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Efficacy and safety of direct-acting oral anticoagulants compared to vitamin K antagonists in COVID-19 outpatients with cardiometabolic diseases

José Miguel Rivera-Caravaca[1,2,3], Stephanie L. Harrison[1,4], Benjamin J. R. Buckley[1,4], Elnara Fazio-Eynullayeva[5], Paula Underhill[6], Francisco Marín[2] and Gregory Y. H. Lip[1,4,7*]

Abstract

Background: It remains uncertain if prior use of oral anticoagulants (OACs) in COVID-19 outpatients with multimorbidity impacts prognosis, especially if cardiometabolic diseases are present. Clinical outcomes 30-days after COVID-19 diagnosis were compared between outpatients with cardiometabolic disease receiving vitamin K antagonist (VKA) or direct-acting OAC (DOAC) therapy at time of COVID-19 diagnosis.

Methods: A study was conducted using TriNetX, a global federated health research network. Adult outpatients with cardiometabolic disease (i.e. diabetes mellitus and any disease of the circulatory system) treated with VKAs or DOACs at time of COVID-19 diagnosis between 20-Jan-2020 and 15-Feb-2021 were included. Propensity score matching (PSM) was used to balance cohorts receiving VKAs and DOACs. The primary outcomes were all-cause mortality, intensive care unit (ICU) admission/mechanical ventilation (MV) necessity, intracranial haemorrhage (ICH)/gastrointestinal bleeding, and the composite of any arterial or venous thrombotic event(s) at 30-days after COVID-19 diagnosis.

Results: 2275 patients were included. After PSM, 1270 patients remained in the study (635 on VKAs; 635 on DOACs). VKA-treated patients had similar risks and 30-day event-free survival than patients on DOACs regarding all-cause mortality, ICU admission/MV necessity, and ICH/gastrointestinal bleeding. The risk of any arterial or venous thrombotic event was 43% higher in the VKA cohort (hazard ratio 1.43, 95% confidence interval 1.03–1.98; Log-Rank test p = 0.029).

Conclusion: In COVID-19 outpatients with cardiometabolic diseases, prior use of DOAC therapy compared to VKA therapy at the time of COVID-19 diagnosis demonstrated lower risk of arterial or venous thrombotic outcomes, without increasing the risk of bleeding.

Keywords: Coronavirus disease 2019, SARS-CoV-2, Thrombosis, Anticoagulant, Vitamin K antagonist, Direct-acting oral anticoagulants, Bleeding

*Correspondence: gregory.lip@liverpool.ac.uk
[1] Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK
Full list of author information is available at the end of the article

Introduction

Oral anticoagulants (OACs), including vitamin K antagonists (VKAs) and direct-acting OACs (DOACs), have been used for thromboprophylaxis in different clinical scenarios. In the pivotal clinical trials of stroke prevention in atrial fibrillation (AF), DOACs were non-inferior

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to warfarin for preventing stroke/systemic embolism (SE), with lower rates of intracranial haemorrhage (ICH) in comparison with warfarin [1–4]. Similarly, in venous thromboembolism (VTE), dabigatran, rivaroxaban, apixaban and edoxaban were non-inferior to conventional therapy in terms of efficacy and caused less bleeding in a broad spectrum of patients [5–9]. These trials evidences are supported by data from real world and observational studies, where DOACs have demonstrated significantly lower rates for major bleeding and a positive net clinical benefit compared to VKAs [10–13]. In VTE patients, the use of DOACs has also been associated with a lower risk of VTE recurrence even after anticoagulant discontinuation [14, 15].

Coronavirus Disease 2019 (COVID-19) has shown to trigger endothelial dysfunction, inflammatory and hypercoagulable states [16–18]. The risk of thrombosis is increased, and thromboembolic complications are relatively frequent in these patients, particularly in those patients with intensive care unit (ICU) admission [19–22]. Thus, anticoagulation is now well-established for the management of COVID-19 patients [23–25]. However, a common limitation is that most of the evidence to date refers to the hospitalization context. Thus, it remains uncertain if prior OAC therapy in outpatients, especially amongst patients with multimorbidity, would potentially influence the severity and clinical outcomes after COVID-19 diagnosis.

