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Letter to the Editors-in-Chief

Pre-admission anticoagulant therapy and mortality in hospitalized COVID-19 patients: A retrospective cohort study

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1. Introduction

The high risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively termed venous thromboembolism (VTE), in patients with Coronavirus disease 2019 (COVID-19) is now well-established [1]. Current guidelines recommend routine use of prophylactic-dose low-molecular-weight heparin in hospitalized COVID-19 to reduce the risk of macrovascular and microvascular complications [2]. However, it is unknown whether continuing pre-admission therapeutic anticoagulation for other indications than COVID-19 is associated with favorable outcomes by mitigating hypercoagulability. Therefore, we studied whether pre-admission use of Vitamin K Antagonists (VKA) or Direct Oral Anticoagulants (DOACs) was associated with a lower risk of death or ICU admission in hospitalized COVID-19 patients.

2. Methods

Data collected in the Dutch multicenter CovidPredict study were used [3]. Included patients were 18 years or older with confirmed COVID-19. Medical Ethical Committees of the participating centers waived the need for informed consent, but patients were provided the possibility to opt-out if they did not want to participate. Data on patient characteristics, medication, and outcomes were collected retrospectively from electronic health records. Patients using therapeutic anticoagulation usually continued this treatment during hospital stay in the same type and dose (unless admitted to the ICU), while all other patients received thromboprophylaxis with low-molecular-weight heparin in accordance with Dutch guidelines (standard-dose in hospital ward patients, double dose in ICU patients, and doubling of the dose if body weight $>$ 100 kg). Patient outcomes were collected roughly at 3 weeks, and at 6 weeks after hospital admission. The primary outcome in this analysis was all-cause mortality, defined as in-hospital mortality or discharge to a palliative care facility during a follow-up period of a maximum of 21 days after hospital admission. The secondary outcome was ICU admission.

Patients who used a VKA or DOAC prior to hospital admission were 1:1 matched to patients not using therapeutic anticoagulation using a propensity score nearest-neighbor matching approach. The propensity score was calculated using 16 potentially confounding variables. Data on indication for pre-admission therapeutic anticoagulation were not routinely collected. Patient characteristics were compared between the matched cohorts using standard descriptive statistics. A standardized mean difference below 0.1 was considered to indicate a well-balanced variable. Kaplan-Meier analysis was used to study the association between pre-admission therapeutic anticoagulation and 21-day all-cause mortality and ICU admission. Differences between the matched cohorts were assessed with the log-rank test. Cox proportional-hazard models were used to calculated hazard ratios with 95% confidence intervals (CI) with therapeutic anticoagulation as the only covariate. In addition, a sensitivity analysis was performed in patients $\leq$70 years only, since most of the patients in the latter group are usually admitted without any restrictions regarding transfer to ICU.

Next to this, a secondary analysis was performed in which the use of anticoagulant and/or antithrombotic therapy was analyzed. This analysis explored the use of either anticoagulation (VKA or DOAC) or antiplatelet therapy, due to the insinuation that antithrombotic therapy might also inhibit the microvascular thrombosis occurring in COVID-19 patients.

All analysis were performed in R, version 3.6.1 (www.R-project.org).

3. Results and discussion

A total of 3075 patients were included between 27 February 2020 and 1 January 2021. Sixty-nine patients (2.2%) were excluded because of missing data. Mean age of the remaining 3006 patients was 66 years (SD 15), 1177 (39%) were female, 882 (30%) had chronic cardiac disease, 830 (30%) were obese, 818 (28%) had diabetes mellitus, and 297 (10%) had asthma. Upon hospital admission, 1072 patients (36%) were using either anticoagulant or antiplatelet therapy, of whom 445 (15%) used therapeutic anticoagulation, 661 (22%) antiplatelet therapy, and 34 (1%) both therapeutic anticoagulation and antiplatelet therapy. Of the 445 patients using therapeutic anticoagulation, 228 (51%) were using DOAC, 188 (42%) VKA, and 29 (6%) another type of therapeutic anticoagulation (e.g. LMWH).

Patients were admitted to the hospital after a median of 7 days

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(interquartile range [IQR], 5–11) after symptom onset. The first in-hospital measured mean oxygen saturation was 93% (standard deviation (SD 6) and the mean respiration rate 24 breaths per minute (SD 7)). During the 21-day follow-up period, 488 (16.2%) patients were admitted to the ICU and 823 (27%) died.

