29, ≥ 30), cancer (yes, no), lung disease (yes, no), arterial hypertension (yes, no), and current smoking status (yes, no). All the analyses were performed in the statistical programming language R, version 4.2.2 in a fully scripted analysis using dynamic reporting (statistical code available upon request).

## 3. Results

In total, 691 patients were randomized in the two studies: 339 were randomized to receive enoxaparin and 352 to the control group (standard of care). Both study groups and the populations of the two studies were balanced in term of age, sex, and BMI, and key comorbidities such as chronic heart failure or cancer. Descriptive statistics, shown in Table 1, report the number of patients included in the intention-to-treat population per trial and their baseline characteristics. The median time between COVID-19 diagnosis and randomization was 2 days in the ETHIC and 3 days in the OVID trial. A total of 11 (1.6 %) patients (5 from the enoxaparin and 6 from the control group) were excluded from the primary analysis because they had incomplete follow-up at 30 days. In OVID, 363 participants were included before the SARS-CoV-2 vaccination campaign or remained unvaccinated, 9 received a single dose, 25 received two doses, and 11 received three doses, whereas no information was available for 46 participants. In ETHIC, 2 participants received their first dose of vaccine before enrolment and 93 received a first dose of vaccination with a median of 40 days after enrolment.

Overall, 20 (6.0 %) patients in the enoxaparin arm and 20 (5.8 %) in the control arm experienced the primary outcome event (Table 2), resulting in a RR for any unplanned hospitalization and all-cause death of 1.05 (95 % CI 0.57–1.92); Fig. 1. Negligible differences were observed in the effect of enoxaparin on the primary outcomes after adjustment for age (RR 1.05; 95 % CI 0.57–1.93). The RR for the primary efficacy outcome at 90 days was 1.07 (95 % CI 0.61 to 1.86); Table 3. The number of patients that experienced the primary outcome in subgroups of selected demographic and clinical characteristics have been summarised in the *Supplementary Table*.

**Table 1**
Baseline characteristics of patients in the intention-to-treat population randomized to the enoxaparin and control group by trial.

| | OVID (n = 234) | ETHIC (n = 105) | OVID (n = 238) | ETHIC (n = 114) |
|---|---|---|---|---|
| | *Enoxaparin group* | | *Standard of care group* | |
| Age, years | 56 (53–62) | 59 (51–66) | 57 (53–62) | 59 (50–67) |
| Women | 114 (48.7) | 45 (42.9) | 103 (43.3) | 51 (45.1) |
| Body-Mass Index, kg/m$^2$ | 25.7 (4.4) | 30.1 (27.5–31.9) | 26.3 (4.7) | 28.8 (26.3–32.2) |
| Race and ethnic group | | | | |
| Caucasian | 223 (96.1) | 66 (62.9) | 223 (94.9) | 75 (66.4) |
| Black | 0 (0.0) | 4 (4.0) | 3 (1.3) | 1 (0.9) |
| Asian | 6 (2.6) | 29 (28.0) | 5 (2.1) | 31 (27.4) |
| Other | 3 (1.3) | 6 (5.7) | 4 (1.7) | 6 (5.3) |
| Comorbidities | | | | |
| Atherosclerotic disease[a] | 8 (3.4) | 14 (18.4) | 14 (5.9) | 14 (18.4) |
| Arterial hypertension | 53 (22.6) | 56 (73.7) | 62 (26.1) | 58 (67.4) |
| Diabetes mellitus | 18 (7.7) | 24 (31.6) | 20 (8.4) | 26 (30.0) |
| Chronic lung disease[b] | 4 (1.7) | 6 (7.9) | 5 (2.1) | 14 (16.3) |
| Chronic heart failure | 1 (0.4) | 0 | 1 (0.4) | 1 (1.1) |
| History of smoking | 41 (17.5) | 26 (26.0) | 40 (16.8) | 33 (30.0) |
| Cancer | 8 (3.4) | 0 | 14 (5.9) | 2 (2.3) |
| Immunocompromised condition[c] | 1 (0.4) | 1 (1.3) | 1 (0.4) | 3 (3.5) |
| Time from COVID-19 diagnosis to randomization, days | 3 (1–5) | 2 (1–3) | 3 (1–5) | 2 (1–3) |
| Baseline medications | | | | |
| ACE-inhibitors | 10 (4.3) | 13 (12.4) | 14 (5.9) | 12 (10.5) |
| Corticosteroids | 5 (2.1) | 7 (6.7) | 3 (1.3) | 3 (2.6) |
| Antiplatelet agents | 13 (5.6) | 1 (1.0) | 13 (5.5) | 1 (0.9) |
| Statins | 27 (11.5) | 28 (26.7) | 25 (10.5) | 30 (26.3) |

