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The Efficacy and Safety of Prolonged Oral Anticoagulation for the Prevention of Thromboembolic Events in Patients Recovered From COVID-19 1 Year After Hospital Discharge: The SARCOV-19 Prospective Registry

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Abstract

Our objective in this study is to know the predictors of thromboembolic events 1 year after hospitalization for severe COVID-19 and the benefit of preventive oral anticoagulation for 1 month to placebo after release. We conducted a prospective study to determine the benefit of preventive anticoagulation upon discharge from the hospital and to determine the predictive factors of thromboembolic events. We included 720 patients in the SARCOV-19 Registry, with a mean age of 62.07 (±18.11), and 61.1% male. After 1 year, 60 thromboembolic events were observed, 45 in patients on a placebo, and 15 in patients on a direct oral anticoagulant. The predictive factors determined for these events were the presence of cardiac disease, elevation of D-dimer during hospitalization, myocardial damage defined by elevation of troponins more than 6 times normal, and the use of mechanical ventilation. However, the use of preventive anticoagulation protects against thrombotic events and reduces the risk of a thromboembolic event at 1 year with a relative risk of 0.49 compared to a placebo. The prolongation of the preventive anticoagulation at the exit will protect with a decrease of almost 50% of the risk against thrombotic events and this without increasing the risk of bleeding.

Keywords

COVID-19, thromboembolic events, predictors factors, preventive prolonged anticoagulation

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Introduction

It is currently clear that COVID-19 infection is associated with an excessively high thromboembolic risk compared to other infections causing respiratory distress syndrome.[1] Since this thrombotic potential is not only limited to the period of hospitalization but also after discharge, preventive anticoagulation should be discussed after discharge, although there is no consensus on this point to date.[2]

The incidence of these thrombotic events decreased between the different periods of the pandemic. At the beginning of the pandemic with the first strains, the incidence reported in the literature is between 20% and 30%.[3] Over time, and during the evolution of the pandemic as well as the advent of vaccination, the risk of thrombotic events decreased, as reported by Talasaz et al,[4] the incidence of thrombotic events decreased from 13.86% before vaccination to 1.1% after vaccination.

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Outside of COVID-19, several studies have investigated the benefit of thromboembolic prophylaxis after hospitalization, such as the MARINER trial,[5] which objected that the extension of preventive anticoagulation by rivaroxaban over 45 days, decreases 28% of fatal and major thromboembolic events without a significant increase in major bleeding.

Our idea in this work is that the use of preventive anticoagulation by a direct oral anticoagulant over a period of 1 month versus a placebo will protect against thromboembolic events.

Materials and Methods

Study Design, Type, and Objectives

COVID-19 disease is currently considered to be a very elevated thromboembolic power, so that preventive or curative anticoagulation must always be discussed at every stage of the disease, and this thrombogenic power is not limited only during hospitalization, but also after leaving the hospital, especially during the first year in postinfection, which brings us to a debate on the primary prevention of these events on the one hand, and secondary prevention on the other hand.

Our objective is to determine, on the one hand, the predictors of thromboembolic events of any type confendu (myocardial infarction, limb ischemia, mesenteric ischemia, intraaortic or intracardiac thrombus, deep vein or cerebral thrombosis, and pulmonary embolism) and on the other hand, the interest of preventive anticoagulation by an AOD for 1 month on the prevention of thromboembolic events versus placebo, this 1 year after leaving the hospital in patients hospitalized for a severe form of COVID-19 disease, requiring hospitalization in an intensive care unit (ICU). For this, we conducted a prospective study on our SARCOV-19 Registry for a period of 1 year in patients hospitalized in our unit between December 2019 and July 2021, with monthly monitoring of patients included in the study with the completion of a thoracic angioscanner every 6 months, as well as a venous ultrasound, to detect asymptomatic events.

