Risks associated with prior oral anticoagulation use in hospitalized COVID-19 patients – A retrospective cohort study on 5392 patients from a tertiary centre

Bistrović, Petra; Sabljic, Anica; Kovačević, Ivona; Čikara, Tomislav; Kereš, Tatjana; Lucijanić, Tomo; Mitrović, Joško; Delić-Brkljačić, Diana; Manola, Šime; Lucijanić, Marko

Source / Izvornik: **International Journal of Cardiology, 2023, 372, 144 - 149**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.1016/j.ijcard.2022.11.051

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:310444

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

International Journal of Cardiology 372 (2023) 144–149

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Risks associated with prior oral anticoagulation use in hospitalized COVID-19 patients – A retrospective cohort study on 5392 patients from a tertiary centre

Petra Bistrovic [a], Anica Sabljic [b], Ivona Kovacevic [c], Tomislav Cikara [a], Tatjana Keres [d], Tomo Lucijanic [e,f], Josko Mitrovic [g,h], Diana Delic-Brkljacic [g,i], Sime Manola [a,g], Marko Lucijanic [b,g,*]

[a] Cardiology department, Clinical Hospital Dubrava, Zagreb, Croatia
[b] Hematology Department, Clinical Hospital Dubrava, Zagreb, Croatia
[c] Pulmology Department, Clinical Hospital Dubrava, Zagreb, Croatia
[d] Intensive Care Department, Clinical Hospital Dubrava, Zagreb, Croatia
[e] Endocrinology, Diabetology and Metabolic Disease Department, Clinical Hospital Dubrava
[f] Primary respiratory and intensive care center, Clinical Hospital Dubrava, Zagreb, Croatia
[g] University of Zagreb, School of Medicine
[h] Rheumatology, Immunology and Allergology Department, Clinical Hospital Dubrava
[i] Cardiology department, Clinical Hospital Center Sisters of Mercy, Zagreb, Croatia

ARTICLE INFO

Keywords:
SARS-CoV-2
Anticoagulant therapy
Thrombosis
Bleeding
Survival

ABSTRACT

Introduction: There are conflicting data on prior oral-anticoagulant (OAC) use and outcomes of hospitalized COVID-19 patients. Due to uncertainties regarding associated risks with the prior OAC use, we have investigated this issue in a large cohort of hospitalized COVID-19 patients from our institution.

Methods: We have retrospectively evaluated a total of 5392 consecutive COVID-19 patients hospitalized in our tertiary center institution in period 3/2020 to 6/2021. Majority of patients received low-molecular-weight-heparin thromboprophylaxis and corticosteroids during hospitalization. Patients' characteristics and clinical outcomes were documented as a part of a hospital registry project and were evaluated according to the prior non-OAC, warfarin and direct oral anticoagulants (DOAC) use.

Results: Median age was 72 years, median Charlson comorbidity index (CCI) was 4 points. There were 56.2% male patients. Majority of patients had severe (70.5%) or critical (15.8%) COVID-19 on admission. A total of 84.8% patients did not receive prior OAC, 9% were previously anticoagulated with warfarin and 6.2% were previously anticoagulated with DOACs.

In the multivariate regression analyses, prior warfarin use was associated increased in-hospital mortality (OR 1.24, $P = 0.048$) independently of older age (OR 2.12, $P < 0.001$), male sex (OR 1.27, $P < 0.001$), higher CCI (OR 1.26, $P < 0.001$) and severe or critical COVID-19 on admission (OR 22.66, $P < 0.001$). Prior DOAC use was associated with higher occurrence of major bleeding (OR 1.72, $P = 0.045$) independently of higher CCI (OR 1.08, $P = 0.017$).

Conclusion: Prior OAC use could be associated with worse clinical outcomes during COVID-19 hospitalization. These phenomena might be OAC type specific and persist after multivariate adjustments.

1. Introduction

Since the beginning of the COVID-19 pandemic in December of 2019, thromboembolic incidents have taken place among the most frequent and severe complications of acute SARS-CoV-2 infection. Proposed mechanisms of coagulopathy in COVID-19 include endothelial

* Corresponding author at: Hematology Department, University Hospital Dubrava, University of Zagreb School of Medicine, Av. Gojka Suska 6, 10000 Zagreb, Croatia.
E-mail address: markolucijanic@yahoo.com (M. Lucijanic).

https://doi.org/10.1016/j.ijcard.2022.11.051
Received 16 November 2022; Accepted 24 November 2022
Available online 28 November 2022

disfunction due to hyperinflammatory state, as well as involvement of SARS-CoV-2 and associated inflammatory response in the coagulation cascade and mediators of thrombosis themselves [1–4]. To combat the procoagulant effects of COVID, low molecular weight heparin (LMWH) thromboprophylaxis has been accepted as the standard of care in those hospitalized due to COVID-19. However, research suggests a high incidence of thromboembolic incidents and subsequent unfavorable outcomes despite thromboprophylaxis [5–8]. So far, studies on the effect of therapeutic LMWH doses during hospitalization have not shown an effect on survival or prevention of critical disease [9–11]. In light of these reports, oral anticoagulation, particularly in those anticoagulated prior to hospitalization due to COVID-19, has received attention as a possible mean of preventing death, venous thromboembolisms (VTE) and critical COVID, as well as decreasing the need for intensive care and mechanical ventilation. Research published so far has produced conflicting results, mostly varying from prior oral anticoagulation (OAC) use being ineffective to potentially beneficial [12–17]. Our paper aims to investigate the potential risks associated with OAC use prior to hospitalization in a large real-life cohort of hospitalized COVID-19 patients from a tertiary center.