The aim of this study was to compare clinical outcomes 30-days after COVID-19 diagnosis between outpatients with cardiometabolic disease on chronic VKA or DOAC therapy at time of COVID-19 diagnosis, using a propensity score matching (PSM) approach.

Methods

Data from TriNetX, a global federated health research network with real-time updates of anonymised electronic medical records (EMRs) mainly from the United States (US), were used. The network includes healthcare organisations (HCOs, academic medical centres, specialty physician practices and community hospitals), with accumulated data for more than 71 million patients. Approximately, 18 million adult patients had a visit in a TriNetX HCO during 2020.

The inclusion criteria were ≥ 18 years and outpatient with COVID-19 and cardiometabolic disease recorded in EMRs between 20 January 2020 and 15 February 2021. COVID-19 was identified using criteria provided by TriNetX based on Centers for Disease Control and Prevention (CDC) coding guidelines [26]. 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 in the EMRs of the patients (Additional file 1: Table S1). The inclusion date start was set as 20 January 2020 because COVID-19 was first confirmed in the US on this date, and the TriNetX network is predominately US-based [27]. Cardiometabolic disease was defined as the combination of diabetes mellitus (ICD-10-CM code: E08-E13) and any disease of the circulatory system (ICD-10-CM code: I00-I99). In addition, all patients should have OAC therapy in the one-year period prior to COVID-19 recorded in their EMRs, and remained on this therapy at COVID-19 diagnosis. During 1-year period prior to COVID-19 diagnosis, patients must not be hospitalized to ensure they are stable outpatients.

All patients were then stratified by OAC prescription. The DOAC group included outpatients who received either dabigatran, apixaban, rivaroxaban or edoxaban for at least 1 year before COVID-19 diagnosis, whereas the VKA group included outpatients who received warfarin under the same conditions. Patients were excluded if they received concomitant anticoagulant therapy (oral or parenteral). Baseline demographics, comorbidities and medication use were also captured from the patient EMRs.

The searches were run in TriNetX on 30 April 2021, which allowed for at least 30-days of follow-up for all participants from the time all conditions were fulfilled. When the searchers were run, there were 61 participating HCOs within the TriNetX research network.

Follow-up and clinical outcomes

All patients were followed-up for up to 30-days after COVID-19 diagnosis. Primary outcomes included all-cause mortality, ICU admission/mechanical ventilation (MV) necessity, ICH/gastrointestinal bleeding, and the composite of any arterial or venous thrombotic event (any of the following: myocardial infarction, other arterial thrombosis, VTE, or ischemic stroke/transient ischemic attack [TIA]/SE). The secondary outcomes were hospital admission, myocardial infarction, VTE, ischemic stroke/TIA/SE, and all bleeding. Further details about the ICD-10-CM codes used for the identification of every outcome are included in Additional file 1: Table S2.

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

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information. No protected health information or personal data are 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 [28].

Cox proportional Hazard Ratios (HRs) 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.

Results

Overall, 2275 patients (mean age 67.7 ± 12.8 years, 1222 [53.7%] males) with COVID-19 and cardiometabolic disease were included. Of these, 648 (363 [56.0%] males, mean age of 67.9 ± 12.9 years) were on VKA therapy at the time of COVID-19 diagnosis, and 1627 (859 [52.8%] males, mean age 67.6 ± 12.8 years) were on DOACs.

There were no differences between cohorts regarding the main reasons for OAC (i.e. AF or previous pulmonary embolism). Other VTEs were more common in patients taking VKA therapy. In addition, patients on VKA were in general more comorbid, as demonstrated by the higher prevalence of hypertension, heart failure, ischemic heart disease, hyperlipidaemia, overweight/obesity, diseases of the nervous and digestive systems, acute kidney failure/chronic kidney disease, and neoplasms (Table 1). After PSM, 1270 remained in the study, 635 individuals on VKA therapy and 635 on DOACs (i.e. proportion of 1:1), well balanced on age, gender, ethnicity, and comorbidities (Table 1).

Comparisons of clinical outcomes

In the initial populations, all event rates were numerically higher in the COVID-19 patients with cardiometabolic disease on prior VKA, which were significant for any arterial or venous thrombotic event (14.04% vs. 8.54%, p < 0.001), VTE (9.88% vs. 6.82%, p = 0.007), and ischemic stroke/TIA/SE (4.17% vs. 1.72%, p < 0.001). After PSM, the rate of any arterial or venous thrombotic event (14.02% vs. 9.61%, p = 0.015) and ischemic stroke/TIA/SE (4.25% vs. 1.73%, p = 0.008) remained higher in users of VKA compared to users of DOACs. Further details are shown in Table 2.

