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► **To cite this version:**

Stéphane Zuily, Benjamin Lefèvre, Olivier Sanchez, Ombeline Empis de Vendin, Guillaume de Ciancio, et al.. Effect of weight-adjusted intermediate-dose versus fixed-dose prophylactic anticoagulation with low-molecular-weight heparin on venous thromboembolism among noncritically and critically ill patients with COVID-19: the COVI-DOSE trial, a multicenter, randomised, open-label, phase 4 trial. *EClinicalMedicine*, 2023, 60, pp.102031. 10.1016/j.eclinm.2023.102031 . hal-04141301

HAL Id: hal-04141301

<https://hal.univ-lorraine.fr/hal-04141301v1>

Submitted on 26 Jun 2023

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Effect of weight-adjusted intermediate-dose versus fixed-dose prophylactic anticoagulation with low-molecular-weight heparin on venous thromboembolism among noncritically and critically ill patients with COVID-19: the COVI-DOSE trial, a multicenter, randomised, open-label, phase 4 trial



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eClinicalMedicine

2023;60: 102031

Published Online 9 June 2023

<https://doi.org/10.1016/j.eclinm.2023.102031>

1016/j.eclinm.2023.102031

Summary

Background Venous thromboembolism is a major complication of coronavirus disease 2019 (COVID-19). We hypothesized that a weight-adjusted intermediate dose of anticoagulation may decrease the risk of venous thromboembolism COVID-19 patients.

Methods In this multicenter, randomised, open-label, phase 4, superiority trial with blinded adjudication of outcomes, we randomly assigned adult patients hospitalised in 20 French centers and presenting with acute respiratory SARS-CoV-2. Eligible patients were randomly assigned (1:1 ratio) to receive an intermediate weight-adjusted prophylactic dose or a fixed-dose of subcutaneous low-molecular-weight heparin during the hospital stay. The primary outcome corresponded to symptomatic deep-vein thrombosis (fatal) pulmonary embolism during hospitalization (COVI-DOSE [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04373707) number: NCT04373707).

Findings Between May 2020, and April 2021, 1000 patients underwent randomisation in medical wards (noncritically ill) (80.1%) and intensive care units (critically ill) (19.9%); 502 patients were assigned to receive a weight-adjusted intermediate dose, and 498 received fixed-dose thromboprophylaxis. Symptomatic venous thromboembolism occurred in 6 of 502 patients (1.2%) in the weight-adjusted dose group and in 10 of 498 patients (2.1%) in the fixed-dose group (subdistribution hazard ratio, 0.59; 95% CI, 0.22–1.63; $P = 0.31$). There was a twofold increased risk of major or clinically relevant nonmajor bleeding: 5.9% in the weight-adjusted dose group and 3.1% in the fixed-dose group ($P = 0.034$).

Interpretation In the COVI-DOSE trial, the observed rate of thromboembolic events was lower than expected in patients hospitalized for COVID-19 infection, and the study was unable to show a significant difference in the risk of venous thromboembolism between the two low-molecular-weight-heparin regimens.

Funding French Ministry of Health, CAPNET, Grand-Est Region, Grand-Nancy Métropole.

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Keywords: COVID-19; Venous thromboembolism; Heparin; Anticoagulation

Introduction

During the early course of moderate to severe coronavirus disease 2019 (COVID-19), an increased risk of venous thromboembolism was reported despite a conventional dose of thromboprophylaxis using heparin.¹ Therefore, several strategies evaluating increased doses of anticoagulation were proposed to reduce the risk of venous thromboembolism, but at the cost of an excess of bleeding, particularly when using therapeutic-dose anticoagulation.² Risk factors for severe or critical COVID-19 include old age and obesity.³ While frail elderly patients may be more subject to bleeding complications, obesity may require a higher anticoagulation dosage in COVID-19. The majority of published randomized controlled trials have evaluated either fixed-dose or therapeutic-dose thromboprophylaxis.⁴ Few

studies have assessed intermediate dose as in the COVI-DOSE trial. One randomized trial has assessed the effect of weight-adjusted dosing versus fixed dose of low-molecular-weight heparin in trauma patients.⁵ This pilot study did not demonstrate a statistical difference between groups although there was a trend in favor of a lower incidence of deep vein thrombosis with the increased dose. The US Western Association of Trauma suggest the use of enoxaparin 4000 IU bid in severe trauma patients, although strong evidence to support this strategy is lacking. The use of intermediate rather than standard dose low-molecular-weight heparin has been proposed in other high-risk settings, such as morbidly obese inpatients,⁶ cancer patients⁷ and was assessed recently in pregnant women with a history of venous thromboembolism.⁸ To our knowledge, the

Research in context

Evidence before this study

Venous thromboembolism (VTE) has emerged as an important consideration in the management of hospitalized patients with COVID-19. Therefore, whether several strategies of thromboprophylaxis could improve the prognosis of patients with COVID-19 have been the subject of extensive important research. We searched randomized controlled trials on MEDLINE with no date or language restrictions on May 8, 2023, using the title and abstract search terms “anticoagulation” and “COVID-19”, which yielded 28 results, with only a single trial designed to compare weight-adjusted intermediate dose of low-molecular-weight-heparin for thromboprophylaxis in critically ill patients with COVID-19 admitted to the intensive care unit. This was the INSPIRATION trial (NCT04486508), which showed the absence of significant difference in the primary outcome of a composite of adjudicated venous or arterial thrombosis,

treatment with extracorporeal membrane oxygenation, or mortality within 30 days.

Added value of this study

COVI-DOSE was designed to assess the efficacy and safety of weight-adjusted intermediate dose of low-molecular-weight heparin versus fixed-dose in noncritically ill as well as critically ill patients with COVID-19 admitted to the medical ward or the intensive care unit. In this trial, we observed no decrease in the risk of venous thromboembolism but an increased risk of clinically relevant nonmajor bleeding.

Implications of all the available evidence

Our results do not support the use of weight-adjusted intermediate-dose prophylactic anticoagulation with low-molecular-weight heparin in all hospitalised patients with COVID-19.

benefit of a weight-adjusted intermediate prophylactic dose of anticoagulation has not been fully investigated, especially in noncritically ill COVID-19 patients, compared to that of fixed-dose thromboprophylaxis. Thus, the objective of this randomized controlled trial was to assess the benefit of a weight-adjusted intermediate dose versus a lower fixed-dose of low-molecular-weight heparin on the risk of venous thromboembolism in COVID-19 inpatients from medical wards and intensive care units.