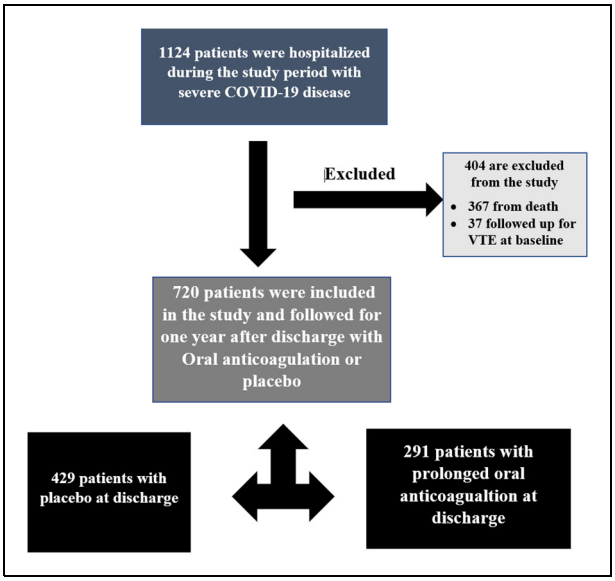

Figure 1. Distribution of patients according to type of thromboprophylaxis.

Study Participation and Data Collection

We included 720 patients who were hospitalized during the study period in our ICU, and whose intrahospital progression was home discharge. We excluded all patients with an antecedent thromboembolic event prior to severe-acute respiratory syndrome-coronavirus-2 (SARS-COV-2) infection, as well as those with a decedent. During hospitalization, anticoagulation management is based on oxygen requirements, levels of fibrinogen, C-reactive protein (CRP), and D-dimer, and whether or not extra-body oxygenation is used. All our patients have received curative anticoagulation by low molecular weight heparin associated or not with aspirin.

At discharge, we randomized our patients into 2 groups (3:2): Group A of patients who received anticoagulation for 1 month and Group B of patients who received a placebo (Figure 1). The medical information was collected between December 2019 and July 2021 by the medical staff of the unit and stored in the database of medical observations used at the university hospital of Mohammed VI King. For each patient, demographic information (sex and age) was taken into account. Medical and surgical history, anamnestic infection data including duration of symptoms, length of hospitalization, symptoms of COVID-19 infection, biological and imaging data, and the treatment used during hospitalization, and then the evolution and follow-up during hospitalization and 1 year after discharge and ensured by regular monthly consultations.

Outcomes and End-Point

The main result of the study is the duration until the first thromboembolic event after leaving the hospital during the first year, and this includes all confendus thromboembolic events (myocardial infarction, limb ischemia, mesenteric ischemia, intraaortic or intracardiac thrombus, deep venous or cerebral thrombosis, and pulmonary embolism), as well as hemorrhagic events.

Statistical Analysis

The objective of the study was to determine the predictors of thromboembolic events 1 year after hospitalization for a severe form of COVID-19 disease and to know the anticoagulation interest after release on protection against thromboembolic.

The data were collected and processed on IBM SPSS statistics software 26.0. The quantitative variables normally distributed were described as mean and standard deviation, and analyzed between the 2 groups by the Student's *t*-test. The nonnormally distributed quantitative variables were described as median and interquartile ranges and analyzed by nonparametric tests. The qualitative variables have been described in numbers, and the analysis between the 2 groups is done by Pearson's

chi-square test or Fisher's exact test. Anonymity and confidentiality were respected in all stages of data processing.

To study predictors, a logistic regression analysis was performed with the associated 95% confidence interval (CI) and bilateral *P*-value reported and a *P*-value below .05 was considered statistically significant. First, a univariate approach was performed for all covariates, and then multivariate analysis was performed for all covariates that had a significant statistical result in univariate analysis with 95% CI associated and bilateral *P*-value were reported. The Kaplan-Meier method was used to estimate survival and the Log-Rank test was used to evaluate assumptions about the observed differences in survival curves. For all statistical tests, a *P*-value below .05 was considered statistically significant.

Ethical Approval

This study was approved by the Mohammed Ist University ethical committee for biomedical research in OUJDA (Morocco) under the number 017/20. Access to patient data was authorized by the Mohammed VI university hospital and approved by the head of the department, and this was after having the signed consent of the patients for participation in the study. For both groups, an informed consent was presented to each patient at discharge, for the explanation of the interest in the study, and the potential benefit expected as well as the complications of the use of prolonged anticoagulation. All included patients granted their participation in the study, with signed consent. Data anonymity was respected in accordance with national and international guidelines.