Data are n (% of available data), or median (Q1-Q3).
[a] Atherosclerotic diseases include the following: acute coronary syndrome, angina, prior myocardial infarction, prior stroke, peripheral arterial disease.
[b] Chronic lung disease: is defined differently in the two trials (OVID: COPD or asthma; ETHIC: COPD, asthma, emphysema or pulmonary fibrosis).
[c] Receiving immunosuppressive therapy or presence of HIV infection.

The secondary efficacy outcome, encompassing major symptomatic venous thromboembolic events and arterial cardiovascular events, occurred in 3 (0.9 %) patients in the enoxaparin group and in 6 (1.8 %) patients in the control group, resulting in a RR of 0.52 (95 % CI 0.13–2.06). VTE was recorded in 7 patients: 2 (0.6 %) in the enoxaparin and 5 (1.5 %) in the standard of care group. The estimated RR for patients in the enoxaparin arm as compared to standard of care in the VTE component of the secondary outcomes at 30 days was 0.42 (95 % CI 0.08–2.13); Table 2. No major bleeding events occurred in the enoxaparin vs. one (0.3 %) in the control group.

## 4. Discussion

In this pooled analysis of ETHIC and OVID trials, prophylactic enoxaparin (compared with no anticoagulation) did not lead to any therapeutic benefit, as defined by all-cause hospitalization and all-cause mortality within 30 days after randomization, among COVID-19 outpatients. These results reinforce the original observations from both individual trials, highlighting the consistency and robustness of the data obtained across various countries and geographic regions. Routine thromboprophylaxis would be safe in terms of bleeding but may be unnecessary to accelerate the recovery from COVID-19 and prevent complications.

These results indicate that the hypothesised anti-inflammatory and

**Table 2**
Primary outcome, secondary efficacy outcomes, and safety outcome events within 30 days after randomization (ITT population).

| Event | Total | Enoxaparin | Standard of care | Missing (%) | RR (95 % CI)[a] |
|---|---|---|---|---|---|
| Primary outcome and components of the primary outcome | | | | | |
| Hospitalization or death | 40 (5.9) | 20 (6.0) | 20 (5.8) | 1.6 | 1.05 (0.57 to 1.92) |
| Hospitalization | 40 (5.9) | 20 (6.0) | 20 (5.8) | 1.6 | – |
| Death | 2 (0.3) | 1 (0.3) | 1 (0.3) | 1.6 | – |
| Secondary efficacy outcomes and components of the secondary efficacy outcomes | | | | | |
| Cardiovascular events | 9 (1.4) | 3 (0.9) | 6 (1.8) | 4.8 | 0.52 (0.13 to 2.06) |
| VTE events | 7 (1.1) | 2 (0.6) | 5 (1.5) | 4.6 | 0.42 (0.08 to 2.13) |
| DVT | 1 (0.2) | 1 (0.3) | 0 (0.0) | 4.6 | – |
| PE | 6 (0.9) | 1 (0.3) | 5 (1.5) | 4.6 | – |
| Arterial events | 2 (0.3) | 1 (0.3) | 1 (0.3) | 4.8 | – |
| Myocardial infarction | 1 (0.2) | 0 (0.0) | 1 (0.3) | 4.6 | – |
| Stroke | 1 (0.2) | 1 (0.3) | 0 (0.0) | 4.6 | – |
| Arterial ischemia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4.6 | – |
| Safety outcome | | | | | |
| Major bleeding | 1 (0.2) | 0 (0.0) | 1 (0.3) | 4.9 | – |

