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

Thrombosis Research 198 (2021) 99–102

Contents lists available at ScienceDirect

Thrombosis Research

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

Letter to the Editors-in-Chief

Association of anticoagulation use with SARS-CoV2 detection☆

The Coronavirus Disease 2019 (COVID-19) pandemic has presented an unprecedented world-wide healthcare challenge, with many aspects of the disease still left to be understood. Significant literature has been dedicated to anticoagulation management during the pandemic, mostly in the form of consensus guidelines [1–3]. Our aim is to determine whether the type of anticoagulation a patient is chronically taking correlates with a higher risk of severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) test positivity. Direct oral anticoagulants (DOACs) are as effective as warfarin in reducing thrombotic events and are associated with lower bleeding risk in patients with non-valvular atrial fibrillation and in most patients on anticoagulation for venous thromboembolic disease (VTE) [4]. However, DOACs are not appropriate for all patients. Given the concern of risk of COVID-19 due to increased potential exposures from frequent laboratory monitoring for warfarin, the consensus recommendations are to consider alternative anticoagulants for eligible patients [3,5,6]. We present data for all patients within the Kaiser Permanente Northern California (KPNC) healthcare delivery system who were on anticoagulation, antiplatelet therapy, or both, in the 3 months prior to the COVID-19 pandemic in California as well as controls suggesting that warfarin can safely be continued in appropriate patients during the COVID-19 pandemic.

KPNC is an integrated healthcare delivery system of hospitals and clinics caring for more than 4 million patients with a commonly accessible electronic medical record system across the diverse community of Northern California. Within this setting, patients on warfarin are managed by a designated pharmacy service that monitors serum protime (PT) and international normalized ratio (INR) results. After regular phlebotomy testing is resulted, pharmacists subsequently communicate with patients any dose adjustments and determine timing of future INR monitoring. During the COVID-19 pandemic, all patients who were unable to complete INR testing as needed were converted to DOACs. All new warfarin prescriptions referred to the service were evaluated for the ability to convert to a DOAC if appropriate, and pharmacists communicated this option to the referring provider. Video teaching was leveraged to increase the use of home INR fingerstick testing. Patients with a stable therapeutic INR, or those close to the therapeutic range, which was determined by their underlying condition, were monitored less frequently. This was done to minimize foot-traffic within the medical centers and reduce potential exposures. The time between INR tests were extended by 1–2 weeks from baseline for eligible patients and was dependent on patients' underlying clinical risk factors and historical INR values. This change in clinical practice occurred during March 2020, which we describe as the care-transition period.

For this retrospective cohort study we reviewed pharmacy medication fills and patient medication lists in the 3 months prior to the COVID-19 pandemic (11/27/2019–2/25/2020) to identify all adults (≥18 years old) who were on warfarin, warfarin and antiplatelets, non-warfarin anticoagulants (DOAC's, low molecular weight heparin), non-warfarin anticoagulants and antiplatelets, and antiplatelets alone. They were compared to a randomly selected group of control patients not on any anticoagulation or antiplatelet therapy. We excluded patients who did not have any health plan membership in the preceding 2 years and patients who were missing information about their sex or date of birth. Positive SARS-CoV2 lab tests between 2/25/2020 and 7/5/2020 were included in the outcome.

We performed logistic regression for the odds of a positive SARS-CoV2 lab test for patients on anticoagulant and/or antiplatelet therapy adjusting for patient age, sex, race/ethnicity, body mass index, Charleston comorbidity index, hypertension, diabetes, and smoking history. Using data from the anticoagulation pharmacy service, we also calculated the average percent time in the therapeutic range (TTR) and 95% confidence intervals of patients on warfarin for 3 time periods: pre-COVID-19 care (January–February 2020), care transition period (March 2020), and post-COVID-19 care changes (April–June 2020) to see if the care changes implemented within KPNC due to the COVID-19 pandemic were associated with changes in TTR rates.