In terms of the primary outcomes after PSM, there were no significant differences in the risks of all-cause mortality, ICU admission/MV necessity, or ICH/gastrointestinal bleeding between patients on VKA or DOACs. Thus, the risk for all-cause mortality was similar comparing the VKA cohort and DOAC cohort (HR 0.70, 95% 0.28–1.74). The risk of ICU admission/MV necessity in the VKA cohort was not significantly different compared to the DOAC cohort (HR 1.31, 95% CI 0.55–3.10), and the risk of ICH/gastrointestinal bleeding was similar (HR 1.29, 95% CI 0.29–5.75). Event-free survival for these three outcomes was not different between cohorts, as assessed by the Kaplan–Meier analyses (Log-Rank tests: p = 0.442 for mortality; p = 0.543 for ICU admission/MV necessity; and p = 0.741 for ICH/gastrointestinal bleeding) (Fig. 1).

The composite outcome of any arterial or venous thrombotic event was inferior in the DOAC cohort in comparison to the VKA cohort, as demonstrated by the 43% higher risk in VKA users (HR 1.43, 95% CI 1.03–1.98) and the lower event-free survival (Log-Rank test p = 0.029) (Fig. 1).

Secondary outcomes

Hospital admission was similar in VKA and DOAC patients (HR 0.98, 95% CI 0.50–1.92). Likewise, there were no significant differences in the risk of myocardial infarction between both groups (HR 1.46, 95% CI 0.41–5.18), nor in the risk of VTE (HR 1.20, 95% CI 0.83–1.74). The risk of all bleeding events was not significantly different in patients previously taking VKA (HR 2.24, 95% CI 0.92–5.44) (Fig. 2).

The risk of suffering an ischemic stroke/TIA/SE at 30-days after COVID-19 diagnosis was 2.42-fold higher in users of VKA compared to DOAC users (HR 2.42, 95% CI 1.20–4.88; Log-Rank test p = 0.011) (Fig. 2).

Sensitivity analysis

A sensitivity analysis was performed including only those patients fulfilling the initial inclusion/exclusion criteria and AF, as this is the most common indication for OAC use. After PSM on a 1:1 proportion, 866 patients (mean age 71.2 ± 11.6 years, 508 [61%] males) with COVID-19, AF and other cardiometabolic disease were included, of which 433 (254 [58.7%] males, mean age of 71.1 ± 12.2 years) were on VKA therapy at the time of

