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SHORT REPORT

Prior use of therapeutic anticoagulation does not protect against COVID-19 related clinical outcomes in hospitalized patients: A propensity score-matched cohort study

Janneke P. Spiegelenberg[1,2] | Marleen M. H. J. van Gelder[3,4] | Martje L. Maas[5] | Marcel M. C. Hovens[6] | Anne Esselink[7] | Anton S. M. Dofferhoff[7] | Rob Janssen[8] | Josephine van de Maat[1,2] | Nico Janssen[1,2] | Marc Blaauw[1,2] | Robert-Jan Hassing[6] | Marjan van Apeldoorn[9] | Angèle Kerckhoffs[9] | Karin Veerman[10] | Jacobien Hoogerwerf[1,2] | Cornelis Kramers[11,12] | Jenneke Leentjens[1,2]

[1]Department of Internal Medicine, Radboud university medical center, Nijmegen, the Netherlands

[2]Radboud Center for Infectious Diseases, Radboud university medical center, Nijmegen, The Netherlands

[3]Department for Health Evidence, Radboud Institute for Health Sciences, Radboud university medical center, Nijmegen, the Netherlands

[4]Radboud REshape Innovation Center, Radboud university medical center, Nijmegen, the Netherlands

[5]Department of Internal Medicine, Bernhoven, Uden, the Netherlands

[6]Department of Internal Medicine, Rijnstate Hospital, Arnhem, the Netherlands

[7]Department of Internal Medicine, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands

[8]Department of Pulmonary Medicine, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands

[9]Department of Internal Medicin and Geriatricts, Jeroen Bosch Hospital, GZ,'s-Hertogenbosch, the Netherlands

[10]Department of Internal Medicine, St. Maartenskliniek, Ubbergen, The Netherlands

[11]Department of Pharmacology-Toxicology, Radboud university medical center, Nijmegen, the Netherlands

[12]Department of Pharmacy, Canisius Willhelmina Hospital, Nijmegen, the Netherlands

Correspondence
Jenneke Leentjens, MD, PhD; Radboud Center for Infectious Diseases, Radboud university medical center, Nijmegen, The Netherlands.
Email: jenneke.leentjens@radboudumc.nl

The hypercoagulable state observed in COVID-19 could be responsible for morbidity and mortality. In this retrospective study we investigated whether therapeutic anticoagulation prior to infection has a beneficial effect in hospitalized COVID-19 patients. This study included 1154 COVID-19 patients admitted to 6 hospitals in the Netherlands between March and May 2020. We applied 1:3 propensity score matching to evaluate the association between prior therapeutic anticoagulation use and clinical outcome, with in hospital mortality as primary endpoint. In total, 190 (16%) patients used therapeutic anticoagulation prior to admission. In the propensity score matched analyses, we observed no associations between prior use of therapeutic anticoagulation and overall mortality (risk ratio 1.02 [95% confidence interval; 0.80–1.30]) or length of hospital stay (7.0 [4–12] *vs*. 7.0 [4–12] days, $P = .69$), although we observed a lower risk of pulmonary embolism (0.19 [0.05–0.80]).

This study shows that prior use of therapeutic anticoagulation is not associated with improved clinical outcome in hospitalized COVID-19 patients.

KEYWORDS

anticoagulation, corona virus disease 2019, direct oral anticoagulants, pulmonary embolism, thromboprophylaxis, thrombosis, vitamin K antagonist

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Besides respiratory failure, COVID-19 also has high rates of thromboembolic complications as seen in multiple retrospective studies.[1–4] In accordance, autopsy studies showed high incidences of macro- and microembolism in patients who were infected by SARS-CoV-2.[5,6] The exact underlying pathophysiology of COVID-19 related thrombotic complications remains unknown, but excessive inflammation, hypoxia, immobilization, thrombotic microangiopathy, diffuse intravascular coagulation and complement activation probably play a role.[7] Importantly, low-molecular-weight heparin (LMWH) thromboprophylaxis seems to decrease mortality in patients with COVID-19.[8]