Methods

Study design and oversight

The COVI-DOSE trial (COVID-19 and dose of anticoagulation) was an investigator-initiated, multicenter, randomized, controlled, parallel-group, phase 4, open-label trial with blinded adjudication of outcomes. The sponsor was the University Hospital of Nancy. The steering committee ([Supplementary appendix](#)) was responsible for the design and oversight of the trial and vouched for the accuracy and completeness of the data and for the fidelity of the trial to the protocol and the statistical analysis plan available at www.thelancet.com. An independent Data Safety Monitoring Board ([Supplementary appendix](#)), monitored patient safety throughout the trial and gave recommendations to the steering committee and the sponsor. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation and was approved by the appropriate French ethics committee (Comité de Protection des Personnes Sud Méditerranée II, reference: 220A08, April 29th 2020). The COVI-DOSE trial was performed in the

setting of the Investigation Network On Venous Thrombo-Embolicism (INNOVTE) and Investigation Network Initiative–Cardiovascular and Renal Clinical Trialists (INI-CRCT), two French research networks on behalf of the French Clinical Research Infrastructure Network (F-CRIN). The COVI-DOSE trial conform to CONSORT 2010 guidelines ([Supplementary appendix](#)). COVI-DOSE [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04373707) number: NCT04373707.

Patients

Patients were enrolled in medical wards or intensive care units from 20 French hospitals. They were eligible to participate in the COVI-DOSE trial if they were adults, hospitalized and presenting with a confirmed or a probable acute respiratory SARS-CoV-2 infection according to World Health Organization classification,⁹ diagnosed by virological test (positive polymerase chain reaction and/or serologic test). Probable cases are suspect cases for whom testing for SARS-CoV-2 is inconclusive or not available in patients with typical SARS-CoV-2 pneumonia. Non-inclusion criteria are available in the full protocol. All included patients provided written informed consent either before enrollment, when possible, or later, when consent was obtained from their authorized representatives before enrollment in critical care settings.

Randomization and masking

Eligible patients were randomly assigned in a 1:1 ratio to receive either an intermediate weight-adjusted prophylactic dose (experimental arm) or a fixed-dose (control arm) of low-molecular-weight heparin. Randomization was performed using a computer-generated allocation sequence, with permuted blocks of two, four and six and stratified according to center and hospitalization setting

at inclusion (medical wards versus intensive care units). The randomization was centrally conducted through an interactive online system.

Treatments

The experimental and control low-molecular-weight heparin regimens are presented in [Table 1](#) and in the protocol available at www.thelancet.com. In the experimental arm and regardless of the hospitalization setting, patients received an increased weight-adjusted intermediate dose of low-molecular-weight heparin ranging from a double standard dose (e.g., enoxaparin 4000 UI twice daily for <50 kg) to a higher dose (e.g., enoxaparin 7000 UI twice daily for ≥ 100 kg). In the control arm, patients admitted to the medical wards received a fixed standard dose of low-molecular-weight heparin (e.g., enoxaparin 4000 UI once daily), while patients from the intensive care units received a fixed doubled standard dose (e.g., enoxaparin 4000 UI twice daily). The heparin doses might have changed during hospitalization and after inclusion based on predefined criteria in case of a) creatinine clearance modifications overtime (both arms) and b) transfert from wards to intensive care unit and vice-versa (control arm only). For instance, regardless of the group of randomization, a patient with a drop of creatinine clearance from >30 to ≤ 30 mL/min will be prescribed a lower dose of low-molecular-weight heparin according to [Table 1](#). For patients randomized in the control arm only, low-molecular-weight heparin doses are doubled in case of transfert from the medical wards to intensive care unit or decreased by 50% in case of transfert from intensive care unit to the medical ward except for patients with a history of mechanical ventilation. The trial treatment was administered during the entire hospital stay (maximal duration of 28 days). Beyond this delay, the treatment and the dose prescribed were left to the discretion of the investigator.

Laboratory (platelet testing) and clinical follow-up of the heparin treatment were applied in accordance with current clinical practice.

Outcomes

The primary outcome was the occurrence of a symptomatic venous thromboembolism event during hospital stay or up to the 28 first days of randomization if the stay was longer. Symptomatic venous thromboembolism was defined by the occurrence of symptomatic deep-vein thrombosis (either proximal or distal), and/or symptomatic pulmonary embolism, or a sudden death for which no other cause could be identified. All events were diagnosed according to current guidelines.¹⁰ Other effectiveness outcomes were the occurrence of a type of venous thromboembolism other than those targeted by the primary objective (superficial vein thrombosis, thrombosis of a catheter/extracorporeal dialysis circuit/extracorporeal membrane oxygenation) and the occurrence of a symptomatic arterial thrombosis. Safety outcomes assessed during hospitalization (up to day 28) were the occurrence of major bleeding¹¹ or clinically relevant nonmajor bleeding.¹² Other outcomes were the net clinical benefit, defined by a composite criterion associating venous thromboembolism and major bleeding, and all-cause mortality, during hospitalization and at day 60 after inclusion. All suspected events were adjudicated by a central independent committee ([Supplementary appendix](#)) whose members were unaware of the treatment assignments.

Sample size and statistical analysis

With a procedure to take into account the competing risk of death¹³ and assuming an estimated 1-month incidence of the primary efficacy outcome of 27% in the fixed-dose group¹⁴ and a 13% incidence of death, we determined that the enrollment of 602 patients (65 events) would provide a power of 80% to detect a 50% reduction with the weight-adjusted dose, at a two-sided type I error of 0.05. The assumption of a 50% risk reduction of intermediate dose versus low dose low-molecular-weight heparin was based on the available studies that compared two prophylactic regimens of LMWH, firstly in trauma patients with an estimation of a relative risk reduction of 63%,⁵ and in a meta-analysis that compared 2 dosing strategies in orthopedic surgery with an estimation of 47%.¹⁵ In February 2021, after the inclusion of 542 patients, based on the lower published incidence of venous thromboembolism¹⁶ and low overall observed rate of the primary outcome, the steering committee, unaware of the group assignment, decided to increase the sample size to 1000 patients (see protocol).

