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ORIGINAL RESEARCH

Anticoagulation Before Hospitalization Is a Potential Protective Factor for COVID-19: Insight From a French Multicenter Cohort Study

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BACKGROUND: Coronavirus disease 2019 (COVID-19) is a respiratory disease associated with thrombotic outcomes with coagulation and endothelial disorders. Based on that, several anticoagulation guidelines have been proposed. We aimed to determine whether anticoagulation therapy modifies the risk of developing severe COVID-19.

METHODS AND RESULTS: Patients with COVID-19 initially admitted in medical wards of 24 French hospitals were included prospectively from February 26 to April 20, 2020. We used a Poisson regression model, Cox proportional hazard model, and matched propensity score to assess the effect of anticoagulation on outcomes (intensive care unit admission or in-hospital mortality). The study enrolled 2878 patients with COVID-19, among whom 382 (13.2%) were treated with oral anticoagulation therapy before hospitalization. After adjustment, anticoagulation therapy before hospitalization was associated with a better prognosis with an adjusted hazard ratio of 0.70 (95% CI, 0.55–0.88). Analyses performed using propensity score matching confirmed that anticoagulation therapy before hospitalization was associated with a better prognosis, with an adjusted hazard ratio of 0.43 (95% CI, 0.29–0.63) for intensive care unit admission and adjusted hazard ratio of 0.76 (95% CI, 0.61–0.98) for composite criteria intensive care unit admission or death. In contrast, therapeutic or prophylactic low- or high-dose anticoagulation started during hospitalization were not associated with any of the outcomes.

CONCLUSIONS: Anticoagulation therapy used before hospitalization in medical wards was associated with a better prognosis in contrast with anticoagulation initiated during hospitalization. Anticoagulation therapy introduced in early disease could better prevent COVID-19–associated coagulopathy and endotheliopathy, and lead to a better prognosis.

Key Words: anticoagulant ■ coagulopathy ■ COVID-19 ■ mortality ■ SARS-CoV-2

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CLINICAL PERSPECTIVE

What Is New?

- Oral anticoagulant therapy before hospitalization is associated with a better prognosis for patients with coronavirus disease 2019.

What Are the Clinical Implications?

- Anticoagulation in early disease could better prevent coronavirus disease 2019–associated coagulopathy and endotheliopathy.
- Introduction of anticoagulation in ambulatory patients in case of close contacts with confirmed patients with coronavirus disease 2019 represents a new potential therapeutic approach.

Nonstandard Abbreviations and Acronyms

CCF	Critical COVID-19 France
DOAC	direct oral anticoagulant
PH	proportional hazard
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VKA	vitamin K antagonist

Since December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic spread rapidly throughout China[1,2] with a higher transmission capacity and a higher mortality compared with SARS-CoV-1 epidemic of 2003.[3] Coronavirus disease 2019 (COVID-19) clinical manifestations are first dominated by respiratory symptoms. Patients may experience severe cardiovascular damages[4,5] associated with a coagulopathy characterized by an increase in procoagulant factors such as fibrinogen, and high levels of D-dimer that have been associated with a worsening of the disease and higher mortality.[6–8] Increased incidence of venous thromboembolism, in particular pulmonary embolism, has been observed in several reports,[9–12] and microvascular thrombosis in the lungs has been observed in autopsy series and during COVID-19 acute respiratory distress syndrome.[13–16] Moreover, SARS-CoV-2 has been shown to induce vascular damage, and we recently described that circulating markers of endothelial lesion are a predictive factor for intensive care unit (ICU) referral and mortality, reinforcing the hypothesis of a COVID-19–associated microvascular dysfunction.[17,18] The COVID-19–associated coagulopathy has led many medical societies to propose different anticoagulation strategies.[19,20] Results showing that prophylactic anticoagulation with low-molecular-weight heparin (LMWH) improved critically ill patients' prognosis argued for the use of prophylactic anticoagulation in patients with COVID-19.[20–23] No protective effect of anticoagulation before hospitalization for COVID-19 on survival has been observed until now, in 2 small retrospective cohorts.[24,25]

Using data from a multicenter French cohort (n=2848), we aimed to determine whether anticoagulation therapy before hospitalization was an independent predictor for developing a severe form of the disease. Moreover, since several anticoagulation strategies based on recent national and international guidelines[19,26] were used and still remain a matter of debate, we also aimed to analyze different prophylactic or therapeutic anticoagulation strategies introduced during hospitalization on patients' clinical outcomes.

METHODS

Detailed data are available on request from the authors.

Study Settings and Population

From February 26 to April 20, 2020, consecutive patients with a diagnosis of SARS-CoV-2 infection and hospitalized in medical wards were included (none of the patients were directly admitted to the ICU). Patients were aged over 18 years old and were included in a retrospective multicentric (24 centers) observational study, which was named the CCF (Critical COVID-19 France) study and initiated by the French Society of Cardiology. Following World Health Organization criteria, SARS-CoV-2 infection was determined by positive results from real-time reverse transcriptase-polymerase chain reaction of nasal or pharyngeal swabs or lower respiratory tract aspirates (confirmed case) or by typical imaging characteristics on chest computed tomography (CT) when laboratory testing was inconclusive (probable case).[27]

Institutional Review Board Approval and Informed Consent

The CCF study was declared and authorized at the French data protection committee (authorization no. 2207326v0) and conducted in accordance with the ethical standards established in the 1964 Declaration of Helsinki and its later amendments (NCT04344327). Because an anonymized hospital database was used, informed consent from individual patients was not obtained.

Data Collection and Anticoagulation Regimen

All data were collected by local investigators in an electronic case-report form via the Research Electronic Data Capture software (Vanderbilt University, Nashville, TN) hosted by a secured server from the French Institute of Health and Medical Research at the Paris

Cardiovascular Research Centre. Patients' baseline information included demographic characteristics, coexisting medical conditions, cardiovascular comorbidities, and chronic medications. Clinical parameters and biological findings were recorded at admission. On the chest CT scan, the degree of pulmonary lesions with ground-glass opacities and areas of consolidation was categorized as low/moderate (<50% involvement) or severe (≥50% involvement). Data on pharmacologic therapies, mode of respiratory support, complications, and final vital status were also gathered during the hospitalization. Oral anticoagulation regimen at admission was categorized into 2 groups: (1) none and (2) oral anticoagulation therapy with a vitamin K antagonist (VKA) or direct oral anticoagulant (DOAC) anti-IIa (dabigatran) or anti-Xa (rivaroxaban or apixaban). The anticoagulation regimen prescribed during hospitalization was categorized into 3 groups: (1) prophylactic low dose (daily LMWH or twice-daily subcutaneous unfractionated heparin), (2) prophylactic high dose (double the preventive dose), and (3) therapeutic regimen. All medical interventions, including anticoagulation and pharmacologic treatments for COVID-19, were performed at the discretion of the referring medical team.