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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 VKA N = 648	COVID-19 patients on prior DOAC N = 1627	p-value	SMD	COVID-19 patients on prior VKA N = 635	COVID-19 patients on prior DOAC N = 635	p-value	SMD
Age (years), mean (SD)	67.90 12.88	67.61 12.79	0.636	0.022	67.80 12.90	68.29 12.26	0.492	0.039
Male sex	363 56.02%	859 52.80%	0.164	0.065	353 55.59%	371 58.43%	0.308	0.057
Ethnicity								
Not Hispanic or Latino	494 76.24%	1133 69.64%	0.002	0.149	482 75.91%	481 75.75%	0.948	0.004
Hispanic or Latino	65 10.03%	117 7.19%	0.024	0.101	64 10.08%	59 9.29%	0.635	0.027
Unknown Ethnicity	89 13.74%	377 23.17%	0.481	0.245	89 14.02%	95 14.96%	0.632	0.027
Comorbidities								
Diabetes mellitus	648 100%	1627 100%	1.000	0.000	635 100%	635 100%	1.000	<0.001
Hypertension	613 94.60%	1479 90.90%	0.003	0.143	600 94.49%	602 94.80%	0.803	0.014
Heart failure	270 41.67%	574 35.28%	0.004	0.132	265 41.73%	249 39.21%	0.360	0.051
Ischemic heart disease	322 49.69%	721 44.32%	0.020	0.108	314 49.45%	311 48.98%	0.866	0.009
Atrial fibrillation	393 60.65%	984 60.48%	0.941	0.003	386 60.79%	389 61.26%	0.863	0.010
Peripheral vascular disease	105 16.20%	239 14.69%	0.363	0.042	103 16.22%	96 15.12%	0.589	0.030
Hyperlipidemia	570 87.96%	1322 81.25%	<0.001	0.187	557 87.72%	553 87.09%	0.735	0.019
Cerebrovascular disease	170 26.24%	367 22.56%	0.062	0.086	166 26.14%	160 25.20%	0.700	0.022
Cerebral infarction	81 12.50%	176 10.82%	0.253	0.052	81 12.76%	85 13.39%	0.739	0.019
Pulmonary embolism	124 19.14%	266 16.35%	0.111	0.073	121 19.06%	121 19.06%	1.000	0.000
Other venous embolism and thrombosis	195 30.09%	391 24.03%	0.003	0.137	187 29.45%	189 29.76%	0.902	0.007
Overweight/obesity	397 61.27%	913 56.12%	0.025	0.105	387 60.94%	389 61.26%	0.908	0.006
Diseases of the respiratory system	543 83.80%	1307 80.33%	0.056	0.090	532 83.78%	523 82.36%	0.501	0.038
Diseases of the nervous system	528 81.48%	1264 77.69%	0.046	0.094	517 81.42%	518 81.58%	0.942	0.004
Diseases of the digestive system	526 81.17%	1230 75.60%	0.004	0.136	514 80.94%	508 80.00%	0.671	0.024
Acute kidney failure and chronic kidney disease	287 44.29%	582 35.77%	<0.001	0.175	277 43.62%	272 42.84%	0.777	0.016
Diseases of liver	130 20.06%	290 17.82%	0.214	0.057	129 20.32%	136 21.42%	0.629	0.027
Neoplasms	351 54.17%	766 47.08%	0.002	0.142	341 53.70%	345 54.33%	0.822	0.013
Pharmacological therapy								
Beta blockers	495 76.39%	1228 75.48%	0.647	0.021	485 76.38%	485 76.38%	1.000	<0.001
ACE inhibitors	396 61.11%	836 51.38%	<0.001	0.197	385 60.63%	385 60.63%	1.000	<0.001
Angiotensin II inhibitors	237 36.57%	621 38.17%	0.479	0.033	236 37.17%	231 36.38%	0.771	0.016
Alpha blockers	549 84.72%	1282 78.80%	0.001	0.154	537 84.57%	542 85.35%	0.695	0.022
Antilipemic agents	366 56.48%	863 53.04%	0.137	0.069	359 56.54%	349 54.96%	0.572	0.032
Calcium channel blockers	477 73.61%	1091 67.06%	0.002	0.144	466 73.39%	463 72.91%	0.849	0.011
Diuretics	455 70.22%	1065 65.46%	0.030	0.102	445 70.08%	438 68.98%	0.670	0.024

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Table 1 (continued)

	Initial populations					Propensity score matched populations				
	COVID-19 patients on prior VKA N = 648		COVID-19 patients on prior DOAC N = 1627				COVID-19 patients on prior VKA N = 635		COVID-19 patients on prior DOAC N = 635		
					p-value	SMD				p-value	SMD
Antiarrhythmics	401	61.88%	988	60.73%	0.609	0.024	396	62.36%	387	60.95%	0.603	0.029
Antiplatelets	495	76.39%	1228	75.48%	0.647	0.021	485	76.38%	485	76.38%	1.000	<0.001
Blood glucose regulation agents (including oral antidiabetics and insulin)	554	85.50%	1389	85.37%	0.947	0.003	545	85.83%	545	85.83%	1.000	<0.001

ACE: Angiotensin-converting enzyme; DOAC: direct-acting oral anticoagulant; SD: standard deviation; SMD: standardized mean difference; VKA: vitamin K antagonist

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Table 2 Primary and secondary outcomes in patients on VKAs or DOAC at COVID-19 diagnosis, before (unmatched) and after propensity score matching