Because of the overt COVID-19 associated coagulopathy, anticoagulation in COVID-19 receives much attention. Consequently, all guidelines recommend administration of prophylactic LMWH for all hospitalized patients with COVID-19.[9,10] Nevertheless, recent reports show that despite the use of apparently adequate thrombosis prophylaxis, the incidence of venous thromboembolism (VTE) in COVID-19 patients who were admitted to a hospital ward appears to be much higher compared to patients with other infectious diseases.[2–4,11] Higher dose of anticoagulation is especially interesting in patients with history of cardiovascular disease who are at higher risk for adverse events in COVID-19.[12] However, there are no rigorous trials on therapeutic anticoagulation, and retrospective studies that address the effect of therapeutic anticoagulation prior to or at hospital admission on clinical outcomes show conflicting results, and often compare very heterogeneous cohorts that lack statistical power to draw firm conclusions (summarized in Table 1).

The aim of this study was to investigate the effect of therapeutic anticoagulation used prior to hospitalization on morbidity and mortality in a large cohort of hospitalized COVID-19 patients.

What is already known about this subject

- Patients with COVID-19 have a hypercoagulable state with increased risk of thrombotic events.
- Several studies investigated the association between therapeutic anticoagulation prior to hospitalization and mortality with ambivalent results, probably due to methodological limitations.

What this study adds

- A rigorous statistical analysis with thorough adjustment for confounding to properly investigate the treatment effect of prior therapeutic anticoagulation on different clinically relevant outcomes in a large cohort of hospitalized COVID-19 patients.
- This study provides convincing evidence that therapeutic anticoagulation used prior to infection is associated with a decreased risk of pulmonary embolism, but not with mortality and other disease severity parameters.

2 | METHODS

2.1 | Patients

We included all patients aged ≥18 years with confirmed COVID-19 admitted to 1 of the 6 participating hospitals in the Netherlands (one academic hospital [Radboudumc, Nijmegen], and 5 teaching hospitals [Canisius Wilhelmina Hospital, Nijmegen; Sint Maartenskliniek, Nijmegen; Rijnstate, Arnhem; Bernhoven, Uden; Jeroen Bosch Hospital, 's-Hertogenbosch]) between 1 March and 31 May 2020. The diagnosis COVID-19 was made with an in-house real-time reverse transcriptase–polymerase chain reaction (PCR) positive for SARS-CoV-2 on a deep naso-oropharyngeal swab. In addition, patients with negative PCR but with clinical symptoms consistent with COVID-19 and a computed tomography (CT) scan of the chest showing a very high suspicion of typical pulmonary involvement of COVID-19 (COVID-19 reporting and data system score of 5 defined by the Dutch Radiology Society) were included.[13] Patients were excluded when COVID-19 was not PCR or radiographically confirmed, or when patients had insufficient clinical documentation because they were transferred to or from another hospital due to capacity constraints.

The index date was the day of hospital admission. Patients were followed until hospital discharge or death. Data on the occurrence of thrombotic events, length of hospital stay, intensive care unit (ICU) admission, type of oxygen ventilation, and mortality were obtained from the patients' records (EPIC, EPIC Systems Corporation, Verona, WI, USA; HiX, ChipSoft, Amsterdam, The Netherlands;

TABLE 1 Summary of published studies on the effect of prior anticoagulation on COVID-19 outcome