2. Methods

We retrospectively analyzed prior OAC use in consecutive hospitalized COVID-19 patients treated at our institution from 3/2020 to 6/2021. All patients were adults and Caucasian. Patients were diagnosed by either PCR or antigen test in the presence of compatible SARS-CoV-2 symptoms. Data on prior OAC use, clinical and laboratory parameters were recorded through the analysis of written and electronical medical records and are a part of the hospital registry project. Inclusion criteria were hospitalization due to COVID-19, age above 18 years and available data on prior OAC use. Flow-chart depicting the patient selection process is presented in Fig. 1. Indications for OAC treatment included atrial fibrillation with CHA2DS2VASc score over 2 and VTE (deep venous thrombosis and pulmonary embolism) prior to admission due to COVID, whereas other potential causes (such as mechanical valves, antiphospholipid syndrome, etc.) were labeled as “other”. COVID-19 severity on admission was defined according to the World Health Organization as mild, moderate, severe and critical [18]. Comorbidities were evaluated as particular entities and as a summarized measure of Charlson comorbidity index (CCI). Majority of patients received LMWH thromboprophylaxis and corticosteroids during hospitalization in dose intensity per assessment of treating physicians. Study was approved by the Institutional Review Board (nm. 2021/2503–04). Due to retrospective nature of the study, need for the informed consent was waived.

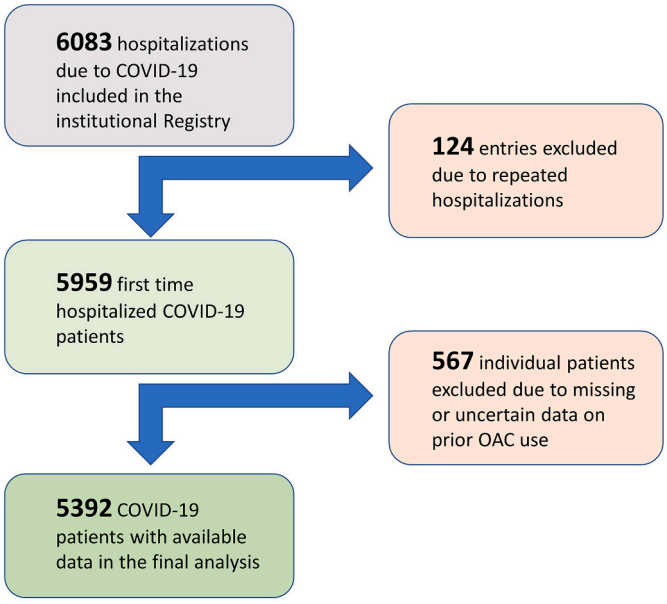

Fig. 1. Flow chart depicting the patient selection process.

Primary objective was to evaluate association of prior warfarin and direct oral anticoagulant (DOAC) use with clinical outcomes (length of hospitalization, death, need for high flow oxygen therapy (HFOT), need for mechanical ventilation (MV), need for intensive care unit (ICU), occurrence of arterial and venous thrombotic events, bacteremia and major bleeding) during hospitalization. Length of hospitalization was considered from the date of admission to the date of hospital discharge or death. Deaths were evaluated as deaths from any cause if occurring during hospitalization and no specific causes of death were analyzed. Venous and arterial thromboses proven by objective imaging and laboratory methods were considered. Due to analysis of Registry level data, venous thromboses mostly represent symptomatic events evaluated by the indication of treating physician. Presence of bacteremia was considered in the case of positive blood-cultures which were sampled based on clinical reasoning of treating physicians. Major bleeding was defined by the International Society on Thrombosis and Haemostasis criteria [19].

Statistical methods: normality of distribution of numerical variables was evaluated using the Kolmogorov-Smirnov test. Due to non-normal distribution, numerical variables were presented as medians and interquartile ranges (IQR) and were compared between subgroups using the Kruskal-Wallis ANOVA test with post-hoc test by Conover. Categorical variables were presented as frequencies and percentages and were compared between groups using the chi squared test. Clinical outcomes of interest were evaluated during hospitalization period. Independent contribution of prior OAC use with outcomes of interest were evaluated using the logistic regression. Multivariate models were adjusted for age, sex, CCI and COVID-19 severity. P values <0.05 were considered to be statistically significant. All analyses were performed using the MedCalc statistical program version 20.109 (MedCalc Software Ltd., Ostend, Belgium).