Outcomes	Initial populations			Propensity score matched populations		
	COVID-19 patients on prior VKA (N = 648)	COVID-19 patients on prior DOAC (N = 1627)	p-value	COVID-19 patients on prior VKA (N = 635)	COVID-19 patients on prior DOAC (N = 635)	p-value
All-cause mortality	10 (1.54%)	22 (1.35%)	0.913	10 (1.57%)	11 (1.73%)	0.826
ICU admission/MV necessity	12 (1.85%)	21 (1.29%)	0.378	12 (1.89%)	10 (1.57%)	0.667
ICH/gastrointestinal bleeding	10 (1.54%)	12 (0.74%)	0.145	10 (1.57%)	10 (1.57%)	1.000
Any arterial or venous thrombotic event	91 (14.04%)	139 (8.54%)	<0.001	89 (14.02%)	61 (9.61%)	0.015
Hospital admission	17 (2.62%)	42 (2.58%)	0.891	17 (2.68%)	17 (2.68%)	1.000
Myocardial infarction	10 (1.54%)	13 (0.80%)	0.190	10 (1.57%)	10 (1.57%)	1.000
Venous thromboembolism	64 (9.88%)	111 (6.82%)	0.007	62 (9.76%)	50 (7.87%)	0.235
All bleeding events	16 (2.45%)	18 (1.11%)	0.084	16 (2.52%)	10 (1.57%)	0.235
Ischemic stroke/TIA/SE	27 (4.17%)	28 (1.72%)	<0.001	27 (4.25%)	11 (1.73%)	0.008

DOAC: direct-acting oral anticoagulant; ICH: intracranial haemorrhage; ICU: intensive care unit; MV: mechanical ventilation; SE: systemic embolism; TIA: transient ischemic attack; VKA: vitamin K antagonist

COVID-19 diagnosis, and 433 (254 [58.7%] males, mean age 71.3 ± 11.0 years) were on DOACs.

Overall, the risk for the primary outcomes in this sensitivity analysis between patients on VKA or DOACs was similar compared to the main analysis. Thus, there were no significant differences in VKA or DOAC-treated patients regarding all-cause mortality (HR 1.36, 95% CI 0.47–3.91; Log-Rank test p = 0.570), ICU admission/ MV necessity (HR 1.35, 95% CI 0.57–3.19; Log-Rank test p = 0.499), and ICH/ gastrointestinal bleeding (HR 0.34, 95% CI 0.07–1.67; Log-Rank test p = 0.162). The risk of composite outcome of any arterial or venous thrombotic event was higher in the VKA cohort compared to the DOAC cohort (HR 1.80, 95% CI 1.04–3.12), with a significantly lower event-free survival (Log-Rank test p = 0.033).