Outcomes

The time from diagnosis to death or ICU admission for ventilation support (including invasive, noninvasive, or high-flow oxygen) were used as a composite primary outcome to define ICU-free survival. The secondary outcome was the time from diagnosis to death only for the selected population of patients secondarily referred to the ICU after the medical ward. Outcomes were assessed using the electronic medical record.

Statistical Analysis

Continuous data were expressed as mean (SD) and categorical data as proportion. Patients were compared according to the use of oral anticoagulation therapy (VKA or DOAC) before hospitalization using the Mann–Whitney test for continuous variables and Fisher exact test for categorical variables.[28] In the multivariable analysis, we used Poisson regression to assess the association between the use of oral anticoagulation therapy before hospitalization and outcomes.[29,30] The model included as covariates sex, age, cardiovascular comorbidities (history of high blood pressure, dyslipidemia, body mass index, type 2 diabetes mellitus, and current smoking), plasma creatinine level (μmoL/L), C-reactive protein (mg/L), fraction of inspired oxygen, and the degree of pulmonary lesions with ground-glass opacities, and areas of consolidation. For the survival analysis, the start of the study was triggered by the diagnosis of SARS-CoV-2 infection and hospitalization in a medical ward. The end of the study was defined either by the death of the patient during the hospitalization or by discharge alive from the hospital. Vital status was ascertained through April 20, 2020, with the potential period of follow-up ranging from 1 to 54 days. If the patient was still hospitalized on April 20, 2020, the vital status was coded as alive. Survival time was calculated as the difference between the date of the diagnosis of SARS-CoV-2 infection and the date of event occurrence (ICU admission and in-hospital death) or the date of hospital discharge or the length of hospital stay for patients still hospitalized at the end of the study (April 20, 2020). We used a Cox proportional hazard (PH) model adjusted for the same potential confounders included in the Poisson regression model to investigate the relationships between the use of oral anticoagulation therapy and outcomes. Kaplan–Meier method was used to represent the Cox PH model results according to the use or not of oral anticoagulation therapy before hospitalization for COVID-19.

We performed 3 sensitivity analyses: (1) To take into account the retrospective design and to avoid the bias caused by censored data (n=513), we performed a complete data analysis for mortality risk: the same Poisson regression analysis in the population of patients who were discharged alive from hospital or dead in hospital (total patients analyzed n=2335) and thus excluded patient with censored outcome; (2) to explore the individual effect of in-hospital anticoagulation therapy (unfractionated heparin or LMWH) on the one hand, and of anticoagulation treatment before hospitalization (VKA or DOAC) on the other hand, and the magnitude of each effect on outcome, we decided to rerun the Cox PH models in the selected population without anticoagulation before hospitalization (n=2466) for the subgroup of patients who were hospitalized in the ICU and for those who stayed in the medical ward using the outcome (in-hospital mortality); (3) to adjust for bias caused by nonrandom allocation of potential covariates, we performed a propensity-matched analysis of patients who were on oral anticoagulation therapy (VKA or DOAC) before hospitalization for COVID-19 infection compared with those who were not and rerun the Cox PH model adjusted only for plasma creatinine level, C-reactive protein, fraction of inspired oxygen, and the degree of pulmonary lesions with ground-glass opacities and areas of consolidation. Missing data were handled using multiple random forest imputation using chained equation (10 sets of imputations). All analyses were 2-sided and a $P<0.05$ was considered statistically significant. Statistical analysis was performed using R studio software including R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

During the study period, 2878 consecutive patients who were hospitalized for SARS-CoV-2 infection in the

medical ward were included. The demographic and clinical characteristics of the patients with COVID-19 according to use of anticoagulation before hospitalization are provided in Table 1. For analysis of anticoagulation before hospitalization assessment, we excluded 30 patients who were treated by heparin or LMWH because the regimen (therapeutic or prophylactic doses) was not known. Among the study population, 382 of 2848 (13.4%) patients were treated with oral anticoagulation therapy before hospitalization, physicians decided to pursue anticoagulation for 341 (90.0%) patients and to use prophylactic low dose for 58 (15.2%), prophylactic high dose for 9 (2.4%), and therapeutic dose for 274 (71.7%) during hospitalization. Among the remaining 2466 patients, 1478 (59.9%) received prophylactic low dose, 261 (10.6%) received prophylactic high dose, and 246 (10.0%) were treated with therapeutic anticoagulation during hospitalization. Patients receiving oral anticoagulation before hospitalization were older ($P<0.001$) and had significantly more cardiovascular risk factors, that is, more high blood pressure, diabetes mellitus, and dyslipidemia (Table 1). Overall, 352 of 2848 (12.4%) patients including 84 (2.9%) under oral anticoagulation therapy died in the medical ward or the ICU. The mean time of follow-up was 8.7 days (6.5) (Table 1).

Therapeutic Anticoagulation Before Hospitalization Decreased In-Hospital Mortality or ICU Admission

In the whole population and after adjustment, male sex, body mass index, C-reactive protein, fraction of inspired oxygen, and parenchymal opacification in chest CT scan were significantly associated with ICU admission and in-hospital mortality (Table 2). Therapeutic oral anticoagulation before hospitalization was associated with a better outcome, with a relative risk (RR) of 0.45 (95% CI, 0.32–0.62; $P<0.001$) for ICU admission and relative risk of 0.72 (95% CI, 0.57–0.90; $P=0.006$) for ICU admission or in-hospital mortality. The use of prophylactic high-dose or therapeutic anticoagulation during hospitalization was significantly associated with higher ICU admission and in-hospital mortality (relative risk, 2.00; 95% CI, 1.49–2.70; $P<0.001$; and relative risk, 1.62; 95% CI, 1.21–2.18; $P=0.001$, respectively) (Table 2). To take into account the retrospective design and to avoid the bias caused by censored data (n=513), the same multivariable analysis was performed in the selected population of patients without censored outcome (patients who were discharged alive from the hospital or dead in the hospital; total patients analyzed, n=2335) and found the same protective effect of therapeutic anticoagulation before hospitalization for COVID-19 and worse outcome for receiving prophylactic high-dose or therapeutic-dose anticoagulation during hospitalization (Table S1). Effect of oral anticoagulation before hospitalization on outcomes was confirmed by using the Kaplan–Meier curve and multivariable adjusted Cox PH model (Figures 1 and 2). In the multivariable adjusted Cox regression model, the adjusted hazard ratio for the effect of oral anticoagulation before hospitalization was 0.70 (95% CI, 0.55–0.88; $P=0.003$; Figure 2). In this multivariable adjusted Cox regression model, we also confirmed that male sex and chest CT scan with ≥50% opacification were associated with a high risk of ICU transfer or in-hospital mortality (Figure 2). In sensitivity analysis, the propensity matching yielded 382 patients who received oral anticoagulation and 1528 patients who did not before hospitalization, with balanced variables between the groups (Table S2). In this propensity-matched population, there was still a statistically significant difference in outcome between the 2 groups: adjusted hazard ratios for the effect of oral anticoagulation before hospitalization were 0.43 (95% CI, 0.29–0.63; $P=<0.001$), 0.76 (95% CI, 0.61–0.98; $P=0.04$) and 1.09 (95% CI, 0.83–1.55; $P=0.49$), respectively, for ICU admission, ICU admission or in-hospital mortality (combined outcome), and for in-hospital mortality (Table 3).