Results

Characteristics of the Patients

The average age of our patients was 62.07 (18.11) with a difference between patients presenting a thromboembolic complication: 66.23 (12.52) compared to patients not presenting these complications: 61.69 (18.5). There was no difference between the 2 groups. Diabetes is the most common comorbidity in our population, but with no difference between the 2 groups, the presence of heart disease is associated with an over-risk of thromboembolic events ($P = .035$). For the biological results, the difference is noted for D-dimers above 2 g/L, ultrasensitive troponin above 6 times normal, and CRP above 300 mg/L. For the chest imaging results, no difference was noted between the 2 groups.

The most common complication during hospitalization is thrombocytopenia (<80 G/L) with one at 16%, then sepsis at 11.5%, and finally DIC at 2.1%, and with a significant difference between the 2 groups for all complications.

During hospitalization, the corticoid most used is methylprednisone at 45.6%, and tocilizumab is used at 15.1%. The use of mechanical ventilation is observed in 7.8% with a significant difference between the 2 groups. Whether or not aspirin was used as an adjunct to aspirin anticoagulation during hospitalization did not differ between the 2 groups.

For the duration of anticoagulation, an extension of the duration of anticoagulation of more than 3 months is associated with a reduction in events compared to the limited intake of 3 months.

Predictive Factors of Thromboembolic Events

After multivariate analysis, the presence of heart disease is associated with an increased risk with an OR at 2.231 ($P = .039$) to develop a thromboembolic event. A rate of D-dimers above 2 g/L ($P = .001$) and troponin above 6 times normal ($P = .003$) are thus a risk factor for thromboembolic events with consecutive OR at 2.981 and 4.672. Antecedent to the use of mechanical ventilation during hospitalization is associated with an increase of 2.332 of the risk of thromboembolic, and finally, the use of preventive anticoagulation is a protective factor with a decrease of almost 68% of the risk of developing thromboembolic event (OR = 0.379 and $P = .007$). These decreases ranged from 23% to 87% compared to placebo (Tables 1 and 2).

Benefits of Prolonged Anticoagulation

A total of 60 patients had thromboembolic events of 8.4% with a significant difference between patients who received limited anticoagulation or not with a relative risk of 0.49 (95% CI, 0.27-0.86), the most common event is myocardial ischemia with a percentage of 26.7% on total events, followed by deep venous thrombosis or pulmonary embolism with 34%. Ischemic cerebrovascular accidents are around 18.3% but without the impact of the duration of preventive anticoagulation on these events (Table 3).

The Kaplan-Meier curve objective is a significant difference in the incidence of thromboembolic events which is significant by the Log-Rank test ($P = .008$) (Figure 2).

For hemorrhagic events, in total, we observed 23 hemorrhagic events or 3.2%, of which 87% of these events are minor events (such as epistaxis, exteriorized hemorrhage of low nonthreatening abundance), and only 13% are major events, 67% of which were on polish anticoagulation but no different than limited preventive anticoagulation ($P = .358$).

Discussion

In our cohort, we demonstrated superiority in protection against thromboembolic events in the group receiving preventive anticoagulation with an AOD after hospital discharge versus the placebo group, with a persistent 50% reduction in risk, and this without potentiation of the risk of bleeding events.

In the MICHELLE randomized trial,[6] which compared the benefit of extending preventive anticoagulation with rivaroxaban 10 mg daily for 35 days in patients with at least 3 days of prior ICU stay for COVID-19 infection, all of whom received preventive anticoagulation with heparin during hospitalization: 3.14% under rivaroxaban developed a thromboembolic event versus 9.43% in the placebo group, with a relative risk of 0.33 ($P = .0293$) for all combined thromboembolic events without superiority over hemorrhagic events.

Table 1. General Characteristics of our Patients.