Concerning the secondary outcomes, the risks of hospital admission (HR 0.94, 95% CI 0.46–1.90; Log-Rank test p = 0.859), myocardial infarction (OR 0.58, 95% CI 0.17–1.97; Log-Rank test p = 0.372), VTE (HR 1.48, 95% CI 0.69–3.19; Log-Rank test p = 0.315), and all bleeding events (HR 1.14, 95% CI 0.44–2.96; Log-Rank test p = 0.782), was also similar in patients previously taking VKA or DOACs. The risk of ischemic stroke/TIA/SE was increased in VKA users (HR 3.69, 95% CI 1.37–9.93), and Kaplan–Meier analysis demonstrated a significantly lower event-free survival in the VKA-treated cohort (Log-Rank test p = 0.006).
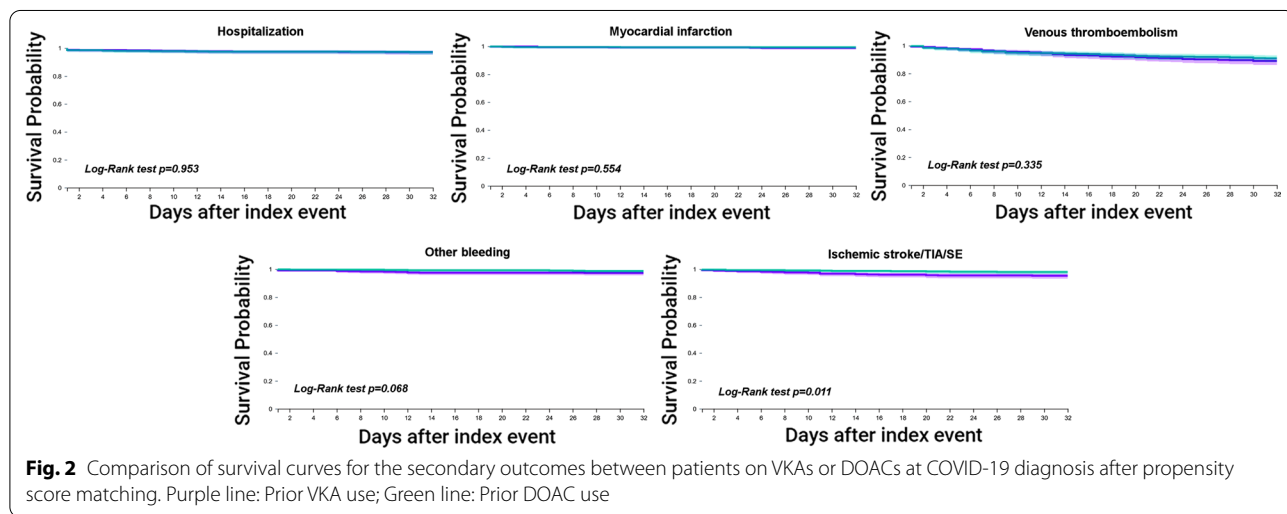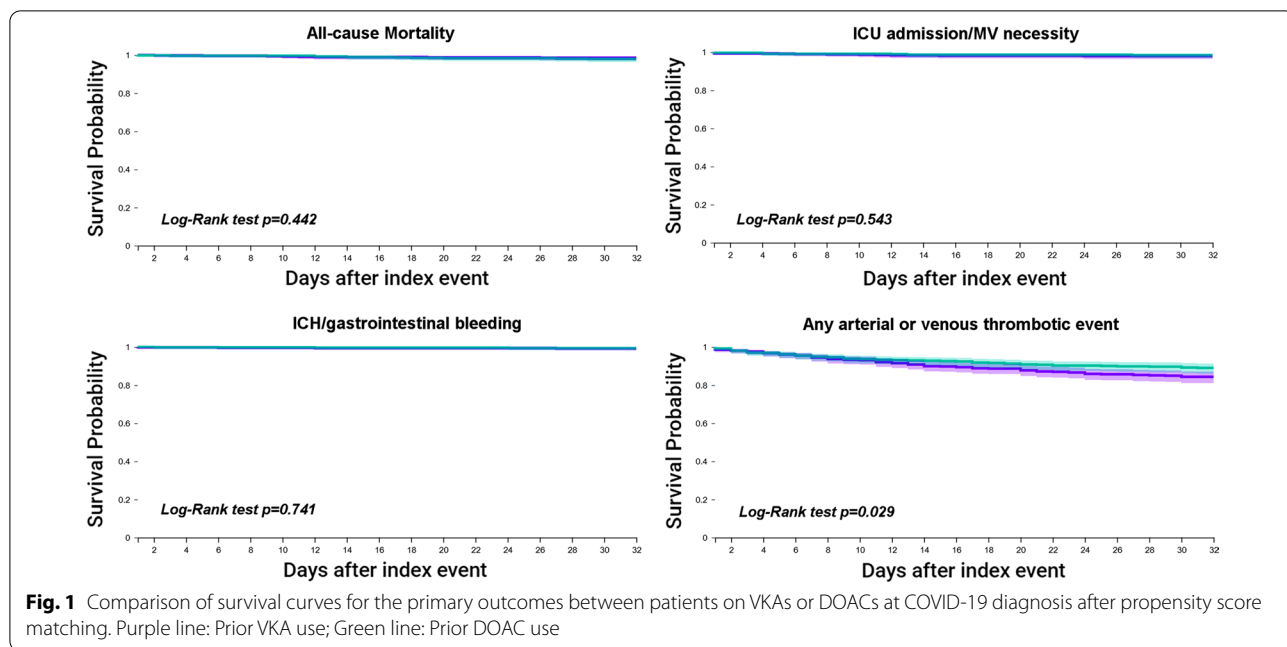
Discussion

In this study including COVID-19 *outpatients* with cardiometabolic disease, patients taking VKA before COVID-19 diagnosis showed a 43% higher 30-day risk of any arterial/venous thrombotic event and ischemic stroke/ TIA/SE, compared to patients taking DOAC, adjusting for comorbidities using PSM. These results were consistent also in COVID-19 patients with AF and other cardiometabolic disease.

