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ORIGINAL ARTICLE

Stability of vitamin K antagonist anticoagulation after COVID-19 diagnosis

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Abstract

Background: Coagulopathy has been reported in severely ill patients with coronavirus disease 2019 (COVID-19). It is unclear whether outpatients with COVID-19 who are treated with vitamin K antagonists (VKAs) have unstable anticoagulation.

Objective: To assess the stability of VKA therapy in patients with COVID-19 through a case-crossover study.

Methods: Between February and July 2020, we included patients who tested positive for COVID-19 from two anticoagulant clinics in the Netherlands. We collected international normalized ratios (INRs) determined between 26 weeks before infection and 12 weeks after. Time in therapeutic range (TTR) and the variance growth rate (VGR) were calculated within patients.

Results: Fifty-one patients with COVID-19 (mean age, 84 years) were included, of whom 15 (29%) were men. Mean TTR in the 26 weeks before COVID-19 was 80% (95% confidence interval [CI], 75-85) compared to 59% (95% CI, 51-68) in the 6 weeks after infection. Mean TTR difference was −23% (95% CI, −32 to −14) with a time above therapeutic range of 38% (95% CI, 30-47) in the 6 weeks after infection. The TTR rose again to 79% (95% CI, 69-89) between 6 and 12 weeks after infection. Also, VGR increased, with a mean increase of 4.8 (95% CI, 2.1-7.5) in the 6 weeks after infection. In the 26 weeks before infection, we registered 19 of 641 (3%) of INR ≥5.0 compared with 35 of 247 (14%) in the 6 weeks after (risk ratio, 4.4; 95% CI, 2.7-7.3).

Conclusions: COVID-19 is associated with a strong decrease in TTR and in therapeutic stability in patients taking VKAs. Additional monitoring in these patients is advised to maximize therapeutic stability.

KEYWORDS
anticoagulants, coronavirus, coumarins, COVID-19, international normalized ratio, prothrombin time

Essentials

- Quality of vitamin K antagonist therapy after coronavirus disease 2019 (COVID-19) is unknown.
- Between February and July 2020, we included patients with COVID-19 from two Dutch anticoagulant clinics.
- Time in therapeutic range was 23% lower after COVID-19, with a doubling of time above range.
- We encourage maintaining a strict control of international normalized ratio after COVID-19.

1 | INTRODUCTION

The novel coronavirus disease, classified as coronavirus disease 2019 (COVID-19), is a viral pneumonia caused by the newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-COV-2).[1,2] As of January 6, 2021, over 80 million cases of COVID-19 have been reported worldwide.[3]

Besides primarily affecting the respiratory system, COVID-19 may also affect coagulation.[4,5] The development of coagulopathy has been associated with a poor prognosis,[6] and abnormal levels of coagulation parameters such as D-dimer and prolonged prothrombin time (PT) have been found in the more severely ill patients with COVID-19,[7-9] yet not in all.[10-12] More than half of hospital-admitted patients with COVID-19 present a PT prolongation, compared with only 28% of patients admitted with community-acquired pneumonia.[13] The mechanism behind these changes in coagulation parameters is currently unclear. Reasons include a host inflammatory response, effects of viral pneumonia in general, or a specific feature of SARS-COV-2 itself.[14]

While these abnormalities have been recorded in hospitalized or severely ill patients, data are lacking on coagulation measures in outpatient settings. In patients treated with vitamin K antagonists (VKAs), whose anticoagulant effect is monitored through international normalized ratio (INR) measurement, the above-mentioned coagulation abnormalities could lead to unstable control of anticoagulation. This could be highly relevant, as it might influence their thrombosis and bleeding risk. A recent report showed an increase in the number of INRs above therapeutic range during the lockdown period in 30 patients treated with VKAs, of whom 10 patients were COVID-19 positive.[15] Two anticoagulation clinics reported that their whole population of VKA users maintained a consistent time in therapeutic range during the first period of the COVID-19 pandemic, describing no differences with the months prior.[16,17] However, no research has been performed specifically into stability of VKA treatment in patients who are COVID-19 positive.

Our aim was to investigate the stability of anticoagulant treatment with VKAs in patients with newly diagnosed COVID-19 through a case-crossover study, in a cohort of outpatients from two anticoagulation clinics in the Netherlands.

