Risk of Thrombotic Events and Other Complications in Anticoagulant Users Infected With SARS-CoV-2: An Observational Cohort Study in Primary Health Care in SIDIAP (Catalonia, Spain)

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Abstract

Background

The risk of thromboembolic events and COVID-19 complications in anticoagulated patients once hospitalized has been widely analyzed. We aim to assess these outcomes in primary health care (PHC) patients chronically treated with oral anticoagulants (OAC) in comparison with non-treated.

Methods

Cohort study including adults with COVID-19 diagnosis in the PHC records in Catalonia, Spain; from March to June 2020. Patients were matched between exposed and non-exposed to OAC based on age and gender in a 1:2 design. Data source is the Information System for Research in Primary Care (SIDIAP).

Results

We included 11,828 (33.3%) patients previously exposed to OAC, who were matched by age and sex to 23,656 (66.7%) non-exposed to OAC. Their mean age was 79.3 and 51% were women. Anticoagulated patients had a higher risk of hospital admission (OR 1.30, 95% CI 1.22-1.38), and of stroke and pulmonary embolism than non-anticoagulated (OR 2.5, 95% CI 2.04-3.06). The risk of pneumonia was not different between groups (OR 1.09, 95% CI 0.95-1.26). We found a lower risk of death in patients exposed to OAC (OR 0.88, 95% CI 0.83-0.93).

Conclusions

OAC users in our study had more comorbidities and were older than non-users, well known risks for hospitalization being confirmed with our results. We also found in our study that OAC exposure was not associated to an increased risk in the mortality rate, although we cannot assess the effect of the interventions applied during hospital admission on the COVID-19 outcomes, as our database is a PHC database.

EUPAS register: EUPAS37205

Background

Coronavirus disease 2019 (COVID-19) is a viral respiratory illness caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), emerged as a global public health crisis in 2020.¹⁻³ Previous research has highlighted that patients with prior cardiovascular conditions are at higher risk for adverse outcomes from COVID-19⁴ and also may predispose patients to thrombotic events⁵⁻⁷ due to both direct and indirect effects of infection, such as severe illness, hypoxia or hypercoagulability.^{5,8,9}

On the one hand, anticoagulant therapy, as low-molecular weight heparins (LMWH) or oral anticoagulants (OAC), is routinely used to treat thrombotic complications in COVID-19 patients admitted to hospital.¹⁰⁻¹²

On the other hand, patients who are chronically anticoagulated for conditions such as atrial fibrillation are at higher risk of thrombotic events,⁴ and guidelines have previously established the considerations on the use of OAC in COVID-19 patients.^{10,13} Ambulatory patients already on OAC could then be thought of having less risk for thrombosis event during the COVID-19 infection though the effects of OAC in the occurrence and prognosis of complications of SARS-CoV-2 in patients chronically treated with OAC are still unknown, as little data are currently available on the prognosis and risk factors of patients exposed to OAC prior to COVID-19 infection.^{5,14}

Most studies are focused on analyzing the risk of thromboembolic events and complications from the COVID-19 infection in patients on anticoagulant treatment once hospitalized.^{15–17}

Methods

We aimed to assess these outcomes in primary health care (PHC) patients who are chronically treated with OAC in comparison with a group of non-treated with OAC.

Study design

Cohort study including adult patients with COVID-19 diagnosis registered as confirmed (by polymerase chain reaction, PCR) or as probably (not confirmed by PCR) in the PHC records in Catalonia, Spain; from the pandemics' onset (March 2020) to June 30th, 2020. Patients were matched in pairs between exposed and non-exposed to OAC based on age and gender in a 1:2 design.

Data source

The study data source is the Information System for Research in Primary Care (SIDIAP),¹⁸ which captures clinical information of approximately 5,8 million people from Catalonia, Spain (around 80% of the Catalan population). This information is pseudonymized, originated from different data sources: 1) ECAP (electronic health records in PHC of the Catalan Health Institute); including socio-demographic characteristics, residents in nursing homes/long-term facilities, comorbidities registered as International Classification of Disease (ICD)-10 codes,¹⁹ specialist referrals, clinical parameters, toxic habits, sickness leave, date of death, laboratory test data, and drug prescriptions issued in PHC, registered as chemical classification system (ATC) codes;²⁰ 2) pharmacy invoice data corresponding to the PHC drug prescriptions; 3) database of diagnoses at hospital discharge²¹ and 4) COVID-19 data from the Catalan Agency of Health Quality and Evaluation (AQuAS).²²