Regarding anticoagulation therapy introduced during hospitalization, we reran multivariable analysis in the subgroup of patients without oral anticoagulation before hospitalization (n=2466). For the entire population, we did not observe a significant association between the use of anticoagulation during hospitalization for any regimen (prophylactic low or high dose and therapeutic dose) and in-hospital mortality (Table 4). The results were similar for patients admitted to the ICU or for patients who stayed in the medical ward (Table 4).

DISCUSSION

In this retrospective study, we demonstrated that an early anticoagulation before COVID-19 hospitalization improves the outcome of patients with COVID-19. Using a multicenter French study of patients hospitalized for COVID-19, we provide evidence that previous oral anticoagulation with VKA or DOAC significantly decreased ICU admission or in-hospital mortality. Furthermore, in patients without anticoagulation before hospitalization, anticoagulation started during hospitalization (heparin or LMWH) was not associated with a better prognosis. Importantly, this is the first study evaluating anticoagulation in patients with COVID-19 that provides a clear description of baseline patient characteristics.[21,24,31]

Table 1. Patient Characteristics and Outcomes According to the Use of Oral Anticoagulation Before Hospital Admission

	Total Population	No Oral Anticoagulation	Oral Anticoagulation	
	n=2878	n=2466*	n=382	*P* Value
Age, y, mean (SD)	66.63 (16.96)	64.81 (16.83)	78.34 (12.55)	<0.001
Male sex, n (%)	1666 (57.9)	1412 (57.3)	233 (61.0)	
Time from onset illness to hospitalization, days, mean (SD)	6.76 (4.66)	6.95 (4.58)	5.72 (5.03)	<0.001
Cardiovascular comorbidites				
Body mass index, kg/m^2, mean (SD)	27.82 (6.03)	27.88 (6.04)	27.63 (6.07)	0.47
High blood pressure, n (%)	1453 (50.5)	1149 (46.6)	291 (76.2)	<0.001
Diabetes mellitus, n (%)	677 (23.5)	558 (22.6)	112 (29.3)	0.016
Dyslipidemia, n (%)	800 (27.8)	632 (25.6)	157 (41.1)	<0.001
Current smoking, n (%)	378 (13.1)	309 (12.5)	60 (15.7)	0.20
History of venous thromboembolism, n (%)	212 (7.4)	113 (4.6)	83 (21.7)	<0.001
History of atrial fibrillation, n (%)	416 (14.5)	118 (4.8)	293 (76.7)	<0.001
Medication				
Beta blockers, n (%)	735 (25.5)	526 (21.3)	201 (52.6)	<0.001
ACE inhibitors, n (%)	506 (17.6)	402 (16.3)	102 (26.7)	<0.001
ARBs, n (%)	469 (16.3)	381 (15.5)	86 (22.5)	0.001
Any diuretic medication, n (%)	564 (19.6)	378 (15.3)	179 (46.9)	<0.001
Antiplatelet therapy, n (%)	627 (21.8)	575 (23.3)	47 (12.3)	<0.001
Immunosuppresive drug, n (%)	147 (5.1)	122 (4.9)	17 (4.5)	0.77
Diabetes mellitus oral drug, n (%)	451 (15.7)	377 (15.3)	70 (18.3)	0.15
Statins, n (%)	653 (22.7)	527 (21.4)	122 (31.9)	<0.001
Anticoagulation characteristics				
Oral anticoagulation therapy, n (%)				…
Direct oral anticoagulants	232 (8.1)	…	232 (60.7)	
Vitamin K antagonists	150 (5.2)	…	150 (39.3)	
Heparin	30 (1.0)	…	…	
Anticoagulation indication, n (%)				…
Atrial fibrillation	370 (12.9)	…	260 (68.1)	
Venous thromboembolism	212 (7.4)	…	83 (21.7)	
Unknown	39 (1.3)		39 (10.2)	
Direct oral anticoagulants, type, n (%)				…
Rivaroxaban	85 (3.0)	…	85 (22.3)	
Apixaban	132 (4.6)	…	132 (34.6)	
Dabigatran	15 (0.5)	…	15 (3.9)	
In-hospital anticoagulation, n (%)				<0.001
None	337 (11.7)	313 (12.7)	23 (6.0)	
Prophylactic low dose	1549 (53.8)	1478 (59.9)	58 (15.2)	
Prophylactic high dose	271 (9.4)	261 (10.6)	9 (2.4)	
Therapeutic dose	533 (18.5)	246 (10.0)	274 (71.7)	
Unknown	188 (6.5)	168 (6.8)	18 (4.7)	
Biology				
Hemoglobin—g/L, mean (SD)	131.2 (19.9)	132.1 (19.3)	126.9 (22.2)	<0.001
Platelet count—×10^9/L, mean (SD)	220.44 (99.21)	221.72 (99.71)	209.72 (92.20)	0.02
Plasma creatinine level—µmol/L, mean (SD)	98.24 (95.63)	93.70 (86.95)	126.73 (137.06)	<0.001
Creatinine clearance (Cockcroft-Gault), mL/min, mean (SD)		102.57 (109.56)	83.85 (250.52)	0.02

(*Continued*)