2 | METHODS

As part of the research program initiated by the Dutch COVID & Thrombosis Coalition,[18] we collected patient characteristics from twoanticoagulation clinics in the Netherlands (Leiden, Amsterdam) from their computerized patient records, consistingof year of birth, sex, co-medication, year of VKA initiation, indication for VKA treatment and INR target range.

2.1 | Study population

We included outpatients aged ≥18 years treated with a VKA for any indication, who were registered by the anticoagulation clinic as testing positive for COVID-19 between February 27, 2020, which is the date of the first reported COVID-19 case in the Netherlands, and July 10, 2020.

At the anticoagulation clinics, appointments are made to monitor the INR. Frequencies of appointments depend on the INR value and individual monitoring time: Appointments are planned at a maximum of 6 weeks apart, although they are routinely scheduled more often. At each appointment, a standardized short questionnaire is taken (and electronically stored) by a trained nurse to document changes in comedication, the occurrence of bleeding events, scheduled invasive procedure, and onset of comorbidities, among which was COVID-19. COVID-19 was defined as a positive polymerase chain reaction (PCR) test for SARS-COV-2. We retrieved this information from the electronic patient files, and all reported positive tests were checked and confirmed by the anticoagulation clinics' treating physicians. We also included patients with suspected COVID-19, defined as patients with suspected SARS-COV-2 infection who were not tested at the time of data extraction, presumably due to the limited testing capacity in the Netherlands at that time. The date of COVID-19 positivity was defined as the day of the confirmed positive test for positive patients and the day of registered suspected infection for suspected patients.

2.2 | Variables measured

To measure the INR, venous blood is drawn into vacuum tubes containing 0.1-volume 0.109 mol/L trisodium citrate as anticoagulant. Blood is centrifuged (10 minutes at 2800 *g*) within 4 hours of collection, upon which the INR is measured. Another performed method to measure the INR is by using a point-of-care device (CoaguChek XS PRO, Roche Diagnostics, Basel, Switzerland).

For each included patient, INR measurements were collected from 26 weeks before the diagnosis of COVID-19 up to a maximum of 12 weeks after. The time in therapeutic range (TTR) was calculated by linear interpolation according to the Rosendaal method[19] in three

different time frames: from 26 weeks before COVID-19 up to the date of confirmed COVID-19 positivity, from the date of COVID-19 positivity to 6 weeks after, and from 6 weeks after COVID-19 positivity to 12 weeks after. The 6-week time window was identified as a sufficiently short hazard time after COVID-19, in which we would have been able to observe an immediate risk after infection. We expected that any effect of a transient risk factor for anticoagulation instability, such as an acute infection, would be visible shortly after diagnosis. Moreover, 6 weeks is the maximum length of time between consecutive appointments, and therefore we would have been able to include at least two INR measurements for each patient. In addition, we considered a TTR >70% as sufficient anticoagulation stability, as a consensus from the European Society of Cardiology indicates that an average individual TTR should be >70% for optimal efficacy and safety outcomes while the patient is taking a VKA.[20]

The INR variability was assessed with two methods[21,22]: the variance growth rate (VGR) of Fihn et al and of Cannegieter et al. The method of Fihn et al represents the degree to which a patient's achieved INR deviates from the target INR, while the method of Cannegieter et al evaluates the degree to which a patient's INR deviates from the previous one. With this second method, a patient is defined as stable if the INRs are around the same value every time, even if this means that, for example, the INR is constantly below the lower limit of the therapeutic range. INR variability assessed with the methods of Fihn et al and Cannegieter et al were calculated for the three time windows mentioned above, that is, in the 26 weeks before, in the 6 weeks after, and between 6 and 12 weeks after the confirmed positivity to COVID-19.

TABLE 1 Demographic and clinical characteristics

	Patients who were COVID-19 positive
General	
Patients, n	51
Age, mean (SD)	84 (11)
Men, n (%)	15 (29)
Years since start of treatment, median (IQR)	8 (4-10)
Indication for anticoagulant treatment	
Atrial fibrillation, n (%)	39 (76)
Venous thromboembolism, n (%)	6 (12)
Mechanic heart valve, n (%)	4 (8)
Ischemic heart disease, n (%)	1 (2)
Vascular, n (%)	2 (4)
Other, n (%)	3 (6)
INR target range	
Low (2.0-3.0), n (%)	50 (98)
High (2.5-3.5), n (%)	1 (2)
Vitamin K antagonist	
Acenocoumarol, n (%)	35 (69)
Phenprocoumon, n (%)	16 (31)
Comedication	
Antihypertensive, n (%)	25 (49)
Antidiabetic, n (%)	15 (30)
Antiplatelet, n (%)	4 (8)

Abbreviations: COVID-19, coronavirus disease 2019; INR, international normalized ratio; IQR, interquartile range; SD, standard deviation.