3. Results

We evaluated a total of 5392 patients hospitalized due to COVID-19. Median age was 72 years, IQR (62–81), median CCI was 4 points, IQR (2–6). There were 3029 (56.2%) male patients. Severe and critical COVID-19 symptoms were present in 3799 (70.5%) and 850 (15.8%) patients, respectively. During hospitalization a total of 1190 (22.1%) patients required high-flow oxygen therapy (HFOT) and 946 (17.5%) required mechanical ventilation (MV) support. A total of 1819 (33.7%) patients died. Among evaluated patients, a total of 4571 (84.8%) did not receive prior-to-COVID anticoagulant therapy, 484 (9%) were previously anticoagulated with warfarin and 337 (6.2%) were previously anticoagulated with DOACs.

Atrial fibrillation was the indication for OAC use in 62.6% of those receiving warfarin and 67.7% in patients on DOACs, VTE was the indication in 11% patients on warfarin and 11.6% patients on DOACs.

Patients’ characteristics at the time of hospital admission, stratified according to the prior anticoagulant therapy status, are shown in Table 1. Patients who were not anticoagulated were significantly younger, had lower CCI and better ECOG functional status on admission, longer duration of symptoms prior to admission, less arterial hypertension, diabetes mellitus, hyperlipoproteinemia, atrial fibrillation, prior venous thromboembolisms, chronic kidney disease and dementia in comparison to both warfarin and DOAC prior-anticoagulated patients ($P < 0.05$ for all analyses). Non anticoagulated patients also had significantly higher CRP in comparison to warfarin and lower IL-6 in comparison to DOAC prior-anticoagulated patients, as well as higher ferritin, higher D-dimers, higher absolute lymphocyte count, higher hemoglobin, higher platelets and lower procalcitonin in comparison to both warfarin and DOAC prior-anticoagulated patients ($P < 0.05$ for all

Table 1
Patients' characteristics between baseline characteristics.

	No anticoagulation (1)	Warfarin (2)	DOAC (3)	P value
Age (years), median and IQR	71 (60–81)	79 (72–85)	80 (72.75–54)	< 0.001* (1 vs 2. 1 vs 3)
Sex				0.439
Female	1987 (43.5%)	224 (46.3%)	152 (45.1%)	
Male	2584 (56.5%)	260 (53.7%)	185 (54.9%)	
CCI, median and IQR	4 (2–5)	5 (4–7)	6 (4–7)	< 0.001* (1 vs 2. 1 vs 3)
COVID-19 severity				0.410
Mild	415 (9.1%)	35 (7.2%)	24 (7.1%)	
Moderate	230 (5%)	23 (4.8%)	16 (4.7%)	
Severe	3224 (70.5%)	339 (70%)	236 (70%)	
Critical	702 (15.4%)	87 (18%)	61 (18.1%)	
ECOG status, median and IQR	2 (1–3)	3 (2–4)	3 (2–4)	< 0.001* (1 vs 2. 1 vs 3)
Duration of symptoms (days), median and IQR	6 (2−10)	4 (1–8)	5 (1–9)	< 0.001* (1 vs 2. 1 vs 3. 2 vs 3)
Arterial hypertension	2960 (64.8%)	402 (83.1%)	296 (87.8%)	< 0.001* (1 vs 2. 1 vs 3)*
Diabetes mellitus	1320 (28.9%)	165 (34.1%)	119 (35.3%)	= 0.004
Hyperlipoproteinemia	946 (20.7%)	155 (32%)	119 (35.3%)	< 0.001* (1 vs 2. 1 vs 3)*
Obesity	1346 (29.4%)	150 (31%)	98 (29.1%)	= 0.763
Atrial fibrillation	368 (8.1%)	303 (62.6%)	228 (67.7%)	< 0.001* (1 vs 2. 1 vs 3)*
Prior VTE	92 (2%)	83 (17.1%)	46 (13.6%)	< 0.001* (1 vs 2. 1 vs 3)*
Chronic kidney disease	438 (9.6%)	106 (21.9%)	65 (19.3%)	< 0.001* (1 vs 2. 1 vs 3)*
Active malignancy	400 (8.8%)	42 (8.7%)	32 (9.5%)	= 0.893
Dementia	754 (16.5%)	132 (27.3%)	74 (22%)	< 0.001* (1 vs 2. 1 vs 3)*
CRP (mg/L), median and IQR	91 (41.1–153)	77.75 (36.1–139.9)	82.6 (39.875–137.2)	= 0.026* (1 vs 2)*
Ferritin (μg/L), median and IQR	809 (432.5–1489.5)	643 (342.5–1215.5)	628.5 (344–1252)	<0.001* (1 vs 2. 1 vs 3)*
D-dimers (mg/L FEU), median and IQR	1.34 (0.71–3.3)	0.46 (0.93–2.17)	1.15 (0.62–2.55)	< 0.001* (1 vs 2. 1 vs 3. 2 vs 3)*
WBC ($x10^9$/L), median and IQR	7.9 (5.7–11.2)	5.5 (7.6–10.9)	5.7 (7.75–11.05)	0.318
Absolute neutrophils ($x10^9$/L), median and IQR	6.3 (4.3–9.36)	6.03 (3.99–9.2)	6.14 (4.195–9.165)	= 0.575
Absolute lymphocytes ($x10^9$/L), median and IQR	0.8 (0.57–1.2)	0.73 (0.5–1.1)	0.78 (0.5–1.09)	<0.001* (1 vs 2. 1 vs 3)*
Hemoglobin (g/L), median and IQR	130 (116–142)	124 (111–139.75)	127 (110–139)	< 0.001* (1 vs 2. 1 vs 3)*
Platelets ($x10^9$/L), median and IQR	223 (166–297)	199 (152–267)	156.5 (203–280.5)	<0.001* (1 vs 2. 1 vs 3)*
IL-6 (pg/mL), median and IQR	42.77 (15.35-96.58)	52.72 (20.145–108.75)	113.3 (23.7–230)	= 0.006* (1 vs 3)*
Procalcitonin (ng/mL), median and IQR	0.21 (0.089–0.702)	0.28 (0.11–1.01)	0.29 (0.12-1.1)	<0.001* (1 vs 2. 1 vs 3)*