The primary analysis was performed in the intention-to-treat population (all the patients who underwent randomization). Time-to-event thrombotic outcome was estimated by competing risk analysis using the Kalbfleisch and Prentice method.¹⁷ Patients were censored at

Experimental arm Increased weight-adjusted dose of low-molecular-weight heparin		
Creatinine clearance ^a	Weight at inclusion	Increased weight-adjusted dose
>30	<50 kg	4000 UI (0.4 mL) BID
	50 à < 70 kg	5000 UI (0.5 mL) BID
	70 à < 100 kg	6000 UI (0.6 mL) BID
	≥ 100 kg	7000 UI (0.7 mL) BID
15–30	all weights	3000 UI (0.3 mL) BID
Control arm Lower-dose of low-molecular-weight heparin		
Creatinine clearance ^a	Standard Dose: For patients hospitalized in a medical ward	Doubled Standard Dose: For patients hospitalized in an intensive care unit
>50	4000 UI (0.4 mL) OD	4000 UI (0.4 mL) BID
>30–50		
15–30	2000 UI (0.2 mL) OD	2000 UI (0.2 mL) BID

Example of Enoxaparin (see full protocol for other molecules). ^aCockcroft and Gault formula (mL/min/1.73 m²); OD: once daily; BID: bi-daily.

Table 1: Low-molecular-weight heparin regimens according to groups of randomization.

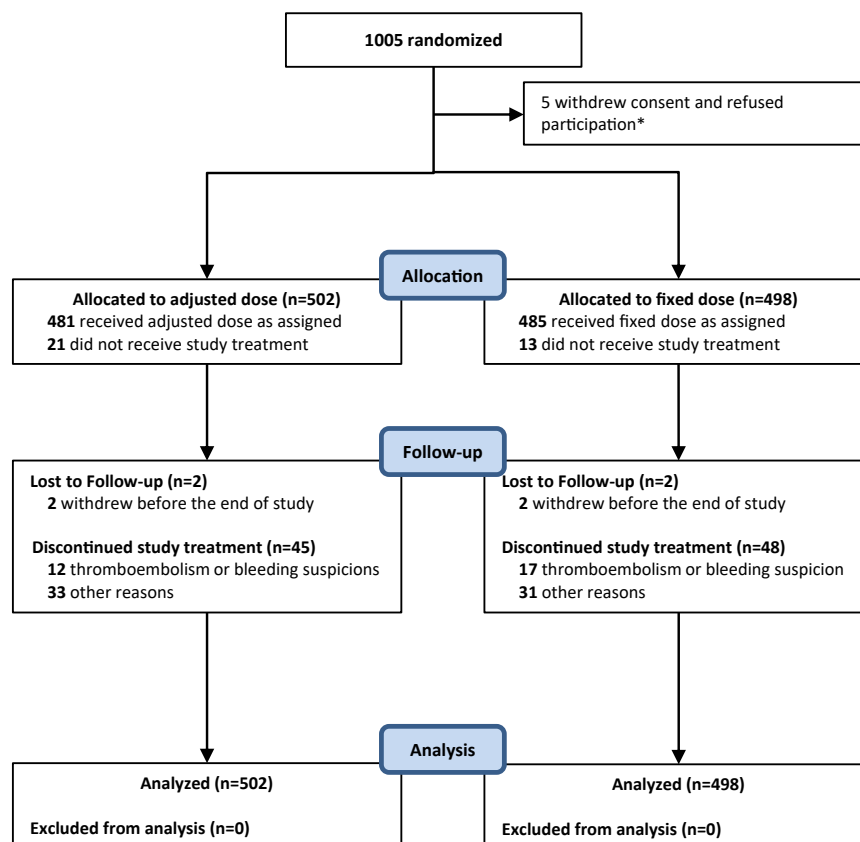
the time of their last follow-up assessment. Cumulative incidences are presented with corresponding 95% confidence intervals (95% CIs). Subdistribution hazard ratios (SubHR) with corresponding 95% CIs were calculated, and the resulting P value was reported. The SubHR for the incidence of bleeding and other outcomes were analyzed with the same methods and population as for the primary analysis. Consistency of the treatment effect was tested across the following subgroups: strata of randomization, time period of randomization, age, sex, body mass index, creatinine clearance, corticosteroid use and respiratory support. Statistical analyses were performed using SAS version 9.4 software (SAS Institute, Inc.). Graphs were constructed with the use of R software, version 4.0.2. A threshold of $P = 0.05$ for two-tailed tests was considered significant.

Role of the funding source

The study sponsor and the funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 13, 2020, and April 29, 2021, 1005 patients were included in 20 centers: 506 were randomly assigned to receive a weight-adjusted prophylactic dose of low-molecular-weight heparin, and 499 received a fixed prophylactic dose. In five patients (0.5%, four in the experimental group and one in the control group), consent was either withdrawn or lacking; thus, 1000 patients were considered in the intention-to-treat analysis. The study flow chart is shown in Fig. 1. Four (0.4%) patients were lost to follow-up, and 42 (4.2%) died from another cause than either thrombosis or bleeding. Patients were included mainly in medical units (801 patients, 80.1%) and to a lesser extent in intensive care units (199 patients, 19.9%). The median (interquartile range [IQR]) duration of hospitalization was 8 days (5–13) in both groups. According to WHO classification, COVID-19 cases were classified as confirmed (89.6%) (using polymerase chain reaction in 99.1%) or probable cases (10.4%). Respiratory supports were not equally distributed between patients randomized in medical wards



*French legislation precludes any reporting of data from these patients.

Fig. 1: Flow chart. Between May 2020 and April 2021, 1005 patients were included in 20 centers: 502 were randomly assigned to receive a weight-adjusted prophylactic dose of low-molecular-weight heparin, and 498 received a fixed prophylactic dose. Thus, 1000 patients were considered in the intention-to-treat analysis.

versus intensive care units, respectively: Supplemental oxygen ≤ 15 L/min (85% versus 68%), noninvasive ventilation with high flow O₂ support >15 L/min (0% versus 17%), invasive mechanical ventilation \pm ECMO (0% versus 14%), and none (14.9% versus 0.5%). At

randomization, the characteristics of the two groups were well balanced (Table 2).

