A JOINT ANALYSIS OF TWO RANDOMIZED CONTROLLED TRIALS ON ENOXAPARIN FOR COVID-19

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BACKGROUND

The coronavirus disease 2019 (COVID-19) carries a high risk of vascular thrombosis (both venous thromboembolism and arterial thrombosis). The American Society of Hematology issued a conditional recommendation in favor of therapeutic over prophylactic anticoagulation in acutely ill COVID-19 patients. Therapeutic dosing was found superior to prophylactic dosing in reducing organ support-free days (OR 1.27, 95% CI 1.03-1.58) in an analysis from three randomized trials (REMAP-CAP, ACTIV-4a, and ATTACC) in 2244 hospitalized patients (not in ICU). Nevertheless, other outcomes were not statistically different, including thrombosis, survival to hospital discharge, and bleeding.

This joint analysis of two randomized-controlled trials (RCTs) aims to assess the safety and efficacy of enoxaparin at therapeutic dose compared to prophylactic dose in people hospitalized with COVID-19.

METHODS

A joint analysis of two RCTs, COVID-19 HD and EMOS-COVID, was performed.

Both studies enrolled inpatients with COVID-19 and the following **inclusion criteria**:

- *respiratory compromise* (as identified by respiratory rate ≥25 breaths/min or arterial oxygen saturation ≤93% at rest or PaO2/FiO2 ≤300 mmHg for COVID-19 HD and by PaO2/FiO2 ≤250 mmHg for EMOS-COVID)

  and/or

- *coagulopathy* (D-dimer > 2000 ng/ml for both RCTs or sepsis-Induced coagulopathy score >4 for COVID-HD).

In both RCTs patients were randomly assigned to two arms: enoxaparin at prophylactic dose (standard 4.000 IU; in the EMOS-COVID 6000 IU if body weight >100 kg) or at therapeutic dose (70 IU/Kg every 12 h).

The **primary efficacy endpoint** of the joint analysis was **clinical worsening**, defined as **the occurrence of the first event among**: *in-hospital death*; *acute myocardial infarction*; symptomatic *arterial or venous thromboembolism*; need of either *Continuous Positive Airway Pressure (CPAP) or Non-Invasive Ventilation (NIV)* in patients who were in standard oxygen therapy at randomization; need for *invasive mechanical ventilation* in any patient. The primary outcome was assessed as time-to-event, described with hazard ratio (HR) and with Kaplan-Meier survival estimate.

High dose enoxaparin did not reduce clinical worsening in non-critically-ill patients with **COVID-19** compared to standard-dose enoxaparin.

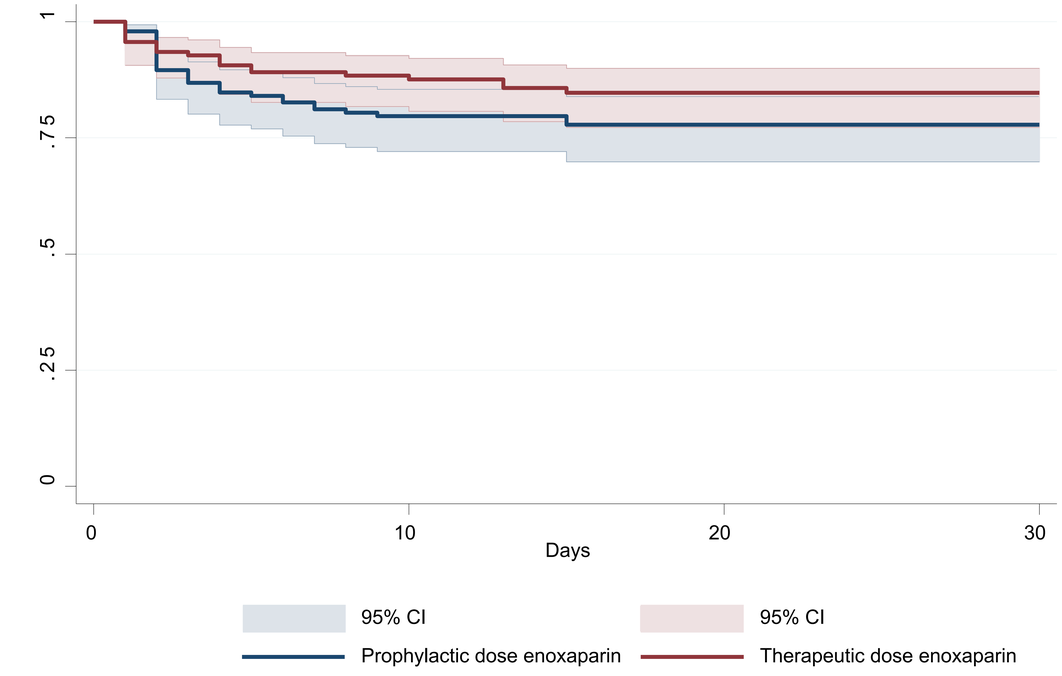


Figure. Kaplan-Meier survival estimate of clinical worsening

RESULTS

COVID-19 HD enrolled 142 people between July 2, 2020 and February 15, 2022, while EMOS-COVID enrolled 141 people from July 27, 2020 to June 5, 2021, resulting in 283 people included in this joint analysis. Baseline characteristics of the two groups are depicted in the Table. The Figure shows the Kaplan-Meier survival estimates of clinical worsening. 31/144 (21.53%) patients in the prophylactic-dose group and 21/139 (15.1%) in the therapeutic-dose group reached the primary outcome (p=0.16).

No major bleeding was observed during the study time.

	Therapeutic Dose (n= 139)		Prophylactic Dose (n= 144)		Total (n= 283)	
Age (Years, mean - SD)	61.4	10.3	60.8	11.2	61.1	10.7
BMI						
Kg/m² (mean – SD)	29.8	5.5	29.6	4.4	29.7	5.0
≥30	59	42.5%	66	45.8%	125	44.2%
<30	80	57.5%	78	54.2%	158	55.8%
Sex (n %)						
F	40	28.8%	36	25%	76	26.9%
M	99	71.2%	108	75%	207	73.1%
Respiratory Support at Screening time						
None or standard oxygen therapy	81	58.3%	87	60.4%	168	59.4%
CPAP / NIV	58	41.7%	57	39.6%	115	40.6%
Laboratory tests						
WBC (10^3/mmc, mean - SD)	8.0	3.3	8.3	3.6	8.2	3.4
PLT (10^3/mmc, mean - SD)	255.1	94.2	258.9	102.8	257.0	98.5
Creatinine (mg/dl, mean - SD)	0.8	0.2	0.8	0.2	0.8	0.2
INR (mean - SD)	1.1	0.1	1.1	0.1	1.1	0.1
aPTT ratio (mean - SD)	1.1	0.9	1.0	0.1	1.0	0.7
D-dimer (ng/ml, median – IQR)	840	530-1302	860	580-1246	852.5	567.5-1261.5
Sepsis Induced Coagulopathy score (mean – SD)	2.3	0.6	2.4	0.7	2.3	0.6

Table. Baseline characteristics of the participants

CONCLUSIONS

The results of this joint analysis did not highlight significant differences in clinical worsening between people with COVID-19 that received enoxaparin at therapeutic compared to prophylactic dose.

ADDITIONAL KEY INFORMATION

ClinicalTrials.gov identifiers: COVID-19 HD (NCT044082359), EMOS-COVID (NCT04646655)

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