Among 188,438 adults on anticoagulant and/or antiplatelet therapy between 11/27/2019 and 2/25/2020 and 188,438 randomly selected adult controls not on these medications, we identified 1029 patients within KPNC who tested positive for SARS-CoV2 between 2/25/2020 and 7/5/2020. Of 30,242 patients on warfarin (with or without antiplatelets) 73 (0.24%) tested positive for SARS-CoV2, and of 34,331 patients on a non-warfarin anticoagulant (with or without antiplatelets) 87 (0.25%) tested positive for SARS-CoV2 (Table 1). When compared to patients who were not on anticoagulants or anti-platelets, patients on warfarin alone (odds ratio (OR) 0.87, 95% confidence interval (CI) 0.64–1.17) or warfarin and an antiplatelet (OR 1.05, CI 0.55–2.01) were not at increased risk of testing positive for SARS-CoV2 adjusting for demographic and clinical characteristics (Table 2). This was also true when comparing patients on non-warfarin anticoagulants alone (OR 1.01, CI 0.76–1.35), antiplatelets alone (OR 1.12, CI 0.92–1.35), and antiplatelets along with non-warfarin anticoagulants (OR 1.35, CI 0.78–2.32) to control patients.

Patients within the 60 to 79-year-old age group were at lower risk of a positive SAR-CoV2 test compared to patients aged 18–29 years (OR age 60–69: 0.61, CI 0.46–0.80; OR age 70–79: 0.52, CI 0.39–0.71). Consistent with previously reported data, we found patients who are African American (OR 1.69, CI 1.33–2.16), Asian (OR 1.46, CI 1.19–1.80), or Hispanic (OR 3.52, CI 3.01–4.12) were more likely to test positive for SARS-CoV2 [7]. Patients who were obese were more likely to test positive than healthy weight patients (OR 1.28, CI 1.08–1.52). In our data, hypertension, diabetes,

☆ The authors have no relevant financial disclosures to disclose.

https://doi.org/10.1016/j.thromres.2020.11.034
Received 27 August 2020; Received in revised form 27 September 2020; Accepted 23 November 2020
Available online 2 December 2020

Table 1
Characteristics of 376,876 Kaiser Permanente Northern California Patients on anticoagulants or antiplatelets and controls (positive SARS-CoV2 N = 1029).

	Warfarin[c] N = 30,242%	Non-warfarin anticoagulant[d] N = 34,331%	Antiplatelet N = 123,865%	None N = 188,438%
Age, years				
18–29	1	1	1	23
30–39	2	2	3	22
40–49	4	3	5	18
50–59	9	9	16	16
60–69	19	22	30	12
70–79	31	36	28	6
80+	35	27	18	3
Median (IQR)	75 (66–83)	74 (66–81)	69 (60–77)	43 (31–58)
Sex				
Male	56	54	55	49
Female	44	46	45	51
Race/ethnicity				
African American	7	6	9	6
Asian	9	10	16	19
Hispanic	12	9	15	20
White	66	69	53	39
Missing/other	6	6	7	16
Body mass index[a]				
Underweight	2	2	1	1
Healthy weight	24	25	23	28
Overweight	32	34	35	30
Obese	43	39	40	28
Unknown	<0.5	<0.5	1	13
Median (IQR)	29 (25–34)	28 (25–33)	29 (25–33)	27 (24–31)
Charlson comorbidity index				
0	13	16	17	82
1–2	29	34	38	15
≥3	57	50	45	4
Median (IQR)	3 (1–5)	3 (1–5)	2 (1–4)	0 (0–0)
Hypertension				
Yes	46	47	45	5
No	54	53	55	95
Diabetes				
Yes	31	26	36	5
No	69	74	64	95
Smoking status[a]				
Ever	51	50	49	26
Never	49	49	50	62
Unknown	<0.5	<0.5	<0.5	12
Any SARS-CoV2 test[b]				
Yes	12	12	10	5
No	88	88	90	95
Positive SARS-CoV2 test[b]				
Yes	0.24 (N = 73)	0.25 (N = 87)	0.31 (N = 390)	0.25 (N = 479)
No	99.76	99.75	99.69	99.75

IQR: inter-quartile range.
[a] Includes information from 10 years prior to 2/25/2020.
[b] Includes SARS-CoV2 test results between 2/25/2020 and 7/5/2020.
[c] Includes 3223 (11%) patients who are on both warfarin and antiplatelet.
[d] Includes 4224 (12%) patients who are on or non-warfarin anticoagulant and antiplatelet.

Table 2
Odds ratio of testing positive for SARS-CoV2 between 2/25/2020 and 7/5/2020 N = 376,876 (positive SARS-CoV2 N = 1029).