	Whole Population	TE Events	No TE Events	*P*-value
Age (*SD*)	62.07 (18.11)	66.23 (12.52)	61.69 (18.50)	**.001**
Sex (%)				
Male	447 (62.1%)	42 (5.8%)	405 (56.3%)	Ref
Female	273 (37.9%)	18 (2.5%)	255 (35.4%)	.118
BMI (*SD*)	26.65 (10.88)	26.15 (3.67)	26.7 (11.31)	.597
Length of hospitalization	7.24 (7.23)	6.92 (6.6)	7.27 (7.28)	.848
Comorbidities				
Diabetes (%)	490 (68.1%)	25 (3.5%)	205 (28.5%)	.063
Arterial hypertension (%)	230 (31.9%)	23 (3.2%)	207 (28.7%)	.167
Heart disease	103 (14.3%)	14 (1.9%)	89 (12.4%)	**.035**
Obesity (%)	103 (14.3%)	9(1.3%)	94(13.1%)	.497
Smoking (%	52 (7.2%)	7 (1%)	45 (6.3%)	.131
COPD (%)	10 (1.4%)	2 (0.3%)	8 (1.1%)	.2
Stroke (%)	28 (3.9%)	2 (0.3%)	26 (3.6%)	.582
CKD (%)	43 (6%)	4 (0.6%)	39 (5.4%)	.490
Clinical characteristics (%)				
Fever	568 (78.9%)	44 (6.1%)	524 (72.8%)	.174
Dyspnea	518 (71.9%)	47 (6.5%)	471 (65.4%)	.158
Asthenia	461 (64%)	41 (5.7%)	420 (58.3%)	.282
Headache	340 (47.2%)	26 (3.6%)	314 (43.6%)	.311
Biological findings (%)				
Ferritin (μg/L)				
(a) <300	211 (29.3%)	14 (1.9%)	197 (27.4%)	Ref
(b) 300-600	95 (13.2%)	11 (1.5%)	84 (11.7%)	.149
(c) >600	414 (57.5%)	35 (4.9%)	379 (52.6%)	.09
D-dimer (mg/L)				
(a) <0.5	327 (45.4%)	26 (3.6%)	301 (41.8%)	Ref
(b) 0.5-1	88 (12.2%)	8 (1.1%)	80 (11.1%)	.729
(c) 1-2	94 (13.1%)	6 (0.8%)	88 (12.2%)	.614
(d) >2	211 (29.3%)	20 (2.8%)	191 (26.6%)	**.03**
Fibrinogen (g/L)				
(a) 2-4	82 (13.6%)	10 (1.7%)	72 (12%)	Ref
(b) <2	410 (68.2%)	29 (4.8%)	381 (63.4%)	.122
(c) 4-8	93 (15.5%)	7 (1.2%)	86 (14.3%)	.302
(d) >8	16 (2.7%)	2 (0.3%)	14 (2.3%)	.973
LDH (IU/L)				
(a) <600	403 (60.5%)	26 (3.9%)	377 (56.6%)	Ref
(b) 600-1000	193 (29%)	13 (2%)	180 (27%)	.896
(c) >1000	70 (10.5%)	14 (2.1%)	56 (8.4%)	.378
Troponin US (ng/mL)				
(a) <3 N	363 (58.2%)	24 (3.8%)	339 (54.3%)	Ref
(b) 3-6 N	225(36.1%)	21 (3.4%)	204 (32.7%)	.230
(c) >6 N	36 (5.8%)	12 (1.9%)	24 (3.8%)	**.001**
TP (%)				
(a) >70%	495 (72.3%)	36 (5.3%)	459 (67%)	Ref
(b) 50-70%	157 (22.9%)	16 (2.3%)	141 (20.6%)	.242
(c) <50%	33 (4.8%)	8 (1.2%)	25 (3.6%)	.872
Plaquette (G/L)				
(a) 150-450	527 (76.5%)	44 (6.4%)	483 (70.1%)	Ref
(b) <150	121 (17.6%)	11 (1.6%)	110 (16%)	.792
(c) >450	41 (6%)	5 (0.7%)	36 (5.2%)	.462
Creatinine sanguine (mg/L)				
(a) 6-12	439 (69.4%)	27 (4.3%)	412 (65.1%)	Ref
(b) >12	194 (30.6%)	28 (4.4%)	166 (26.2%)	.562
CRP (mg/L)				
(a) <100	228 (34.3%)	19 (2.9%)	209 (31.4%)	Ref
b) 100-200	215 (32.3%)	21 (3.2%)	194 (29.2%)	.526
(c) 200-300	147 (22.1%)	13 (2%)	134(20.2%)	.09