2.3 | Statistical analysis

We defined the 26 weeks before the infection as an unexposed period for each patient, using a case-crossover design. This design, in which each patient acts as his own control, is powerful and efficient in minimizing possible confounding.[23,24] It can be used for a transient and brief exposure, such as COVID-19, which creates a hazard for an acute outcome (eg, changes in INR). Therefore, we used the paired sample *t* test to compare the measures of TTR and VGR in the 6 weeks and between 6 and 12 weeks after the date of infection with the measures in the 26 weeks before the date of infection that was used as a reference category. For TTR, we also calculated the relative mean difference by subtracting the measurement in the 26 weeks before infection from the measurement after infection, dividing it by the value in the 26 weeks prior and multiplying the result by 100%. Mean monitoring time of INR (ie, days between consecutive INR measurements) was also calculated for the three aforementioned times frames. Furthermore, we calculated the percentage of INRs ≥5 and ≥8 for each time window. We calculated the risk ratios (RRs) and 95% confidence intervals (95% CIs) of having an INR ≥5 or ≥8 after COVID-19, compared with the measure in the 26 weeks before infection. For each day before and after the index date, the percentage of patients in, above, and under therapeutic range was computed, using linear interpolation according to the Rosendaal methods.[19] Two separate analyses were conducted: (i) including only patients with a confirmed COVID-19, and (ii) including also patients with suspicion of COVID-19.

3 | RESULTS

3.1 | General characteristics

Fifty-one patients were registered as positive (ie, confirmed by PCR testing) for COVID-19 by the anticoagulation clinic (Table 1), which is 0.2% of the total population followed by the anticoagulation clinic during the study period (27 853 individuals). Of those, 15 (29%) were men, and the mean age at the time of SARS-COV-2 infection was 84 years (standard deviation [SD], 11). The majority of patients were treated with VKAs because of atrial fibrillation (39; 76%) and the second-most-common indication was venous thromboembolism (6; 12%). Patients had been taking VKAs for a median of 8 years (interquartile range [IQR], 4-10) before their COVID-19 diagnosis. Acenocoumarol was the anticoagulant used in 35 patients (69%). Moreover, 13 patients were recorded as suspected of COVID-19 at the anticoagulation

clinics (Table S1). Suspect patients were slightly younger than positive patients (mean age, 80 years; SD, 13) and 5 were men (39%). The indication of venous thromboembolism (6; 46%) for VKA treatment was more prevalent among suspected as compared with positive cases, and the most frequently used anticoagulant in this group was phenprocoumon (10; 77%). During the follow-up, 9 patients died (18%). These patients were older compared to the patients who survived (mean age, 88 years; SD, 8), 5 were men (56%), and the most common indication for anticoagulation was atrial fibrillation (7; 78%). The mean time until death after COVID-19 diagnosis was 12 days (SD, 6).

3.2 | Time in therapeutic range

Mean TTR in the 26 weeks before COVID-19 diagnosis was 80% (95% CI, 75-85), whereas mean TTR in the 6 weeks after infection was 59% (95% CI, 51-68). Mean difference between the TTR calculated in the 26 weeks before and in the 6 weeks after the infection was −23% (95% CI, −32 to −14). Time above therapeutic range was 38% (95% CI, 30-47) in the 6 weeks after infection, whereas time above therapeutic range was 17% (95% CI, 13-22) in the 26 weeks before (Table 2), with a mean difference of 24% (95% CI, 14-33). In the time frame between 6 and 12 weeks after the infection, mean TTR was 79% (95% CI, 69-89), with a mean difference with the 26 weeks before infection of −1.3% (95% CI, −13 to 10). Mean TTR in the 26 weeks before COVID-19 was not different in the 9 deceased patients (80%; 95% CI, 64-95) compared with patients with COVID-19 who survived. Due to the short time to death after COVID-19 diagnosis, INR measurements were available only for 5 of the deceased patients after the index date. Of those, only 1 patient had a significant drop in TTR (from 100% to 56%), whereas for the remaining 4 patients, only a few INR measurements (1-4) were available and were all within the therapeutic range.