Author, date of publication	Design, methods	Primary outcome	OAC	Patients	Findings
Tremblay *et al.*, July 2020[13]	Retrospective cohort study, PSM & Cox proportional-hazard models	All-cause mortality	Prior DOAC + VKA before admission	Hospitalized patients - OAC $n = 139$ - control $n = 417$	HR 1.208 (95% CI, 0.750–1.946)
Rossi, July 2020[14]	Retrospective cohort study, Cox proportional-hazards models	All-cause mortality	Prior DOAC before admission	Nonhospital patients aged >60 y - DOAC $n = 26$ - control $n = 44$	HR 0.38 (CI 95%, 0.17–0.58)
Lachant, Oct 2020[15]	Retrospective cohort study without correction for confounders	Thrombotic events	Prior OAC before admission	Hospitalized and nonhospitalized patients - OAC n = 107	0 thrombotic events in OAC group
Rivera-Caravaca, Oct 2020[16]	Retrospective cohort study, PSM & Cox proportional-hazard models	All-cause mortality	Prior DOAC + VKA before admission	Hospitalized patients: - OAC $n = 109$ - control $n = 109$	HR 1.53 (95% CI, 1.08–2.16)
Fröhlich *et al.*, Jan 2021[17]	Retrospective cohort study, multivariable logistic regression model	In-hospital all-cause mortality or need for invasive or noninvasive ventilation or ECMO implant	Prior DOAC + VKA before admission	Hospitalized patients registered in health insurance company AOK - VKA $n = 223$ - DOAC $n = 508$ - control $n = 5059$	VKA: OR 0.57 (95% CI, 0.40–0.83) DOAC: OR 0.71 (95%, CI 0.56–0.91)
Harrison *et al.*, Jan 2021[18]	Retrospective cohort study, multivariable logistic regression model with IPTW on propensity score	In-hospital mortality at 21 days from the first test	DOAC + VKA before and during admission	Hospitalized patients - DOAC $n = 104$ - warfarin $n = 28$ - control $n = 894$	DOAC: OR 0.44 (95% CI, 0.20–0.90) warfarin: OR, 0.29 (95% CI, 0.02–1.62)
Schiavone *et al.*, Jan 2021[19]	Retrospective cohort study, multivariable logistic regression	Mortality	Prior DOAC + VKA before admission	Hospitalized patients - OAC $n = 65$ - control $n = 779$	No association with the use of OACs
Chocron *et al.*, February 2021[20]	Retrospective cohort study, Cox proportional-hazard model	ICU admission and composite outcome for ICU admission and/or death	Prior DOAC + VKA before admission	Hospitalized patients - OAC $n = 382$ - control $n = 1528$	ICU admission: HR 0.43 (95% CI 0.29–0.63) ICU & death: HR 0.76 (95% CI 0.61–0.98)
Flam *et al.*, March 2021[21]	Retrospective cohort study, Cox proportional-hazards regression	Hospital admission and composite outcome for ICU admission and/or death	Prior DOAC before admission	Non-hospitalized patients with AF registered in the national patient register of Sweden - DOAC $n = 103\,703$ - control $n = 36\,875$	Hospital admission: HR 1.00 (CI 95%, 0.75–1.33) ICU admission or death: HR 0.76 (CI 95%, 0.51–1.12)

PSM, propensity score matching; ICU, intensive care unit; IPTW, inverse probability of treatment weighting; OAC, oral anticoagulant; DOAC, direct oral anticoagulant; VKA, vitamin K antagonist; AF, atrial fibrillation; ECMO, extracorporeal membrane oxygenation.

xCare EPD, NEXUS, Nieuwegein, The Netherlands) and recorded in our database using a standardized case report form in the good clinical practice-compliant data management system Castor (Castor Electronic Data Collection, Amsterdam, the Netherlands). CT pulmonary angiograms were performed at the discretion of the treating clinician. Common indications for CT pulmonary angiogram included high D-dimer levels and/or progressive hypoxemia. The study was carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees and informed consent. The Institutional Review Boards of the participating hospitals waived the need for informed consent due to the observational nature of this study.

2.2 | Outcomes

The primary outcome was all-cause in hospital mortality. Secondary outcomes included admission to the ICU, need for invasive mechanical ventilation, critical respiratory status (defined as a composite endpoint of the need for invasive mechanical ventilation and/or need of venturi mask and/or nonrebreathing mask), imaging-proved pulmonary embolism (PE) and length of hospital stay.

