



# Prophylactic or therapeutic doses of heparins for COVID-19 infection? A retrospective study

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## Abstract

**Background** Coronavirus disease 19 (COVID-19) is a global outbreak. COVID-19 patients seem to have relevant coagulative abnormalities, even if they are not typical of disseminated intravascular coagulopathy (DIC) of the kind seen in septicemia. Therefore, anticoagulant therapy with heparins is increasing in interest for a clinical approach to these patients, particularly if older. Studies comparing if prophylactic doses are more effective than therapeutic ones are still missing.

**Methods** Data were collected in the Geriatric Section of the Dolo Hospital, ULSS 3 “Serenissima”, Venice from 31st March to 01st May 2020. Heparins (calciparin, fondaparinux, enoxaparine) were divided into prophylactic or therapeutic doses. People previously treated with oral anticoagulants were removed. Vital status was assessed using administrative data. Cox’s regression analysis, adjusted for potential confounders, was used for assessing the strength of the association between heparins and mortality. The data were reported as hazard ratio (HR) with 95% confidence intervals (CIs).

**Results** 81 older people (mean age 84.1 years; females = 61.9%) were included. No significant differences in terms of demographic and clinical characteristics emerged between people treated with prophylactic or therapeutic doses, including age, gender, X-rays findings or severity of disease. Therapeutic doses were not associated to a better survival rate (HR 1.06; 95% CI 0.47–2.60;  $p=0.89$ ), even after adjusting for 15 confounders related to mortality (HR 0.89; 95% CI 0.30–2.71;  $p=0.84$ ).

**Conclusions** Our paper indicates that in older people affected by COVID-19 there is no justification for using therapeutic doses instead of prophylactic ones, having a similar impact on mortality risk.

**Keywords** COVID-19 · Heparin · Mortality

## Introduction

Coronavirus disease 19 (COVID-19) is a global outbreak. COVID-19 patients seem to have relevant coagulative abnormalities [1]. These alterations could appear both as thrombotic microangiopathy or disseminated intravascular coagulation, like in other severe infections [1]. Moreover, many patients also develop venous or arterial thrombosis [1].

Patients who died for COVID-19 pneumonia showed significantly increased higher levels of D-dimer and fibrin degradation products (FDP), longer prothrombin time (PT), with also later lower value of fibrinogen and anti-thrombin. All these data revealed an increased coagulation activation in COVID-19 patients, with an increased risk of death [2]. Moreover, severe patients are also often immobilized, with an elevated additional risk for venous thromboembolism development. Therefore, anticoagulant therapy with heparins is increasing in interest for a clinical approach to these patients, particularly if older. Anticoagulant therapy seems to be important to reduce fibrin deposition, microthrombi formation and prothrombotic state in these patients [2].

In a recent paper, the administration of Low Molecular Weight Heparin (LMWH) at prophylactic dose was highly recommended for all patients with COVID-19 infection that required hospitalization, in absence of contraindications [3]. Nevertheless, is not clear if the benefit in term of survivance

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with prophylactic doses of LMWH is limited only to patients that develop sepsis-induced coagulopathy during the course of COVID-19 infection [4]. It is also possible that patients with more severe infection could benefit from even higher doses of LMWH, several trials are investigating that point [1].

Studies comparing if prophylactic doses are more effective than therapeutic ones are still missing. Given this background, the aim of the present paper is to investigate the benefit in terms of mortality between the prophylactic or therapeutic dose of LMWH in older patients and COVID-19.

## Methods

### Participants

Data were collected in the Geriatric Section of the Dolo Hospital, ULSS 3 “Serenissima”, Venice from 31st March to 01st May 2020. The protocol of the study was approved by our Local Ethical Committee.

### COVID-19 diagnosis

To all the patients, a nasopharyngeal swab test with an RT-PCR assays (Copan UTM System, Copan, Italy) for the identification of SARS-CoV-2 was administered.

### Exposure: heparins

People previously treated with oral anticoagulants (e.g. for atrial fibrillation) were removed. Heparins (calciparin, fondaparinux, enoxaparin) were then divided in prophylactic or therapeutic doses. The decision for treating a patient with prophylactic or therapeutic doses was based on clinical, bio-humoral, radiological findings, giving higher doses of heparins to people at higher risk of mortality [5], since no univocal guidelines exist for therapy with heparins for COVID-19 [5]. The mean duration of treatment was 11 days.

### Outcome: mortality

Vital status was assessed using administrative data, recording the date of death. The mean follow-up period was 31 days.

### Clinical parameters

For the aims of this study, we collected several information, including (1) Demographics (age, sex); (2) clinical signs at the admission (temperature, systolic and diastolic blood pressure, Arterial Oxygen saturation, SpO<sub>2</sub>); (3) presence of comorbidities, verified through medical history, medications,

laboratory and radiological tests; (4) X-ray findings suggestive of COVID-19 infection and divided in pulmonary thickening and/or interstitial pneumonia; (5) bio-humoral findings: we collected several bio-humoral laboratory tests: for the aims of this paper, we have reported only those more strongly related to heparin use. These measurements were made using standard laboratory procedures.

