Full Length Article

Direct-acting oral anticoagulants use prior to COVID-19 diagnosis and associations with 30-day clinical outcomes

José Miguel Rivera-Caravaca [a,b], Benjamin J.R. Buckley [a,c], Stephanie L. Harrison [a,c], Elnara Fazio-Eynullayeva [d], Paula Underhill [e], Francisco Marín [b], Gregory Y.H. Lip [a,c,f,*]

[a] Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom
[b] Department of Cardiology, Hospital Clínico Universitario Virgen de la Arrixaca, University of Murcia, Instituto Murciano de Investigación Biosanitaria (IMIB-Arrixaca), CIBERCV, Murcia, Spain
[c] Cardiovascular and Metabolic Medicine, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, United Kingdom
[d] TriNetX LLC., Cambridge, MA, United States
[e] TriNetX LLC., London, United Kingdom
[f] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

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ABSTRACT

Background: It is unclear if direct-acting oral anticoagulants (DOACs) use before hospitalization due to COVID-19 diagnosis would potentially impact the severity and clinical outcomes thereafter. We compared 30-day hospitalization/re-hospitalization and clinical outcomes between patients on chronic DOAC therapy and patients not on oral anticoagulation (OAC) therapy at time of COVID-19 diagnosis.
Methods: We used data from TriNetX, a global federated health research network. Patients aged ≥18 years who were treated with DOACs at time of COVID-19 diagnosis between 20 January 2020 and 28 February 2021 were included, and matched with patients not on OAC therapy from the same period. All patients were followed-up at 30-days after COVID-19 diagnosis. The primary outcomes were all-cause mortality, hospitalization/re-hospitalization, venous thromboembolism (VTE) and intracranial hemorrhage (ICH).
Results: 738,423 patients were included. After propensity score matching (PSM), 26,006 patients remained in the study (13,003 on DOACs; 13,003 not on OAC). DOAC-treated patients (mean age 67.1 ± 15.4 years, 52.2% male) had higher relative risks (RRs) and lower 30-days event-free survival as compared to patients not on OAC for all-cause mortality (RR 1.27, 95% CI 1.12–1.44; Log-Rank test $p = 0.010$), hospitalization/re-hospitalization (RR 1.72, 95% CI 1.64–1.82; Log-Rank test $p < 0.001$) and VTE (RR 4.51, 95% CI 3.91–5.82; Log-Rank test $p < 0.001$), but not for ICH (RR 0.90, 95% CI 0.54–1.51; Log-Rank test $p = 0.513$).
Conclusion: In COVID-19 patients, previous DOAC therapy at time of diagnosis was not associated with improved clinical outcomes or lower hospitalization/re-hospitalization rate compared to patients not taking OAC therapy.

1. Introduction

The novel Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), is a respiratory infection which may present with a broad picture of symptoms ranging from mild upper respiratory symptoms to acute respiratory distress syndrome and severe pneumonia [1].

From the early stage of the pandemic, some patients with COVID-19 present with multi-organ involvement, including a higher risk of thrombosis [2]. Indeed, COVID-19 can induce changes in the clotting system, platelet activation and artery dysfunction, that ultimately lead to vascular inflammation, a hypercoagulable state and endothelial dysfunction [3,4]. As a result, thromboembolic complications are not rare in these patients, with an estimated VTE incidence of 25% [2,5–7]. Thus, anticoagulation is now established as one of the main therapies for the management of COVID-19 patients [8–10].

Direct-acting oral anticoagulants (DOACs) have demonstrated appropriate efficacy/safety profile in different settings; however, previous studies have reported drug-drug interactions of DOACs with some antiviral treatments used in COVID-19 patients, which may even increase plasma levels of DOACs [11–13]. However, it is unclear if chronic DOAC therapy before the diagnosis of COVID-19 would potentially

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impact the severity and clinical outcomes after COVID-19 diagnosis, since most of the evidence in relation to anticoagulation and COVID-19 refers to the in-hospital setting.

In the present study, we aimed to compare hospitalization and clinical outcomes 30-days after COVID-19 diagnosis between patients on chronic DOAC therapy at time of COVID-19 diagnosis and patients not on OAC therapy in this time frame, using a propensity score matching (PSM) approach.