Abbreviations: IQR – interquartile range; CCI – Charlson comorbidity index; ECOG – Eastern Cooperative Oncology Group; CRP – C reactive protein; WBC – white blood cells; IL – interleukin.

analyses). In the OAC subgroup, patients on warfarin experienced significantly shorter duration of symptoms prior to hospitalization and had lower D-dimer levels on admission compared to those on DOACs (P < 0.05 for all analyses). There were no statistically significant differences in sex and in COVID-19 severity on admission between non-anticoagulated patients and patients receiving different OACs ($P > 0.05$ for both analyses).

Associations of prior OAC use with clinical outcomes during hospitalization are presented in Table 2 and Fig. 2. Both patients who received prior warfarin or DOACs experienced significantly higher in-hospital mortality in comparison to non-prior-anticoagulated patients (47.1% vs 46% vs 31.4%, $P < 0.001$). Patients receiving prior DOACs experienced significantly higher major bleeding rates in comparison to non-anticoagulated patients whereas similar rates compared to warfarin anticoagulated patients (5% vs 2.8% vs 4.1%, $P = 0.022$). There were no significant associations with duration of hospital stay, HFOT and MV support, admission to ICU, bacteremia, arterial or venous thrombosis rates during hospitalization regarding prior anticoagulation status ($P > 0.05$).

We further performed a series of multivariate logistic regression models assessing the relationships of prior OAC use with clinical outcomes during hospitalization. Models were adjusted for clinically meaningful parameters (age, sex, CCI and COVID-19 severity on admission) and are presented in Table 3. Relationship of prior warfarin use with the increased mortality remained statistically significant (OR 1.24, $P = 0.048$) independently of older age (OR 2.12, $P < 0.001$), male sex (OR 1.27, P < 0.001), higher comorbidity burden (OR 1.26, P < 0.001) and severe or critical COVID-19 on admission (OR 22.66, P < 0.001). Similarly, relationship of prior DOAC use with occurrence of major bleeding (OR 1.72, $P = 0.045$) remained statistically significant independently of higher comorbidity burden (OR 1.08, $P = 0.017$).

Table 2
Associations of prior OAC use with clinical outcomes during hospitalization (hospitalization >10 days, in-hospital mortality, HFOT, MV, ICU stay, bacterial sepsis, arterial and venous thromboses, major bleeding).

Outcome	No anticoagulation (1)	Warfarin (2)	DOAC (3)	P value
Duration of hospitalization (days), median and IQR	10 (6–15)	10 (6–17)	10 (6–16)	= 0.559
Death during hospitalization	1436 (31.4%)	228 (47.1%)	155 (46%)	**< 0.001* (1 vs 2, 1 vs 3)***
HFOT	1116 (22.2%)	104 (21.5%)	70 (20.8)	= 0.782
MV	788 (17.2%)	96 (19.8%)	62 (18.4%)	= 0.330
ICU	1030 (22.5%)	119 (24.6%)	80 (23.7%)	= 0.540
Bacteriaemia	481 (10.5%)	47 (9.7%)	26 (7.7%)	= 0.098
Arterial thrombosis	232 (5.1%)	29 (6%)	19 (5.6%)	= 0.437
VTE	277 (6.1%)	27 (5.6%)	13 (3.9%)	=0.242
Major bleeding	127 (2.8%)	20 (4.1%)	17 (5%)	**= 0.022* (1 vs 3)***

* Statistically significant at level $P < 0.05$. Abbreviations: HFOT – high flow oxygen therapy; MV – mechanical ventilation; ICU – intensive care unit; VTE – venous thromboembolism.