### Statistical analysis

After verifying the normality of the continuous variables included, we reported the data as mean with standard deviations (SDs) or, in case of categorical variables, as percentages (%). Independent groups *T*-test was used for continuous variables, Chi-square test (with Fisher’s correction) for categorical parameters. For D-dimer, due to non-normal distribution, data are reported as median (with interquartile range) and the Kruskal–Wallis test was used for comparing any difference in the median.

For assessing the association between heparins’ dosages and mortality, we used a Cox’s regression analysis, adjusted for potential confounders. Confounders (i.e. age, sex, and presence of obesity, diabetes, cancer, COPD, dementia, Parkinson’s disease, renal failure, acute myocardial infarction, stroke, heart failure, high blood pressure, pressure sores, hepatic cirrhosis) were included in this model only if they reached, at the univariate analyses, a *p*-value < 0.10. The data were reported as hazard ratio (HR) with their 95% confidence intervals (CIs).

Threshold of statistical significance was set to 5%. All statistical analyses were performed with SPSS 21.0.

## Results

Overall, 88 older people were recovered in our ward. After excluding 7 persons treated with oral anticoagulants, 81 older people (mean age 84.1 years; females = 61.9%) were finally included.

Table 1 shows the most important descriptive findings, by a dose of LMWH used during the hospitalization. No significant differences in terms of demographic and clinical characteristics emerged between people treated with prophylactic or therapeutic doses, including age, gender, X-rays findings or presence of comorbidities. The only bio-humoral parameter significantly different was serum creatinine levels ( $1.61 \pm 1.11$  in prophylactic doses vs.  $1.22 \pm 0.52$  in therapeutic doses; *p* value = 0.04) (Table 1). No significant difference in the mean duration of the therapy emerged between the two groups ( $10.8 \pm 8.7$  vs.  $10.7 \pm 8.3$  days; *p* = 0.94).

As shown in Fig. 1, the cumulative incidence of deaths was similar between subjects taking a prophylactic or therapeutic dose of LMWH, being 50% in both groups (log rank

**Table 1** Descriptive findings of the participants included, by dose of LMWH

Parameter	Prophylactic doses ( <i>n</i> = 57)	Therapeutically doses ( <i>n</i> = 24)	<i>p</i> value
Age (years)	84.1 (11.9)	87.1 (8.0)	0.25
Females (%)	43.9	29.2	0.32
Temperature	37.4 (1.5)	36.9 (0.9)	0.61
Systolic blood pressure	125 (29)	126 (25)	0.99
Diastolic blood pressure	76 (16)	76 (13)	0.99
SpO <sub>2</sub>	93.0 (5.1)	92.1 (6.4)	0.59
Comorbidities, in alphabetical order			
Cancer (%)	7.0	12.5	0.42
Cirrhosis (%)	1.8	0.0	0.99
COPD (%)	17.5	8.3	0.49
Dementia (%)	64.9	54.2	0.45
Diabetes (%)	22.8	29.2	0.58
Heart failure (%)	3.5	4.2	0.99
Hypertension (%)	61.4	66.7	0.80
Obesity (%)	10.5	4.2	0.67
Parkinson's disease (%)	5.3	8.3	0.63
Pressure sores (%)	15.8	4.2	0.27
Previous AMI (%)	7.0	8.3	0.99
Renal failure (%)	17.5	12.5	0.75
Stroke (%)	7.0	4.2	0.99
X-ray findings			
Pulmonary thickening (%)	27.8	16.7	
Interstitial pneumonia (%)	33.3	45.8	
Both (%)	22.2	29.2	
Main bio-humoral findings			
D-dimer	1651 (640–2981)	744 (695–7489)	0.29
Creatinine	1.61 (1.11)	1.22 (0.52)	0.04
Hemoglobin	12.2 (2.4)	12.7 (2.1)	0.43
Platelets	215 (84)	245 (91)	0.15

Data are reported as mean (with standard deviation) for continuous variables and percentages for categorical variables, except for D-dimer for which the data are reported as median (with interquartile range). Independent groups *T*-test was used for continuous variables (Kruskall–Wallis test for D-dimer), chi-square test (with Fisher's correction) for categorical parameters

test, *p* value = 0.89). Therapeutic doses were not associated to a better survival rate (HR 1.06; 95% CI 0.47–2.60; *p* = 0.89), even after adjusting for 15 confounders related to mortality (HR 0.89; 95% CI 0.30–2.71; *p* = 0.84).