	OR	95% CI
Medication		
Warfarin N = 27,019	0.87	0.64–1.17
Non-warfarin anticoagulant N = 30,107	1.01	0.76–1.35
Antiplatelet N = 123,865	1.12	0.92–1.35
Warfarin and antiplatelet N = 3223	1.05	0.55–2.01
Non-warfarin anticoagulant and antiplatelet N = 4224	1.35	0.78–2.32
None N = 188,438	1.00	Ref
Age, years		
18–29	1.00	Ref
30–39	1.19	0.93–1.52
40–49	1.03	0.80–1.33
50–59	0.97	0.75–1.24
60–69	0.61	0.46–0.80
70–79	0.52	0.39–0.71
80+	0.91	0.67–1.24
Sex		
Male	1.00	Ref
Female	1.05	0.92–1.19
Race/ethnicity		
African American	1.69	1.33–2.16
Asian	1.46	1.19–1.80
Hispanic	3.52	3.01–4.12
White	1.00	Ref
Missing/other	1.50	1.17–1.93
Body mass index[a]		
Underweight	0.96	0.54–1.72
Healthy weight	1.00	Ref
Overweight	1.00	0.83–1.19
Obese	1.28	1.08–1.52
Charlson comorbidity index		
0	1.00	Ref
1–2	1.40	1.15–1.71
≥3	2.09	1.63–2.69
Hypertension		
Yes	0.97	0.81–1.15
No	1.00	Ref
Diabetes		
Yes	1.16	0.97–1.39
No	1.00	Ref
Smoking status[a]		
Ever	0.86	0.75–0.98
Never	1.00	Ref

OR: odds ratio; CI: confidence interval.
[a] Also adjusts for unknown status.

female sex, and smoking status were not associated with a higher risk of a positive SARS-CoV2 test (Table 2).

Between January and June 2020 an average of 35,096 patients had their INR's monitored through the anticoagulation pharmacy service. The TTR of these patients remained stable between 72 and 73% during this period. March 2020 was the month during which transitions in care for patients on warfarin occurred, allowing patients with more stable INR levels over time to extend testing intervals by an additional 1–2 weeks on average. The TTR percentages in January and February 2020 were 72.7% (CI 72.4–72.9) and 72.4% (CI 72.2–72.7) respectively, with no significant differences noted in April, May, and June 2020 where they were 72.4% (CI 72.1–72.7), 72.3% (CI 72.1–72.6) and 72.2% (CI 71.9–72.4) respectively (Fig. 1). For comparison, the percentage of patients within KPNC with TTR in 2019 was 72.8% with the 95% CI between 73.1% and 72.4% (Fig. 2).

To our knowledge, this is the first report to examine the association between chronic anticoagulation use and risk of contracting COVID-19 in a