4. Discussion

Results from our large real-life cohort of COVID-19 patients from an institutional registry demonstrate that prior OAC use could be associated

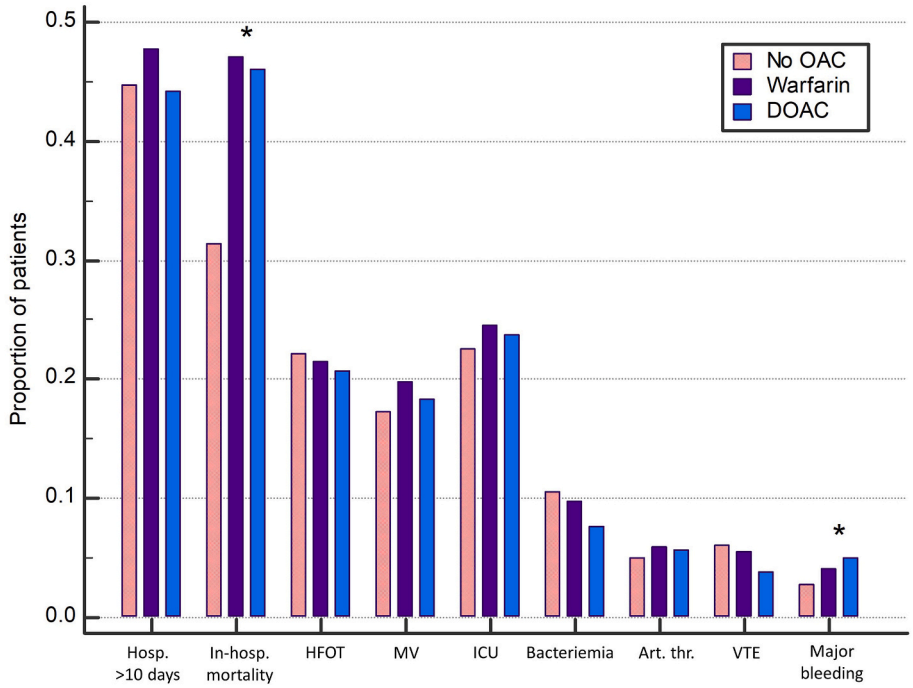

Fig. 2. Overview of clinical outcomes during hospitalization stratified according to prior oral anticoagulant therapy use. (* denotes statistically significant difference).

Table 3
Multivariate logistic regression models assessing independent contribution of prior OAC use, age, sex, comorbidity burden and COVID-19 severity on admission to the risk of developing investigated clinical outcomes (hospitalization >10 days, in-hospital mortality, HFOT, MV, ICU stay, bacterial sepsis, arterial and venous thromboses, major bleeding).

Outcome	Warf vs no prior OAC	DOAC vs no prior OAC	Age > 70 years	Male sex	CCI	Severe or critical COVID-19
Hospitalization > 10 days	*P* = 0.526 OR = 1.06 (0.88 to 1.29)	*P* = 0.483 OR = 0.92 (0.73 to 1.16)	*P* = 0.153 OR = 0.91 (0.80 to 1.04)	*P* = 0.244 OR = 1.07 (0.96 to 1.19)	**P < 0.001*** OR = 1.05 (1.02 to 1.07)	**P < 0.001*** OR = 1.50 (1.28 to 1.77)
In-hospital mortality	**P = 0.048*** OR = 1.24 (1.00 to 1.533)	*P* = 0.347 OR = 1.13 (0.88 to 1.44)	**P < 0.001*** OR = 2.12 (1.83 to 2.47)	**P < 0.001*** OR = 1.27 (1.12 to 1.45)	**P < 0.001*** OR = 1.26 (1.22 to 1.29)	***P* ≤0.001*** OR = 22.66 (14.50 to 35.42)
HFOT	*P* = 0.814 OR = 0.97 (0.76 to 1.23)	*P* = 0.587 OR = 0.93 (0.70 to 1.23)	*P* = 0.675 OR = 0.97 (0.82 to 1.14)	**P ≤0.001*** OR = 1.45 (1.26 to 1.66)	*P* = 0.177 OR = 0.98(0.95 to 1.01)	*P* = 0.997 OR -
MV	*P* = 0.189 OR = 1.18(0.92 to 1.51)	*P* = 0.674 OR = 1.07 (0.79 to 1.43)	*P* = 0.081 OR = 0.86 (0.72 to 1.02)	**P < 0.001*** OR = 1.68 (1.44 to 1.96)	*P* = 0.258 OR = 1.02 (0.99 to 1.05)	P = 0.997 OR -
ICU	*P* = 0.230 OR = 1.15(0.92 to 1.45)	*P* = 0.517 OR = 1.09 (0.83 to 1.43)	**P < 0.001*** OR = 0.76 (0.65 to 0.89)	**P < 0.001*** OR = 1.63(1.42 to 1.87)	*P* = 0.161 OR = 1.02 (0.99 to 1.05)	**P < 0.001*** OR = 7.89 (5.47 to 11.39)
Bacterial sepsis	*P* = 0.604 OR = 0.92 (0.66 to 1.27)	*P* = 0.109 OR = 0.71 (0.47 to 1.08)	***P* = 0.021*** OR = 0.78 (0.63 to 0.96)	**P < 0.001*** OR = 1.58 (1.31 to 1.91)	*P* = 0.128 OR = 1.03 (0.99 to 1.07)	**P < 0.001*** OR = 5.16 (3.20 to 8.31)
Arterial thrombosis	*P* = 0.795 OR = 0.95 (0.63 to 1.43)	*P* = 0.680 OR = 0.90 (0.55 to 1.47)	*P* = 0.430 OR = 0.89 (0.67 to 1.19)	*P* = 0.612 OR = 1.06 (0.83 to 1.37)	P < 0.001* OR = 1.16 (1.11 to 1.22)	*P* = 0.208 OR = 0.80 (0.57 to 1.13)
VTE	*P* = 0.847 OR = 1.04 (0.69 to 1.58)	*P* = 0.253 OR = 0.72 (0.40 to 1.27)	*P* = 0.377 OR = 0.88 (0.66 to 1.17)	***P* = 0.020*** OR = 0.76 (0.60 to 0.96)	***P* = 0.018*** OR = 0.93 (0.88 to 0.99)	**P < 0.001*** OR = 2.91 (1.79 to 4.72)
Major bleeding	*P* = 0.195 OR = 1.39 (0.85 to 2.27)	**P = 0.045*** OR = 1.72 (1.01 to 2.92)	*P* = 0.355 OR = 0.84 (0.58 to 1.22)	*P* = 0.742 OR = 1.06 (0.77 to 1.45)	**P = 0.017*** OR = 1.08 (1.01 to 1.15)	*P* = 0.198 OR = 1.412 (0.84 to 2.39)