Table 1. Continued

	Total Population	No Oral Anticoagulation	Oral Anticoagulation	
	n=2878	n=2466*	n=382	*P* Value
Glomerular filtration rate (MDRD), L/min per 1.73 m^2, mean (SD)	81.62 (29.51)	83.92 (28.59)	67.28 (30.86)	<0.001
White blood cells—$\times 10^9$/L, mean (SD)	7.33 (5.14)	7.34 (5.35)	7.17 (3.41)	0.55
Lymphocytes—$\times 10^9$/L, mean (SD)	1.31 (3.46)	1.34 (3.68)	1.13 (1.67)	0.29
C-reactive protein, mg/L, mean (SD)	90.34 (77.11)	90.87 (78.38)	86.67 (67.44)	0.33
FiO_2, %, mean (SD)	28.62 (12.11)	28.63 (12.10)	28.71 (12.23)	0.91
PaO_2 mm Hg, mean (SD)	80.89 (29.08)	81.30 (29.28)	79.08 (27.74)	0.26
In-hospital outcomes				
Parenchymal opacification in chest CT scan >50%, n (%)	430 (14.9)	377 (15.3)	51 (13.4)	<0.001
Time from hospital admission to ICU admission, mean (SD)	8.74 (6.50)	8.62 (6.56)	9.48 (6.07)	0.02
Time from hospital admission to in-hospital death, mean (SD)	8.68 (6.93)	8.86 (7.39)	8.14 (5.28)	0.41
Noninvasive mechanical ventilation, n (%)	81 (2.8)	69 (2.8)	11 (2.9)	0.99
Invasive mechanical ventilation, n (%)	370 (12.9)	341 (13.8)	27 (7.1)	<0.001
Reasons for ICU admission, n (%)				<0.001
Septic shock	2 (0.1)	0 (0.0)	2 (0.5)	
Acute respiratory failure	522 (18.1)	480 (19.5)	39 (10.2)	
Acute cardiac failure	9 (0.3)	6 (0.2)	2 (0.5)	
Other	5 (0.2)	5 (0.2)	0 (0.0)	
In-hospital mortality etiology, n (%)				<0.001
Acute respiratory failure	309 (10.7)	236 (9.6)	70 (18.3)	
Acute cardiac failure	13 (0.5)	8 (0.3)	4 (1.0)	
Cardiac arrest	19 (0.7)	12 (0.5)	7 (1.8)	
Other	15 (0.5)	12 (0.5)	3 (0.8)	

ACE indicates angiotensin-converting-enzyme inhibitors; ARBs, angiotensin II receptor blockers; CT, computed tomography; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; LMWH, low molecular weight heparin; MDRD, modification of diet in renal disease; and PaO_2, partial pressure of oxygen.
*Patients treated with LMWH or unfractionated heparin at admission were excluded because the therapeutic or prophylactic regimen was unknown.

Based on the rationale that SARS-CoV-2 infection is associated with endothelial dysfunction,[17,18] COVID-19–induced coagulopathy might be a consequence of endothelial injury.[2,32] We indeed previously described that patients with COVID-19 treated with therapeutic anticoagulation had a lower level of circulating endothelial cells, a marker of endothelial lesion.[33] This protective effect of anticoagulation therapy on endothelial dysfunction could explain the protective effect of anticoagulation on microvascular thrombosis and coagulopathy observed in patients with COVID-19. Indeed, endotheliitis has been described during COVID-19 and could be at the origin of impaired microcirculatory function affecting particularly the lungs and kidneys.[34] From patients' autopsies, this endotheliitis has been described associated with an angiogenic process in the lungs.[35] Moreover, the central involvement of endothelial compartment in COVID-19 outcome and pathophysiology is supported by the higher level of circulating endothelial cells in patients who are COVID-19 positive versus negative, associated with the increased plasma levels of angiopoietin-2 and E-selectin correlated to ICU transfer.[17,33] In the present study, we observed that anticoagulation administered before hospitalization for COVID-19 had a significant positive impact on ICU admission or in-hospital mortality by contrast with patients without anticoagulation. Our results are not in line with those of Tremblay et al,[24] who recently reported that they used a propensity score to compare patients who were anticoagulated versus nonanticoagulated before hospitalization. Of note, the logistic regression model they used to calculate the propensity score was not adjusted on relevant cardiovascular comorbidities such as hypertension, diabetes mellitus, smoking, or renal function and could explain the divergent results in the literature. This makes the association between anticoagulation and outcomes difficult to analyze since endothelial dysfunction during COVID-19 mostly results from these comorbidities.[36] Moreover, in a cohort of 449 patients with COVID-19

Table 2. Poisson Regression Model According to ICU Admission (A)

	ICU Admission			ICU Admission or In-Hospital Mortality			In-Hospital Mortality		
	RR	95% CI	*P* Value	RR	95% CI	*P* Value	RR	95% CI	*P* Value
Oral anticoagulation prior admission (DOAC or VKA)	0.45	0.32–0.62	<0.01	0.72	0.57–0.90	<0.01	0.94	0.68–1.26	0.68
In-hospital anticoagulation									
Prophylactic low dose	1.15	0.81–1.66	0.44	1.07	0.82–1.40	0.61	1.10	0.76–1.61	0.62
Prophylactic high dose	2.92	2.02–4.31	<0.01	2.00	1.49–2.70	<0.01	1.11	0.65–1.86	0.69
Therapeutic dose	2.64	1.81–3.92	<0.01	1.62	1.21–2.18	<0.01	1.35	0.89–2.06	0.16
Age, y	0.98	0.97–0.98	<0.01	1.01	1.00–1.01	<0.01	1.06	1.04–1.06	0.00
Male sex, n (%)	1.46	1.21–1.77	<0.01	1.35	1.16–1.56	<0.01	1.28	1.02–1.61	0.03
High blood pressure, n (%)	1.09	0.88–1.33	0.41	1.04	0.88–1.22	0.61	1.17	0.90–1.52	0.22
Diabetes mellitus, n (%)	1.12	0.90–1.37	0.31	1.13	0.95–1.32	0.15	1.39	1.08–1.76	<0.01
Dyslipidemia, n (%)	1.22	0.99–1.50	0.05	1.07	0.91–1.25	0.39	1.01	0.80–1.26	0.93
Current smoker, n (%)	1.10	0.86–1.37	0.44	1.02	0.83–1.23	0.84	1.25	0.91–1.68	0.15
Body mass index, kg/m^2, mean (SD)	1.02	1.01–1.04	<0.01	1.01	0.99–1.02	0.09	1.00	0.98–1.02	0.72
Plasma creatinine level—µmol/L, mean (SD)	1.00	0.99–1.01	0.47	1.00	1.00–1.01	<0.01	1.00	1.00–1.01	<0.01
C-reactive protein, mg/L, mean (SD)	1.00	1.01–1.02	<0.01	1.00	1.00–1.01	<0.01	1.00	1.00–1.01	<0.01
FiO_2, %, mean (SD)	1.02	1.01–1.02	<0.01	1.02	1.01–1.02	<0.01	1.02	1.01–1.02	<0.01
Parenchymal opacification in chest CT scan >50%	1.61	1.32–1.94	<0.01	1.44	1.22–1.69	<0.01	1.18	0.89–1.54	0.23

In-hospital mortality or ICU admission as a composite event to define ICU-free survival (B) and to in-hospital mortality (C). CT indicates computed tomography; DOAC, direct oral anticoagulant; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; RR, relative risk; and VKA, vitamin K antagonist.

in Wuhan, China, a prophylactic dose of LMWH used in 99 patients decreased mortality only in a specific subgroup of patients with a sepsis-induced coagulopathy.[21] In our study, we have tried to discern the specific and individual effect of the anticoagulation before hospitalization and anticoagulation initiated during hospitalization. In our population, no beneficial effect of prophylactic anticoagulation was reported, as recently described by Lynn et al.[37] Even for prophylactic high doses or therapeutic anticoagulation introduced