We observed that the percentage of patients in therapeutic range decreased ≈9 to 11 days before the date of registered COVID-19, while we recorded a concomitant increase of patients above therapeutic range (Figure 1). After ≈30 days from the day of infection, the percentage of patients in therapeutic range rose again to values >70%.

We repeated the aforementioned analysis combining data of patients who were COVID-19 positive with suspected patients (Table S2 and Figure S1). Results were similar to the analysis on positive patients only.

3.3 | Variance growth rate of INR

The VGR calculated according to the method of Cannegieter et al in 26 weeks before COVID-19 was 1.4 (95% CI, 0.8-2.0) and increased to 5.7 (95% CI, 3.0-8.5) in the 6 weeks after infection, with a mean difference of 4.8 (95% CI, 2.1-7.5). Between 6 and 12 weeks from COVID-19, mean VGR of Cannegieter et al was 3.6 (95% CI, 0-7.4) with a mean increase of 2.5 (95% CI, −1.4 to 6.4) relative to 26 weeks before infection. Similarly, VGR calculated with the method of Fihn et al was 0.8 (95% CI, 0.5-1.1) in the 26 weeks before COVID-19 and rose to 1.9 (95% CI, 1.0-2.7) in the 6 weeks after infection, with a mean difference of 1.2 (95% CI, 0.3-2.0) (Table 3). The VGR of Fihn et al was 1.1 (95% CI, 0.2-2.0) between 6 and 12 weeks after infection, with a mean increase from 26 weeks before infection of 0.2 (95% CI, −0.8 to 1.2). We repeated both analyses including patients with suspected COVID-19 and the analyses yielded similar results (Table S3).

3.4 | Percentage of INR ≥5.0 and INR ≥8.0

In the 26 weeks before COVID-19 diagnosis, 641 INR measurements were available, whereas 247 and 154 INR measurements were available in the 6 weeks after and between 6 and 12 after, respectively. Per patient, a median of 1.5 (IQR, 2) INR measurements were available each month in the 26 weeks before COVID-19 diagnosis. The median number of INR measurements each month per patient was instead 2 (IQR, 2) in the first 6 weeks after diagnosis and 1.3 (IQR, 1.7) between 6 and 12 weeks after. Mean monitoring time between INR was 20 days (95% CI, 17-22) in the 26 weeks before infection, whereas it was 15 days (95% CI, 13-18) in the 6 weeks after infection and remained 15 days (95% CI, 13–17) between 6 and 12 weeks after infection.

TABLE 2 Stability of anticoagulation before and after COVID-19 in positive patients

	Mean TTR, % (95% CI)	Mean difference TTR, % (95% CI)	Relative mean difference TTR, % (95% CI)	Mean time above range, % (95% CI)	Mean difference time above range,% (95% CI)	Mean time below range, % (95% CI)	Mean difference time below range, % (95% CI)
26 weeks before COVID-19	80 (75 to 85)	reference	reference	17 (13 to 22)	reference	3 (1 to 4)	reference
6 weeks after COVID-19	59 (51 to 68)	−23 (−32 to −14)	−25 (−37 to −14)	38 (30 to 47)	24 (14 to 33)	2 (0.2 to 4)	−0.7 (−3 to 1)
6–12 weeks after COVID-19	79 (69 to 89)	−1.3 (−13 to 10)	5 (−11 to 21)	18 (8 to 27)	1 (−11 to 13)	3 (0.5 to 5)	0.3 (−2 to 3)

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; TTR, time in therapeutic range.