Previous studies have shown that cardiometabolic multimorbidity is common among patients with COVID-19, and it is associated with a higher risk of hospitalization and a worsened prognosis [29–32]. In particular, diabetes is frequent in these patients [33, 34], and associated with an increased risk of complications, likely due to clustering with other conditions [29]. Simultaneously, several cardiovascular diseases, including hypertension, cerebrovascular disease and coronary artery disease, are prevalent in COVID-19 patients, and are associated with a higher risk of adverse outcomes [35]. Given that the presence of cardiometabolic disease is not uncommon in patients with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, this might have major implications for prognosis in this condition.

It is well established that COVID-19 increases the risk of arterial and venous thrombosis [20, 21], leading to the research focus on thromboinflammation and antithrombotic therapy, particularly in anticoagulation therapy [23, 25, 36, 37]. Many patients had preexisting cardiovascular diseases and were already on OAC therapy when they were diagnosed of COVID-19 [38]. Hence, the role of prior OAC therapy in the context of COVID-19 is gaining interest. For example, a recent study concluded that prior use of therapeutic anticoagulation was not associated with improved survival in hospitalized COVID-19 patients [39]. Similarly, a small study found that regular VKA use in hospitalized

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Fig. 1 Comparison of survival curves for the primary outcomes between patients on VKAs or DOACs at COVID-19 diagnosis after propensity score matching. Purple line: Prior VKA use; Green line: Prior DOAC use

Fig. 2 Comparison of survival curves for the secondary outcomes between patients on VKAs or DOACs at COVID-19 diagnosis after propensity score matching. Purple line: Prior VKA use; Green line: Prior DOAC use

frail older patients with COVID-19 was associated with increased mortality during the first week [40]. On the contrary, a retrospective study concluded that COVID-19 patients on OAC at the time of infection and throughout their disease course had significantly lower risk of all-cause mortality at 21 days [41]. Indeed, OAC therapy was associated with lower risk of all-cause mortality in elderly AF patients with COVID-19 [42], and more recently, the ACTION trial showed that among patients admitted with COVID-19 and elevated D-dimer, therapeutic anticoagulation was not superior to prophylactic anticoagulation; and rivaroxaban for stable patients and enoxaparin for unstable patients

increased major bleeding without improving clinical outcomes [43, 44].

Nevertheless, a common limitation of most studies (both, those with positive and negative results in favour of OACs) is the hospitalization setting. Such patients have already suffered deterioration of their baseline status, which has led to hospitalization and may be a manifestation of a more severe state of the SARS-CoV-2 infection, with an increased risk of thrombosis, mortality, ICU admission, and MV. In these more severe patients, several confounding factors may be acting when evaluating the potential role of previous OAC, and the differences between VKA and DOAC may be non-existent.

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As a result, COVID-19 *outpatients* with cardiometabolic diseases under anticoagulation therapy are a population with scarce data, and their management could be particularly complex. A recent study concluded that OAC therapy in high-risk AF patients was associated with a lower risk of receiving a positive COVID-19 test and severe COVID-19 outcomes [45]. In turn, preadmission and in-hospital OAC therapy (either VKA or DOAC) were positively associated with higher survival in a study including elderly AF patients with COVID-19 [46]. Although these prior studies did not observe differences between VKA and DOACs, we found that VKA users had a higher risk of thromboembolism, which supported several previous studies demonstrating that DOAC therapy is more effective and even as safe as VKA therapy [47, 48].

DOACs have recently demonstrated to be superior in comparison to VKAs among patients with different conditions. For example, DOACs was associated with lower long-term all-cause mortality than VKAs in AF patients who were successfully discharged after transcatheter aortic valve replacement [49]. In addition, in patients with left ventricular thrombi, there is a significant reduction in stroke with the use of DOACs, without an increase in bleeding [50], and among diabetic AF patients, DOACs are associated with a lower risk of thromboembolism, major bleeding, and major adverse limb events than VKAs [51].

Nonetheless, the published data for DOACs in the field of COVID-19 is conflicting. In the context of hospitalization, many of the COVID-19 patients with prior DOAC therapy will be switched to heparins because they are expected to receive medications interacting with DOACs, or have coagulation system and homeostasis disorders [52, 53]. For this reason, it is necessary to act before hospitalization in these especially vulnerable patients. Since our results show that within 30 days of COVID-19 diagnosis there is an increased risk of complications in patients on prior VKA, whenever possible, a change to a DOAC should be considered. This may not only reduce the risk of adverse events in the case of COVID-19, but also the need for monitoring and therefore the number of visits to health care centers and the social contact that this implies, which can contribute to a lower risk of infection [54]. Some societies consider that DOAC could be maintained even during hospitalization, based on clinical conditions and assessment for drug–drug interactions [21, 55, 56].