2.3 | Potential confounders

We identified potential confounders a priori by performing a literature review. Directed acyclic graphs were subsequently drawn to visualize causal assumptions to identify confounders (Figure S1 in the online supplement). Age, sex, body mass index (BMI), medical history of chronic pulmonary disease, diabetes mellitus, active malignancy, hypertension, obstructive coronary heart disease, myocardial infarction, nonischaemic cardiomyopathy, heart failure, previous heart surgery, electronic heart device, cerebrovascular accidents, and/or peripheral artery disease, use of immunosuppressive medication, and no-ICU policy were identified as confounders that were available in our database.

2.4 | Statistical analysis

Descriptive statistics were used to compare the patients with and without prior therapeutic anticoagulation and to estimate the prevalence of the outcomes. Categorical parameters were presented as counts with percentages, continuous parameters with medians and interquartile ranges, based on their non-normal distribution tested with the Shapiro–Wilk test. Comparisons were performed using Mann–Whitney *U* test or χ^2 test as appropriate. To compare the outcomes while adjusted for potential confounding resulting from the nonrandomized design of our observational study, we applied propensity score-matching methods. In our database, 174 (15%) patients had missing information for BMI. Therefore, we first imputed BMI values with single imputation using predicted values from multivariable models including age, sex, hypertension, diabetes mellitus and the outcome mortality. Propensity scores were generated using a multivariable logistic regression model with prior therapeutic anticoagulation use as outcome and the 17 variables previously stated as predictors. The patients with therapeutic anticoagulation were subsequently matched in a 1:3 ratio with patients without therapeutic anticoagulation prior to admission on these propensity scores with Nearest Neighbor Matching techniques without replacement and a calliper width of 0.1 of the standard deviation of the logit of the propensity score. To evaluate the balance of measured confounders between exposed and unexposed groups, we calculated the standardized mean difference. A standardized mean difference <0.25 indicated balance of matched cohorts.[22]

Associations between prior therapeutic use of anticoagulants and the outcomes overall in hospital mortality, admission to ICU, occurrence of PE, critical respiratory state and the need for invasive mechanical ventilation were estimated as risk ratios with 95% confidence intervals. Estimating the differences in length of hospital stay between the 2 groups was performed using Mann–Whitney *U* test stratified by mortality.

In our secondary analysis, we compared vitamin K antagonists (VKAs) *vs.* no therapeutic anticoagulation, direct oral anticoagulants (DOACs) *vs.* no therapeutic anticoagulation and VKA *vs.* DOAC on the before mentioned outcome parameters. Matching was performed using the R-software/studio Version 1.3.1093 and statistical analysis were performed using STATA/SE 16.0 (Stata Corp, TX, USA).

3 | RESULTS

Of the 1316 patients who were hospitalized with proven COVID-19 between 1 March and 31 May 2020, 239 patients were excluded because of reasons depicted in Figure 1. Of the 1154 patients included in this study, 92 (8%) used VKA and 98 (8%) used DOAC, and 964 (84%) patients did not use therapeutic anticoagulation prior to COVID-19 diagnosis; 76% of patients used OAC because of atrial fibrillation, 13% because of VTE in history, 4% because of mechanical valve replacement, 2 patients because of a cardiac arrest in history and, in 5% of patients, the reason of chronic OAC use was unknown. All patients in the exposed group were continued on therapeutic anticoagulation during hospitalization. Among patients who did not use therapeutic anticoagulation prior to admission, 856 (89%) received prophylactic LMWH during hospitalization. COVID-19 was confirmed by a positive PCR test in 1124 (97%) patients or considered confirmed by clinical features in combination with a CT scan with a very high level of suspicion (CO-RADS 5) in 30 (3%) patients.