Data are n (% of available data) or % of available data.
CI, confidence interval; DVT, deep vein thrombosis; ITT, intention-to-treat; PE, pulmonary embolism; RR, risk ratio; VTE, venous thromboembolism.
[a] From one-stage random effects model for individual patient data meta-analysis with loglink function.

antiviral effects of heparins in the setting of COVID-19 are less potent than initially thought. This result could be due to the pathogenesis of COVID-19-associated coagulopathy or [14], as previously postulated, to the prophylactic dose of enoxaparin being insufficient. A previous study has shown that higher dose regimes showed moderate benefit in the probability of survival and hospital discharge with the reduced need for organ support in non-critically ill patients [15]. In the outpatient setting, all studies focusing on anticoagulant thromboprophylaxis and anti-platelet treatments performed so far could not demonstrate a benefit of primary prevention to prevent hospitalizations or lead to a faster improvement [16–19]. These findings could be cautiously extrapolated to other patient groups with acute respiratory conditions that are being treated in an outpatient setting.

This individual patient data meta-analysis revealed an interesting observation that the risk of combined thromboembolic and arterial events, as well as the combined occurrence of DVT and PE within 30 days, was lower in patients receiving enoxaparin than in the control group. Although the statistical significance was not reached due to the relatively low number of events, the numerical variance in the occurrence of these outcomes, including PE, hints at the potential benefits of enoxaparin treatment. The relative risk reduction, approximately 50 %, is in line with prior primary thromboprophylaxis trials on LMWH in hospitalized medically ill patients. These findings warrant further investigation to explore the potential clinical significance of these observations. A prospective meta-analysis of all studies focusing on primary thromboprophylaxis with different anticoagulant agents, including parenteral and oral anticoagulants, in outpatients with COVID-19 is being completed (PROSPERO repository ID: CRD42022362776) and may help to elucidate this hypothesis.

There are limitations to the conclusions that can be drawn from our analysis and it is important to be discerning whilst interpreting these findings. Although ETHIC and OVID shared a very similar study design, patients in the OVID study were older and presented with respiratory symptoms, while patients from the ETHIC study were younger and were deemed eligible in the presence of additional risk factors for severe disease, independent of age. A further limitation of this pooled analysis is that the association of treatment regarding secondary outcomes and across patient subgroups could not be assessed due to the small number of events and a low sample size. Finally, we could not fully explain the higher incidence of PE over DVT events. It appears unlikely that this occurred as a consequence of bias (i.e. diagnostic suspicion bias, referral bias). It may rather reflect the predominance of pulmonary events