(continued)

Table 1. (continued)

	Whole Population	TE Events	No TE Events	*P*-value
(d) >300	75 (11.3%)	6 (0.9%)	69 (10.4%)	**.02**
Leucocytes (/mm^3)				
(a) 4000-10,000	410 (76.5%)	23 (3.2%)	387 (53.8%)	Ref
(b) >10,000	310 (17.6%)	37 (5.1%)	273 (37.9%)	.762
Lymphocyte (/mm^3)				
(a) 1000-4000	247 (34.3%)	21 (2.9%)	226 (31.4%)	Ref
(b) <1000	409 (56.8%)	37 (5.1%)	372 (51.7%)	.08
(c) >4000 m	64 (8.9%)	2 (0.3%)	62 (8.6%)	.172
Imagerical findings				
0-25%	154 (21.3%)	12 (1.7%)	142 (19.7%)	Ref
25-50%	130 (18.1%)	15 (2.1%)	115 (16%)	.286
50-75%	224 (31.1%)	16 (2.2%)	208 (28.9%)	.813
75-100%	212 (29.4%)	17 (2.4%)	195 (27.1%)	.937
Complication during hospitalization				
CIVD	15 (2.1%)	5 (0.7%)	10 (1.4%)	**.005**
Sepsis	83 (11.5%)	13 (1.8%)	70 (9.7%)	**.014**
Thrombopenia	115 (16%)	15 (2.1%)	100 (13.9%)	**.04**
Management				
Methylprednisone	328 (45.6%)	21 (2.9%)	307 (42.7%)	.055
Dexamethasone	150 (20.8%)	15 (2.1%)	135 (18.8%)	.249
Tocilizumab	109 (15.1%)	6 (0.8%)	103 (14.3%)	.166
Plasmapheresis	5 (0.7%)	1 (0.1%)	4 (0.6%)	.354
Prone position	321 (44.6%)	28 (3.9%)	293 (40.7%)	.418
High-flow oxygen therapy	252 (35%)	23 (3.2%)	229 (31.8%)	.332
CPAP	42 (5.8%)	7 (1%)	35 (4.9%)	.051
Noninvasive ventilation	98 (13.6%)	10 (1.4%)	88 (12.2%)	.29
Mechanical ventilation	56 (7.8%)	9 (1.3%)	47 (6.5%)	**.035**
Anticoagulation during hospitalization				
Oral anticoagulant alone	287 (40.1%)	28 (3.9%)	259 (36.2%)	Ref
Oral anticoagulant with aspirin	428 (59.9%)	32 (4.5%)	396 (55.4%)	.173
Anticoagulation at discharge				
Placebo	429 (59.6%)	45 (6.3%)	384 (53.3%)	Ref
OAD during 1 month	291 (40.4%)	15 (2.1%)	276 (38.3%)	**.007**

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CIVD, intravascular disseminated coagulation; LDH, lactate dehydrogenase; CPAP, continuous positive airway pressure; OAD, obstructive airway disease.
Note: Values that are statistically significant indicated in bold.

Table 2. Predictive Factors of Thromboembolic Events.

Variable	OR	(95% CI)	*P*-value
Age	1.268	(0.987-1.789)	.384
Heart disease	**2.231**	(1.04-4.786)	**.039**
D-dimer (mg/L)			
(a) >2	**2.981**	**(1.256-2.871)**	**.003**
Troponin US (ng/mL)			
(a) >6 N	**4.672**	**(2.793-8.093)**	**.001**
CRP (mg/l)			
(a) >300	**1.987**	**(0.678-2.679)**	.987
CIVD	**3.409**	**(0.91-4.782)**	.69
Sepsis	**1.493**	**(0.691-3.605)**	.372
Thrombopenia (**<**80 G/L**)**	**1.163**	**(0.531 -2.547)**	.706
Mechanical ventilation	**2.332**	**(1.09-5.318)**	**.04**
Anticoagulation at discharge			
Placebo	**Ref**		
OAD during 1 month	**0.379**	**(0.188-0.765)**	**.007**

Abbreviations: CRP, C-reactive protein; CIVD, intravascular disseminated coagulation; OAD, obstructive airway disease.
Note: Values that are statistically significant indicated in bold.