* Statistically significant at level $P < 0.05$. Odds ratios with 95% confidence intervals are shown. Abbreviations: Warf – warfarin; OAC – oral anticoagulant therapy; DOAC = direct oral anticoagulants; CCI – Charlson comorbidity index; HFOT – high flow oxygen therapy; MV – mechanical ventilation; ICU – intensive care unit; VTE – venous thromboembolism; OR – odds ratio.

with worse clinical outcomes during COVID-19 hospitalization in comparison to no prior anticoagulation. These phenomena might be OAC type specific and persist after multivariate adjustments. There are several important points we would like to emphasize.

Previously published studies regarding prior OAC use have produced conflicting results. In the study by Chocron et al., patients admitted with prior OAC therapy were compared to those without. The composite primary outcome included time from diagnosis to death, ICU transfer

and ventilatory support (mechanical, ventilation, non-invasive mechanical ventilation (NIV) and high-flow oxygen therapy). Their results showed a significant difference in ICU admission and in-hospital mortality favoring those who were anticoagulated, which was attributed to a potentially preventative effect on coagulopathy caused by COVID. However, there is no data available on thromboembolic incidents during hospitalization [12]. A study by Frochlich et al. found that patients on both DOAC and warfarin had improved primary outcomes (death, NIV, ECMO and MV), while Hozayen et al. found that those on prior OAC treated as out-patient COVID-19 were less likely to be admitted to hospital [13,15]. Other authors have not found statistical differences between the groups when comparing all cause mortality, ICU admission, critical COVID and mechanical ventilation [14,16,17]. Tremblay et al. also compared thromboembolic incidents between those on prior OAC and no prior OAC and found no statistical difference, while Spiegelenberg et al. results show fewer pulmonary embolisms in those who were anticoagulated prior to admission [14,16].

Adverse events caused by prior OAC use have also been reported. A study by Menager et al. found increased seven-day in hospital mortality in geriatric patients on long term warfarin therapy, attributing this effect to the potential interaction of depleted vitamin K levels with cytokine regulation [20]. Nawaz et al. reported more venous thromboembolic incidents in a 90-day period from admission, more transfusions, as well as longer admissions as potential unfavorable outcomes of prior OAC therapy. Yet, the study does not differentiate between OAC types and was not adjusted for comorbidities [21]. Prior OAC use in comparison to no prior anticoagulation might be a marker of frailty predisposing these patients to worse outcomes [22].

Studies investigating anticoagulation during hospitalization for COVID-19 imply clinical benefit [23], especially among patients admitted due to respiratory failure [24].