Twenty-one patients (4.2%) in the experimental arm and 13 (2.6%) in the control arm did not receive any study dose of low-molecular-weight heparin. The result

Characteristics at inclusion	Weight-adjusted dose (N = 502)	Fixed dose (N = 498)	Standardized difference
Median age (IQR) — years	62.2 (53.1–70.6)	61.8 (51.6–71.0)	0.02
Age ≥ 70 years — no (%)	134/502 (26.7)	138/498 (27.7)	-0.02
Male sex — no (%)	331/502 (65.9)	335/498 (67.3)	-0.03
Median body weight (IQR) - kg	83.0 (72.0–95.0)	81.7 (72.0–93.0)	0.06
Body weight - no (%)			0.08
<50 kg	9 (1.8)	8 (1.6)	
50–70 kg	95 (18.9)	94 (18.9)	
70–100 kg	308 (61.4)	317 (63.8)	
≥ 100 kg	90 (17.9)	78 (15.7)	
Median body mass index ^a (IQR) — kg/m ²	28.3 (24.9–32.2)	28.1 (24.8–31.3)	0.06
Body mass index ≥ 30 kg/m ² - no (%)	184/496 (37.1)	158/485 (32.6)	0.09
Creatinine clearance (Cockcroft-Gault) — no (%)			0.11
<50 mL/min	21 (4.2)	29 (5.9)	
50–90 mL/min	149 (29.7)	160 (32.3)	
≥ 90 mL/min	331 (66.1)	306 (61.8)	
Hospitalization in medical wards at inclusion	407 (81.1)	394 (79.1)	0.05
Known past medical history — no (%)			
Hypertension	195/492 (39.6)	204/495 (41.2)	-0.03
Diabetes mellitus	112/491 (22.8)	104/495 (21.0)	0.04
Hypercholesterolemia	111/491 (22.6)	112/491 (22.8)	0.00
Coronary heart disease	45/495 (9.1)	33/494 (6.7)	0.09
Sleep apnea	44/494 (8.9)	41/492 (8.3)	0.02
Chronic respiratory disease	31/494 (6.3)	19/494 (3.8)	0.11
Active cancer	19/490 (3.9)	23/489 (4.7)	-0.04
Venous thromboembolism	19/495 (3.8)	26/494 (5.3)	-0.07
Stroke	18/491 (3.7)	16/489 (3.3)	0.02
Chronic kidney disease	11/495 (2.2)	10/495 (2.0)	0.01
Heart failure	10/494 (2.0)	12/494 (2.4)	-0.03
Treatment at baseline — no (%)			
Antiplatelet agent	97/502 (19.3)	95/496 (19.2)	0.00
Renin-angiotensin system blockers	138/495 (27.9)	160/494 (32.4)	-0.10
Corticosteroid use (10 mg/day or more)	57/493 (11.6)	48/495 (9.7)	0.06
COVID-19 specific treatments — no (%)			
Dexamethasone	384/473 (81.2)	390/486 (80.2)	0.02
Tocilizumab	7/468 (1.5)	9/484 (1.9)	-0.03
Respiratory support — no (%)			0.06
Supplemental oxygen ≤ 15 L/min	404/494 (81.8)	401/491 (81.7)	
Noninvasive ventilation with high flow O ₂ support >15 L/min	14/494 (2.8)	19/491 (3.9)	
Invasive mechanical ventilation \pm ECMO	14/494 (2.8)	14/491 (2.8)	
No supplemental oxygen therapy	62/494 (12.6)	57/491 (11.6)	
Study drug compliance			
At least one dose of study drug (modified ITT)	481/502 (95.8)	485/498 (97.4)	-0.09
Full compliance	436/481 (90.6)	437/485 (90.1)	0.02
Treatment discontinuation	45/481 (9.4)	48/485 (9.9)	-0.02
Due to thromboembolism or bleeding suspicion	12	17	
Other reasons	33	31	

Abbreviations: ECMO: Extracorporeal membrane oxygenation; IQR: Interquartile range. ^aThe body mass index is the weight in kilograms divided by the square of the height in meters.

Table 2: Baseline demographic, clinical and therapeutic characteristics of the patients.

was unchanged in the modified-ITT population (patients receiving at least one dose of study treatment). Among patients who started treatment (99.6% enoxaparin and 0.4% tinzaparin), study drug compliance was evaluated and is described in Table 2. The median duration of trial-drug administration was 7 days in both groups, with a median daily dose of 12,000 UI (interdecile range: 10,000–14,000) in the experimental arm and 4000 UI (interdecile range: 4000–8000) in the control arm. The median (IQR) follow-up was 65 days (61–75) in the experimental arm and 64 days (61–75) in the control arm. Steroid use during hospitalization did not differ between experimental and control arms (81.2% versus 80.2%, respectively), nor did tocilizumab use (1.5% versus 1.9%, respectively).

During the hospital stay, symptomatic venous thromboembolism occurred in 6 out of 502 patients (1.2%) in the experimental arm and 10 of 498 patients (2.1%) in the control arm, yielding a SubHR of 0.59 (95% CI: 0.22–1.63; $P = 0.31$) (Fig. 2, Table 3). The median (IQR) time to event was 4.0 days (2.0–14.0) in the experimental arm and 13.0 days (8.0–19.0) in the control arm (Table 3). Descriptive subgroup analyses for the primary outcome are provided in Fig. 3. The risk of symptomatic venous thromboembolism was not significantly different across groups of treatment in patients admitted to medical wards (SubHR: 0.32, 95% CI: 0.06–1.59) or intensive care units (SubHR: 1.10, 95% CI: 0.28–4.39) or according to BMI below 30 (SubHR: 0.62, 95% CI: 0.15–2.58) or ≥ 30 (SubHR: 0.53, 95% CI: 0.13–2.18).

The frequency of major bleeding events occurring during hospitalization did not differ between the

experimental and control arms (1.0% versus 1.3%, respectively, Table 4). A significantly higher rate of major or clinically relevant nonmajor bleeding was observed in the experimental versus control arms (5.9% versus 3.1%, respectively, SubHR: 1.95, 95% CI: 1.05–3.63, $P = 0.034$), with differences between medical wards (experimental versus control groups: 6.1% and 1.9%, respectively) and intensive care units (experimental versus control groups: 5.3% and 7.8%, respectively). Clinically relevant nonmajor bleeding occurred in 4.9% and 1.9% of the experimental and control arms, respectively (SubHR: 2.69, 95% CI: 1.25–5.77). During the entire follow-up study (up to day 60), 26 patients (5.4%) died in the experimental arm, and 31 (6.5%) died in the control arm (HR: 0.83, 95% CI: 0.49–1.40); a net clinical benefit was observed in 15 (3.1%) and 23 patients (4.8%), respectively (SubHR: 0.64, 95% CI: 0.34–1.23).