2. Methods

We used data from TriNetX, a global federated health research network with real-time updates of anonymised electronic medical records (EMRs), predominately in the United States (US). The network is comprised of healthcare organisations (HCOs), including academic medical centres, specialty physician practices and community hospitals. Approximately, 18 million adult patients had a visit in a TriNetX HCO during 2020.

For this study, patients within the TriNetX research network with COVID-19 between 20 January 2020 and 28 February 2021, were included. The patients were stratified by whether they had (or not) a recording of receiving DOACs in the one-year period prior to COVID-19 recorded in their EMRs. The DOAC group was composed by patients with COVID-19 aged ≥18 years who received either dabigatran, apix-aban, rivaroxaban or edoxaban between the above period, and should be on DOAC therapy for at least one year before COVID-19 diagnosis and remained on this therapy at COVID-19 diagnosis. Patients cannot have concomitant anticoagulant therapy (oral or parenteral, i.e. warfarin, acenocoumarol, phenprocoumon, desirudin, defibrotide, argatroban, betrixaban, lepirudin, fondaparinux, heparin, bivalirudin, enoxaparin, dalteparin, tirofiban, and eptifibatide). The non-OAC group included patients with COVID-19 aged ≥18 years between the same period who were not on any anticoagulant therapy (either oral or parenteral).

The start date was chosen as 20 January 2020 because COVID-19 was first confirmed in the US on this date, and the TriNetX network is pre-dominately US-based [14]. COVID-19 was identified using criteria provided by TriNetX based on Centres for Disease Control and Prevention (CDC) coding guidelines [15]. COVID-19 status was determined using codes in EMRs or a positive test result identified with COVID-19-specific laboratory codes. Specifically, COVID-19 was identified by one or more of the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes or a positive laboratory test result (using LOINCs) in the EMRs of the patients (Supplementary Table 1) (the date of the first recorded value, either an ICD-10-CM code or confirmed COVID-19 by a laboratory test result, was used as the index date). A recent study has showed that hospitals appear to provide reasonably accurate COVID-19 diagnosis codes in administrative data [16]. The searches were run in TriNetX on 6 of May 2021, which allowed for at least 30-days of follow-up for all participants from the time all conditions (COVID-19 and DOAC or COVID-19 and no OAC) were ful-filled. When the searchers were run, there were 60 participating HCOs within the TriNetX research network.

The following data were also available from the patient EMRs: baseline demographics, comorbidities (e.g. hypertension, coronary artery disease, diabetes mellitus, heart failure, previous stroke, peripheral vascular disease, prior gastrointestinal hemorrhage and prior intracerebral hemorrhage, using ICD-10 codes) and medication use (e.g. anti-platelets, beta-blockers, calcium channel blockers, anti-arrhythmics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and diuretics).

2.1. Follow-up and clinical outcomes

All patients were followed-up at 30-days after COVID-19 diagnosis. Clinical outcomes recorded as primary included all-cause mortality, hospitalization/re-hospitalization (if the patient was already

hospitalized at time of COVID-19 diagnosis), venous thromboembolism (VTE) and intracranial hemorrhage (ICH). The secondary outcomes were the composite of ischemic stroke/transient ischemic attack (TIA)/ systemic embolism (SE); the composite of ICH/gastrointestinal bleeding; myocardial infarction; and the composite of any thrombotic or throm-boembolic event. Further details about the ICD-10-CM codes used for the identification of every outcome are included in Supplementary Table 2.

2.2. Ethical issues

As a federated network, research studies using TriNetX do not require ethical approval. To comply with legal frameworks and ethical guidelines guarding against data re-identification, the identity of participating HCOs and their individual contribution to each dataset are not disclosed. The TriNetX platform only uses aggregated counts and statistical summaries of de-identified information. No Protected Health Information or Personal Data is made available to the users of the platform.

2.3. Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD), and tested for differences with independent-sample *t*-tests. Categorical variables were expressed as absolute frequencies and percentages, and tested for differences with chi-squared test.

The TriNetX platform was used to run 1:1 PSM using logistic regression. The platform uses 'greedy nearest-neighbour matching' with a caliper of 0.1 pooled standard deviations and difference between propensity scores ≤0.1. We assessed covariate balance between groups using standardised mean differences (SMDs). Any baseline characteristic with a SMD between cohorts lower than 0.1 is considered well matched [17].