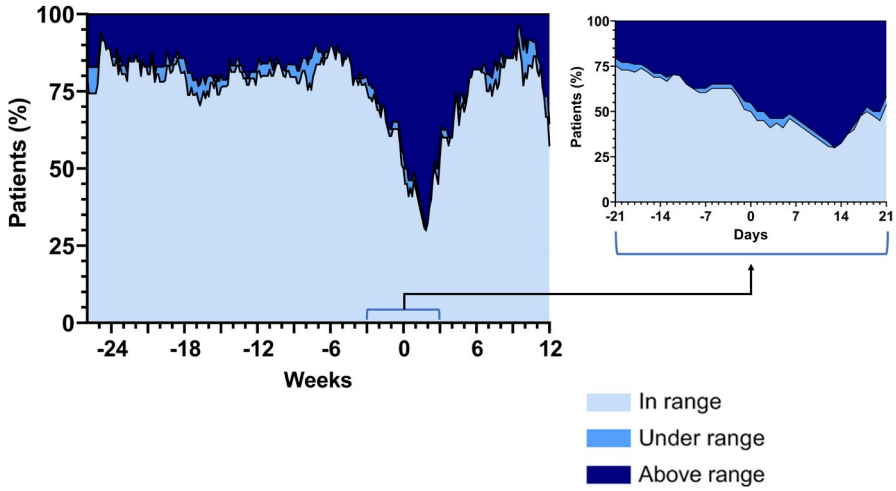

FIGURE 1 Percentage of patients in, above and under therapeutic range over time. Day 0 is the date of positive COVID-19 test. On the right side, a blow-up figure of the time frame between 3 weeks before and after COVID-19

TABLE 3 Variance growth rate according to Cannegieter et al and Fihn et al before and after COVID-19 in positive patients

	Mean VGR Cannegieter et al (95% CI)	Mean difference VGR Cannegieter et al (95% CI)	Mean VGR Fihn et al. (95% CI)	Mean difference VGR Fihn et al (95% CI)
26 weeks before COVID-19	1.4 (0.8 to 2.0)	reference	0.8 (0.5 to 1.1)	reference
6 weeks after COVID-19	5.7 (3.0 to 8.5)	4.8 (2.1 to 7.5)	1.9 (1.0 to 2.7)	1.2 (0.3 to 2.0)
6-12 weeks after COVID-19	3.6 (0 to 7.4)	2.5 (−1.4 to 6.4)	1.1 (0.2 to 2.0)	0.2 (−0.8 to 1.2)

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; VGR, variance growth rate.

In the 26 weeks before COVID-19, 19 of 641 (3%) INR samples were ≥5.0 (13 patients) compared with 35 of 247 (14%) in 18 patients in the 6 weeks after infection (RR, 4.8; 95% CI, 2.8-8.2). Between 6 and 12 weeks after infection, we registered 10 of 154 (6%) INRs ≥5.0 in 7 patients (RR, 2.1; 95% CI, 1.0-4.6). Moreover, 3 of 641 (0.5%) of INR samples were ≥8.0 (3 patients) in the 26 weeks before the infection compared with 10 of 247 (4%) in 8 patients in the 6 weeks after (RR, 8.6; 95% CI, 2.4-31.2). Between 6 and 12 weeks after infection, we registered 6 of 154 (4%) INRs ≥8.0 in 5 patients (RR, 8.3; 95% CI, 2.1-32.9) (Table 4). The results of both analyses repeated adding suspect patients also showed a higher risk of supratherapeutic INRs after COVID-19 (Table S4).

4 | DISCUSSION

The results of this case-crossover analysis showed that in patients using VKA treatment, 6 weeks after COVID-19, the quality of anticoagulation control was lower compared to the weeks before infection. Time in therapeutic range was 23% lower in patients who were COVID-19 positive during the 6 weeks after infection, with two times more INR values above therapeutic range. Interestingly, the mean TTR was restored between 6 and 12 weeks after infection. Moreover, the variability of the INR was increased in the 6 weeks after infection, with a more pronounced result found by the method of Cannegieter et a. than the method of Fihn et al. Between 6 and 12 weeks after infection the increase in VGR was less pronounced. In addition, in the 6 weeks after COVID-19, we registered an almost five times higher proportion of INR ≥5.0 and an eight times higher proportion of INR ≥8.0 compared to the 26 weeks before COVID-19. This is clinically relevant because INRs ≥5.0 are strongly associated with a higher risk of bleeding complications,[25] and withholding of VKA or even administration of an antidote can be required.[26] Between 6 and 12 weeks after infection the proportion of higher INRs was still increased but less prominently compared with the percentage in the first 6 weeks after infection. The unstable control of INR is reflected by the shorter mean number of days between consecutive INR measurements observed in the three different time frame. The mean monitoring time was 20 days in the 26 weeks before infection and dropped to 15 days in both the 6 weeks after and between 6 and 12 weeks after.