Baseline patient characteristics are shown in Table 2. Patients who used therapeutic anticoagulation prior to hospitalization were older, more likely to be male, and more likely to have cardiovascular comorbidities or a no-ICU policy compared to patients who did not use prior therapeutic anticoagulation. Subsequent propensity score matching retained 164 (86%) patients who used prior therapeutic

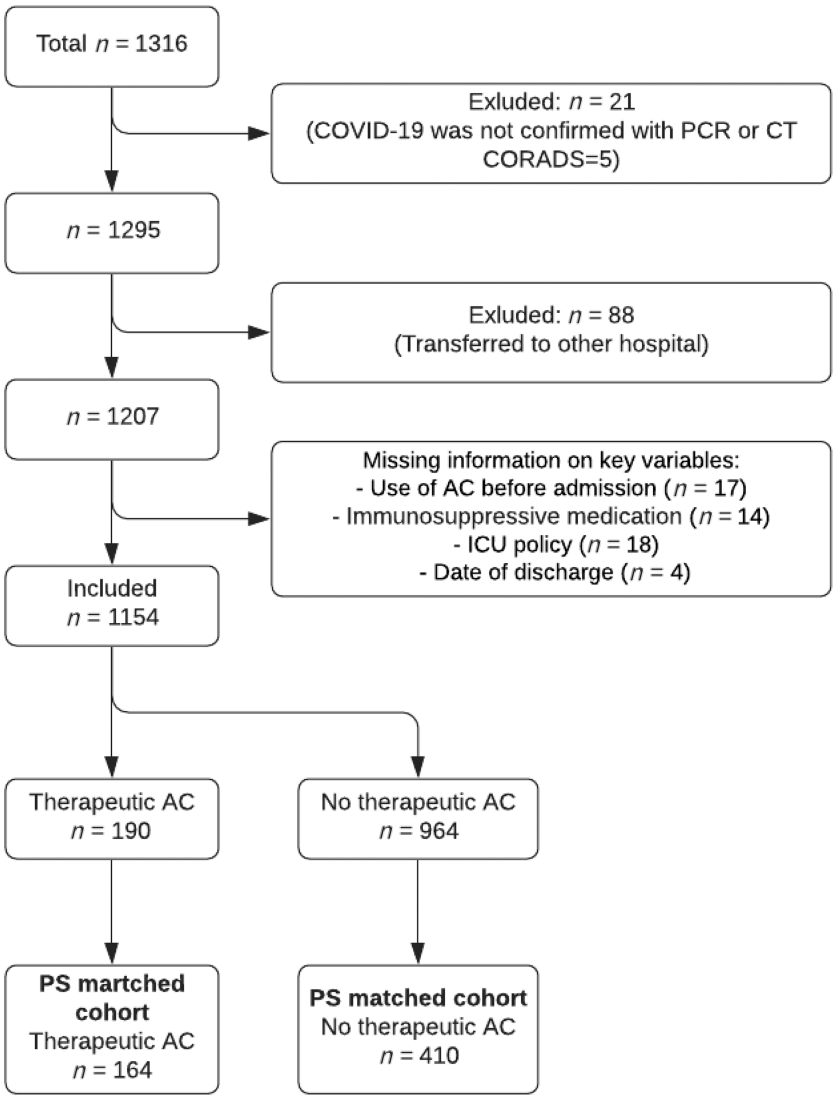

FIGURE 1 Flow chart displaying included database sample matched by propensity-score. PCR, reverse transcriptase polymerase chain reaction; CORADS, COVID-19 reporting and data system score; AC, anticoagulation; ICU, intensive care unit; PS, propensity score; CT, computed tomography

anticoagulation and 410 unexposed patients. The main covariates were balanced between the groups after the propensity score matching (Table 2).

The results from the total cohort and the propensity score-matched analysis on the associations between therapeutic anticoagulation use and the dichotomous outcomes are presented in Table 3A. In the crude total cohort analysis, therapeutic anticoagulation use was associated with an increased risk of mortality and decreased risks of ICU admission, mechanical ventilation and PE. In the propensity score-matched analyses, however, no associations between therapeutic anticoagulation use and the outcomes were observed, except for a decreased risk of PE among patient with therapeutic anticoagulation (risk ratio 0.19 [95% confidence interval 0.05–0.80]; Table 3, Figure S2). In addition, therapeutic anticoagulation use was not associated with length of hospital stay (Table 3B).

Similar to the primary analysis, no associations were found between VKA or DOAC use prior to admission and COVID-19 related clinical outcome parameters after propensity score matching (see Tables S1–S6).