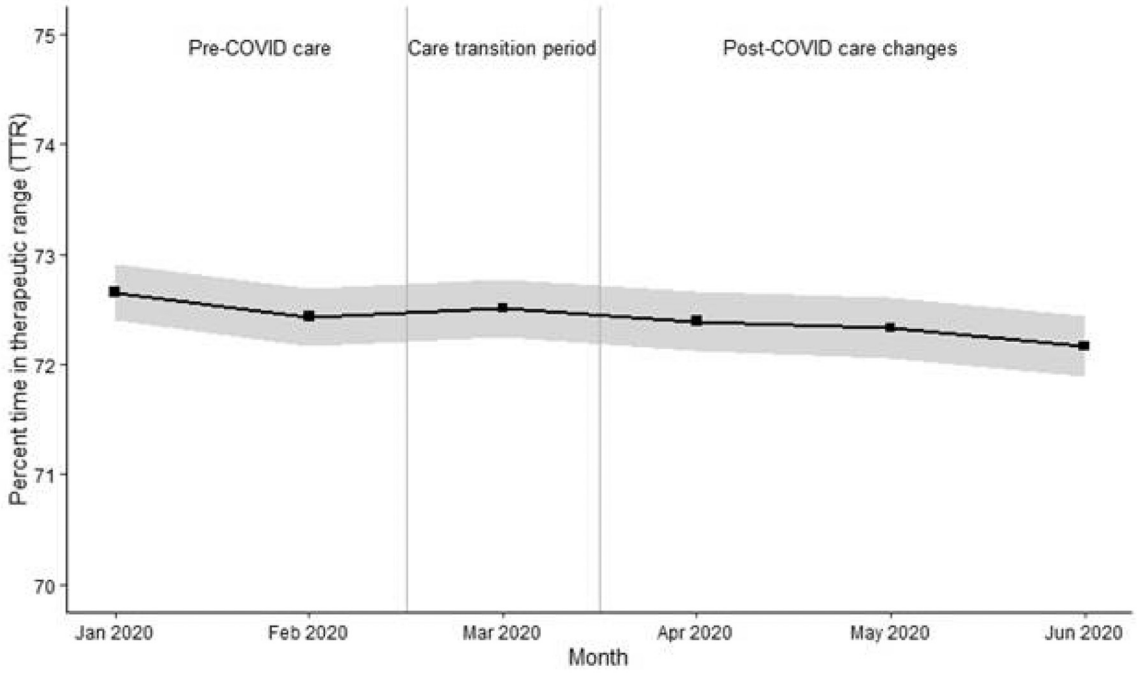

Fig. 1. Graph showing the percentage of patients on warfarin with INRs in the therapeutic range.

Key Findings:

1) Patients with an indication for chronic warfarin can safely continue warfarin therapy with appropriate precautions during the COVID-19 pandemic.
2) Chronic warfarin therapy is not associated with a higher rate of positively testing for SAR-CoV2.
3) Patients on warfarin during the COVID-19 pandemic maintained TTR rates consistent with those prior to the COVID-19 pandemic.

Fig. 2. Summary of key findings.

large integrated healthcare system. Our experience demonstrates that with an effective protocol to manage warfarin, the medication can be continued safely and effectively without an increase in the risk of a positive SARS-CoV2 test. We conclude that an effective TTR could be maintained even with slightly prolonged intervals of INR testing in patients with a history of stable tests. Notably, we chose to use TTR rates as the standard indicator of efficacy for warfarin rather than analyzing rates of bleeds or development of thrombosis as clinical adverse events, as these have been shown to be under-reported by patients during the pandemic [8].

We were also able to confirm observations supported in the literature that patients with obesity and a higher number of comorbidities have an elevated risk of a positive SARS-CoV2 test [9]. Consistent with Chinese data, we also found that while older people in their 70s and 80s have worse outcomes, younger patients may have an increased risk of testing positive for SARS-CoV2 [10].

Within KPNC, we have a dedicated pharmacy team that monitors INR levels and guides patients regarding warfarin dose adjustments and future INR monitoring. Mitigation strategies to prevent COVID-19 transmission included an expansion of use of home INR self-tests, which was initially restricted to patients with limited mobility and other comorbidities, and active attempts to convert eligible patients to DOAC's. Most patients had their INR monitored via routine visits to phlebotomy labs within our medical centers. During the COVID-19 pandemic, however, we have been taking precautions to limit the number of patients in the medical center, including within the phlebotomy laboratory. All staff, including phlebotomists, wear personal protective equipment, and patient contact areas are thoroughly cleaned between patients.

A limitation of the study is the fact that our data can only include patients tested for SARS-CoV2 within the KPNC system. We anticipate very few KPNC members were tested outside of KPNC because of the ease of testing and wait times relative to testing in the local area outside of KP, however we do not have data confirming how many patients tested outside KPNC. Also, this data may not be applicable to a patient population with a lower mean TTR, as they may require more frequent blood draws to effectively manage their warfarin dosing, which may subsequently increase the risk of potential exposures. Nevertheless, because of our large patient population, these limitations do not invalidate our conclusions, and provide valuable insight to the impact of SARS-CoV2 risk among patients on anticoagulants. Further research can be aimed to report the long-term outcomes and SARS-CoV2 risk among anticoagulated patients, including survival rates among COVID-19 patients taking different anticoagulants.

Our current study, however, does provide valuable knowledge to the management of patient who warrant anticoagulation during the COVID-10 pandemic. We demonstrate that with an integrated system in which TTR rates can be effectively maintained at 70% or higher, and appropriate infection control precautions can be employed, there is no increased risk of a positive SARS-CoV2 test among patients taking warfarin compared to patients who are on DOAC's or the general population.

