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Letter to the Editors-in-chief

A perfect storm: Root cause analysis of supra-therapeutic anticoagulation with vitamin K antagonists during the COVID-19 pandemic



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King's College Hospital hosts a busy anticoagulation clinic in south London within the epicentre of the COVID-19 outbreak in the UK [1]. After the UK entered a period of 'lockdown' from 23/03/2020, the Government advised shielding of elderly and vulnerable patients and limiting hospital visits. UK guidance for anticoagulation services was issued ([Guidance for the safe switching of warfarin to direct oral anticoagulants \(DOACs\) for patients with non-valvular AF and venous thromboembolism \(DVT / PE\) during the coronavirus pandemic](#)) with recommendations around maintaining safe anticoagulation whilst minimising exposure to COVID-19 infection [2]. These included switching to direct oral anticoagulants (DOACs) where appropriate, self-testing INRs, increasing the INR test interval for previously stable patients, and temporarily suspending anticoagulation with VKA therapy where this could no longer be safely continued. Despite implementation of these recommendations, we noted frequent high INR readings in clinical practice during this period. Routine practice at our institution is to perform root cause analysis on all INR results above > 8.0 . We report on the frequency of supra-therapeutic INR values during the COVID-19 pandemic compared to the previous year and during lockdown and describe the findings of the root cause analysis.

Methods

All INR results taken within our hospital and community anticoagulation service during a 6-week period were identified (01/03/2020–17/04/2020) centred around the lockdown date of 23/03/2020. We then compared these to the results from the same period in 2019. All cases with excessive elevation of the INR (> 8.0) were selected. Data was collated from the anticoagulant clinic record and electronic patient records, which included patient characteristics, INR test frequency, drug compliance, co-medications, and changes in diet and alcohol intake as well as patient-reported events including bleeding. Bleeding events were defined by ISTH criteria [3,4]. Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated to compare the incidence of high INRs during each time period. Root cause analysis was performed according to routine clinical practice, and the results reviewed by a panel of three in-house anticoagulation specialists. COVID-19 was defined as a risk factor for a high INR reading if the disease was possible or confirmed [5].

Results

During the 2020 reporting period, 30/3214 (0.9%) INR samples received were > 8.0 ($n = 30$ patients), compared to 6/4079 (0.1%) ($n = 6$ patients) during the same period in the previous year (OR 6.3, 95% CI, 2.6–15.2; $p < .001$).

The time in therapeutic range during this period in 2020 was 69.6% compared with 73.7% in 2019.

The characteristics of the patients with an INR > 8 are described in Table 1.

During the pandemic, 22/30 (73%) high INRs occurred during the 3-week lockdown period (OR 3.43, 95% CI, 1.52–7.73; $p < .003$). Risk factors for a high INR were identified during root cause analysis. These included COVID-19 infection (10 confirmed, 6 possible, totaling 16/30, 53%), antibiotic therapy (17/30, 57%), inpatient admission (12/30, 40%), recent hospital discharge within the previous 4 weeks (5/30, 17%), missed test date (3/30, 10%), entering an end of life treatment pathway (3/30, 10%), higher target INR (3/30, 10%), other interacting drugs (2/30, 7%) and prolonged test interval (1/30, 3%). The majority (13/16, 81%) of patients with possible or confirmed COVID-19 were prescribed antibiotics. In (2/30, 7%) patients the elevated INR was unexplained. (3/30, 10%) patients experienced bleeding: 2 minor bleeding, and 1 major bleed (spontaneous retroperitoneal haemorrhage), with no recorded deaths due to bleeding.

Discussion

Our data reveals a significant increase in high INR results during the COVID-19 pandemic, with the majority occurring after the introduction of a lockdown. The reasons for this are likely multifactorial, however more than half of our cases had COVID-19 (possible or confirmed) and/or antibiotic use. The use of antibiotics in patients with COVID-19 appears to be common. Given the high prevalence of COVID-19 in the community, it is important to reinforce the need for prescribers of antibiotics and patients to maintain good channels of communication with anticoagulation clinics regarding co-prescribing of interacting drugs. Subclinical derangements of coagulation and liver impairment have been reported in COVID-19 which might contribute to the problem [6,7]. Reduced vitamin K status has also been reported in patients with COVID-19 [8]; this could be associated with malabsorption due to small

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Table 1
Patient characteristics for those with an INR > 8 in 2019 and 2020.

Patient characteristics	2020 n = 30		2019 n = 6	
	n	%	n	%
Gender (male)	16	53	4	67
Age (years), mean [sd]	71 [14.5]	–	70 [16.7]	–
Ethnicity				
White	16	53	4	67
Black	8	27	2	33
Hispanic	4	13	–	–
Asian	2	7	–	–
Care home resident	3	10	1	17
Indication for anticoagulation				
AF	12	40	–	–
APS	2	7	–	–
VTE*	8	27	6	100
LV Thrombus	2	7	–	–
Aortic valve replacement	2	7	–	–
Mitral valve replacement	1	3	–	–
CVA embolic	2	7	–	–
INR target range				
2–3	26	87	3	50
2.5–3.5	2	7	3	50
3–4	2	7	–	–

Abbreviations: AF, atrial fibrillation; APS, antiphospholipid syndrome; VTE, venous thromboembolism; LV, left ventricular thrombus; CVA, cerebral vascular accident; SD, standard deviation.