Risk Ratios (RR) with 95% confidence intervals (CI) for 30-days outcomes were calculated following PSM. Kaplan-Meier survival curves were also produced with Log-Rank tests after PSM. No imputations were made for missing data. Two-sided *p*-values <0.05 were accepted as statistically significant. Statistical analysis was performed using the TriNetX Analytics function in the online research platform.

3. Results

An overall cohort of 738,423 patients with COVID-19 was included. Of these, 13,229 (6899 [52.15%] males, mean age 67.30 ± 15.43 years) were on DOAC therapy at the time of COVID-19 diagnosis, and 725,194 (315,061 [43.45%] males, mean age 45.50 ± 18.10 years) were not on OAC therapy at this time period.

Patients from the cohort with previous DOAC therapy were older and had a significantly higher proportion of males, non-Hispanic/Latino patients and comorbidity (Table 1). After PSM, there were 26,006 patients who remained in the study, 13,003 individuals included in each cohort (1:1), and both were well-balanced on age, gender and ethnicity, apart from all the included comorbidities (Table 1).

3.1. Comparisons of clinical outcomes in propensity score matched populations

After PSM, the risks for all outcomes except ICH were significantly higher in the DOAC cohort, as summarized in the Fig. 1. Regarding the primary outcomes, the RR for all-cause mortality was 1.27 (95% CI 1.12–1.44) in the DOAC population, with decreased survival probability (Log-Rank test *p* = 0.010) (Fig. 2). There was also a higher risk of hospitalization/re-hospitalization (RR 1.72, 95% CI 1.64–1.82) and a higher risk of VTE (RR 4.51, 95% CI 3.91–5.82) in previous DOAC users, with Kaplan-Meier analysis showing that 30-day survival probability was lower in these patients (Log-Rank tests *p* < 0.001) (Fig. 2). The risk of ICH was not significantly different between both cohorts (RR 0.90,

Table 1

Comparison of clinical characteristics of the study cohort before and after propensity score matching.