We saw that during the 26 weeks before COVID-19, the percentage of patients in therapeutic range was stable through time and sharply decreased 9 to 11 days before the actual date of registered COVID-19 positivity, with a concomitant increase in the percentage of patients above therapeutic range. This period just before the infection could reflect the latency between the day of the onset of infection and/or symptoms and the day the results of the test for SARS-COV-2 were available. Another possible explanation could be related to the interpolation assumption, that states that INRs linearly

TABLE 4 Percentage of INR ≥5.0 and ≥8.0 before and after COVID-19 in positive patients

	INR ≥5.0		INR ≥8.0	
	High INR/all INR (%)	RR (95% CI)	High INR/all INR (%)	RR (95% CI)
26 weeks before COVID-19	19/641 (3%)	Reference	3/641 (0.5%)	Reference
6 weeks after COVID-19	35/247 (14%)	4.8 (2.8-8.2)	10/247 (4%)	8.6 (2.4-31.2)
6-12 weeks after COVID-19	10/154 (6%)	2.1 (1.0-4.6)	6/154 (4%)	8.3 (2.1-32.9)

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; INR, international normalized ratio; RR, risk ratio.

increase/decrease from one measurement to the following one. If, for example, the date of COVID-19 registered positivity is between one INR in range and one INR out of range, the linear interpolation would result in a high INR not only after but also before infection. At the end of our follow-up period, between 80 and 84 days after the infection, the percentages of patients in therapeutic range slightly decreased again, but not declining below 70%. We believe this could be due to the relatively low number of patients with such long follow-up, as only 19 patients had an INR determination between 80 and 84 days after infection.

Explanations for the unstable INR in previously stable patients during COVID-19 are probably multifactorial and difficult to identify clearly. The VGR assessed with the method of Cannegieter et al yielded the greatest mean increase, suggesting that INR instability is mainly caused by deviation from the previous measurement, rather than deviation from the target INR. A factor that could contribute to such instability is a change in diet during illness. A reduced intake of food during the illness, particularly of vitamin K–containing food, could have contributed to the higher number of supratherapeutic INRs.[27] Reduced vitamin K status has also been reported in patients who were COVID-19 positive.[28] Moreover, a recent review showed that patients who were COVID-19 positive are frequently treated with antibiotics.[29] Changes in prescribed medication during COVID-19, some of which could have interactions with VKA, could have determined the observed instability.[30] In our population, 26 (50%) patients changed medication around the time of COVID-19 diagnosis (within 14 days before until 14 days after the date of COVID-19–positive test), of whom 23 (45%) were treated with interacting medication and 24 (47%) with antibiotics. However, mean TTR in the 6 weeks after infection was lower in patients who did not initiate possible interacting medication (53%; 95% CI, 40-65) compared with patients treated with a possible interacting drug (68%; 95% CI, 57-80). Moreover, mean difference between TTR calculated in the 26 weeks before and in the 6 weeks after was similar between patients who did not initiate possible interacting medication and patients who did (−23%; 95% CI, −41 to −15; and −16%; 95% CI, −30 to 3). However, our limited sample size and the small group sizes do not allow us to draw firm conclusions on the contribution of interactive medication to the observed instability. In addition, nonadherence to prescribed VKA dosage during illness could also be a concurrent cause of deviation from the target INR. However, only a VKA overdosage could explain the observed increased rate of supratherapeutic INR. It cannot be excluded that SARS-COV-2 itself had an effect on anticoagulant intensity through its effects on coagulation parameters that are related to anticoagulant control.[7-9,13,31] Acute respiratory infections are a demonstrated risk factor for overanticoagulation,[32] independently from antibiotic treatments[33]; however, their exact contribution to TTR variability has not been previously evaluated in the literature. Nevertheless, as it is not possible to disentangle which component of COVID-19 illness contributes to our findings, we do not mean to infer a causal relation between SARS-COV-2 per se and decreased TTR.