COVID-19 classification

Subjects were classified according to the following criteria: confirmed cases are those with a confirmed COVID-19 diagnostic record, PCR + and/or a positive serology test. Those with a non-confirmed diagnosis or test (possible or unclear) along with any individual with a record of hospitalization, pneumonia and/or death related to COVID-19 were considered possible cases. During the first wave of the COVID-19

pandemics in Catalonia, PCR tests were not routinely conducted to all patients with compatible symptoms, due to the unavailability of laboratory kits to do the tests. Thus, we needed to capture those patients with possible diagnosis of COVID-19, such as those admitted to hospital with pneumonia or other COVID-19 symptoms who were not tested. We designed an algorithm to classify patients as “COVID possible” when there was not a test result available. The date of COVID-19 diagnosis was set to be the first of all records used per patient.

To guarantee that our algorithm is not far from the Catalan population, the resulting cohort was compared to the official COVID-19 cases provided by the AQUAS during the pandemic (comparison in supplementary material, Figure S1).^{22,23}

Drug exposure

Patients were classified as exposed to OAC if they had at least one dispensation of either direct OAC (DOAC) or vitamin K antagonists (VKA) during the three previous months to the COVID-19 diagnosis date.

Variables

At baseline, the variables captured were: sex, age, geographical area, MEDEA socioeconomic index (deprivation index based on five indicators of socio-economic position. The higher this is, the worse the deprivation is, and it allows analyzing health inequalities),²⁴ body mass index (BMI), residence in nursing homes, smoking habit, comorbidities, and drug exposure to OAC and to comedications which might be associated with the COVID-19 prognosis and/or the events studied: antiplatelets, non-steroidal anti-inflammatory drugs, systemic corticosteroids and LMWH.

Main outcomes: diagnosis of pneumonia, thrombotic composite outcome containing stroke and pulmonary embolism, hospital admission, and mortality. The risk of these events was analyzed comparing patients exposed to OAC with non-exposed.

Statistical analysis

Quantitative variables were described as the mean and standard deviation, whereas categorical variables were described as the proportion over the exposed and non-exposed individuals. Univariate analysis was done by means of Student's t-test and Chi-square test as appropriate.

For each outcome, we fitted a conditional logistic regression model (clogit) to estimate an odds ratio (OR) comparing the prevalence of each outcome among individuals exposed to OAC to those non-exposed to the drug. The clogit accounted for matched pairs and was fitted including other covariables such as smoking habits, comorbidities and concomitant drugs. Variable selection was performed using the AIC-based stepwise backward procedure and we used the Wald test on the fitted coefficient to determine whether the log-odds was significantly different from zero at a 0.05 level. All analyses were performed in R software (v3.6.3).

We conducted a sensitivity analysis of the risk of the events excluding those patients living in nursing homes or long-term care facilities.

Results

We included 35,484 patients in our study; 11,828 (33.3%) had been previously exposed to OAC, and they were matched by age and sex to 23,656 (66.7%) who were not exposed to OAC. Their mean age was 79.3 years-old (SD 11.8), 51% were women and 70.1% were living in the Barcelona metropolitan area. The most frequent comorbidities were hypertension (69.7%) and respiratory diseases (30.4%). Those exposed to OAC had a higher frequency of comorbidities than non-exposed. Table 1 includes all baseline sociodemographic and clinical characteristics of patients included in the study.

Table 1
Baseline sociodemographic and clinical characteristics of patients included in the study.