	Initial populations				Propensity score matched populations			
	COVID-19 patients on prior DOAC	COVID-19 patients non on prior OAC	*p*-Value	SMD	COVID-19 patients on prior DOAC	COVID-19 patients non on prior OAC	*p*-Value	SMD
	N = 13,229	*N* = 725,194			N = 13,003	N = 13,003		
Age (years), mean (SD)	67.30 15.43	45.50 18.10	<0.001	1.297	67.10 15.43	68.20 15.20	<0.001	0.071
Male sex	6899 52.15%	315,061 43.45%	<0.001	0.175	6783 52.17%	6633 51.01%	0.063	0.023
Ethnicity								
Not Hispanic or Latino	9587 72.47%	409,278 56.43%	<0.001	0.340	9418 72.43%	9264 71.25%	0.034	0.026
Hispanic or Latino	1107 8.37%	99,631 13.74%	<0.001	0.172	1103 8.48%	1028 7.91%	0.090	0.021
Unknown Ethnicity	2535 19.16%	216,285 29.82%	<0.001	0.250	2482 19.09%	2711 20.85%	<0.001	0.044
Comorbidities								
Hypertension	9265 70.04%	165,148 22.77	<0.001	1.076	9083 69.85%	9624 74.01%	<0.001	0.093
Heart failure	3975 30.05%	18,109 2.50%	<0.001	0.805	3836 29.50%	3728 28.67%	0.140	0.018
Ischemic heart disease	4806 36.33%	39,699 5.29%	<0.001	0.820	4688 36.05%	4810 36.99%	0.116	0.020
Atrial fibrillation	6653 50.29%	16,592 2.29%	<0.001	1.300	6435 49.49%	6063 46.63%	<0.001	0.057
Peripheral vascular disease	1297 9.80%	9080 1.25%	<0.001	0.381	1259 9.68%	1400 10.78%	0.004	0.036
Cerebrovascular disease	2706 20.46%	23,322 3.22%	<0.001	0.554	2646 20.35%	2640 20.30%	0.926	0.001
Cerebral infarction	1371 10.36%	8940 1.23%	<0.001	0.398	1331 10.24%	1251 9.62%	0.097	0.021
Transient cerebral ischemic attack and related syndromes	754 5.70%	6202 0.86%	<0.001	0.275	729 5.61%	751 5.78%	0.556	0.007
Arterial embolism and thrombosis	246 1.86%	1185 0.16%	<0.001	0.170	242 1.86%	223 1.72%	0.374	0.011
Venous thromboembolism	2663 20.13%	7851 1.08%	<0.001	0.651	2567 19.74%	2632 20.24%	0.314	0.013
Hyperlipidemia	6649 50.29%	105,577 14.56%	<0.001	0.825	6509 50.06%	6870 52.83%	<0.001	0.056
Overweight/obesity	4884 36.92%	111,303 15.35%	<0.001	0.507	4791 36.85%	4592 35.32%	0.010	0.032
Diabetes mellitus	4841 36.92%	78,775 10.86%	<0.001	0.635	4734 36.41%	5112 39.31%	<0.001	0.060
Cardiac and vascular implants and grafts	2553 19.30%	15,110 2.08%	<0.001	0.580	2475 19.03%	2572 19.78%	0.128	0.019
Disorders of thyroid gland	3230 24.42%	67,422 9.30%	<0.001	0.412	3157 24.28%	3532 27.16%	<0.001	0.066
Diseases of the respiratory system	10,406 78.66%	336,788 46.44%	<0.001	0.706	10,196 78.41%	10,489 80.67%	<0.001	0.056
Chronic obstructive pulmonary disease	2403 18.17%	20,440 2.82%	<0.001	0.517	2334 17.95%	2429 18.68%	0.128	0.019
Asthma	2027 15.32%	65,932 9.10%	<0.001	0.191	1982 15.24%	2229 17.14%	<0.001	0.052
Sleep apnea	3232 24.43%	47,271 6.52%	<0.001	0.511	3166 24.35%	3027 23.28%	0.043	0.025
Diseases of liver	1683 12.72%	34,550 4.76%	<0.001	0.285	1656 12.74%	1949 14.99%	<0.001	0.065
Acute kidney failure and chronic kidney disease	4495 33.98%	38,380 5.29%	<0.001	0.774	4375 33.65%	4467 34.35%	0.229	0.015
Neoplasms	4878 36.87%	120,821 16.66%	<0.001	0.469	4791 36.85%	5115 39.34%	<0.001	0.051
History of gastrointestinal hemorrhage	764 5.78%	6754 0.93%	<0.001	0.272	741 5.70%	730 5.61%	0.768	0.004
History of intracranial hemorrhage	128 0.97%	1472 0.20%	<0.001	0.100	124 0.95%	192 1.48%	0.001	0.048
Pharmacological therapy								
Beta blockers	8802 66.54%	92,780 12.79%	<0.001	1.315	8586 66.03%	8895 68.41%	<0.001	0.051
ACE inhibitors	4764 36.01%	66,931 9.23%	<0.001	0.676	4648 35.75%	4784 36.79%	0.079	0.022
Angiotensin II inhibitors	3696 27.94%	40,958 5.65%	<0.001	0.625	3589 27.60%	3648 28.06%	0.414	0.010
Alpha blockers	2548 19.26%	28,408 3.92	<0.001	0.494	2480 19.07%	2359 18.14%	0.054	0.024
Antilipemic agents	7868 59.48%	98,185 13.54%	<0.001	1.086	7680 59.06%	7903 60.78%	0.005	0.035
Calcium channel blockers	6051 45.74%	61,071 8.42%	<0.001	0.925	5902 45.39%	5621 43.23%	<0.001	0.044
Diuretics	7893 59.66%	86,494 11.93%	<0.001	1.148	7680 59.06%	7888 60.66%	0.009	0.033
Antiplatelets	7135 53.94%	88,003 12.14%	<0.001	0.992	6969 53.60%	7407 56.96%	<0.001	0.068

95% CI 0.54–1.51; Log-Rank test *p* = 0.513).