Analysis of all patients in the cohort without matching showed that, patients using pre-admission therapeutic anticoagulation were older (mean age 76.2 vs 64.3 years; $P < 0.001$), more often male (67% vs 60%, $P = 0.009$), and more often had diabetes (37% vs 26%; $P < 0.001$) or chronic kidney disease (22% vs 9%; $P < 0.001$) than those not using therapeutic anticoagulation. After matching, a total of 380 patients using therapeutic anticoagulation were paired with 380 not using therapeutic anticoagulation at hospital admission. In total, 65 anticoagulant using patients could not be matched, of which 55 due to missing data, and 10 patients since no matched control patients could be found using the pre-defined conditions. The time between symptom onset and hospital admission (7.0 days vs 7.0 days; $P = 0.02$), oxygen saturation on admission (93% vs 93%; $P = 0.585$), and mean respiratory rate (23/min vs 23/min; $P = 0.822$) were similar between patients with pre-admission therapeutic anticoagulation and matched controls. After matching, standardized mean differences were <0.1 for all matching variables except center (see Table 1).

During a median follow-up of 21 days [IQR, 8–21] in the matched cohort, pre-admission use of therapeutic anticoagulation was neither associated with all-cause mortality (HR, 0.95; 95% CI, 0.75–1.20; Fig. 1) nor with ICU admission (HR, 0.75; 95%,CI 0.50–1.15). These results did not materially change in the secondary analysis of anticoagulant and/or antiplatelet therapy (HR for mortality, 1.07 [95%,CI 0.85–1.37] and HR for ICU admission, 0.96 [95%,CI 0.57–1.08]).

In the sensitivity analysis including only patients ≤70 years, 98 patients using anticoagulant therapy prior to admission could be matched to 98 patients not using anticoagulant therapy prior to admission. In this cohort, pre-admission use of therapeutic anticoagulation was also not associated with all-cause mortality (HR, 1.06; 95% CI, 0.56–2.00) or with ICU admission (HR, 0.96; 95% CI, 0.52–1.79).

In this multicenter retrospective cohort study of more than 3000 hospitalized patients with COVID-19, we did not find an association between pre-admission therapeutic anticoagulation and mortality or ICU admission. Results were similar both using a broader definition of antithrombotic therapy including antiplatelet agents and in an analysis restricted to patients ≤70 years, in which treatment restrictions are less often applied.

Our findings are in line with a previous retrospective cohort study by Tremblay and colleagues [4], in which no significant difference was found in survival or time to mechanical ventilation between patients using pre-admission anticoagulant therapy and those not using therapeutic anticoagulation. In contrast, Paranjpe and colleagues [5] showed that in-hospital use of treatment-dose anticoagulation was associated with lower mortality and longer time to mechanical ventilation. Besides these observational studies, recently a combined analysis of three international randomized controlled trials (ATTACC, ACTIV-4, and REMAP-CAP) showed that therapeutic-dose heparin was superior to standard of care with respect to organ-support free days in hospitalized ward patients, while there was no benefit in ICU patients [6]. Potential explanation for the different findings of the present study and this RCT include residual confounding (despite the propensity score matching approach) and selection bias. With respect to the latter, in CovidPredict only hospitalized patients were included. If the hypothesis holds that anticoagulation is associated with a favorable disease course in patients with COVID-19, those with therapeutic anticoagulation may have been admitted less frequently to the hospital, resulting in selection of patients with more severe COVID-19 trajectory while subsequent worse

Table 1
Patient characteristics overall and in matched groups with asterisk is also used in propensity score matched model.