Our study showed a higher mortality rate during hospitalization in patients with prior OAC, however after adjustments for potential confounders, a statistically significant difference regarding in-hospital mortality persisted for warfarin vs prior non-anticoagulated patients only. Patients who were non-anticoagulated prior to COVID-19 indeed demonstrated features of more pronounced inflammation and activation of coagulation in comparison to anticoagulated patients at the time of hospital admission. However, severity of COVID-19 symptoms at the time of hospital admission did not significantly differ between patient subgroups. It should be noted that determinants of worse prognosis like older age, higher comorbidity burden and worse functional status were overrepresented among anticoagulated patients which significantly reflects on mortality. In addition, difficulties exist in conversion of even optimally anticoagulated warfarin patients to LMWH, which is the standard of anticoagulant care for hospitalized COVID-19 patients. INR values in therapeutic, and often below therapeutic range, associated with warfarin use introduce uncertainties regarding optimal timing of start of LMWH therapy. This might result in pro-coagulant interventions aimed at normalization of prothrombin time and unknown periods without protective anticoagulation, which may also add to increased mortality. Our study is the first to report of a significant risk of major bleeding in patients on prior non-vitamin K oral anticoagulants in comparison to non-prior anticoagulated patients, that persisted independently of comorbidities after adjustments for other clinically relevant parameters. These phenomena could be a consequence of difficulties with timely conversion to prophylactic/therapeutic doses of LMWH and periods of overlap of DOAC and LMWH therapies, especially considering there are no readily available tests for anticoagulant activity for DOACs.

Main limitations of our work are single-centre experience, retrospective study design and inability to discriminate between different DOAC subtypes. We could not accurately evaluate post-admission anticoagulation strategies due to reason that large majority of patients received LMWH either in prophylactic or full therapeutic doses, and due to overlap in anticoagulation strategies in same patients depending on COVID-19 clinical course and physicians' reasoning. Our results are representative for treatment of severe or critical COVID-19 patients at a high-volume tertiary level institution and might not be generalized to other clinical contexts. Due to complexity of propensity score matching for evaluation of three subgroups of patients, presentation of univariate and subsequently adjusted associations of OAK subtype with outcomes of interest was used as preferred and more comprehensible approach. Variables for multivariate adjustment were chosen due to their recognized negative prognostic significance. CCI was utilized as a summary measure providing cumulative comorbidity burden instead of particular comorbidities to maintain statistical power and reduce overfitting. Main strengths of our work are data based on a uniformly treated cohort of real-life patients and large sample size, as well as a detailed overview of patients' characteristics and a number of clinical outcomes recorded as a part of a hospital registry project. Due to limitations of the study design and differences in clinical profile of patients exposed to different OAC types prior to hospitalization it is difficult to be certain whether differences in prognosis differ due to the patient or anticoagulant itself. Our results complement the understanding of this important clinical topic but should be only considered hypothesis generating.

In conclusion, prior warfarin use is associated with increased mortality, whereas DOAC use increases the chances of major bleeding incidents in comparison to no prior anticoagulation among hospitalized COVID-19 patients. Additional research is needed in order to further define potential risks of prior OAC therapy.

Funding

None.

Ethical approval

The study was approved by the University Hospital Dubrava Review Board (nm. 2021/2503–04).

Declaration of Competing Interest

None.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Petra Bistrovic, Anica Sabljic, Ivona Kovacevic, Tomislav Cikara, Tatjana Keres, Tomo Lucijanic, Josko Mitrovic, Diana Delic-Brkljacic, Sime Manola and Marko Lucijanic. The first draft of the manuscript was written by Petra Bistrovic and Marko Lucijanic and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

This paper is a part of the project "Registar hospitalno liječenih bolesnika u Respiracijskom centru KB Dubrava"/"Registry of hospitalized patients in Clinical Hospital Dubrava Respiratory center".

References

[1] Z. Wu, J.M. McGoogan, Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China, JAMA 323 (2020) 1239.
[2] H. Mei, L. Luo, Y. Hu, Thrombocytopenia and thrombosis in hospitalized patients with COVID-19, J. Hematol. Oncol. (2020) 13.
[3] C. Agbuduwe, S. Basu, Haematological manifestations of COVID-19: from cytopenia to coagulopathy, Eur. J. Haematol. 105 (2020) 540–546.