In terms of secondary outcomes, the RR of the composite ischemic stroke/TIA/SE was 1.59 (95% CI 1.31–1.92; Log-Rank test *p* < 0.001). Similarly, there were significantly higher risks of ICH/gastrointestinal bleeding (RR 1.27, 95% CI 1.02–1.59), myocardial infarction (RR 1.49, 95% CI 1.19–1.86), and the composite of thrombotic and thromboembolic events (RR 2.81, 95% CI 2.55–3.11). Kaplan-Meier analysis also demonstrated that patients from the DOAC cohort had poorer survival probabilities for myocardial infarction and the composite outcome (Log-Rank tests *p* = 0.004 and *p* < 0.001; respectively), but not for ICH/gastrointestinal bleeding (Log-Rank test *p* = 0.120) (Supplementary Fig. 1).

3.2. Sensitivity analyses

In order to investigate further the clinical outcomes, we performed two sensitivity analyses.

In the first one, previous atrial fibrillation (AF) or VTE were not used for adjusting the PSM. Thus, 26,466 patients remained in the study after PSM; 13,233 patients in the previous DOAC cohort and 13,233 patients in the cohort without previous OAC. The matched cohorts were balanced for all other variables shown in the main analysis, but not in terms of AF (50.22% vs. 18.02%; *p* < 0.001; SMD = 0.722) and VTE (20.09% vs. 7.27%; *p* < 0.001; SMD = 0.380). Even so, the risk for all-cause mortality was higher in the DOAC cohort (RR 1.65, 95% CI 1.45–1.88), as well as the risk for hospitalization/re-hospitalization (RR 1.89, 95% CI 1.79–2.00), and VTE (RR 9.14, 95% CI 7.55–11.06) (Log-Rank tests *p* < 0.001). However, there were no difference in terms of ICH between cohorts (RR 1.40, 95% CI 0.79–2.48; Log-Rank test *p* = 0.362). KM curves for these outcomes are shown in Supplementary Fig. 2.

Another sensitivity analysis was performed accounting for the severity of COVID-19 infection. This analysis showed 25,978 patients overall after PSM (12,989 on previous DOAC:12,989 not on previous OAC), and both cohorts were balanced in terms of hospitalization at inclusion (34.79% vs. 34.40%; *p* = 0.506; SMD = 0.008), intensive care unit (ICU) stay at inclusion (13.74% vs. 13.00%; *p* = 0.083; SMD = 0.022) and mechanical respiratory assistance requirements at inclusion (5.27% vs. 4.67%; *p* = 0.026; SMD = 0.028). The results were similar to those found for the main analysis, with a significantly increased risk for all-cause mortality (RR 1.35, 95% CI 1.19–1.53), hospitalization/re-hospitalization (RR 1.58, 95% CI 1.50–1.66), and VTE (RR 4.39, 95% CI 3.82–5.05) (Log-Rank tests *p* < 0.001) in the DOAC cohort, without
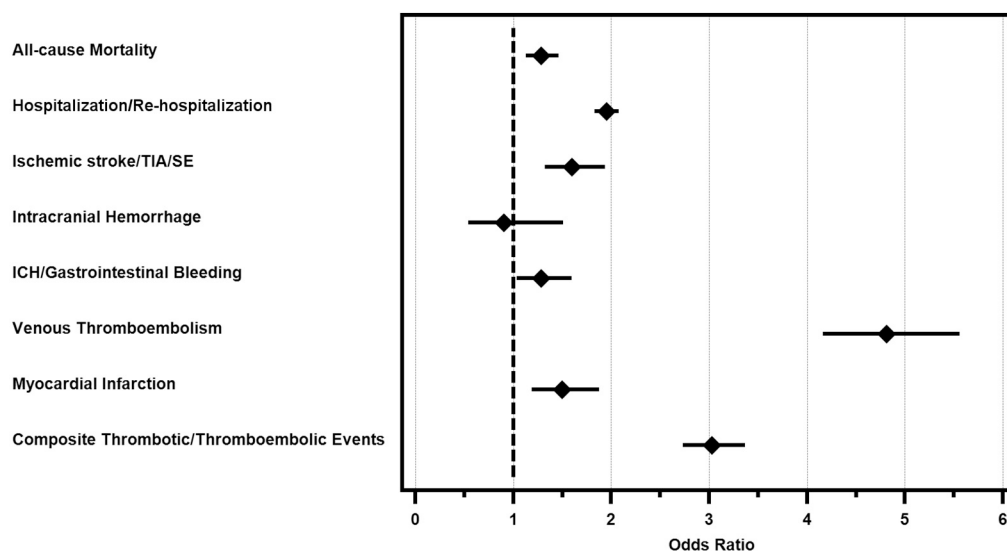
Fig. 1. Forest plot of odds ratios for outcomes in the DOAC population after propensity score matching.
TIA = transient ischemic attack; SE = systemic embolism; ICH = intracranial hemorrhage.

differences regarding ICH risk (RR 0.82, 95% CI 0.49–1.36; Log-Rank test $p = 0.308$) (Supplementary Fig. 3).