N (%)	Overall 35,484	OAC non- exposed 23,656	OAC exposed 11,828	P-value**
Sex, male	17376 (49.0)	11584 (49.0)	5792 (49.0)	1 (matched)
Age, mean (SD)	79.30 (11.84)	79.30 (11.84)	79.30 (11.84)	1 (matched)
Smoker	14898 (42.0)	9592 (40.5)	5306 (44.9)	< 0.001
Non-smoker	20586 (58.0)	14064 (59.5)	6522 (55.1)	
BMI, mean (SD)	28.32 (5.28)	27.83 (5.02)	29.14 (5.59)	< 0.001
Obesity* (%)	10172 (39.2)	6973 (42.7)	3199 (33.4)	< 0.001
	Missing, 9545(26.9)			
COVID-19 diagnosis	17616 (49.6)	12017 (50.8)	5599 (47.3)	< 0.001
positive	17868 (50.4)	11639 (49.2)	6229 (52.7)	
possible				
Nursing home	11037 (31.1)	7897 (33.4)	3140 (26.5)	< 0.001
MEDEA†				
Unknown	11991 (33.8)	8150 (34.5)	3841 (32.5)	< 0.001
Rural areas	6744 (19.0)	4673 (19.8)	2071 (17.5)	
Urban, quintiles 1st -3rd	15483 (43.6)	10389 (43.9)	5094 (43.0)	
Urban, quintiles 4th -5th	8010 (22.6)	5117 (21.7)	2893 (24.4)	
Comorbidities***				
Chronic kidney disease	9015 (25.4)	5395 (22.8)	3620 (30.6)	< 0.001

* IMC > 30 or ICD-10 diagnosis

** Obtained from a Chi-square test in categorical variables, and t-test in numerical variables

*** Starting or active one year before COVID-19 diagnosis

**** Registered dispensation three months before COVID-19 diagnosis

†OAC; oral anticoagulants. SD; standard deviation. BMI; body mass index. MEDEA deprivation index based on five indicators of socio-economic position. The higher this is, the worse the deprivation.²⁴ LMWH; low-molecular weight heparins. NSAID; nonsteroidal anti-inflammatory drugs.

N (%)	Overall 35,484	OAC non- exposed 23,656	OAC exposed 11,828	P-value**
Diabetes mellitus	10501 (29.6)	6618 (28.0)	3883 (32.8)	< 0.001
Heart failure	5285 (14.9)	1892 (8.0)	3393 (28.7)	< 0.001
Hypertension	24728 (69.7)	15730 (66.5)	8998 (76.1)	< 0.001
Ischemic coronary disease	4346 (12.2)	2302 (9.7)	2044 (17.3)	< 0.001
Respiratory disease	10775 (30.4)	6315 (26.7)	4460 (37.7)	< 0.001
Thromboembolism	762 (2.1)	173 (0.7)	589 (5.0)	< 0.001
Concomitant Drugs****				
Antiplatelets	7247 (20.4)	6488 (27.4)	759 (6.4)	< 0.001
LMWH	863 (2.4)	436 (1.8)	427 (3.6)	< 0.001
NSAID	12074 (34.0)	6851 (29.0)	5223 (44.2)	< 0.001
Systemic corticosteroids	2687 (7.6)	1420 (6.0)	1267 (10.7)	< 0.001
* IMC > 30 or ICD-10 diagnosis				
** Obtained from a Chi-square test in categorical variables, and t-test in numerical variables				
*** Starting or active one year before COVID-19 diagnosis				
**** Registered dispensation three months before COVID-19 diagnosis				
†OAC; oral anticoagulants. SD; standard deviation. BMI; body mass index. MEDEA deprivation index based on five indicators of socio-economic position. The higher this is, the worse the deprivation. ²⁴ LMWH; low-molecular weight heparins. NSAID; nonsteroidal anti-inflammatory drugs.				

The frequencies of events of interest which were assessed after the diagnosis of COVID-19 are shown in Table 2. Patients exposed to OAC showed a higher frequency of stroke and pulmonary embolism (1% vs 0.7%, p-value = 0.001 and 1.1% vs 0.4%, p < 0.001, respectively) and of hospital admission (15.3% vs 12.1% p < 0.001) than the non-exposed, and lower frequency of death (16.6% vs 17.7% p = 0.008). The frequency of pneumonia was not different between groups (2.6% vs 2.8%, p-value = 0.247).

Table 2
Number of events of interest after the COVID-19 diagnosis

N (%)	Overall	OAC non-exposed	OAC exposed	p-value**
	35,484	23,656	11,828	
Pneumonia	939 (2.6)	609 (2.6)	330 (2.8)	0.247
Stroke	272 (0.8)	155 (0.7)	117 (1.0)	0.001
Pulmonary embolism	213 (0.6)	88 (0.4)	125 (1.1)	< 0.001
Hospital admission	4664 (13.1)	2860 (12.1)	1804 (15.3)	< 0.001
Death	6156 (17.3)	4194 (17.7)	1962 (16.6)	0.008
†OAC; oral anticoagulants. SD; standard deviation.				