Also for postdischarge thromboprophylaxis, a large meta-analysis from 10,148[7] patients showed that extending preventive anticoagulation after hospital discharge in these patients for <35 days with direct oral anticoagulation protects against all-cause mortality and thrombosis with OR: 0.62; 95% CI: 0.42-0.94, $P = .023$; $I^2 = 30.2\%$, and this without an increase in bleeding events.

For patients treated at home, in the controlled, randomized, double-blind ACTIV-4B trial,[8] which studied the benefit of thromboprophylaxis with aspirin 75 mg daily or apixaban (5-10 mg daily) versus placebo in patients with symptomatic COVID-19 infection treated at home. The results were negative in terms of all-cause mortality, fatal thromboembolic events, and hospitalization between the 2, although this trial was stopped early because the number of events was rare compared to what was expected. Similarly, another randomized, controlled, single-blind trial (OVID)[9] compared the benefit of thromboprophylaxis with enoxaparin 40 mg daily for 14 days. No difference was observed between the 2 groups with

Table 3. Benefits of Prolonged Anticoagulation.

Variable	Placebo (429)	Prolonged Anticoagulation During 1 Month (291)	Relative Risk (95% CI)	*P*-Value
Thromboembolic events (total)	45 (6.3%)	15 (2.1%)	0.49 (0.27-0.86)	.007
Stroke	6 (0.8%)	5 (0.7%)		.479
PE and VTE	15 (2.5%)	5 (0.7%)		.047
Myocardial ischemia	16 (2.77%)	4 (0.7%)		.002
Limb's ischemia	8 (1.12%)	1 (0.2%)		.038
Bleeding events (total)	8 (1.12%)	15 (2.1%)	1.15 (0.82-3.28)	.358
Minor events	7 (1.09%)	13 (1.8%)		
Major events	1 (0.1%)	2 (0.2%)		

Abbreviations: PE, pulmonary embolism; VTE, deep vein thrombosis.