4. Discussion

In the present study including a large cohort of patients with COVID-19, we demonstrate that chronic DOAC therapy before COVID-19 diagnosis was not associated with improved clinical outcomes or hospitalization at 30-days, compared to non-OAC therapy, after adjusting for comorbidities using PSM.

As far as we are aware, the present study represents the largest cohort of patients investigating the efficacy and safety of previous DOAC use before COVID-19 diagnosis. Importantly, our analysis is balanced by PSM and included both outpatients and inpatients. Although our results confirm some previous observations, the topic remains controversial and reinforces the hypothesis that OAC-treated patients are particularly vulnerable and still have an inherent pro-inflammatory state.

COVID-19 increases the risk of both arterial and venous thrombotic complications. For this reason, anticoagulation is one of the target therapies in the management of patients with COVID-19. Thus, the American Society of Hematology guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19 suggest using prophylactic-intensity over intermediate- or therapeutic-intensity anticoagulation for patients with COVID-19–related acute illness who do not have suspected or confirmed VTE [18]. Recently, the INSPIRATION trial supported this, showing that among COVID-19 patients admitted to the ICU, intermediate-dose prophylactic anticoagulation, did not result in a significant difference in the composite outcome of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days, compared with standard-dose prophylactic anticoagulation [19]. Indeed, an interim analysis of combined data from the REMAP-CAP, ATTACC, and ACTIV-4a trials showed that inpatients with severe disease, receiving prophylactic anticoagulation at therapeutic doses did not reduce the requirement for organ support [20]. These results reinforced the hypothesis that more aggressive anticoagulation therapy does not have much benefit as expected.

On the other hand, a recent real-world observational study demonstrated that early initiation of prophylactic anticoagulation compared with no anticoagulation among COVID-19 patients admitted to hospital was associated with a decreased risk of 30-day mortality and no increased risk of serious bleeding events [21]; however, the frequency of DOAC use was low in this study. A large cohort study simulating an

intention-to-treat trial analyzed the effect of anticoagulation therapy on mortality, showing that patients with moderate or severe illness benefited from anticoagulation in the first 48 h of hospitalization, with a similar efficacy for apixaban compared to enoxaparin in decreasing mortality [22]. Unfortunately, most of the evidence thus far is focused on *hospitalized* patients (and in-hospital outcomes) and there are limited data about the role of previous antithrombotic therapies before COVID-19 diagnosis on the progression and prognosis of the disease. In particular, information about COVID-19 patients who are not yet hospitalized is scarce.

One small study in an Italian cohort of elderly patients with COVID-19 concluded that chronic DOAC intake was an independently associated with a decreased mortality risk (HR 0.38, 95% CI 0.17–0.58; $p = 0.010$) [23]. Similarly, another study in Italy showed that elderly patients with COVID-19 on chronic OAC treatment for AF had lower all-cause mortality rate ratio compared to their PSM non-anticoagulated counterpart [24]. A further cohort study including hospitalized COVID-19 patients from Germany showed that pre-existing therapy with both DOACs or VKAs was associated with a lower risk for the primary endpoint (all-cause mortality or need for invasive or non-invasive ventilation or extracorporeal membrane oxygenation) [25]. Similarly, in COVID-19 patients initially admitted in medical wards of French hospitals, previous OAC with VKA or DOACs significantly decreased ICU admission or in-hospital mortality [26].

