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Direct-acting Oral Anticoagulants Use Prior to COVID-19 Diagnosis and Associations with 30-day Clinical Outcomes

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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: 738,423patients 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.

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 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.

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, apixaban, 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, ie. 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 predominately 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 fulfilled. 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 haemorrhage and prior intracerebral haemorrhage, using ICD-10 codes) and medication use (e.g. antiplatelets, beta-blockers, calcium channel blockers, anti-arrhythmics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and diuretics).

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 thromboembolic event. Further details about the

ICD-10-CM codes used for the identification of every outcome are included in Supplementary Table 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.

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

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<0.05 were accepted as statistically significant. Statistical analysis was performed using

the TriNetX Analytics function in the online research platform.

Results

An overall cohort of 738,423 patients with COVID-19 was included. Of these, 13,229 (6,899 [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).

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 Figure 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) (Figure 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) (Figure 2). The risk of ICH was not significantly different between both cohorts (RR 0.90, 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 Figure 1).

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

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 suggests 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 ACTIV4a 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 hours 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 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.

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.

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.

Figure legends

Figure 1. Forest plot of odds ratios for outcomes in the DOAC population after prosensity score matching.

TIA = transient ischemic attack; SE = systemic embolism; ICH = intracranial hemorrhage.

Figure 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.

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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 = 13229	N = 725194			N = 13003	N = 13003		
Age (years), mean (SD)	67.30 15.43	45.50 18.10	<0.001	1.297	67.10 15.4	68.2 15.2	<0.001	0.071
Male sex	6899 52.15%	3150 61 43.45%	<0.001	0.175	6783 52.1%	6633 51.01%	0.063	0.023
Ethnicity								
Not Hispanic or Latino	9587 72.47%	4092 78 56.43%	<0.001	0.340	9418 72.43%	9264 71.25%	0.034	0.026
Hispanic or Latino	1107 8.37%	9963 1 13.74%	<0.001	0.172	1103 8.48%	1028 7.91%	0.090	0.021
Unknown Ethnicity	2535 19.16%	2162 85 29.82%	<0.001	0.250	2482 19.09%	2711 20.85%	<0.001	0.044
Comorbidities								
Hypertension	9265 70.04%	16351 48 22.77%	<0.001	1.076	9083 69.85%	9624 74.01%	<0.001	0.093
Heart failure	3975 30.05%	1810 9 2.50%	<0.001	0.805	3836 29.50%	3728 28.67%	0.140	0.018
Ischemic heart disease	4806 36.33%	3969 5.29%	<0.001	0.820	4688 36.05%	4810 36.99%	0.116	0.020
Atrial fibrillation	6653 50.29%	16592 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%	2332 2 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

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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	19.7%	2632	20.24%	0.314	0.013
Hyperlipidemia	6649	50.29%	105577	14.56%	<0.001	0.825	6509	50.05%	6870	52.83%	<0.001	0.056
Overweight/obesity	4884	36.92%	111303	15.35%	<0.001	0.507	479	36.85%	4592	35.32%	0.010	0.032
Diabetes mellitus	4841	36.92%	78775	10.86%	<0.001	0.6.5	73 4	36.41%	5112	39.31%	<0.001	0.060
Cardiac and vascular implants and grafts	2553	19.30%	15110	2.08%	<0.001	0.580	2475	19.03%	2572	19.78%	0.128	0.019
Disorders of thyroid gland	3230	24.42%	67422	9.30%	<0.001	0.412	3157	24.28%	3532	27.16%	<0.001	0.066
Diseases of the respiratory system	10406	78.66%	3?67?8	46.44%	<0.001	0.706	10196	78.41%	10489	80.67%	<0.001	0.056
Chronic obstructive pulmonary disease	2403	18.17%	20440	2.82%	<0.001	0.517	2334	17.95%	2429	18.68%	0.128	0.019
Asthma	2027	15.32%	65932	9.10%	<0.001	0.191	1982	15.24%	2229	17.14%	<0.001	0.052
Sleep apnea	3232	24.43%	47271	6.52%	<0.001	0.511	3166	24.35%	3027	23.28%	0.043	0.025
Diseases of liver	1683	12.72%	34550	4.76%	<0.001	0.285	1656	12.74%	1949	14.99%	<0.001	0.065
Acute kidney failure and	4495	33.98%	38380	5.29%	<0.001	0.774	4375	33.65%	4467	34.35%	0.229	0.015

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chronic kidney disease											
Neoplasms	4878	36.87%	120821	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%	92780	12.79%	<0.001	1.315	8786	66.03%	8895	68.41%	<0.001	0.051
ACE inhibitors	4764	36.01%	66931	9.23%	<0.001	0.6?6	4648	35.75%	4784	36.79%	0.079	0.022
Angiotensin II inhibitors	3696	27.94%	40958	5.65%	<0.001	0.625	3589	27.60%	3648	28.06%	0.414	0.010
Alpha blockers	2548	19.26%	28408	3.22	<0.001	0.494	2480	19.07%	2359	18.14%	0.054	0.024
Antilipemic agents	7868	59.48%	9815?	13.54%	<0.001	1.086	7680	59.06%	7903	60.78%	0.005	0.035
Calcium channel blockers	6051	45.7?%	61?07	8.42%	<0.001	0.925	5902	45.39%	5621	43.23%	<0.001	0.044
Diuretics	7893	59.?6%	86494	11.93%	<0.001	1.148	7680	59.06%	7888	60.66%	0.009	0.033
Antiplatelets	7135	53.94%	88003	12.14%	<0.001	0.992	6969	53.60%	7407	56.96%	<0.001	0.068

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Figure 1. Forest plot of odds ratios for outcomes in the DOAC population after prosensity score matching. TIA = transient ischemic attack; SE = systemic embolism; ICH = intracranial hemorrhage.

Figure 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.

Declaration of interests

☐The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

X The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Highlights

- It is unclear if chronic DOAC therapy has some impact on COVID-19 prognosis.

- Prior DOAC users before COVID-19 were matched with patients non on anticoagulants.

- All-cause mortality, hospitalization and VTE were higher in DOAC-treated patients.

- Chronic DOAC therapy at time of COVID-19 diagnosis did not improve clinical outcomes.