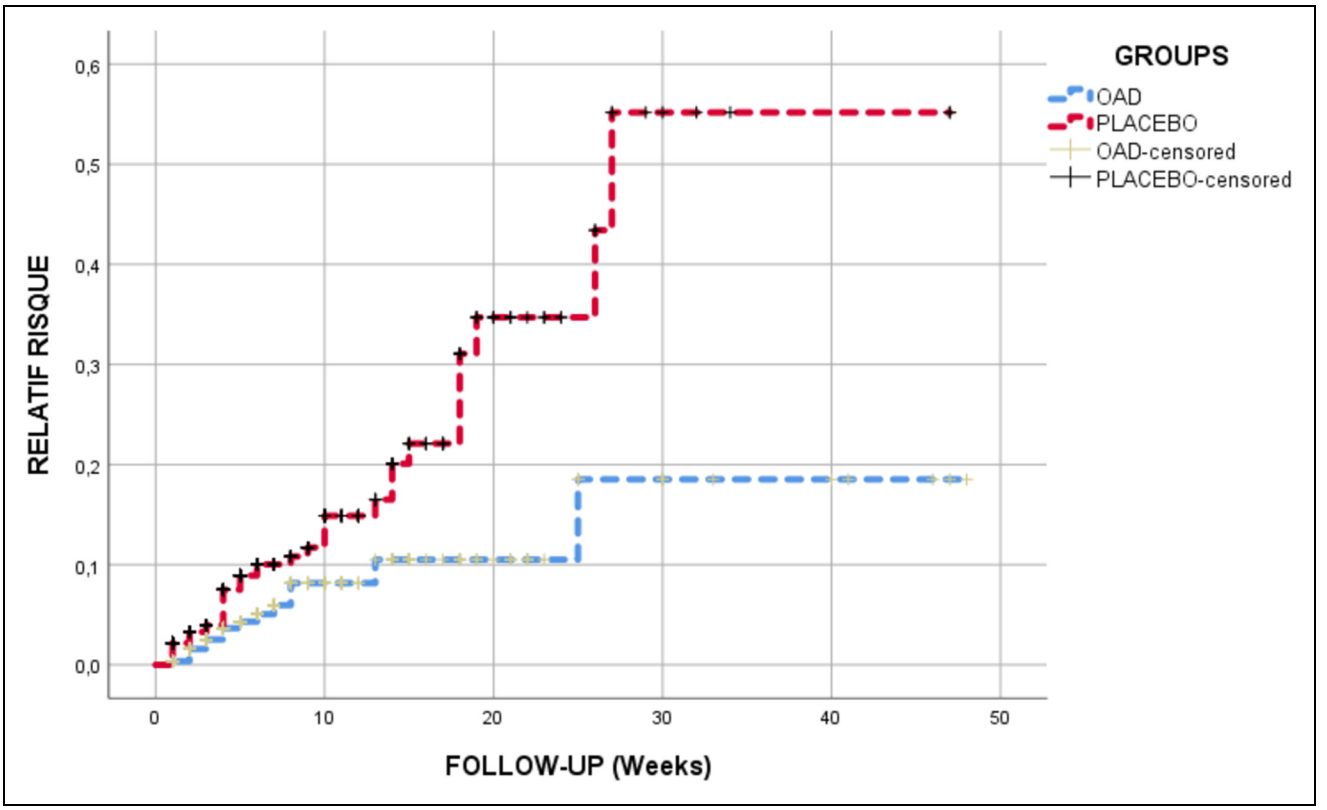

Figure 2. The kaplan meier curve shows a significant difference between the placebo group and the OAD group with regard to the main outcome at 1 year after discharge.

the primary composite outcome of any untoward hospitalization and all-cause death within 30 days of randomization (relative risk: 0-98; 95% CI: 0-37 to 2-56; $P = 0$-96).

In the prospective registry CORE-19,[10] which studied the predictors of thromboembolic events as well as mortality during the 90 days after discharge from hospital for COVID-19 infection, the incidence of thrombovenous embolic is 1.55% and 1.71% for arterial, and the extension of preventive anticoagulation at exit protected against these events with an OR at 0.54 (0.47-0.81) (*P*-value = .003).

To our knowledge, this is the first registry that studies the predictive factors of thromboembolic events in patients admitted to ICUs for a severe COVID-19 infection and this 1 year after their discharge from the hospital. In our register, the objective risk factors were the rate above 2000 ng/mL (OR = 2.981), the presence of heart disease (2231), myocardial distress (OR = 4.67), and the use of mechanical ventilation during the first hospitalization (OR = 2.332)., in the CORE-19 Registry that studies all patients infected with COVID-19 regardless of severity, the factors determined are the presence of coronary artery disease or peripheral vascular pathology (OR = 2.04), the presence of chronic renal failure (OR = 2.1), and the age above 75 (OR = 3.66), although the rise in the rate is not significant.

The question of the value of preventive anticoagulation after the hospital's sorite after a COVID-19 infection remains a matter of debate, and until today no consensus has been reached. In this

regard, several clinical trials are underway to evaluate the efficacy and safety of this anticoagulation quoting: The XACT trial (NCT04640181) which evaluates 150 randomized patients (1:1) to receive enoxaparin in hospital or rivaroxaban orally (10, 15, or 20 mg/day) until they are discharged from hospital for 28 days with a composite primary outcome of a combination of all-cause death or mortality at 30 days, mechanical ventilation, intubation or transfer to an ICU. The ACTIV-4c trial (NCT04650087) recruited 4000 patients in the United States to evaluate the efficacy and safety of anticoagulants and antiplatelet drugs (apixaban, aspirin, or placebo) administered to patients who left the hospital. The main objective is to reduce myocardial infarction, stroke, arterial and venous thrombosis, and death within 30 days of hospital discharge for patients with moderate or severe COVID-19.

Conclusion

COVID-19 infection remains a general disease with a very important thrombotic component, especially in the severe form of the disease, For this, the discussion of putting the patient under preventive anticoagulation upon discharge from the hospital must always be taken seriously, given the initial results that are encouraging in this direction.

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Declaration of Conflicting Interests

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