However, Sivaloganathan et al. demonstrated that patients taking antithrombotic therapy (anticoagulant or antiplatelet agents) at the time of infection with COVID-19, did not have a significantly different mortality risk to those patients not taking these drugs [27]. A further recent study showed no difference in the risk of acute respiratory distress syndrome at admission or death during hospitalization, between COVID-19 patients treated with antiplatelets or anticoagulants pre-admission, compared to those untreated [28]. Likewise, anticoagulant use pre-COVID-19 diagnosis was not associated with a decreased risk for all-cause mortality, mechanical ventilation or hospital admission in a retrospective study from the New York City health system, suggesting that previous anticoagulant use did not protect against development of severe COVID-19 [29]. Data from a preliminary analysis of the HOPE COVID-19 Registry evidenced a significantly lower survival and higher mortality risk in COVID-19 patients on OAC therapy at hospital admission compared to patients without prior OAC at admission [30]. Other study showed that chronic anticoagulants or antiplatelets use was not associated with a lower risk of any primary outcome in COVID-19
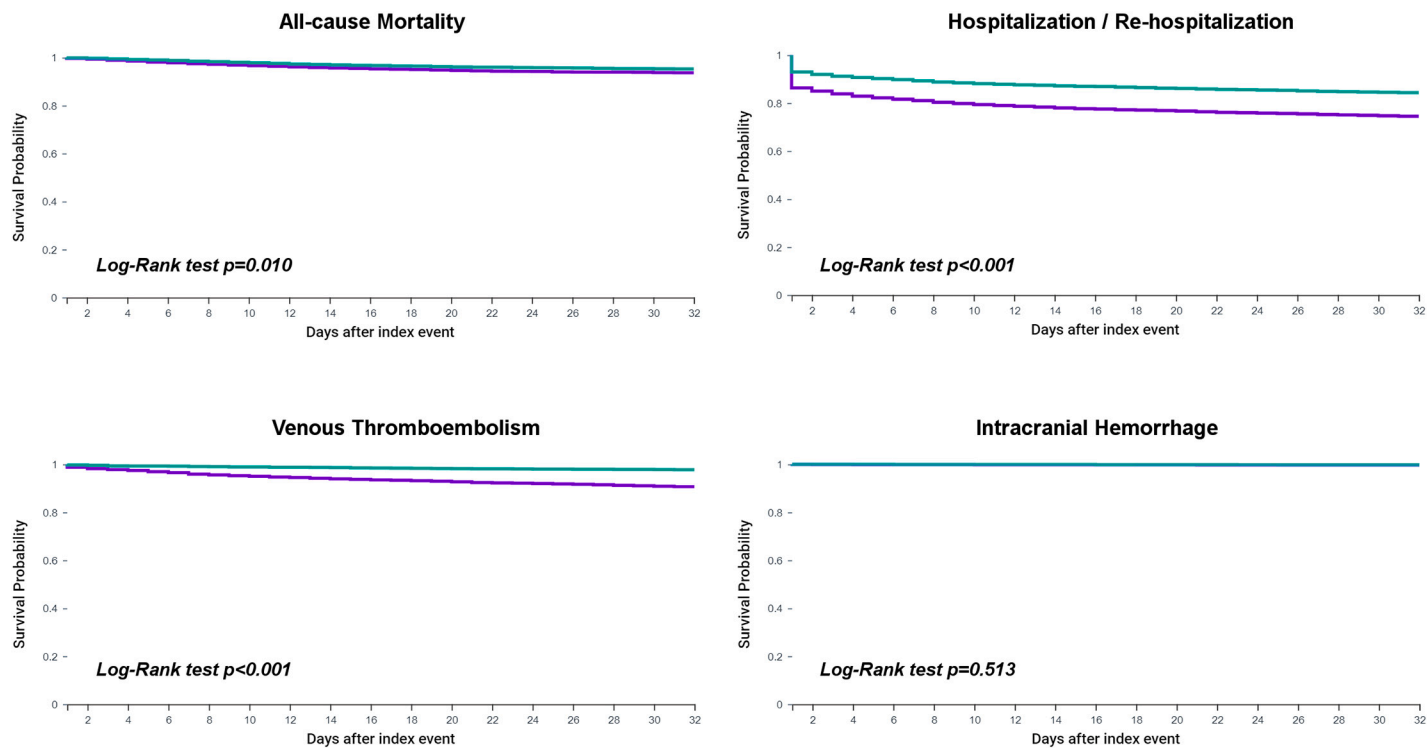
Fig. 2. Comparison of survival curves for the primary outcomes between patients on DOACs or not at COVID-19 diagnosis after propensity score matching. Purple line = Prior DOAC use. Green line = Not prior OAC use. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

patients, including hospitalization, mortality, VTE, emergency department visit, ICU stay, invasive ventilator use or any outcome (OR anticoagulants vs. none 1.21, 95% CI 0.93–1.56) [31]. Finally, a nationwide register-based cohort study in Sweden demonstrated that ongoing DOAC use at the time of SARS-CoV-2 infection was not associated with reduced risk of COVID-19 hospitalization nor the composite of ICU admission or death due to COVID-19 [32].