During hospitalization, three symptomatic venous thromboses of other sites (0.6%) occurred in both groups (three jugular vein thrombi, two catheter-related thrombi, and one upper-limb superficial vein thrombus). One case of symptomatic arterial thrombosis (0.2%) was observed in the experimental arm (radial thrombosis), and two (0.4%) were observed in the control arm (one ischemic stroke and one myocardial infarction).

Discussion

The COVI-DOSE study, which involved 1000 COVID-19 patients hospitalized in medical wards or intensive care units, did not show that an intermediate weight-adjusted prophylactic dose of low-molecular-weight heparin

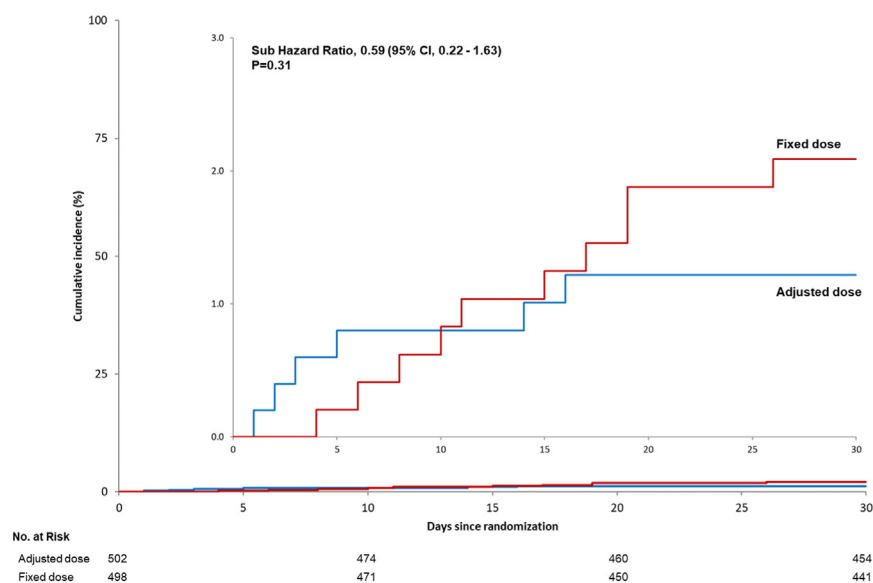


Fig. 2: Cumulative Event Rates for the Primary Outcome. The curves are shown for the first occurrence of the primary outcome of adjudicated symptomatic recurrent venous thromboembolism defined as symptomatic deep-vein thrombosis or pulmonary embolism or venous thromboembolism-related death during the hospital stay. The inset shows the same data on an expanded y-axis.

	Weight-adjusted dose (N = 502)	Fixed dose (N = 498)	Subhazard ratio (95% Confidence Interval)	P value
Symptomatic venous thromboembolism during hospitalization or until day 28 ^b	6/502 (1.2)	10/498 (2.1)	0.59 (0.22–1.63)	0.31
Components of the primary outcome				
Deep-vein thrombosis ^c	0	2		
Pulmonary embolism	3	8		
Pulmonary embolism-related deaths ^d	3	0		
Primary outcome, by site of hospitalization ^b				
Medical ward	2/407 (0.5)	6/394 (1.6)	0.32 (0.06–1.59)	
Intensive care units	4/95 (4.2)	4/104 (3.9)	1.10 (0.28–4.39)	

^aThe analysis of primary outcome was for adjudicated events, performed in the intention-to-treat population. ^bKalbfleisch and Prentice method accounting for the competing risk associated with the risk of death. ^cOne case of proximal and one case of distal deep-vein thrombosis. ^dOne fatal pulmonary embolism and two sudden deaths where pulmonary embolism could not be ruled out.