4 | DISCUSSION

The main findings of this study are that therapeutic anticoagulation used prior to SARS-CoV-2 infection is associated with a lower risk for PE but is not associated with a decreased risk of other COVID-19 related outcomes in hospitalized COVID-19 patients, including in-hospital mortality. In addition, we did not observe differences in outcomes between DOAC or VKA-treated subgroups.

The acute inflammatory phenomenon in COVID-19 amplifies hypercoagulability and increases the risk of thrombosis even under prophylaxis of LMWH.[3,4] It has been hypothesized that therapeutic anticoagulation used prior to infection could improve the prognosis of COVID-19 by hampering coagulation activation. Indeed, a previous study showed that the use of therapeutic anticoagulation at hospital admission resulted in a much lower incidence of VTE compared to thromboprophylaxis alone.[15] Other studies, however, showed ambivalent results on COVID-19 severity and mortality due to comparison of dissimilar cohorts and lack of proper statistical adjustments for imbalances in baseline characteristics including comorbidities (Table 1).

TABLE 2 Characteristic of the total cohort and the study population matched on propensity score for patients with therapeutic anticoagulation use and unexposed patients

	Total cohort						Propensity score-matched cohort					
	Therapeutic AC use ($n = 190$)		No therapeutic AC use ($n = 964$)				Therapeutic AC use ($n = 164$)		No therapeutic AC use ($n = 410$)			
Characteristic	***n***	**(%)**	***n***	**(%)**	***P*-value**	**St. Diff.[1]**	***n***	**(%)**	***n***	**(%)**	***P*-value**	**St. Diff.[1]**
Age, median (IQR), y	76	(72–82)	68	(57–76)	<.001	0.89a	76	(71-82)	76	(70–82)	.70	0.035
Females	55	(29)	364	(38)	.02	0.19	53	(32)	132	(32)	.98	0.0026
BMI, median (IQR), kg/m^2	27.6	(24.0–31.1)	27.6	(25.0–30.8)	.73	0.03	27.6	(24.4–31.7)	27.7	(24.8–30.8)	.91	0.010
Cardiovascular disease												
Hypertension	112	(59)	341	(35)	<.001	0.49a	96	(58)	213	(52)	.15	0.13
Obstructive CAD	52	(27)	96	(10)	<.001	0.46a	42	(26)	83	(20)	.16	0.13
Myocardial infarction	30	(16)	80	(8)	<.001	0.23	22	(13)	59	(14)	.76	0.028
Heart failure	40	(21)	17	(2)	<.001	0.64a	17	(10)	17	(4)	.004	0.24
Nonischaemic cardiomyopathy	12	(6)	15	(2)	<.001	0.25a	8	(5)	14	(3)	.41	0.073
Previous heart surgery	18	(9)	25	(3)	<.001	0.29a	13	(8)	24	(6)	.36	0.082
Electronic heart device	13	(7)	12	(12)	<.001	0.29a	7	(4)	11	(3)	.33	0.086
CVA	37	(19)	99	(10)	<.001	0.26a	34	(21)	73	(18)	.42	0.074
Peripheral artery disease	20	(11)	41	(4)	<.001	0.24	18	(11)	33	(8)	.27	0.10
Diabetes mellitus	52	(27)	210	(22)	.09	0.13	47	(29)	110	(27)	.66	0.041
Chronic pulmonary disease	53	(28)	225	(23)	.18	0.10	43	(26)	107	(26)	.98	0.0028
Active malignancy	43	(23)	169	(18)	.10	0.13	38	(23)	91	(22)	.80	0.023
Immunosuppressant use	23	(12)	102	(11)	.54	0.05	19	(12)	55	(13)	.56	0.055
No ICU policy	114	(60)	268	(28)	<.001	0.69a	92	(56)	218	(53)	.53	0.059

AC, anticoagulation; BMI, body mass index; CAD, coronary artery disease; CVA, cerebrovascular accident; ICU, intensive care unit; IQR, interquartile range.