The results of the conditional logistic regression model are shown in Fig. 1. Patients exposed to OAC had a higher risk of hospital admission (OR 1.30, 95% CI 1.22–1.38), and the composite endpoint composed by stroke and pulmonary embolism than non-anticoagulated patients (OR 2.5, 95% CI 2.04–3.06). The risk of pneumonia was not different between exposure groups (OR 1.09, 95% CI 0.95–1.26). The risk of death was lower for patients exposed to OAC compared to non-exposed (OR 0.88, 95% CI 0.83–0.93).

When we analyzed these results excluding those patients living in nursing homes/long-term care facilities, we obtained the same results, maintaining the thread of the results of all the PHC population (Table 3).

Table 3
Risk of events of interest excluding patients living in long-term facilities

Outcome	Adjusted OR	95% CI	p-value
Pneumonia	1.05	0.87–1.26	0.607
Stroke + Pulmonary embolism	3.35	2.58–4.35	< 0.001
Hospital admission	1.24	1.14–1.35	< 0.001
Death	0.91	0.83–0.99	0.037
OR obtained by fitting a conditional logistic model adjusted by matched samples with AIC-based stepwise variable selection algorithm.			

Discussion

We analyzed the thromboembolic and fatal outcomes in a COVID-19 cohort (n = 35,484 patients), comparing those individuals who were exposed to OAC to those non-exposed, matched by age and sex. In our study, those patients exposed to OAC had a higher risk of hospital admission (OR 1.30, 95% CI 1.22–1.38) and thromboembolic events – stroke and pulmonary embolism (OR 2.5, 95% CI 2.04–3.06) – than

those who were not treated with OAC. Those patients exposed to OAC had a lower risk of mortality than non-exposed (OR 0.88, CI 95% 0.83–0.93). We found no differences in the risk of pneumonia between groups. Similar results were found when we excluded the population living in nursing homes, which had a higher rate of COVID-19 infection and negative outcomes during the first wave of the pandemic when compared with the general population.²³

Patients with cardiovascular conditions have been reported as having a higher risk for adverse events from COVID-19 and thrombotic events.^{4–7} For instance, Inciardi et al. analyzed data of 99 COVID-19 patients with pneumonia, 53.5% of them had previous cardiovascular diseases, and found a higher mortality in this subgroup of patients (RR 2.35, 95% CI 1.08–5.09). They did not report on the use of comedications.²⁵

As anticoagulant therapy as LMWH is used to treat thrombotic complications in COVID-19 patients, chronic treatment with OAC may play a role in lowering the risk of thrombotic events caused by SARS-CoV-2 infection, and in this alignment, some studies have previously assessed complications in COVID-19 patients according to their previous exposure to OAC, finding different results. Rivera-Caravaca et al. studied 1,002 patients from Ecuador, Germany, Italy and Spain who were admitted to hospital due to COVID-19 and were previously treated with OAC. They found a HR of 1.53 (CI95% 1.08–2.16) for mortality when compared OAC users with non-users.²⁶

Russo et al. enrolled 192 COVID-19 patients to study the risk of suffering acute respiratory distress syndrome (ARDS) and/or death during hospitalization. They found no protective effect for these events in the 26 (13.5%) patients who were OAC users admitted to hospital.²⁷

Denas et al. conducted a population-based propensity score-matched study in the Veneto Region, Italy. They included 4,697 COVID-19 patients older than 65 and matched 559 anticoagulated patients to 559 non-exposed. They found a rate ratio of all-cause mortality higher in non-anticoagulated patients (32.2% vs 26.5%), although the estimate was not statistically significant; HR 0.81, 95%CI 0.65–1.01. The authors discussed a possible role of OAC in reducing the mortality in that group of patients, although taking into account that they might have been switched to LMWH during hospitalization and other interventions might have also affected the outcomes.²⁸ Similar results, finding OAC exposure as having a protecting role, are shown in an Italian study [HR for death 0.38 (0.17–0.58)].²⁹ Our findings do not show a higher risk among those exposed to OAC, risk that also do not show when analyzing a subpopulation of those patients not in long-term facilities.