CRediT authorship contribution statement

J. Kavecansky developed the study, analyzed the data and wrote the manuscript
J. Dusendang developed the study, collected the data, analyzed the data and contributed to the manuscript
J. Tavakoli analyzed the data and contributed to the manuscript
J. Schmittdiel developed the study, analyzed the data and contributed to the manuscript
G. Ho analyzed the data and contributed to the manuscript
J. Loyles collected the data and contributed to the manuscript
A. Pai conceived and designed the study, analyzed the data and wrote the manuscript

Acknowledgements

The authors would like to thank Dr. Douglas Corley for his insights into the project.

References

[1] M.Y. Abou-Ismail, A. Diamond, S. Kapoor, Y. Arafah, L. Nayak, The hypercoagulable state in COVID-19: incidence, pathophysiology, and management [published online ahead of print, 2020 Jun 20], Thromb. Res. 194 (2020) 101–115, https://doi.org/10.1016/j.thromres.2020.06.029.
[2] R. Emert, P. Shah, J.G. Zampella, COVID-19 and hypercoagulability in the outpatient setting, Thromb. Res. 192 (2020) 122–123, https://doi.org/10.1016/j.thromres.2020.05.031.
[3] G. Barnes, A. Burnett, A. Allen, et al., Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum, J. Thromb. Thrombolysis 50 (2020) 72–81.
[4] Amin A, Keshishian A, Dina O, et al. Comparative clinical outcomes between direct oral anticoagulants and warfarin among elderly patients with non-valvular atrial fibrillation in the CMS medicare population [published correction appears in J Thromb Thrombolysis. 2020 Jun 20;:]. J. Thromb. Thrombolysis 2019;48(2):240–249. doi:https://doi.org/10.1007/s11239-019-01838-5.
[5] J.M. Connors, J.H. Levy, COVID-19 and its implications for thrombosis and anticoagulation, Blood. 135 (23) (2020) 2033–2040, https://doi.org/10.1182/blood.2020006000.
[6] C.S. Kow, W. Sunter, A. Bain, S.T.R. Zaidi, S.S. Hasan, Management of outpatient warfarin therapy amid COVID-19 pandemic: a practical guide [published online ahead of print, 2020 May 26], Am. J. Cardiovasc. Drugs (2020) 1–9, https://doi.org/10.1007/s40256-020-00415-z.
[7] Rentsch CT, Kidwai-Khan F, Tate JP, et al. Covid-19 by race and ethnicity: a national cohort study of 6 million United States veterans. Preprint. medRxiv. 2020; 2020.05.12.20099135. Published 2020 May 18. doi:https://doi.org/10.1101/2020.05.12.20099135.
[8] G. Mantica, N. Riccardi, C. Terrone, A. Gratarola, Non-COVID-19 visits to emergency departments during the pandemic: the impact of fear, Public Health 183 (2020) 40–41, https://doi.org/10.1016/j.puhe.2020.04.046.
[9] Zhou Y, Chi J, Lv W, Wang Y. Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (Covid-19) [published online ahead of print, 2020 Jun 26]. Diabetes Metab. Res. Rev. 2020;e3377. doi:https://doi.org/10.1002/dmrr.3377.
[10] C. Huang, Y. Wang, X. Li, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [published correction appears in Lancet. 2020 Jan 30;:], Lancet. 395 (10223) (2020) 497–506, https://doi.org/10.1016/S0140-6736(20)30183-5.

Juraj Kavecansky[a,*], Jennifer R. Dusendang[b], Jahan Tavakoli[c], Julie Schmittdiel[b], Gwendolyn Ho[d], Jodi Loyles[e], Ashok Pai[f]
[a] *Kaiser Permanente, Antioch, CA, United States of America*
[b] *Kaiser Permanente, Division of Research, Oakland, CA, United States of America*
[c] *Kaiser Permanente, San Francisco, CA, United States of America*
[d] *Kaiser Permanente, Sacramento, CA, United States of America*
[e] *Kaiser Permanente, Pharmacy Services, Oakland, CA, United States of America*
[f] *Kaiser Permanente, Oakland, CA, United States of America*

[*] Corresponding author at: Department of Hematology Oncology, Kaiser Permanente, United States of America.
E-mail address: Juraj.Kavecansky@kp.org (J. Kavecansky).