[1]Standardized differences to compare the distribution of covariates between the exposure groups.

[a]St. Diff >0.25, the covariate is not balanced between the 2 groups.

TABLE 3A Risk estimates for COVID-19 outcome associated with therapeutic anticoagulation *vs.* no therapeutic anticoagulation in the total cohort and the propensity score (PS)-matched cohort

	Total cohort					PS-matched cohort				
	Therapeutic AC use ($n = 190$)		No therapeutic AC use ($n = 964$)			Therapeutic AC use ($n = 164$)		No therapeutic AC use ($n = 410$)		
Outcome	*n*	(%)	*n*	(%)	Crude RR (95% CI)	*n*	(%)	*n*	(%)	PS-matched RR (95% CI)a
Deceased	75	(39)	207	(22)	1.84 (1.48–2.28)	60	(37)	147	(36)	1.02 (0.80–1.30)
ICU admission	20	(11)	193	(20)	0.53 (0.34–0.81)	20	(12)	61	(15)	0.82 (0.51–1.31)
Mechanical ventilation	16	(8)	134	(14)	0.61 (0.37–0.99)	16	(10)	42	(10)	0.95 (0.55–1.65)
Critical respiratory state	83	(44)	362	(38)	1.16 (0.97–1.39)	68	(41)	176	(43)	0.97 (0.78–1.20)
Pulmonary embolism	2	(1)	77	(8)	0.13 (0.03–0.53)	2	(1)	26	(6)	0.19 (0.05–0.80)

AC = anticoagulation, CI = confidence interval, ICU = intensive care unit, RR = relative risk.
[a]The propensity scores included the following characteristics: age, sex, body mass index, active malignancy, chronic pulmonary disease, diabetes mellitus, hypertension, obstructive coronary artery disease, myocardial infarction, heart failure, nonischaemic cardiomyopathy, previous heart surgery, electronic heart device, cerebrovascular accident, peripheral artery disease, immunosuppressive medication, no ICU policy.

TABLE 3B Associations between therapeutic AC use and length of hospital stay in the total cohort and the propensity score (PS)-matched cohort

	Total cohort					PS-matched cohort				
	Therapeutic AC use ($n = 190$)		No therapeutic AC use ($n = 964$)			Therapeutic AC use ($n = 164$)		No therapeutic AC use ($n = 410$)		
Length of hospital stay	Days	(IQR)	Days	(IQR)	*P*-value	Days	(IQR)	Days	(IQR)	*P*-value
All patients	7.0	(4.0–11.0)	7.0	(4.0–13.0)	.47	7.0	(4.3–11.8)	7.0	(4.0–12.0)	.69
Deceased										
Yes	6.0	(4.0–9.0)	7.0	(5.0–12.0)	.06	6.5	(4.0–10.8)	7.0	(4.0–10.0)	.61
No	7.0	(5.0–13.0)	7.0	(4.0–13.0)	.51	7.0	(5.0–12.8)	7.0	(4.0–12.0)	.40

AC = anticoagulation, IQR = interquartile range.
[a]The propensity scores included the following characteristics: age, sex, body mass index, active malignancy, chronic pulmonary disease, diabetes mellitus, hypertension, obstructive coronary artery disease, myocardial infarction, heart failure, nonischaemic cardiomyopathy, previous heart surgery, electronic heart device, cerebrovascular accident, peripheral artery disease, immunosuppressive medication, no ICU policy.

Tremblay *et al.* also used a propensity score-matched comparison and found no statistically significant difference in mortality, time to mechanical ventilation, or hospitalization when comparing patients with and without therapeutic oral anticoagulation prior to SARS-CoV-2 infection.[23] However, they included both ambulatory and hospitalized patients, and only adjusted for age, sex, race, Charlson comorbidity index and obesity in their propensity-score analysis while we illustrated that adjustment for more potential confounders is relevant. Moreover, they did not include thrombotic complications as an outcome parameter whereas our study showed a benefit on PE incidence, but not on other clinical endpoints.