Tremblay et al. conducted a study in 3,772 COVID-19 patients treated with OAC, antiplatelets or non-treated with antithrombotics. They did two propensity score matchings, comparing OAC-treated vs non-treated and antiplatelets-treated vs non-treated. The HR for all-cause mortality, mechanical ventilation and hospital admission were not significant. The Kaplan-Meier survival analyses did not show differences between groups. They did not exclude the possibility that anticoagulation during COVID-19

infection may be useful but they did not find that previous treatment with OAC may protect from severe forms of COVID-19.³⁰

In a study in France, 90% of COVID-19 patients admitted to the ICU because of pulmonary thromboembolism were receiving prophylactic anticoagulant (LMWH) treatment according to critically ill patients' guidelines, but the study did not analyze if these patients were already on prophylactic anticoagulant treatment due to previously indications such as atrial fibrillation.³¹

We found that OAC users were more frequently hospitalized than non-users. This outcome has not been assessed in the cited studies above, as all patients included in those studies were already hospitalized for SARS-CoV-2 infection.^{15,16,31,32} Our study includes those hospitalized and those who not, and it reveals that anticoagulated patients had more comorbidities and were older, well known risks for hospitalization being confirmed with our results.

Among the limitations of our study there is the reliability of the COVID-19 diagnoses; we included patients without a confirmed result as during the first wave of the pandemic in our setting PCR test were not always performed. This limitation has been described in other research as during the beginning of the pandemic diagnosis test for COVID-19 were not widely available, and clinical algorithms have been used to assess COVID-19 diagnosis.³³ Another limitation is the lack of hospital information: we cannot capture ICU admission, ventilation or treatments administered during the admission, which clearly have influence in the prognosis and outcomes of COVID-19.

We also found in our study that OAC exposure was not associated to an increased risk in the mortality rate, although we cannot assess the effect of the interventions applied during hospital admission on the mortality, scales of prognosis, complications, treatments and specific outcomes in COVID-19 hospital admitted patients, as our database is a PHC database and does only record the dates of admission and diagnoses and cause of discharge.

Some strengths of our study include the large number of patients included, representativeness for general population, and complete socio-demographic data. We must highlight that our cohort are PHC patients, so we have estimated the risk of death and hospitalization for a different population from the only hospitalized ones that are usually studied.

Conclusions

OAC users in our study had more comorbidities and were older than non-users, well known risks for hospitalization being confirmed with our results.

We found that OAC exposure was not associated to an increased risk in the mortality rate in our study, although we cannot assess the effect of the interventions applied during hospital admission on the COVID-19 outcomes, as our database is a PHC database.

We must highlight that our cohort are PHC patients, so we have estimated the risk of death and hospitalization for a different population from the only hospitalized ones that are usually studied.

List Of Abbreviations

AQuAS

Catalan Agency of Health Quality and Evaluation

ATC

anatomical therapeutic chemical classification

BMI

body mass index

CI

confidence interval

COVID-19

coronavirus disease 2019

DOAC

direct oral anticoagulants

ECAP

electronic health records in primary care of the Catalan Health Institute

ICD

international classification of diseases

IDIAPJGol

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LMWH

low-molecular weight heparins

MEDEA

socioeconomic index

OAC

oral anticoagulants

OR

odds ratio

PCR

polymerase chain reaction

PHC

primary health care

SARS-CoV-2

severe acute respiratory syndrome-coronavirus-2

SD

standard deviation

SIDIAP

information system for research in primary care
VKA
vitamin K antagonists

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Research Ethics Committee of IDIAPJGol (approval on June 3rd 2020) and the SIDIAP's scientific committee. This is a database research study which has been conducted according to the guidelines of the Declaration of Helsinki (Fortaleza, Brazil 2013) and does not require consent from the people included to participate or for publication. The need for consent was waived by the Research Ethics Committee of IDIAPJGol as it is deemed unnecessary according to European legislation (Regulation [EU] 2016/679).

Availability of data and materials

Data for this study can be accessed at request to the corresponding author.

Competing interests

The authors declare that they do not have conflict of interests.

Consent for publication

All authors give their consent for the publication of all results related with this study.

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Author's contributions

MGS, AGL, CV, DO and RM designed the study. DO conducted the statistical analysis. MGS, AGL, CV, DO and RM interpreted the results. MGS and AGL wrote the first version of the manuscript. MGS, AGL, CV, DO and RM reviewed and approved the final version of the manuscript.

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Figures

Figure 1

Risk of events of interest according to the conditional logistic regression model Adjusted OR in exposed to OAC (95% CI)

Supplementary Files

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