Due to our relatively small sample size and follow-up time, we were not able to evaluate whether the instable INR control we found results in higher frequency of bleeding or thrombosis. However, it is established that INR instability is a general risk factor for adverse outcomes, such as bleeding and thrombotic events.[21,34,35] For an INR of 5.0 to 5.5, the incidence of bleeding events is estimated as 4.8 per 100 patient-years, raising to 75 per 100 patient-years when the INR is ≥6.5.[36] Some other limitations of our study should be noted. First, information on the severity of COVID-19 was not available in the electronic chart of the anticoagulation clinics. Therefore, we cannot comment on whether severity of disease can influence the instability of anticoagulation. Furthermore, presumably due to the strict policy of testing at the time our data were collected, some patients who were COVID-19 positive may not have been tested and were therefore not included in our analysis. This is reflected in our limited sample size of 51 patients who were COVID-19 positive. The total number of patients followed by the two anticoagulation clinics was 27 853 individuals in the study period, which means that the 0.2% of the population followed by the anticoagulation clinic tested positive for COVID-19. This percentage is similar to data from the Netherlands: as of July 14, 2020, a total of 51 146 residents in the Netherlands tested positive for COVID-19 since the beginning of the pandemic,[37] which represents 0.3% of the total population (17 280 397). Regardless, we expect that missing some patients would not have influenced our results other than possibly slightly lower precision. This is further supported as repeating the analysis including suspect patients did not change our results. In addition, we observed an increased frequency of INR measurements after COVID-19 diagnosis compared with before, which could lead to an increased number of out-of-range INRs due to overtesting. However, INR controls at the anticoagulation clinics during the first wave of

COVID-19 were delayed as much as possible in stable patients,[38] to reduce unnecessary contact and the risk of infection. Therefore, we believe that the reduced monitoring time is a consequence of the increased rate of INRs above range and not vice versa. A strength of our study is the case-crossover design through which patients are compared with themselves. This design strongly reduces problems with incomparability of groups (minimizing confounding) and with sampling bias otherwise introduced in selection of controls.

We showed a strong reduction of anticoagulant therapy stability after COVID-19 diagnosis: TTR decreased in 23% with a doubling of time above therapeutic range. On the basis of our results, we encourage maintaining a strict INR control during COVID-19 because of the higher incidence of supratherapeutic INRs that could increase the bleeding risk.

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AUTHOR CONTRIBUTIONS

EC, SCC, and NvR designed the research. EC, FJvdM, and MCN collected the data. EC and NvR analyzed the data. EC and NvR wrote the manuscript. EC, SCC, NvR, FJvdM, MCN, and WML revised the article for important intellectual content.

RELATIONSHIP DISCLOSURE

Dr Van der Meer reports grants from CSL Behring, Pfizer, Bayer, Novo Nordisk, Sobi, Roche, OctaPharma outside the submitted work. The other authors declare no conflict of interest.