[4] M. Lucijanic, I. Krecak, E. Soric, M. Sedinic, A. Sabljic, L. Derek, et al., Thrombocytosis in COVID-19 patients without myeloproliferative neoplasms is associated with better prognosis but higher rate of venous thromboembolism. Blood, Cancer J. (2021) 11.
[5] L. Wang, L. Zhao, F. Li, J. Liu, L. Zhang, Q. Li, et al., Risk assessment of venous thromboembolism and bleeding in COVID-19 patients, Clin. Respir. J. 16 (2022) 182–189.
[6] F.A. Klok, M.J.H.A. Kruip, N.J.M. Van Der Meer, M.S. Arbous, D.A.M.P. J. Gommers, K.M. Kant, et al., Incidence of thrombotic complications in critically ill ICU patients with COVID-19, Thromb. Res. 191 (2020) 145–147.
[7] J. Thachil, N. Tang, S. Gando, A. Falanga, M. Cattaneo, M. Levi, et al., ISTH interim guidance on recognition and management of coagulopathy in COVID-19, J. Thromb. Haemost. 18 (2020) 1023–1026.
[8] M. Lucijanic, N. Piskac Zivkovic, M. Ivic, M. Sedinic, B. Brkljacic, A. Mutvar, et al., Asymptomatic deep vein thromboses in prolonged hospitalized COVID-19 patients, Wien. Klin. Wochenschr. 133 (2021) 1281–1288.
[9] D.M. Smadja, G. Bonnet, N. Gendron, O. Weizman, L. Khider, A. Trimaille, et al., Intermediate- vs. standard-dose prophylactic anticoagulation in patients with COVID-19 admitted in medical Ward: a propensity score-matched cohort study, Front. Med. (Lausanne) 8 (2021), 747527.
[10] M. Sholzberg, G.H. Tang, H. Rahhal, M. Alhamzah, L.B. Kreuziger, F.N. Áinle, et al., Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial, BMJ. n2400 (2021).
[11] R.F. Comes, Rodríguez BAE, C.F. Ortolá, M.L. Hernández-Sanz, J.T. Herrera, F. H. Martínez, et al., Effectiveness of thromboprophylaxis with low molecular weight heparin in critically ill patients with COVID-19. An observational, prospective, multicenter study, Rev. Esp. Anestesiol. Reanim. (2022).
[12] R. Chocron, V. Galand, J. Cellier, N. Gendron, T. Pommier, O. Bory, et al., Anticoagulation before hospitalization is a potential protective factor for COVID-19: insight from a French multicenter cohort study, J. Am. Heart Assoc. 10 (8) (2021) e018624, https://doi.org/10.1161/JAHA.120.018624. PMID: 33550816; PMCID: PMC8174166.
[13] S.M. Hozayen, D. Zychowski, S. Benson, P.L. Lutsey, J. Haslbauer, A. Tzankov, et al., Outpatient and inpatient anticoagulation therapy and the risk for hospital admission and death among COVID-19 patients, EClinicalMedicine. 41 (2021), 101139.
[14] J.P. Spiegelenberg, M.M.H.J. van Gelder, M.L. Maas, M.M.C. Hovens, A. Esselink, A.S.M. Dofferhoff, et al., Prior use of therapeutic anticoagulation does not protect against COVID-19 related clinical outcomes in hospitalized patients: a propensity score-matched cohort study, Br. J. Clin. Pharmacol. 87 (2021) 4839–4847.
[15] G.M. Fröhlich, E. Jeschke, U. Eichler, H. Thiele, L. Alhariri, M. Reinthaler, et al., Impact of oral anticoagulation on clinical outcomes of COVID-19: a nationwide cohort study of hospitalized patients in Germany, Clin. Res. Cardiol. 110 (2021) 1041–1050.
[16] D. Tremblay, M. van Gerwen, M. Alsen, S. Thibaud, A. Kessler, S. Venugopal, et al., Impact of anticoagulation prior to COVID-19 infection: a propensity score–matched cohort study, Blood. 136 (2020) 144–147.
[17] M. Protasiewicz, K. Reszka, W. Kosowski, B. Adamik, W. Bombala, A. Doroszko, et al., Anticoagulation prior to COVID-19 infection has no impact on 6 months mortality: a propensity score-matched cohort study, J. Clin. Med. (2022) 11.
[18] World Health Organization, Clinical Management of COVID-19: Interim Guidance, 27 May 2020, World Health Organization, Geneva, 2020.
[19] S. Kaatz, D. Ahmad, A.C. Spyropoulos, S. Schulman, Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH, J. Thromb. Haemost. 13 (2015) 2119–2126.
[20] P. Ménager, O. Brière, J. Gautier, J. Riou, G. Sacco, A. Brangier, et al., Regular use of VKA prior to COVID-19 associated with lower 7-day survival in hospitalized frail elderly COVID-19 patients: the GERIA-COVID cohort study, Nutrients. 13 (2020).
[21] H. Nawaz, A. Choudhry, W.J. Morse, O. Zarnowski, H. Patel, H. Amin, Do admitted COVID-19-positive patients on anticoagulation therapy have a reduced hospital stay and disease severity? Cureus. 14 (2022), e23382.
[22] J.M. Rivera-Caravaca, I.J. Núñez-Gil, D. Vivas, M.C. Viana-Llamas, A. Uribarri, V. M. Becerra-Muñoz, et al., Clinical profile and prognosis in patients on oral anticoagulation before admission for COVID-19, Eur. J. Clin. Investig. 51 (2021), e13436.
[23] G.N. Nadkarni, A. Lala, E. Bagiella, H.L. Chang, P.R. Moreno, E. Pujadas, et al., Anticoagulation, bleeding, mortality, and pathology in hospitalized patients with COVID-19, J. Am. Coll. Cardiol. 76 (2020) 1815–1826.
[24] F. Santoro, I.J. Núñez-Gil, M.C. Viana-Llamas, C. Maroun Eid, R. Romero, I. Fernández Rozas, et al., Anticoagulation therapy in patients with coronavirus disease 2019: results from a multicenter international prospective registry (health outcome predictive evaluation for Corona virus disease 2019 [HOPE-COVID19]), Crit. Care Med. 49 (2021) e624–e633.