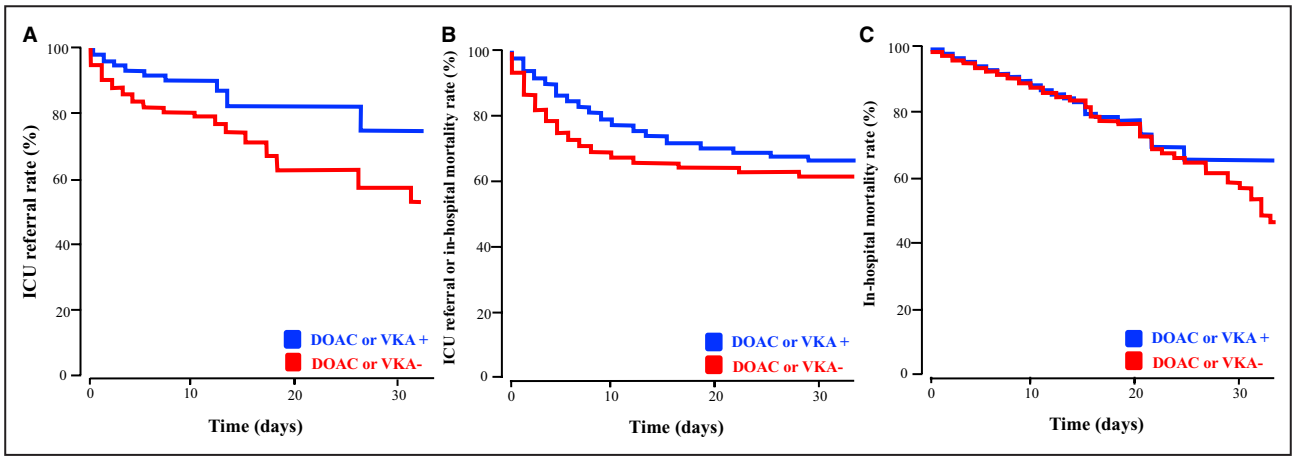

Figure 1. Survival curves of Cox proportional hazard model according to admission to ICU admission.
A, Admission to in-hospital mortality, or ICU admission as a composite event to define ICU-free survival (**B**) and to admission to in hospital mortality (**C**). Cox proportional hazards model is adjusted for sex, age, cardiovascular comorbidities (history of high blood pressure. dyslipidemia. body mass index, type 2 diabetes mellitus, and current smoking), plasma creatinine level (µmol/L), C-reactive protein (mg/L), and fraction of inspired oxygen. The degree of pulmonary lesions with ground-glass opacities and areas of consolidation and the use of in hospital anticoagulation (preventive low or high dose and therapeutic dose anticoagulation). DOAC indicates direct oral anticoagulant; ICU, intensive care unit; and VKA, vitamin K antagonist.

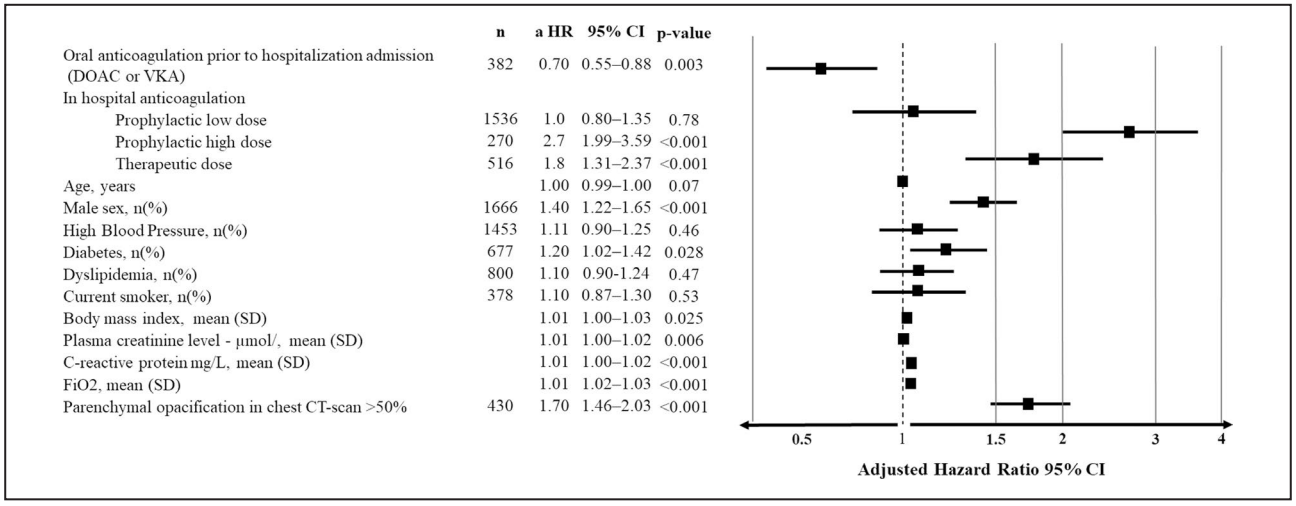

Figure 2. Forest plot of Cox proportional hazard model in the entire population (n=2748), according to admission to in-hospital mortality or ICU admission as a composite event to define ICU-free survival.
aHR indicates adjusted hazard ratio; CT, computed tomography; DOAC, direct oral anticoagulant; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; and VKA, vitamin K antagonist.

during hospitalization, an increase of patients with unfavorable outcome was observed. This finding is supported by the recent description of Paranjpe et al,[31] who found that patients who received anticoagulation were more likely to require invasive mechanical ventilation. We hypothesize that prehospital anticoagulation (VKA or DOAC) is more likely efficient at the early step of disease by preventing COVID-19–associated coagulopathy and endotheliopathy. Once the endotheliitis condition is reached, the COVID-19 worsens and the anticoagulation therapy loses its protective effect.

The clinical course of COVID-19 consists of 2 main phases: viral infection followed by immune and inflammatory response. Both phases are associated with coagulopathy and potential need of anticoagulation but probably with several different objectives. In both phases, anticoagulation could decrease microthrombosis in small lung vessels and delay aggravation in the early phase or decrease the burst of thromboinflammation and associated microthrombosis. Early anticoagulation before hospitalization for COVID-19 could also help, besides the coagulopathy associated with endothelial lesion, directly on the inhibition of the entry of SARS-CoV-2 into endothelial cells. Indeed, cell entry of SARS-CoV-2 depends on the binding of the viral spike proteins to cellular receptors and on spike-protein priming by host cell proteases. It has been demonstrated that serine protease TMPRSS2 is necessary for spike-protein priming.[38] Thus, a TMPRSS2 inhibitor has been proposed as a treatment option. If virus entrance inside cells is dependent on a serine protease action, anticoagulation, by blocking the coagulation cascade, could directly limit the virus entrance in endothelial but also in other cells. This hypothesis needs to be tested in preclinical models of infection.