This is also the first study to investigate the effects of therapeutic anticoagulation subgroups, ie vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs), in hospitalized COVID-19 patients. There are different hypotheses as to why VKA could have unfavourable effects, and DOACs, by contrast, could be of benefit in COVID-19. Dofferhof *et al.* detected reduced extrahepatic vitamin K status in patients with COVID-19 and showed that low vitamin K status was related to poor prognosis in these patients.[24] VKAs are evident causes of reduced vitamin K status, but the relationship between VKA *vs.* other therapeutic anticoagulation on the prognosis of COVID-19 patients has never been studied before.

Our study has several limitations that need to be addressed. Most importantly, its observational and retrospective nature limit causal inference, although the propensity score matching increases the credibility of our observations. Noteworthy, propensity score matching is often criticized because of its dependence on the included covariates. Confounders not included in the propensity score could lead to significant bias. However, in our study, the prior visualization of relevant covariates in the directed acyclic graph and the subsequent high and relevant number of included covariates in the propensity score matching, make this a valid approach. It is possible that a history of atrial fibrillation (AF) is a potential confounder since AF is the most important indication for prescribing therapeutic oral anticoagulation.

However, patients with AF are at higher risk for poor prognosis as they are older and more likely to have other cardiovascular risk factors.[25] In our study we have thoroughly corrected for these confounders and thus reduced the risk for residual confounding. Although our database represents 1 of the largest matched cohorts of anticoagulation users in the literature (Table 1), the relatively small sample size could potentially lead to a type II error. However, in our study, we found no suggestion of an effect on mortality with a risk ratio close to 1. Furthermore, the increased risk observed for PE is in line with previous studies. Nevertheless, our study population might have been too small to detect small differences in clinical outcomes between the exposure groups. Other limitations are that there was no routine screening for PE, which may have resulted in underdiagnosis of this outcome.

Strengths of our study include the rigorous statistical analysis with thorough adjustment for confounding to properly investigate the treatment effect of prior therapeutic anticoagulation on different clinically relevant outcomes in a large cohort of hospitalized COVID-19 patients. Furthermore, we are the first to investigate the effect of therapeutic anticoagulation subgroups, i.e. vitamin K antagonists and DOACs.

In summary, although prior therapeutic anticoagulation use is associated with reduced PE occurrence, it is not associated with better outcome parameters in hospitalized COVID-19 patients in terms of all-cause mortality, ICU admittance, need for mechanical ventilation and length of hospital stay. Secondary analyses between subgroups also showed no differences in clinical outcomes between VKA- and DOAC-treated patients.

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COMPETING INTERESTS

R. Janssen discloses application of a patent on vitamin K in COVID-19. R. Janssen and A.S.M. Dofferhoff have a scientific collaboration with Kappa Bioscience AS, a manufacturer of vitamin K2 (MK-7). All other authors declare no conflict of interest or competing interest.

CONTRIBUTORS

J.L. is the principal investigator. J.S., M.G., M.M., M.H., A.E., A.D., R.J., C.K. and J.L. designed the study. A.D., J.v.d.M., J.H., N.J, M.v.A., A.K., K.V., M.B. and R.J.H. were responsible for sample collection and laboratory processing. J.S., A.D., R.J., J.v.d.M., J.H., N.J., M.v.A., A.K., K.V., M.B., R.J.H. and J.L. were responsible for data collection and management. J.S., M.G., C.K. and J.L. performed the statistical analyses and drafted the manuscript. M.M., M.H., A.E., A.D., R.J., J.v.d.M., J.H., N.J., M.v.A., A.K., K.V., M.B. and R.J.H. critically revised the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL

The study was approved by the local ethics committee of the Radboud University Medical Centre (number 2020–6344) and carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees and informed consent.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

ORCID

Marleen M. H. J. van Gelder https://orcid.org/0000-0003-4853-4434

Angèle Kerckhoffs https://orcid.org/0000-0002-4309-230X

Jenneke Leentjens https://orcid.org/0000-0003-3356-3910

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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