Table 3: Primary outcome.^a

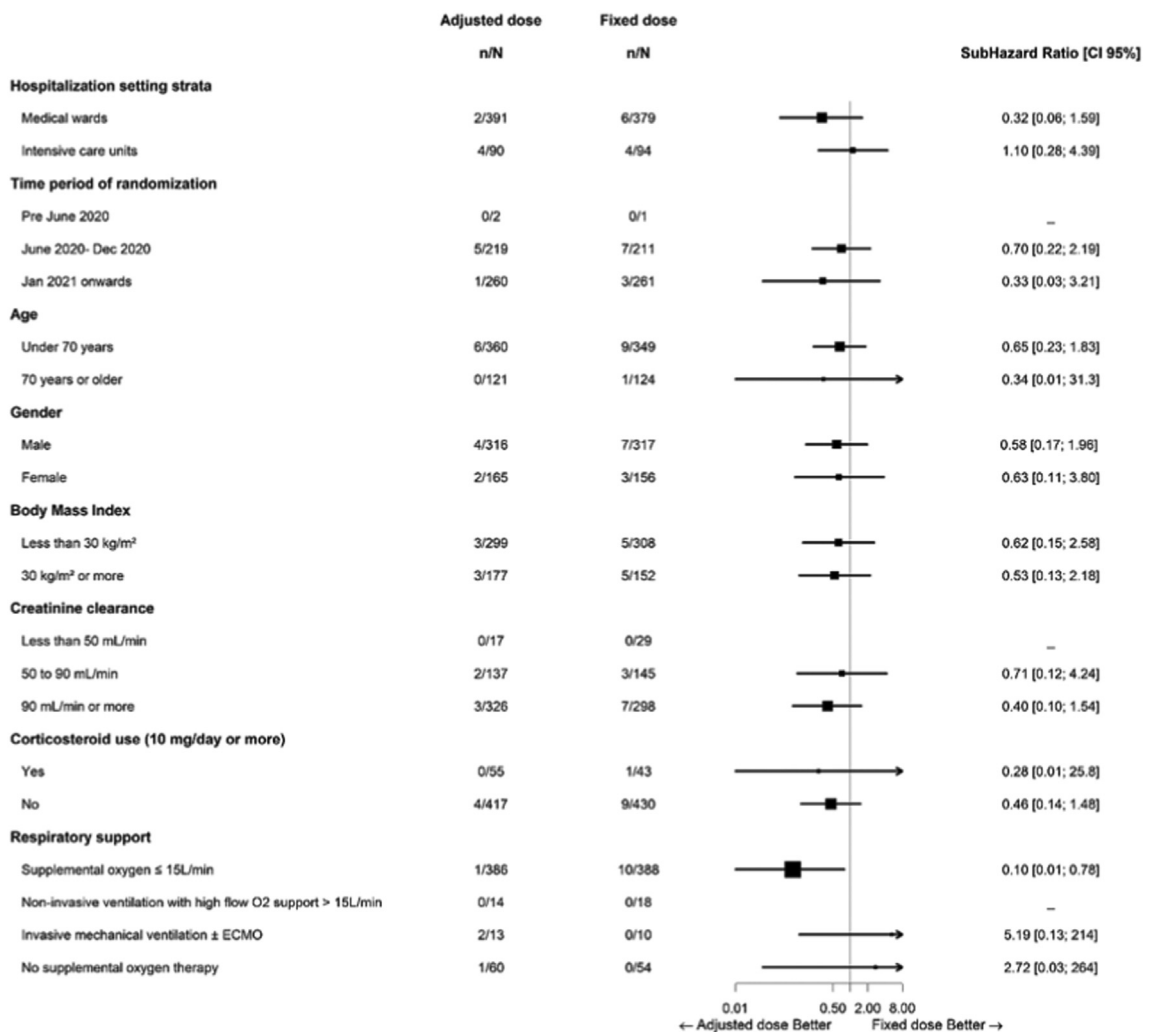


Fig. 3: Descriptive Subgroup Analyses for the Primary Outcome. Subgroup analyses were conducted in the intention-to-treat population. The size of each square indicates the treatment effect, and arrows indicate 95% confidence intervals that extend past the boundary of the graph. Body mass index is the weight in kilograms divided by the square of the height in meters. Abbreviation: ECMO: extracorporeal membrane oxygenation.

	Weight-adjusted dose (N = 502)	Fixed dose (N = 498)	Subhazard ratio (95% Confidence Interval) ^b	P value
	No. of patients with the event/total no. of patients (%)			
Major bleeding or clinically relevant nonmajor bleeding ^b	29/502 (5.9)	15/498 (3.1)	1.95 (1.05–3.63)	0.034
Major bleeding ^b	5 (1.0)	6 (1.3)	0.83 (0.25–2.70)	0.75
Fatality	0	0		
Hemoglobin decrease \geq 2 g/dL	5	6		
Transfusion \geq 2 units	3	3		
Critical site bleeding	0	1 ^c		
Clinically relevant nonmajor bleeding ^b	24/502 (4.9)	9/498 (1.9)	2.69 (1.25–5.77)	0.011
All-cause death ^b	22/502 (4.5)	25/498 (5.2)	0.87 (0.49–1.55)	0.64
Net clinical benefit ^b	10/502 (2.0)	16/498 (3.3)	0.62 (0.28–1.36)	

^aThe analyses of secondary outcomes were for adjudicated events, performed in the intention-to-treat population. ^bKalbfleisch and Prentice method accounting for the competing risk associated with risk of death. ^cRetroperitoneal bleeding.

Table 4: Secondary outcomes during hospitalization (up to day 28).^a

reduced the risk of symptomatic venous thromboembolism compared to that with a fixed prophylactic dose. Importantly, an intermediate dose was associated with a near 2-fold increased risk of clinically relevant nonmajor bleeding.

To our knowledge, few trials compared intermediate weight-adjusted prophylactic doses of low-molecular-weight heparin versus fixed prophylactic doses of low-molecular-weight heparin in COVID-19 patients, most of them included critically ill patients admitted to intensive care units or with laboratory evidence of coagulopathy.^{18–21} These trials failed to demonstrate the benefit of an increased intermediate (nontherapeutic) weight-adjusted dose using low-molecular-weight heparin for several outcomes, including thrombosis, treatment with extracorporeal membrane oxygenation and mortality, probably due to either a lack of power or the absence of a treatment effect or both. Together with these studies, we confirm the lack of superiority of weight-based intermediate dose low-molecular-weight heparin versus standard fixed prophylactic dose in critically ill patients. Similarly, in other trials assessing the effect of therapeutic versus standard dose anticoagulation in critically ill patients, higher doses had no effect on efficacy but induced a higher risk of bleeding.²

Regarding noncritically ill patients, our results suggest a different treatment effect depending on the hospitalization setting at inclusion with a nonsignificantly lower frequency of venous thromboembolism in the medical wards (0.5% versus 1.6%, respectively) not seen in the intensive care units (4.2% versus 3.9%, respectively). Of note, patients from the experimental arm with supplemental oxygen less than 15 L had a significant reduction of the primary outcome. However, because of the risk of the overall type I error rate inflation (subgroup analysis with multiple comparisons), this result may be due to chance. To date, some trials assessing therapeutic dose heparin showed significant reduction

of different primary outcomes such as thrombosis²² or the need for organ support²³ in non-critically ill selected COVID-19 patients (e.g., according to d-dimer results). Data from two years of trials looking at the optimal thromboprophylaxis strategy in hospitalized noncritically ill COVID-19 patients were summarized in the recent ISTH guidelines²⁴: a) therapeutic-dose low-molecular-weight heparin is preferred over standard prophylactic dose in selected COVID-19 ward patients (class of recommendation 1), while b) only data from retrospective observational studies supported the recommendation of the absence of benefit of an intermediate dose versus standard prophylactic dose (class of recommendation 3). The COVI-DOSE randomized controlled trial failed to demonstrate the superiority of an increased weight-adjusted intermediate-dose versus standard fixed-dose low-molecular-weight heparin. The following could have impacted primary outcome measures: First, we recorded a lower frequency of symptomatic venous thromboembolism (<5%) than previously reported at the beginning of the pandemic (up to 31%), and the point estimate of the treatment effect was lower (relative risk reduction of 41%) than expected (50%), probably leading to an underpowered and a nonconclusive trial.^{25,26} This could be explained by the mixing of patients from medical wards and intensive care units as well as several factors that have induced a lower incidence of thrombosis since 2020: the primary outcome was measured during the hospital stay and the average recorded hospital duration was 7 days, the measurement of only symptomatic venous thromboembolism events without systematic screening, lower COVID-19 variant severity in terms of systemic inflammation, and the benefit of steroids,²⁷ SARS-CoV-2 vaccination²⁸ in the overall prognosis. Second, the absence of treatment effect in critically ill patients could be explained by the choice of heparin dose regimen in the control group. Indeed, we observed that the treatment effect was higher in the