Total population, n = 3,006	Anticoagulant use (n=445)	No anticoagulant use (n=2561)	p-value	SMD	Anticoagulant use (n=380)	No anticoagulant use (n=380)	p-value	SMD
Age*, years mean (SD)	76.2 (10.58)	64.3 (14.72)	<0.001	0.929	75.8 (10.83)	75.4 (10.74)	0.623	0.036
Time in pandemic* in days, median [IQR]	46.0 [37.0 - 67.3]	47.0 [38.0 - 74.0]	0.313	0.022	47.0 [37.0-68.0]	44.5 [37.0- 69.0]	0.581	0.019
Women*, n (%)	149 (34)	1028 (40)	0.009	0.138	128 (34)	139 (37)	0.447	0.061
Diabetes*, n (%)	161 (37)	657 (26)	<0.001	0.242	143 (38)	144 (38)	1.000	0.005
Asthma*, n (%)	33 (8)	264 (11)	0.075	0.102	31 (8)	32 (8)	1.000	0.010
Obesity*, n (%)	126 (30)	704 (30)	0.991	0.004	115 (30)	103 (27)	0.378	0.070
Hypertension*, n (%)	260 (59)	1100 (43)	<0.001	0.311	224 (59)	228 (60)	0.824	0.022
Chronic kidney disease*, n (%)	97 (22)	228 (9)	<0.001	0.367	86 (23)	74 (20)	0.328	0.078
Time to admission, days, median [IQR]	7.0 [3.0 - 10.0]	7.0 [5.0 - 11.0]	<0.001	0.197	7.0 [3.0- 10.0]	7.0 [4.0- 13.0]	0.002	0.241
Temperature at admission in °C, mean (SD)	37.7 (1.19)	37.8 (1.14)	0.086	0.087	37.7 (1.20)	37.8 (1.24)	0.439	0.056
Oxygen saturation in %, mean (SD)	93 (6.40)	93 (5.95)	0.996	<0.001	93 (6.45)	93 (5.89)	0.585	0.040
Respiratory rate, breaths-per-minute, mean (SD)	22.9 (7.02)	23.6 (7.27)	0.071	0.096	23.0 (7.16)	23.1 (6.85)	0.822	0.017
ICU admission, n (%)	44 (10)	444 (17)	<0.001	0.219	38 (10)	49 (13)	0.255	0.091
Mortality, n (%)	194 (4)	629 (25)	<0.001	0.410	141 (37)	140 (37)	1.000	0.005

Used abbreviations: SMD: Standardized Mean Difference, SD: Standard Deviation, IQR: Inter Quartile Ranges, ICU: Intensive Care Unit.
The other 8 possible confounding factors used in propensity score matched model: center, chronic cardiac disease, malignancy, liver disease, dementia, organ transplant, autoimmune disorder, and rheumatic disorder.