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REFERENCES

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506.
2. Guan WJ, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708–1720. http://dx.doi.org/10.1056/NEJMoa2002032.
3. European Centre for Disease Prevention and Control, COVID-19 - Situation update worldwide. [cited 2020 19 October]; Available from: https://qap.ecdc.europa.eu/public/extensions/COVID-19/COVID-19.html#global-overview-tab.
4. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system. *JAMA Cardiol*. 2020;5(7):831.
5. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular considerations for patients, health care workers, and health systems during the coronavirus disease 2019 (COVID-19) Pandemic. *J Am Coll Cardiol*. 2020:75(18):2352-2371.
6. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost*. 2020;18(5):1023-1026.
7. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18(4):844-847.
8. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.
9. Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020:18(5):1094-1099.
10. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. *J Thromb Thrombolysis*. 2021;51(4):1107-1110.
11. Fogarty H, Townsend L, Ni Cheallaigh C, et al. COVID19 coagulopathy in Caucasian patients. *Br J Haematol*. 2020;189(6):1044-1049.
12. Di Micco P, Russo V, Carannante N, et al. Clotting factors in COVID-19: epidemiological association and prognostic values in different clinical presentations in an Italian cohort. *J Clin Med*. 2020;9(5):1371.
13. Zhang Y, Zheng L, Liu L, et al. Liver impairment in COVID-19 patients: a retrospective analysis of 115 cases from a single center in Wuhan city, China. *Liver Int*. 2020:40(9):2095-2103.
14. Iba T, Levy JH, Levi M, Connors JM, Thachil J. Coagulopathy of coronavirus disease 2019. *Crit Care Med*. 2020;48(9):1358-1364.
15. Speed V, Patel RK, Byrne R, Roberts LN, Arya R. A perfect storm: root cause analysis of supra-therapeutic anticoagulation with vitamin K antagonists during the COVID-19 pandemic. *Thromb Res*. 2020;192:73-74.
16. Kavecansky J, Dusendang JR, Tavakoli J, et al. Association of anticoagulation use with SARS-CoV2 detection. *Thromb Res*. 2021;198:99-102.
17. Barcellona D, Marongiu F. Thrombosis centres and AVKs monitoring in COVID-19 pandemic. *Intern Emerg Med*. 2020;15(8):1365-1368.
18. Cannegieter SC, ten Cate H, van Gorp ECM, et al.; The Dutch & COVID Thrombosis Coalition study group. Caging the dragon: Research approach to COVID-19-related thrombosis. *Res Pract Thromb Haemost*. 2021;5:278-290.
19. Rosendaal FR, Cannegieter SC, van der Meer FJM, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost*. 1993;69(03):236-239.
20. De Caterina R, Husted S, Wallentin L, et al. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis-Task Force on Anticoagulants in Heart Disease. *Thromb Haemost*. 2013;110(6):1087-1107.
21. Van Leeuwen Y, Rosendaal FR, Cannegieter SC. Prediction of hemorrhagic and thrombotic events in patients with mechanical heart valve prostheses treated with oral anticoagulants. *J Thromb Haemost*. 2008;6(3):451-456.
22. Kent DL, Vermes D, McDonell M, Henikoff J, Fihn SD. A model for planning optimal follow-up for outpatients on warfarin anticoagulation. *Med Decis Making*. 1992;12(2):132–141. http://dx.doi.org/10.1177/0272989x9201200206
23. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol*. 1991;133(2):144-153.
24. Maclure M, Mittleman MA. Should we use a case-crossover design? *Annu Rev Public Health*. 2000;21:193-221.
25. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest

Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e44S-e88S.
26. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy. *Chest*. 2012;141(2):e152S-e184S.
27. Hylek EM, Heiman H, Skates SJ, Sheehan MA, Singer DE. Acetaminophen and other risk factors for excessive warfarin anticoagulation. *JAMA*. 1998;279(9):657-662.
28. Dofferhoff ASM, et al. Reduced Vitamin K Status as A Potentially Modifiable Prognostic Risk Factor in COVID-19. 2020: Preprints.org.
29. Rawson TM, Moore LSP, Zhu N, et al. Bacterial and fungal coinfection in individuals with coronavirus: a rapid review to support COVID-19 antimicrobial prescribing. *Clin Infect Dis*. 2020:71(9):2459-2468.
30. Panneerselvam S, Baglin C, Lefort W, Baglin T. Analysis of risk factors for over-anticoagulation in patients receiving long-term warfarin. *Br J Haematol*. 1998;103(2):422-424.
31. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med*. 2020;58(7):1116-1120.
32. Macedo AF, Bell J, McCarron C, et al. Determinants of oral anticoagulation control in new warfarin patients: analysis using data from Clinical Practice Research Datalink. *Thromb Res*. 2015;136(2):250-260.
33. Clark NP, Delate T, Riggs CS, et al. Warfarin interactions with antibiotics in the ambulatory care setting. *JAMA Intern Med*. 2014;174(3):409-416.
34. Schein JR, White CM, Nelson WW, et al. Vitamin K antagonist use: evidence of the difficulty of achieving and maintaining target INR range and subsequent consequences. *Thromb J*. 2016;14:14.
35. van Rein N, Lijfering WM, Bos MHA, et al. Objectives and design of BLEEDS: a cohort study to identify new risk factors and predictors for major bleeding during treatment with vitamin K antagonists. *PLoS One*. 2016;11(12):e0164485.
36. Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer F, Vandenbroucke JP, Briet E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med*. 1995;333(1):11-17.
37. Rijksinstituut voor Volksgezondheid en Milieu (RIVM) - Wekelijkse update epidemiologische situatie COVID-19 in Nederland July 2020; Available from: https://www.rivm.nl/en/node/163991.
38. Ten Cate H. Thrombosis management in times of COVID-19 epidemy; a Dutch perspective. *Thromb J*. 2020;18:7.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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