Table 3. Hazard Ratios of Cox Proportional Hazard Model According to Admission to ICU Admission (A)

	aHR	95% CI	*P* Value
Oral anticoagulation prior admission (VKA or DOAC) (n=382)			
Admission to ICU admission	0.43	0.29–0.63	<0.001
Admission to in-hospital mortality or ICU admission as a composite event to define ICU-free survival	0.76	0.61–0.98	0.04
Admission to in-hospital mortality	1.09	0.83–1.55	0.49

Admission to in-hospital mortality or ICU admission as a composite event to define ICU-free survival (B) and to admission to in hospital mortality (C) in propensity matched population (n=1528). Cox proportional hazards model is adjusted for sex, age, cardiovascular comorbidities (history of high blood pressure, dyslipidemia, body mass index, type 2 diabetes mellitus, and current smoking), plasma creatinine level (µmol/L), C-reactive protein (mg/L), fraction of inspired oxygen, the degree of pulmonary lesions with ground-glass opacities and areas of consolidation, and the use of in-hospital anticoagulation (preventive low or high dose and therapeutic dose).

Our study has several limitations. Because of its retrospective design, it precludes determination of any causal relationship between the use of oral anticoagulants and outcomes. Moreover, this study has included only patients who were initially hospitalized in the medical ward and did not include patients who were directly admitted to the ICU. This selected population would not be representative of all patients with COVID-19. Despite efforts to control confounders by using different analytical strategies, some potential biases may have been disregarded such as the delay to introduction of anticoagulation, the duration of anticoagulation therapy during hospitalization and its indication. All

Table 4. Hazard Ratios for in Hospital Mortality in the Population Without AC Therapy Prior to Hospitalization (n=2466)

	Population Without Oral Anticoagulant Treatment (VKA or DOAC) Prior to Hospitalization for COVID-19 (n=2466)											
	Entire Population (n=2466)				Medical Population (n=1961)				ICU Population (n=503)			
	n	aHR	95% CI	*P* Value	n	aHR	95% CI	*P* Value	n	aHR	95% CI	*P* Value
In-hospital anticoagulation												
None	313	Ref	…	…	278	Ref	…	…	35	Ref	…	…
Prophylactic low dose	1478	1.04	0.69–1.60	0.85	1261	1.06	0.67–1.65	0.81	217	0.93	0.31–2.80	0.90
Prophylactic high dose	261	0.90	0.51–1.61	0.71	135	0.83	0.47–1.55	0.61	126	0.96	0.28–3.30	0.94
Therapeutic dose	246	1.00	0.61–1.60	0.99	139	0.85	1.07–1.09	0.59	107	0.85	0.27–2.70	0.79

Cox proportional hazard model is adjusted on sex, age, cardiovascular comorbidities (history of high blood pressure, dyslipidemia, body mass index, type 2 diabetes mellitus, and current smoking). Plasma creatinine level (µmol/L). C-reactive protein (mg/L). FiO_2. The degree of pulmonary lesions with ground-glass opacities and areas of consolidation. DOAC indicates direct oral anticoagulant; HR, hazard ratio; ICU, intensive care unit; ref, reference; and VKA, vitamin K antagonist.

efforts were made to adjust the analyses for relevant variables, including cardiovascular comorbidities, patient characteristics, severity of clinical features, and CT scan results. By design, the study can only report associations and cannot investigate causality.

In conclusion, our study is the first to demonstrate a beneficial effect of oral anticoagulation before hospitalization for COVID-19 on disease outcomes. Our results provide new data to suggest introduction of anticoagulation in ambulatory patients in case of close contacts with patients with confirmed COVID-19. Anticoagulation introduction in early disease, in particular in ambulatory patients, could prevent coagulopathy and endothelial-related disease, while an anticoagulation introduction too late, during the thrombo-inflammatory phase, do not provide protective effects. This hypothesis needs to be tested in appropriate prospective randomized studies.

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Supplementary Material

Appendix S1
Tables S1–S2

REFERENCES

1. Guan W-J, Ni Z-Y, Hu YU, Liang W-H, Ou C-Q, He J-X, Liu L, Shan H, Lei C-L, Hui DSC, et al. Clinical characteristics of coronavirus disease 2019