However, there are some indications such as antiphospholipid syndrome or prosthetic heart valves for which DOACs are not approved. In such patients, a switch from VKA to DOACs is not possible, and therefore other interventions are required to achieve and maintain the highest quality of anticoagulation in order to reduce the risk of worse clinical outcomes when on VKAs. These include the identification and modification of causes of poor anticoagulation control with VKAs (eg. potential pharmacologic interactions), routine assessment of adherence to treatment, patient-centred education/counselling and educational programs for healthcare professionals, the use of multidose drug dispensing systems, self-management of VKA therapy, specialized anticoagulation clinics to improve adherence and a more careful follow-up [57, 58]. Due to the COVID-19 pandemic, telemedicine visits and telehealth programs may help to achieve these objectives while minimize exposure risks for both patients and healthcare professionals [59].

Limitations

There are some limitations that need to be acknowledged. First, 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.

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. It should also be noted that we had not access to time in therapeutic range of International Normalized Ratio (INR) for VKA-treated patients, so there are uncertainties about the quality of anticoagulation therapy in these patients. Finally, our main objective was to investigate the association of prior VKA or DOAC therapy with short-term prognosis after outpatient 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 VKAs or DOACs. For the same reason, we have not analyzed the potential role of other pharmacological therapies such as antidiabetics agents or insulin, although we recognize influence of such therapies on outcomes.

Conclusion

In COVID-19 outpatients with cardiometabolic diseases, prior use of DOAC therapy compared to VKA therapy at the time of COVID-19 diagnosis might

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reduce the risk of composite arterial or venous thrombotic outcomes, without increasing the risk of bleeding.

Abbreviations
AF: Atrial fibrillation; CDC: Centres for Disease Control and Prevention; CI: Confidence interval; COVID-19: Coronavirus Disease 2019; DOAC: Direct-acting oral anticoagulant; EMR: Electronic medical record; HCO: Healthcare organisation; HR: Hazard ratio; ICH: Intracranial haemorrhage; ICU: Intensive care unit; INR: International normalized ratio; MV: Mechanical ventilation; OAC: Oral anticoagulant; PSM: Propensity score matching; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; SD: Standard deviation; SE: Systemic embolism; SMD: Standardised mean difference; TIA: Transient ischemic attack; VKA: Vitamin K antagonist; VTE: Venous thromboembolism.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12933-021-01368-6.

Additional file 1: Table S1. ICD-10-CM codes and LOINCs for the identification of COVID-19. **Table S2.** Clinical outcomes and ICD-10-CM codes.

Authors' contributions
JMR-C and GYHL designed the study. EF-E and PU provided TriNetX access and made a critical revision. JMR-C and GYHL acquired data, performed statistical analyses and drafted the manuscript. SLH, BJRB and FM made a critical revision. All authors approved the final content for journal submission and publication. All authors read and approved the final manuscript.

Availability of data and materials
The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because some materials are used for other unpublished projects.

Declarations

Ethics approval and consent to participate
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 are made available to the users of the platform.

Consent for publication
Not applicable.

Competing interests
JMR-C has received a grant from Sociedad Española de Trombosis y Hemostasia (grant for short international training stays 2020), and the First Contact Initiative Grant 2020 from the European Society of Cardiology Council on Basic Cardiovascular Science. SLH has received a grant from Bristol Myers Squibb (BMS). FM: consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and AstraZeneca; research grants from Bayer. GYHL: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally. Other authors report no conflict of interest.

Author details
[1]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK. [2]Department of Cardiology, Hospital Clínico Universitario Virgen de La Arrixaca, University of Murcia, Instituto Murciano de Investigación Biosanitaria (IMIB-Arrixaca), CIBERCV, Murcia, Spain. [3]Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK. [4]Cardiovascular and Metabolic Medicine, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK. [5]TriNetX LLC., Cambridge, MA, USA. [6]TriNetX LLC., London, UK. [7]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

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