## Discussion

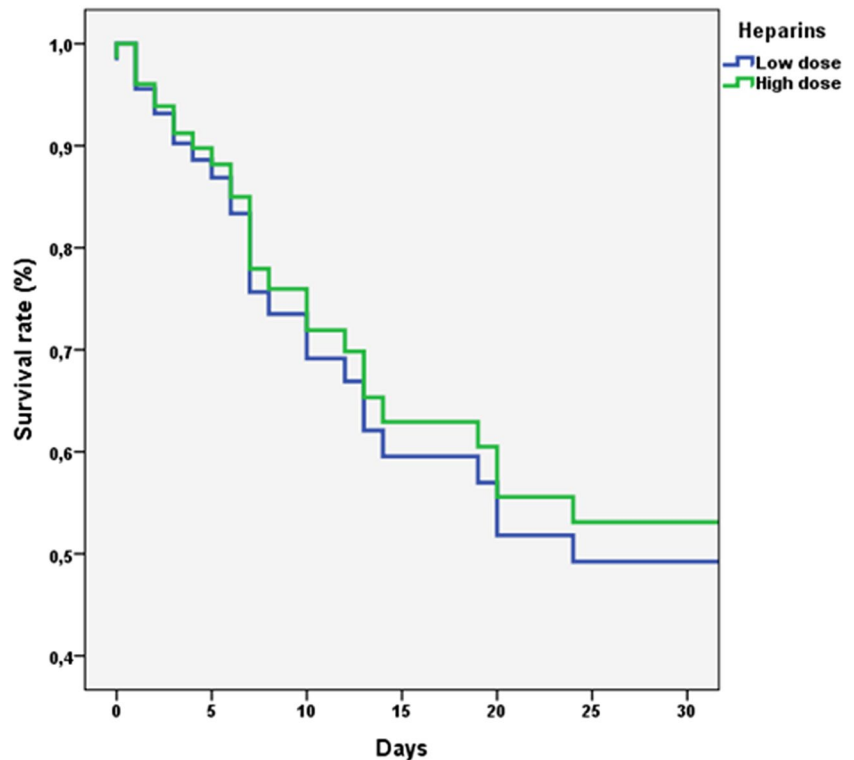
In the present retrospective study, including a group of older people affected by COVID-19, we reported no difference in terms of mortality between subjects taking a prophylactic or therapeutic dose of LMWH. This finding remained unaltered after adjustment for several potential confounders.

In a Chinese study involving 449 subjects with COVID-19 a reduction in mortality in people treated with low doses of LMWH was observed only for patients with

higher D-dimer level or sepsis-induced coagulopathy [6]. While the use of a prophylactic dose of LMWH in all COVID-19 patients is currently encouraged by several scientific associations [7], the use of higher doses is still debated.

The use of a therapeutic dose of LMWH could be suggested by the high incidence of venous thromboembolism in severe COVID-19 patients reported in the literature. In a recent paper, an incidence of 47% of venous thromboembolism was observed in a patient requiring intensive care unit for COVID-19, while in patients admitted to regular ward the incidence of symptomatic venous thromboembolism was 3%, despite the use of a prophylactic dose of LMWH [8]. Similarly, in an Italian study the incidence of venous thromboembolism was 6.6% in patients hospitalized in the normal ward and 27.6% in intensive care unit [9].

**Fig. 1** Survival curves by dose of LMWH



All these data, including our report, seem to highlight that maybe the protective effect of the therapeutic dose of LMWH in COVID-19 could be relevant only in selected or severe patients. Lacking definitive data on LMWH dose for COVID-19 patients, currently, there are only treatment suggestions elaborated by experts in the field of coagulation and based on a patient-tailored approach taking into account laboratory values, particularly D-dimer levels, comorbidities, risk factors, and severity of the infection [10–12].

The findings of our paper should be interpreted within its limitations. First, the retrospective nature of this study that can contain some biases. Second, we did not collect, during the follow-up, hemorrhagic events. Third, we did not calculate any prognostic or severity index that can be important in better tailoring therapy in older people. Third, to know some of the predictors of prognosis in such a frail population would be of importance, since some of these factors could be responsible at the same time of the dose prescription and of mortality. Finally, the sample size is limited (less than 100 participants) and with a short follow-up period. Despite these limitations, we believe that our paper has some strengths, in particular the fact that is the first study exploring this important clinical topic.

In conclusion, our study indicates that in older people affected by COVID-19 admitted to a regular ward, there is no justification for using therapeutic doses instead of prophylactic ones, having a similar impact on mortality risk. Future RCTs are needed to confirm our findings.

**Author contributions** Data analysis and statistical analysis: NV; data collection: MM, FB; drafting: FB, MF, FB; critical revision: FC, PA, AR.

**Funding** None.

**Data availability** Available upon request to the corresponding author.

**Code availability** All statistical analyses were performed with SPSS 21.0.

## Compliance with ethical standards

**Conflict of interest** None to declare.

**Ethics approval** In agreement with the current Italian law [Gazzetta Ufficiale della Repubblica Italiana, Serie Generale n. 76 del 31-03-2008], we informed our local Ethical Committee of this nature that is observational and collect the data regarding normal critical practice.

**Consent to participate** Informed consent was collected orally for hygienic reasons.

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