* Included DVT, PE, renal vein thrombosis, cerebral sinus vein thrombosis, portal vein thrombosis.

bowel COVID-19 involvement and/or reduced dietary intake. Other potential contributory factors include decreased access to green leafy vegetables due to stockpiling [9], increased alcohol consumption [10], and increased paracetamol prescribing which may have increased warfarin sensitivity during lockdown [11]. Furthermore, the psychological impact of social distancing and bereavement may have affected adherence to regular medications during this period [12].

Prior to increasing INR test intervals or switching patients from warfarin to a DOAC during the pandemic (in keeping with UK guidance), the data highlights the importance of careful individual risk assessment, given the high incidence of elevated INRs, frequent prescribing of co-medications and unforeseen consequences of a lockdown.

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Author contributions

VS, RB, LNR collected the data. VS, RKP, RB conducted the root-cause analysis. VS & RKP drafted the manuscript, which was critically reviewed by all authors.

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Declaration of competing interest

VS & RB declare no competing interests. LNR has received speaker fees and travel grant from Bayer, and investigator-initiated research grant and travel grant from Sanofi. RKP has received speaker fees from Bayer. RA reports grants from Bayer, personal fees from Bayer, Pfizer, Medtronic and Sanofi and non-financial support from Bayer, Pfizer and Sanofi.

References

- [1] UK Office for National Statistics, Coronavirus (COVID-19) in the UK, <https://coronavirus.data.gov.uk/>, Accessed date: 19 April 2020 Updated 19/4/2020.
- [2] H. Williams, Guidance for the safe switching of warfarin to direct oral anticoagulants (DOACs) for patients with non-valvular AF and venous thromboembolism (DVT/PE) during the coronavirus pandemic, Royal College of General Practitioners and British Society of Haematology (2020; 26 March), *Guidance for the safe switching of warfarin to direct oral anticoagulants (DOACs) for patients with non-valvular AF and venous thromboembolism (DVT / PE) during the coronavirus pandemic*, Accessed date: 12 May 2020.
- [3] S. Kaatz, D. Ahmad, A. Spyropoulos, S. Schulman, Subcommittee on Control of Anticoagulation, Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH, *J. Thromb. Haemost.* 13 (11) (2015) 2119–2126.
- [4] S. Schulman, C. Kearon, Subcommittee on Control of Anticoagulation of the Scientific, Standardization Committee of the International Society on Thrombosis and Haemostasis, Definition of major bleeding in clinical investigations of anti-hemostatic medicinal products in non-surgical patients, *J. Thromb. Haemost.* 3 (4) (2005) 692–694.
- [5] Public Health England. COVID-19 - investigation and initial clinical management of possible cases (updated 27/4/2020). <https://www.gov.uk/government/publications/wuhan-novel-coronavirus-initial-investigation-of-possible-cases/investigation-and-initial-clinical-management-of-possible-cases-of-wuhan-novel-coronavirus-wn-cov-infection#criteria>. Updated Accessed May 12, 2020.
- [6] H. Han, L. Yang, R. Liu, et al., Prominent changes in blood coagulation of patients with SARS-CoV-2 infection, *Clinical Chemistry and Laboratory Medicine (CCLM)* 1 (ahead-of-print) (2020).
- [7] C. Zhang, L. Shi, F.S. Wang, Liver injury in COVID-19: management and challenges, *Lancet Gastroenterol Hepatol.* 5 (5) (2020) 428–430.
- [8] A.S. Dofferhoff, I. Piscoer, L.J. Schurgers, et al., Reduced Vitamin K Status as A Potentially Modifiable Prognostic Risk Factor in COVID-19, (2020).
- [9] Lisa Bachelor, MPs in plea to government over UK's covid-19 stockpiling, *The Guardian* (21 Mar 2020) 2020 <https://www.theguardian.com/world/2020/mar/21/mps-plea-government-uk-covid-19-stockpiling-coronavirus>.
- [10] J. Marsden, S. Darke, W. Hall, et al., Mitigating and learning from the impact of COVID-19 infection on addictive disorders, *Addiction.* (2020), <https://doi.org/10.1111/add.15080>.
- [11] E.M. Hylek, H. Heiman, S.J. Skates, M.A. Sheehan, D.E. Singer, Acetaminophen and other risk factors for excessive warfarin anticoagulation, *JAMA.* 279 (9) (1998) 657–662.
- [12] J.K. Abdou, V. Auyeung, J.P. Patel, R. Arya, Adherence to long-term anticoagulation treatment, what is known and what the future might hold, *Br. J. Haematol.* 174 (1) (2016) 30–42.

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