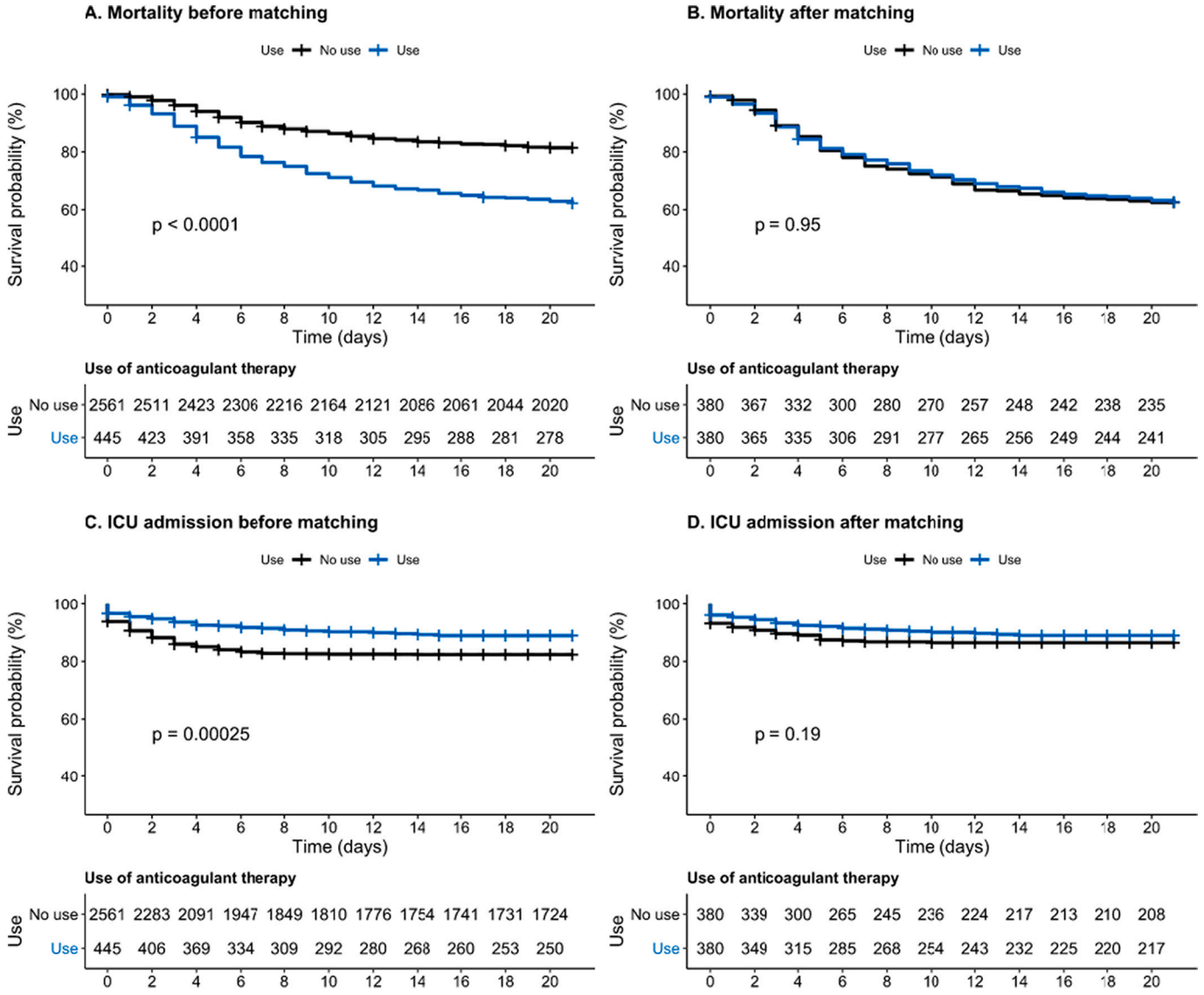

Fig. 1. All-cause mortality (A–B) and ICU admission (C–D) in patients with and without anticoagulant therapy. Time from hospital admission to death and ICU admission overall (A and C) and in the matched groups (B and D).

prognosis. Various studies have been initiated to evaluate the effect of initiation pre-hospital anticoagulation with direct oral anticoagulants on outcomes in COVID-19 patients to address this question [7–9].

There are several limitations of the present study that deserve notion and could explain the disparity with several trials [10,11]. Although we matched groups for time in the pandemic, we cannot exclude that concomitant COVID-19 treatment, which changed rapidly in the last year, influenced the risk estimates by effect modification. Similarly, thrombosis prophylaxis policies may have differed across centers in the beginning of the pandemic. However, results were comparable when restricting the analysis to patients admitted after the release of the Dutch national guidelines on thrombosis prophylaxis [12]. Unfortunately, information on bleeding events was not available, which would be needed to balance the risks and benefits of therapeutic anticoagulation. Information was also not available on restrictions for ICU admission in case of clinical deterioration. If patients with pre-admission therapeutic anticoagulation were less often transferred to the ICU than controls, we may have overestimated the effects on ICU admission and underestimated the effects on mortality. Information on changes in anticoagulant therapy or the dose of low-molecular-weight heparin prophylaxis in control patients during follow-up was not available.

In summary, the present study did not show an association between pre-admission therapeutic anticoagulation and favorable outcomes in hospitalized COVID-19 patients. Peer-reviewed results of large international studies are awaited to further address this question.

CRediT authorship contribution statement

Conceptualization: TFH, SM, MC, and NvE. Formal analysis: TFH, DC, NvE. Supervision: SM, MC and NvE. Investigation: TFH, DC, SM, MC, HtC, NvE. Writing original draft: TFH, DC, and NvE. Validation and visualization: TFH, DC, FHMvO, NvE. Writing, review & editing: TFH, DC, FHMvO, SM, MC, MDdK, EAV, RAD, HtC, NPJ, NG, APV, ACR, MAH, MO, HRB, JPWvdB, AM, MtW, SS, MB, NvE.

Declaration of competing interest

TFH, DC, FHMvO, SM, MDdK, EAV, RAD, NPJ, NG, APV, ACR, MAH, MO, HRB, AM, MtW, SS, and MB have nothing to report.

MC received research support and consultancy fees from Bayer and consultancy fees from Daiichi Sankyo, outside the submitted work. All fund were transferred to his institute.

HtC reports receiving advisory board honoraria from LEO Pharma, Portola/Alexion, Antheos and Pfizer; research support from Bayer and Pfizer; consultancy fees from Alveron; all reimbursements were transferred to CARIM.

JPWvdB received research support and advisory board honoraria from Amgen and UCB which were transferred to his institute.

NvE reports receiving advisory board honoraria from LEO Pharma, Daiichi-Sankyo, and Pfizer which were transferred to his institute.

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Other authors have nothing to report.

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