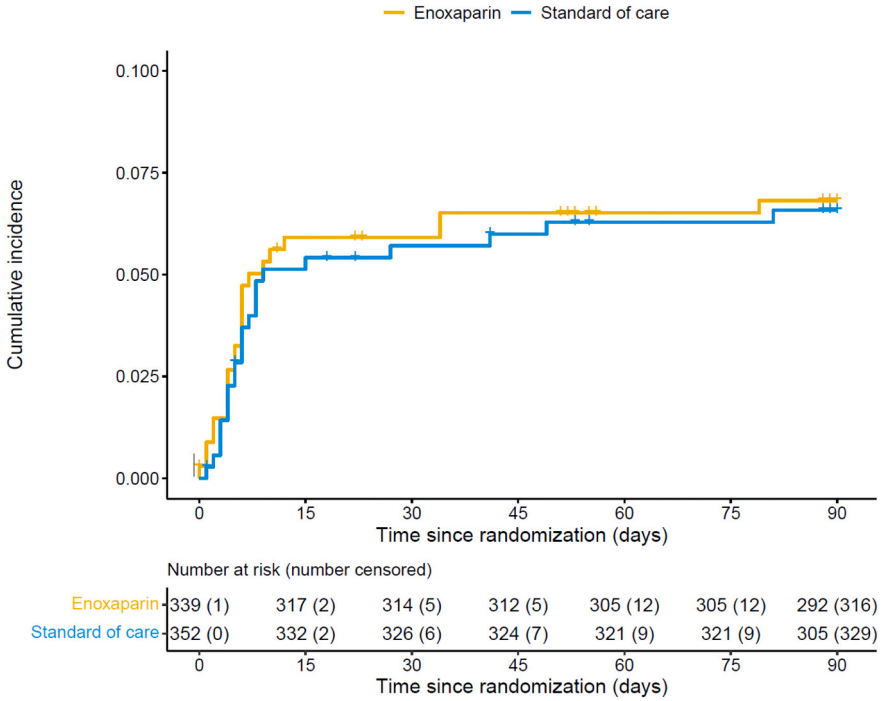


**Fig. 1.** Cumulative incidence of the primary outcome (composite of all-cause hospitalization and all-cause death) over time.

**Table 3**
Primary efficacy outcome, secondary outcome and safety outcome events within 90 days after randomization (ITT population).

| Event | Total | Enoxaparin | Standard of care | Missing (%) | RR (95 % CI)[a] |
|---|---|---|---|---|---|
| Primary efficacy outcomes | | | | | |
| Hospitalization or death | 46 (6.9) | 23 (7.0) | 23 (6.7) | 3.0 | 1.07 (0.61 to 1.86) |
| Hospitalization | 46 (6.9) | 23 (7.0) | 23 (6.7) | 3.0 | – |
| Death | 2 (0.3) | 1 (0.3) | 1 (0.3) | 3.0 | – |
| Secondary study outcomes | | | | | |
| Cardiovascular events | 10 (1.5) | 3 (1.0) | 7 (2.1) | 6.4 | 0.45 (0.12 to 1.73) |
| VTE events | 8 (1.2) | 2 (0.6) | 6 (1.8) | 6.2 | 0.35 (0.07 to 1.73) |
| DVT | 1 (0.2) | 1 (0.3) | 0 (0.0) | 6.2 | – |
| PE | 6 (0.9) | 1 (0.3) | 5 (1.5) | 6.2 | – |
| Other | 1 (0.2) | 0 (0.0) | 1 (0.3) | 6.2 | – |
| Arterial events | 2 (0.3) | 1 (0.3) | 1 (0.3) | 6.4 | – |
| Myocardial infarction | 1 (0.2) | 0 (0.0) | 1 (0.3) | 6.2 | – |
| Stroke | 1 (0.2) | 1 (0.3) | 0 (0.0) | 6.2 | – |
| Arterial ischemia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6.2 | – |
| Safety outcome | | | | | |
| Major bleeding | 1 (0.2) | 0 (0.0) | 1 (0.3) | 6.5 | – |

Data are n (% of available data) or % of available data.
CI, confidence interval; DVT, deep vein thrombosis; ITT, intention-to-treat; PE, pulmonary embolism; RR, risk ratio; VTE, venous thromboembolism.
[a] From one-stage random effects model for individual patient data meta-analysis with loglink function.

observed in the early phases of the pandemic [2,20,21].

In conclusion, we found no evidence of a clinical advantage of administering prophylactic enoxaparin in symptomatic, but clinically stable outpatients with COVID-19. These results should be interpreted taking into consideration the relatively low rate of events.

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## Declaration of competing interest

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2023.08.009.

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