medical wards than in intensive care units. Patients from the control arm admitted to the intensive care units received a double standard-dose of low-molecular-weight heparin in comparison to patients admitted to the medical wards. This could have decreased the difference in doses between the experimental arm (weight-adjusted) and the control arm (double standard dose) especially in low weight patients below 60 kg. However, the potential overlap of dosages was low in the group of patients randomized in intensive care units because low-weight patients under 60 kg were under-represented in this group (3.0%) and in the whole population (7% of patients below 60 kg, mean weight: 83.8 kg [IQR, 72–95]). Importantly, the choice of low-molecular-weight heparin dose regimen prescribed in intensive care unit patients randomized in the control group was supported by French guidelines published in 2020.²⁹

Clinically relevant nonmajor bleeding more than doubled in the experimental arm versus the control arm. At the beginning of the pandemic, the main goal of a randomized controlled trial was to decrease the risk of venous thromboembolism considering the adverse effect of bleeding induced by high doses of anticoagulation.⁴ Bikdeli et al. concluded that, among patients admitted to intensive care units with COVID-19, weight-adjusted intermediate anticoagulation was associated with a 2-fold increased risk –though not reaching significance– of clinically relevant nonmajor bleeding¹⁹ compared with standard-dose prophylactic anticoagulation, which was similar to our finding. Of note, even if non-major bleeding are clinically relevant, only major bleeding have been shown to be strongly associated with mortality and should be the only relevant safety endpoint in a benefit/risk analysis when paired with symptomatic venous thromboembolism (which is also clearly associated with mortality).³⁰ For this reason, we included the net clinical benefit as an outcome and failed at demonstrating its significant improvement between both arms.

Finally, death from any cause was not significantly decreased by our intervention regardless of the hospitalization setting, similar to previous trials performed in intensive care units only.^{18,19}

To our knowledge, our trial is one of the largest randomized controlled trial assessing an intermediate weight-adjusted dose of low-molecular-weight heparin versus a standard dose, especially in noncritically ill patients with COVID-19. Patients were prospectively followed with careful documentation of outcomes and adverse events. Loss to follow-up was very low, as was the rate of withdrawal of consent. For pragmatic reasons and due to the urgent need for evidence, an open-label design was used, which is subject to risk of bias. However, the randomization method used ensured concealment, all analyses were performed on an intention-to-treat basis, and all effectiveness and safety outcomes were adjudicated by a central clinical adjudication committee unaware of the treatment allocation.

In conclusion, among COVID-19 patients hospitalized in medical wards or intensive care units, an intermediate weight-adjusted prophylactic dose versus a standard fixed-dose of low-molecular-weight heparin did not result in a reduction in either the risk of venous thromboembolism or mortality and was associated with a 2-fold increased risk of clinically relevant nonmajor bleeding. Whether an increased intermediate-dose of anticoagulation might reduce the risk of venous thromboembolism and improve the prognosis of COVID-19 requires additional evaluation based on randomized controlled trials or meta-analyses, such as those conducted on behalf of the World Health Organization Rapid Evidence Appraisal for COVID-19 Therapies Working Group²⁷ or the International Network of Venous Thromboembolism (INVENT) Clinical Research Networks.⁴

Contributors

SZ made substantial contributions to conception, interpretation of data for the work, wrote the first draft of the manuscript and revised it critically for important intellectual content, and approved the version to be published; BL made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; OS made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; OeV made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; GdC made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; JBA made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; LK made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; BT made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; HG made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; CSR made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; GL made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; ATD made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; PR made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; SA made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; GT made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; DM made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; RA made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; NM made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; SS made substantial contributions

to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; RLM made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; FM made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; VLM made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; IQ made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; CMY made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; NL made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; MM made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; MD made substantial contributions to acquisition of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; YB made substantial contributions to interpretation of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; FP made substantial contributions to interpretation of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; PMR made substantial contributions to interpretation of data for the work, revised the draft critically for important intellectual content, and approved the version to be published; EP made substantial contributions to conception, analysis of data for the work, wrote the first draft of the manuscript and revised it critically for important intellectual content, and approved the version to be published; FG made substantial contributions to interpretation of data for the work, revised the first draft of the manuscript critically for important intellectual content, and approved the version to be published; PM made substantial contributions to interpretation of data for the work, revised the first draft of the manuscript critically for important intellectual content, and approved the version to be published; LB made substantial contributions to acquisition of data for the work, revised the first draft of the manuscript critically for important intellectual content, and approved the version to be published; PR made substantial contributions to conception, interpretation of data for the work, wrote the first draft of the manuscript and revised it critically for important intellectual content, and approved the version to be published; FC made substantial contributions to conception, interpretation of data for the work, revised the first draft of the manuscript critically for important intellectual content, and approved the version to be published; DW made substantial contributions to conception, interpretation of data for the work, wrote the first draft of the manuscript and revised it critically for important intellectual content, and approved the version to be published; NT made substantial contributions to conception, interpretation of data for the work, wrote the first draft of the manuscript and revised it critically for important intellectual content, and approved the version to be published; SL made substantial contributions to conception, interpretation and analysis of data for the work, wrote the first draft of the manuscript and revised it critically for important intellectual content, and approved the version to be published.

EP and SL have directly accessed and verified the underlying data reported in the manuscript. SZ and SL were responsible for the decision to submit the manuscript.

Data sharing statement

On request, and subject to review, after approval of a proposal, with a signed data access agreement, the COVI-DOSE steering committee will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, COVI-DOSE steering committee can also provide access to the related individual deidentified participant data when data will be available after publication.