in China. *N Engl J Med*. 2020;382:1708–1720. DOI: 10.1056/NEJMoa2002032.
2. Debuc B, Smadja DM. Is COVID-19 a new hematologic disease? *Stem Cell Rev Rep*. 2020:1–5. DOI: 10.1007/s12015-020-09987-4.
3. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, Tamin A, Harcourt JL, Thornburg NJ, Gerber SI, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med*. 2020;382:1564–1567. DOI: 10.1056/NEJMc2004973.
4. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323:1239–1242. DOI: 10.1001/jama.2020.2648.
5. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. 2020;17:259–260. DOI: 10.1038/s41569-020-0360-5.
6. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062. DOI: 10.1016/S0140-6736(20)30566-3.
7. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18:844–847. DOI: 10.1111/jth.14768.
8. Goudot G, Chocron R, Augy J-L, Gendron N, Khider L, Debuc B, Aissaoui N, Peron N, Hauw-Berlemont C, Vedie B, et al. Predictive factor for COVID-19 worsening: insights for high-sensitivity troponin and D-dimer and correlation with right ventricular afterload. *Front Med (Lausanne)*. 2020;7:586307. DOI: 10.3389/fmed.2020.586307.
9. Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, Jeanpierre E, Rauch A, Labreuche J, Susen S, et al. Pulmonary embolism in patients with COVID-19: awareness of an increased prevalence. *Circulation*. 2020;142:184–186. DOI: 10.1161/CIRCULATIONAHA.120.047430.
10. Klok FA, Kruip M, van der Meer N, Arbous MS, Gommers D, Kant KM, Kaptein F, van Paassen J, Stals M, Huisman MV, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: an updated analysis. *Thromb Res*. 2020;191:148–150. DOI: 10.1016/j.thromres.2020.04.041.
11. Klok FA, Kruip M, van der Meer N, Arbous MS, Gommers D, Kant KM, Kaptein F, van Paassen J, Stals M, Huisman MV, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;191:145–147. DOI: 10.1016/j.thromres.2020.04.013.
12. Planquette B, Le Berre A, Khider L, Yannoutsos A, Gendron N, de Torcy M, Mohamedi N, Jouveshomme S, Smadja DM, Lazareth I, et al. Prevalence and characteristics of pulmonary embolism in 1042 COVID-19 patients with respiratory symptoms: a nested case-control study. *Thromb Res*. 2021;197:94–99. DOI: 10.1016/j.thromres.2020.11.001.
13. Fox S, Akmatbekov A, Harbert J, Li G, Brown G, Vander HR. Pulmonary and cardiac pathology in COVID-19: the first autopsy series from New Orleans. medRxiv preprint. 2020.
14. Zhang H, Zhou P, Wei Y, Yue H, Wang YI, Hu M, Zhang S, Cao T, Yang C, Li M, et al. Histopathologic changes and SARS-CoV-2 immunostaining in the lung of a patient with COVID-19. *Ann Intern Med*. 2020;172:629–632. DOI: 10.7326/M20-0533.
15. Liu X, Liu X, Xu Y, Xu Z, Huang Y, Chen S, Li S, Liu D, Lin Z, Li Y. Ventilatory ratio in hypercapnic mechanically ventilated patients with COVID-19–associated acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2020;201:1297–1299. DOI: 10.1164/rccm.202002-0373LE.
16. Diehl J-L, Peron N, Chocron R, Debuc B, Guerot E, Hauw-Berlemont C, Hermann B, Augy JL, Younan R, Novara A, et al. Respiratory mechanics and gas exchanges in the early course of COVID-19 ARDS: a hypothesis-generating study. *Ann Intensive Care*. 2020;10:95. DOI: 10.1186/s13613-020-00716-1.
17. Smadja DM, Guerin CL, Chocron R, Yatim N, Boussier J, Gendron N, Khider L, Hadjadj J, Goudot G, Debuc B, et al. Angiopoietin-2 as a marker of endothelial activation is a good predictor factor for intensive care unit admission of COVID-19 patients. *Angiogenesis*. 2020;23:611–620. DOI: 10.1007/s10456-020-09730-0.
18. Philippe A, Chocron R, Gendron N, Bory O, Beauvais A, Peron N, Khider L, Guerin CL, Goudot G, Levasseur F, et al. Circulating von Willebrand factor and high molecular weight multimers as markers of endothelial injury predict COVID-19 in-hospital mortality. *Angiogenesis*. 2021:1–13. DOI: 10.1007/s10456-020-09762-6.
19. Susen S, Tacquard CA, Godon A, Mansour A, Garrigue D, Nguyen P, Godier A, Testa S, Levy JH, Albaladejo P, et al. Prevention of thrombotic risk in hospitalized patients with COVID-19 and hemostasis monitoring. *Crit Care*. 2020;24:364. DOI: 10.1186/s13054-020-03000-7.
20. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, Clark C, Iba T. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020;18:1023–1026. DOI: 10.1111/jth.14810.
21. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020;18:1094–1099. DOI: 10.1111/jth.14817.
22. Ayerbe L, Risco C, Ayis S. The association between treatment with heparin and survival in patients with Covid-19. *J Thromb Thrombolysis*. 2020;50:298–301. DOI: 10.1007/s11239-020-02162-z.
23. Spyropoulos AC, Ageno W, Barnathan ES. Hospital-based use of thromboprophylaxis in patients with COVID-19. *Lancet*. 2020;395:e75. DOI: 10.1016/S0140-6736(20)30926-0.
24. Tremblay D, van Gerwen M, Alsen M, Thibaud S, Kessler A, Venugopal S, Makki I, Qin Q, Dharmapuri S, Jun T, et al. Impact of anticoagulation prior to COVID-19 infection: a propensity score-matched cohort study. *Blood*. 2020;136:144–147. DOI: 10.1182/blood.2020006941.
25. Russo V, Di Maio M, Attena E, Silverio A, Scudiero F, Celentani D, Lodigiani C, Di Micco P. Clinical impact of pre-admission antithrombotic therapy in hospitalized patients with COVID-19: a multicenter observational study. *Pharmacol Res*. 2020;159:104965. DOI: 10.1016/j.phrs.2020.104965.
26. Spyropoulos AC, Levy JH, Ageno W, Connors JM, Hunt BJ, Iba T, Levi M, Samama CM, Thachil J, Giannis D, et al. Scientific and standardization committee communication: clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost*. 2020;18:1859–1865. DOI: 10.1111/jth.14929.
27. Revel MP, Parkar AP, Prosch H, Silva M, Sverzellati N, Gleeson F, Brady A; European Society of Radiology, the European Society of Thoracic Imaging. COVID-19 patients and the radiology department—advice from the European Society of Radiology (ESR) and the European Society of Thoracic Imaging (ESTI). *Eur Radiol*. 2020;30:4903–4909. DOI: 10.1007/s00330-020-06865-y.
28. Bewick V, Cheek L, Ball J. Statistics review 10: further nonparametric methods. *Crit Care*. 2004;8:196–199.
29. Reichenheim ME, Coutinho ES. Measures and models for causal inference in cross-sectional studies: arguments for the appropriateness of the prevalence odds ratio and related logistic regression. *BMC Med Res Methodol*. 2010;10:66. DOI: 10.1186/1471-2288-10-66.
30. Sedgwick P. Bias in observational study designs: cross sectional studies. *BMJ*. 2015;350:h1286. DOI: 10.1136/bmj.h1286.
31. Paranjpe I, Fuster V, Lala A, Russak AJ, Glicksberg BS, Levin MA, Charney AW, Narula J, Fayad ZA, Bagiella E, et al. Association of treatment dose anticoagulation with in-hospital survival among hospitalized patients with COVID-19. *J Am Coll Cardiol*. 2020;76:122–124. DOI: 10.1016/j.jacc.2020.05.001.
32. Guerin CL, Guyonnet L, Goudot G, Revets D, Konstantinou M, Chipont A, Chocron R, Blandinieres A, Khider L, Rancic J, et al. Multidimensional proteomic approach of endothelial progenitors demonstrate expression of KDR restricted to CD19 cells. *Stem Cell Rev Rep*. 2020:1–13.Nov 17 [epub ahead of print].;10.1007/s12015-020-10062-1.
33. Khider L, Gendron N, Goudot G, Chocron R, Hauw-Berlemont C, Cheng C, Rivet N, Pere H, Roffe A, Clerc S, et al. Curative anticoagulation prevents endothelial lesion in COVID-19 patients. *J Thromb Haemost*. 2020;18:2391–2399. DOI: 10.1111/jth.14968.
34. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020;395:1417–1418. DOI: 10.1016/S0140-6736(20)30937-5.
35. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, Vanstapel A, Werlein C, Stark H, Tzankov A, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. *N Engl J Med*. 2020;383:120–128. DOI: 10.1056/NEJMoa2015432.
36. Sardu C, Gambardella J, Morelli MB, Wang X, Marfella R, Santulli G. Hypertension, thrombosis, kidney failure, and diabetes: is COVID-19 an endothelial disease? A comprehensive evaluation of clinical and basic evidence. *J Clin Med*. 2020;9:1417.

37. Lynn L, Reyes JA, Hawkins K, Panda A, Linville L, Aldhahri W, Kango G, Shah S, Ayanian S, Teufel K. The effect of anticoagulation on clinical outcomes in novel coronavirus (COVID-19) pneumonia in a U.S. cohort. *Thromb Res*. 2020;197:65–68. DOI: 10.1016/j.thromres.2020.10.031.

38. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu N-H, Nitsche A, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181:271–280.e278. DOI: 10.1016/j.cell.2020.02.052.

SUPPLEMENTAL MATERIAL

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Table S1. Poisson regression model according to: ICU admission (A); ICU admission or In-hospital mortality as a composite event to define ICU-free survival (B); and to in-hospital mortality (C) in uncensored population (n=2335).

	Population without censored data - complete data based analysis (n=2335)								
	ICU referral			ICU or in-hospital mortality			In-hospital mortality		
	RR	95% CI	p-value	RR	95% CI	p-value	RR	95% CI	p-value
Oral anticoagulation prior admission (DOAC or VKA)	0.45	[0.32-0.62]	0.000	0.77	[0.59-0.93]	0.050	0.94	[0.68-1.26]	0.68
In hospital anticoagulation,									
Prophylactic low dose	1.15	[0.81-1.66]	0.441	1.09	[0.82-1.40]	0.614	1.10	[0.76-1.61]	0.62
Prophylactic high dose	2.92	[2.02-4.31]	0.000	2.01	[1.49-2.70]	0.000	1.11	[0.65-1.86]	0.69
Therapeutic dose	2.64	[1.81-3.92]	0.000	1.68	[1.21-2.18]	0.001	1.35	[0.89-2.06]	0.16
Age, years	0.98	[0.97-0.98]	0.000	1.01	[1.00-1.01]	0.000	1.06	[1.04-1.06]	0.000
Male sex, n(%)	1.46	[1.21-1.77]	0.000	1.35	[1.16-1.56]	0.000	1.28	[1.02-1.61]	0.031
High blood pressure, n(%)	1.09	[0.88-1.33]	0.408	1.04	[0.88-1.22]	0.605	1.17	[0.90-1.52]	0.23
Diabetes, n(%)	1.12	[0.90-1.37]	0.305	1.13	[0.95-1.32]	0.148	1.39	[1.08-1.76]	0.007
Dyslipidemia, n(%)	1.22	[0.99-1.50]	0.054	1.07	[0.91-1.25]	0.394	1.01	[0.80-1.26]	0.94
Current smoker, n(%)	1.10	[0.86-1.37]	0.439	1.02	[0.83-1.23]	0.837	1.25	[0.91-1.68]	0.15
Body mass index, Kg/m², mean (SD)	1.02	[1.01-1.04]	0.002	1.01	[0.99-1.02]	0.099	1.00	[0.98-1.02]	0.72
Plasma creatinine level - µmol/L, mean (SD)	1.00	[0.99-1.01]	0.474	1.00	[1.00-1.01]	0.001	1.00	[1.00-1.01]	0.000
C-reactive protein, mg/L, mean(SD)	1.00	[1.01-1.02]	0.000	1.00	[1.00-1.01]	0.000	1.00	[1.00-1.01]	0.000
FiO2, mean (SD)	1.02	[1.01-1.02]	0.000	1.02	[1.01-1.02]	0.000	1.02	[1.01-1.02]	0.000
Parenchymal opacification in chest CT-scan >50%	1.61	[1.32-1.94]	0.000	1.44	[1.22-1.69]	0.000	1.18	[0.89-1.54]	0.234

RR= Relative Risk; CI= Confident Interval; ICU =Intensive Care Unit. DOAC=Direct Oral anticoagulant; VKA= Vitamin K antagonist; SD= Standard deviation; CT=Computed tomography.

Table S2. Patients' characteristics and outcomes according to the propensity matching analysis (n=1528).

	Propensity matched population		
	No prior oral AC	oral AC prior to hospitalization	p-value
	n=1146	n=382	
Age, years, mean (SD)**	76.53 (12.28)	77.31 (12.55)	0.051
Male sex, n (%)**	679 (59.2)	233 (61.0)	0.588
Time from onset illness to hospitalization, days, mean(SD)	6.46 (4.59)	5.71 (4.91)	0.007
Cardiovascular comorbidities			
Body mass index, Kg/m², mean (SD)**	27.67 (5.62)	27.56 (5.74)	0.758
High blood pressure, n (%)**	855 (74.6)	295 (77.2)	0.338
Diabetes Mellitus, n (%)**	351 (30.6)	112 (29.3)	0.676
Dyslipidemia, n (%)**	458 (40.0)	161 (42.1)	0.489
Current smoking, n (%)**	855 (74.6)	295 (77.2)	0.338
History of venous thromboembolism n (%)	69 (6.0)	83 (21.7)	<0.001
History of atrial fibrillation n (%)	86 (7.5)	293 (76.7)	<0.001
In hospital anticoagulation, n (%)			
None	134 (11.7)	23 (6.0)	<0.001
Prophylactic low dose	113 (9.9)	9 (2.4)	<0.001
Prophylactic high dose	763 (66.6)	58 (15.2)	<0.001
Therapeutic dose	136 (11.9)	292 (76.4)	<0.001
Biology			
Plasma creatinine level - µmol/L, mean (SD)	108.97 (102.64)	126.56 (136.55)	0.008
Creatinine clairance (Cockcroft-Gault), mL/min mean (SD)	73.93 (55.05)	81.75 (234.82)	0.296
C-reactive protein, mg/L, mean (SD)	92.86 (77.22)	86.28 (66.20)	0.135
FiO2, ¨%, mean (SD)	29.50 (13.02)	28.83 (12.15)	0.378
In hospital outcomes			
Parenchymal opacification in chest CT-scan >50%, n (%)	169 (14.7)	51 (13.4)	0.556
Time from hospital admission to ICU transfer, mean (SD)	6.87 (3.37)	7.63 (3.27)	<0.001
Time from admission to in-hospital mortality, mean (SD)	11.29 (4.54)	11.33 (4.39)	0.860
Non-invasive mechanical ventilation, n (%)	41 (3.6)	11 (2.9)	0.625
Invasive mechanical ventilation, n (%)	146 (12.7)	27 (7.1)	<0.001
Reasons for ICU admission, n (%)			0.046
Septic shock	0 (0.0)	2 (0.5)	
Acute respiratory failure	1142 (99.7)	378 (99.0)	
Acute cardiac failure	2 (0.2)	2 (0.5)	
Other	2 (0.2)	0 (0.0)	
In-hospital mortality, n (%)	218 (19.0)	84 (21.9)	0.235
In-hospital mortality etiology, n (%)			0.095
Acute respiratory failure	193 (88.5)	70 (83.3)	
Acute cardiac failure	8 (3.7)	4 (4.7)	
Cardiac arrest	6 (2.7)	7 (8.3)	
Other	11 (5.1)	3 (3.6)	

CT= Computerized Tomography, ICU = Intensive Care Unit, FiO2=Fraction of inspired oxygen (%), U/ L= Units per Liter.**Covariates used in the propensity score matching.