The published data thus far indicate that the evidence for DOACs in this context is controversial, and the present study (being the largest series) shows that previous chronic DOAC therapy at time of COVID-19 diagnosis was not associated with improved clinical outcomes or lower hospitalization, and instead, an increased risk of mortality, hospitalization/re-hospitalization and VTE. The reasons underlying these observations are complex. Even despite PSM adjusting, patients on DOACs may have increased risk for other reasons, including a baseline pro-inflammatory state. OAC has the potential to reduce this by blocking inflammation hypercoagulability activation in the setting of COVID-19 [33,34], but at the same time the SARS-CoV-2 enhances abnormal coagulation markers [3]. In its severe form, COVID-19 induces a cytokine storm that predispose to thrombotic disease due to excessive inflammation, platelet activation, endothelial dysfunction, and blood stasis [2,35,36]. We could hypothesize that the presence of SARS-CoV-2 infection may increase the already-high thrombotic risk of these patients on DOACs, and a pathophysiological explanation for the observed VTE risk and lower survival on our study.

Currently, there are several ongoing clinical trials in the context of COVID-19, in both inpatients and outpatients [37]. However, patients included in randomized clinical trials (RCTs) are usually more selected, so results from observational studies like this one are still necessary and highly encouraged in order to support and complement RCTs, as well as to provide real-world evidence.

4.1. Limitations

We should acknowledge limitations in relation to this study. The main limitation is that the data were collected from the HCO EMRs and some health conditions may be underreported. Recording of ICD codes in EMR may vary by factors including age, comorbidities, severity of illness, length of in-hospital stay, and in-hospital mortality. Further residual confounding may include lifestyle factors such as alcohol consumption and physical activity, which were not available. Using both ICD-10 codes and laboratory test results to identify COVID-19 patients may have different interpretations and a potential bias. ICD-10 codes alone may be recorded weeks after actual infection, or possibly weeks before a positive laboratory test result if patient received a "clinical" diagnosis and did not seek testing immediately. Unfortunately, we are not able to provide the exact number of patients that were included in the study with an ICD-10 code or with a positive laboratory test result, since we cannot elucidate how many were included according to the specific COVID-19 criteria. However, we can confirm that patients were included only once, i.e. there are not duplicated patients due to more than one COVID-19 criteria fulfilled and the TriNetX platform is updated and reviewed on a monthly basis, so appropriateness of COVID-19 diagnosis is guaranteed.

In addition, the use of ICD codes for the identification of COVID-19 cases also requires validation studies in terms of sensitivity and specificity. Furthermore, propensity scores are a method used to balance covariates, but in observational studies propensity scores are estimated and therefore there is no certainty that the propensity score was 100% accurate. We also could not determine if there was any impact of attending different HCOs because of data privacy restrictions. We examined all deaths of the included patients captured within the TriNetX network; however, deaths outside of the participating HCOs are not well captured. Finally, our main objective was to investigate the impact of prior DOAC therapy on short-term prognosis after COVID-19 diagnosis. For this reason we did not take into account the

anticoagulation therapy once patients were diagnosed of COVID-19, since our interest was on the previous use of DOACs (or not). We acknowledge that this may imply a bias, but the large cohort and the sensitivity analyses performed aim to make these results valid and generalizable.

5. Conclusion

In patients with COVID-19, previous chronic DOAC therapy at time of COVID-19 diagnosis was not associated with improved clinical outcomes or lower hospitalization rate compared to COVID-19 patients not taking OAC therapy, even after adjusting for comorbidities.

Funding

Declaration of competing interest

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi. org/10.1016/j.thromres.2021.06.014.

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