Declaration of interests

Dr. Zuily reports grants from French Ministry of Health, grants from The Grand Est Regional Council, grants from The Grand Nancy Métropole, grants from The Comité ad hoc de pilotage national des essais thérapeutiques et autres recherches sur le COVID-19 (CAPNET, label Priorité Nationale de Recherche–National Research Priority), during the conduct of the study; personal fees from Leo Pharma, personal fees from Bristol Myers Squibb, personal fees from Pfizer, personal fees from Novartis, personal fees from GlaxoSmithKline, personal fees from Amgen, personal fees from Viatrix, personal fees from Sanofi, grants from Boehringer Ingelheim, grants from Bayer, outside the submitted work; Dr. Lefevre reports grants from Gilead, grants from ViiV, outside the submitted work; Dr. Sanchez reports grants and personal fees from Bristol Myers Squibb, grants and personal fees from Pfizer, grants and personal fees from Bayer, grants and personal fees from MSD, grants and personal fees from Boehringer Ingelheim, personal fees from Inari, personal fees from Boston Scientific, personal fees from Sanofi, personal fees from Leo Pharma, personal fees from Chiesi, grants from Oxyvie, outside the submitted work; Dr. Empis De Vendin has nothing to disclose; Dr. De Ciancio has nothing to disclose; Dr. Arlet reports grants from Addmedical, grants and other from Novartis, outside the submitted work; Dr. Khider has nothing to disclose; Dr. Terriat has nothing to disclose; Dr. Greigert has nothing to disclose; Dr. Robert has nothing to disclose; Dr. Louis has nothing to disclose; Dr. Trinh-Duc has nothing to disclose; Dr. Rispal has nothing to disclose; Dr. Accassat reports other from Leo Pharma, other from Janssen, other from MSD, outside the submitted work; Dr. Thiery has nothing to disclose; Dr. Montani reports grants and personal fees from Acceleron, grants and personal fees from Janssen, grants and personal fees from Merck, personal fees from Bayer, outside the submitted work; Dr. Azarian has nothing to disclose; Dr. Meneveau reports grants, personal fees and other from Bayer, grants, personal fees and other from Bristol Myers Squibb, grants, personal fees and other from Pfizer, grants from Medtronic, grants and personal fees from Boston Scientific, grants, personal fees and other from Abbott, personal fees from Inari, personal fees from Terumo, outside the submitted work; Dr. Soudet reports grants and personal fees from Leo Pharma, grants and personal fees from Bristol Myers Squibb, grants and personal fees from Pfizer, outside the submitted work; Dr. Le Mao has nothing to disclose; Dr. Maurier has nothing to disclose; Dr. Le Moing has nothing to disclose; Dr. Quééré reports other from Leo Pharma, outside the submitted work; Dr. Yelnik has nothing to disclose; Dr. Lefebvre reports personal fees and other from Pfizer, other from Eumedica, outside the submitted work; Dr. Martinot reports other from Menarini, other from Overcome, outside the submitted work; Dr. Delrue has nothing to disclose; Dr. Benhamou has nothing to disclose; Dr. Parent reports grants from Oxyvie, personal fees from MSD, outside the submitted work; Dr. Roy reports personal fees and other from Bayer, personal fees and other from Boehringer Ingelheim, personal fees and other from Bristol Myers Squibb, personal fees and other from Pfizer, personal fees and other from Aspen, personal fees and other from Sanofi, outside the submitted work; Ms. Presles has nothing to disclose; Dr. Goehringer has nothing to disclose; Dr. Mismetti reports personal fees from Bayer Healthcare, personal fees from Bristol Myers Squibb, personal fees from Boehringer Ingelheim, personal fees from Sanofi, personal fees from Leo Pharma, personal fees from Aspen, personal fees from Pfizer, outside the submitted work; Dr. Bertolotti reports grants from Bayer, grants and personal fees from MSD, personal fees and other from Leo Pharma, personal fees and other from Bristol Myers Squibb, personal fees and other from Pfizer, outside the submitted work; Dr. Rossignol reports personal fees from AstraZeneca, personal fees from Bayer, personal fees from Boehringer-Ingelheim, personal fees from Cincor, personal fees from KBP, personal fees from Novartis, personal fees from NovoNordisk, personal fees from Roche, personal fees from Vifor/Relypsa, personal fees from Fresenius, personal fees and other from CardioRenal, personal fees from Idorsia, personal fees from Sequana, personal fees from Vifor, non-financial support from G3P, outside the submitted work; Dr. Couturaud reports grants and personal fees (board memberships, symposia or travel) from Bayer, grants and personal fees (board

memberships, symposia or travel) from Bristol-Myers Squibb/Pfizer, personal fees (board memberships, symposia or travel) from Merck Sharp and Dohme, personal fees (board memberships, symposia or travel) from Astra Zeneca, personal fees (board memberships or symposia) from Sanofi, personal fees (board memberships or symposia) from Janssen, personal fees (board memberships, symposia or travel) from Leo Pharma, outside the submitted work; Dr. Wahl has nothing to disclose; Dr. Thilly has nothing to disclose; Dr. Laporte reports personal fees from Lilly/Boehringer Ingelheim, personal fees from Bristol Myers Squibb/Pfizer, personal fees from Merck, personal fees from Leo-Pharma, outside the submitted work.

Acknowledgements

Sources of funding and support: The COVI-DOSE trial was supported by grants from the French Ministry of Health (PHRC-I 2020, grant number N02), the Grand Est Regional Council, the Grand Nancy Métropole and the Comité ad hoc de pilotage national des essais thérapeutiques et autres recherches sur le COVID-19 (CAPNET, label Priorité Nationale de Recherche - National Research Priority).

Substantial contributions: We would like to thank the patients and their families who participated in the COVI-DOSE trial as well as the COVI-DOSE investigators, the members of the data and safety monitoring board (Thomas Lecompte, Emmanuel Oger and Marie-Antoinette Sevestre), the Nancy DRCI team (Saïda Khaled-Jousselin, Yohann Bernard, Amélie Amiot, El Mehdi Siaghy (Director), Valérie Bouaziz, Charlotte Daguin, Véronique Saunier, Laurence Verger and other), the pharmacovigilance team (Madlyne Jacquot and Nadine Petitpain), the Saint-Etienne team (Martin Charly, Laurent Tordella), the INI-CRCT and INNOVTE network teams, the administrative support team and the monitoring support team, all for their devotion to (team) work.

SZ obtained written permission to include the names of all individuals included in the Acknowledgment section.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eclinm.2023.102031>.

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