Adherence to Anticoagulation Ambulatory during the Beginning of Coronavirus Pandemic

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Abstract

Introduction: Treatment with Vitamin K Antagonists is already proven to be significant in reducing thromboembolic events in patients with indications for systemic anticoagulation. In the context of ambulatory adherence, the *SARS-CoV2* coronavirus pandemic emerged as a challenge for managing patients undergoing anticoagulation.

Methods: To avoid crowding and follow the recommended measures of social distancing, the Anticoagulation Ambulatory of the *Hospital Universitário de Santa Maria* started to adopt a differentiated model of care, with a collection of hospital prothrombin time and immediate home return, followed by teleconsultation, with medication adjustment, as necessary. The present study aimed to assess adherence to the new care model, as well as the profile of patients seen. A retrospective cohort study was conducted, analyzing consultations between March and May 2020.

Results: The results demonstrate a low-educated population (76% had completed elementary school at most). The most common indications for the use of oral anticoagulation were atrial fibrillation (33.6%), followed by mechanical aortic valve prosthesis (31.3%) and mechanical mitral valve prosthesis (17.2%). Regarding adherence, especially to blood collection in the scheduled period, there was low adherence in the initial weeks of the pandemic declaration, with substantial improvement in adherence in the last two weeks of analysis.

Conclusion: Determining the clinical characteristics and profile of patients helps to determine the local needs of this population and implement active search strategies to improve adherence rates, which may reduce unfavorable outcomes.

Keywords: cardiac epidemiology, COVID-19, anticoagulation

1. Introduction

Anticoagulant therapy using Vitamin K Antagonists (VKA) is already of great epidemiological importance in reducing thromboembolic events. In the context of atrial fibrillation (AF), it has an established role in the prophylaxis of ischemic stroke (iCVA) and venous thromboembolism (VTE) (SPiAF, 1991). Another indication is the prophylaxis of thromboembolic events in patients with mechanical valve prostheses (Nishimura et al., 2014). Despite the emergence of new direct oral anticoagulants, VKAs continue to be widely used, mainly due to their low cost and easy access (Connolly et al., 2009). Periodic laboratory control of VKA is essential. It is performed on an outpatient basis by evaluating the prothrombin time (PT) and its derivative, the international normalized ratio (INR), which reflects the intensity of the extrinsic pathway of blood coagulation.

In this sense, understanding the patient's clinical condition and the importance of treatment is essential. Educational measures related to both patients and the medical team can increase the time spent in the therapeutic

range (TTR) and reduce the incidence of thromboembolic events (Vinereanu et al., 2017).

In the context of ambulatory adherence, the *SARS-CoV2* coronavirus pandemic emerged as a challenge for managing patients undergoing anticoagulation. Discovered in late 2019, *SARS-CoV2* was identified as the cause of an outbreak of the respiratory disease in Wuhan, a city in Hubei province, China (Wu & McGoogan, 2020). It quickly resulted in an epidemic across China, followed by a growing number of cases in other countries worldwide. In February 2020, the World Health Organization designated the disease as COVID-19 (Sohrabi et al., 2020).

As part of the initial control measures for the coronavirus pandemic, social distancing, protective devices (such as face masks), hygiene measures such as frequent hand washing, and the use of alcohol-gel were implemented. Physical distancing is independently associated with a reduced risk of transmission (Koo et al., 2020). At the beginning of the COVID-19 pandemic in Brazilian territory, many health services significantly reduced or suspended elective medical procedures and outpatient care.

The *Hospital Universitário de Santa Maria (HUSM)*, following the recommendations of the World Health Organization and the Ministry of Health, adopted similar practices, temporarily withholding outpatient care from March 20, 2020. However, the follow-up of patients undergoing anticoagulation requires regular periodicity and contact to maintain the INR within the recommended therapeutic range. To avoid loss of anticoagulation follow-up and control, professionals from the HUSM's Anticoagulation Ambulatory chose to adopt a telephone service model. In this model, the patient was instructed to attend the HUSM on the day determined exclusively to collect a blood sample to perform an INR, returning immediately to their home, thus fulfilling social distancing. The multidisciplinary team then contacted the patients with information about the value of the INR that day and guidance on the need to adjust the dose of the oral anticoagulant. In addition, a regular checklist on adherence and complications, such as bleeding or adverse events, was applied. In this case, the responsible physician resolved the doubts and provided face-to-face service when necessary. The present study aimed to assess adherence to the new care model, as well as the profile of patients seen.

2. Method

Retrospective cohort study, with a sequential sample of patients being followed up at the Anticoagulation Ambulatory of the HUSM, with periodic operation once a week. All cases attended between March 20th and May 8th, 2020; the period considered the beginning of the pandemic by *SARS-CoV2* in Brazil, were considered. Initially, patients' adherence to the ambulatory was evaluated. As part of the active search protocol, missing patients were contacted and submitted to a structured telephone questionnaire. Information was collected about the reasons for not attending the ambulatory and whether there was the development of any complications related to anticoagulation or infectious conditions potentially associated with the *SARS-CoV2* virus.

As this data was already collected in the routine and protocol of the ambulatory, it was not necessary to sign an informed consent form. The confidentiality and privacy of the information obtained were maintained, and there was no conflict of interest. The research was approved by the Research Ethics Committee of the *Universidade Federal de Santa Maria* under the number (CAAE 36845020.0.0000.534).

Data were stored and analyzed by the program in the Statistical Package for Social Sciences – SPSS 21.0. The normality of the distribution of numerical data was verified with the Kolmogorov-Smirnov test. Their description was in mean and standard deviation or median and interquartile range. Categorical data were presented by absolute and relative numbers. Numerical variables were compared using Student's T-test, and the association between categorical variables was verified using Chi-square and Fisher's Exact Tests. The comparison between attendance to appointments on each scheduled date was analyzed using the Generalized Estimating Equations model. Analyzes with $p < 0.05$ were considered statistically significant.

3. Results

The mean age was 61 ± 12.7 years (range 32 to 93 years), most were male (63.6%), more often with incomplete elementary school (50.0%) and retired 36.9 % (Table 1).

Table 1. Sociodemographic characteristics of the sample of patients scheduled to attend the Anticoagulation Outpatient Clinic of the *Hospital Universitário de Santa Maria*, during the *SARS-CoV2* pandemic period, from March to May 2020 (N=132)

Characteristics	N	Frequency N (%)
Age in years	132	61±12.7
Gender	132	
Male		84 (63.6)
Schooling	88	
Illiterate		7 (8.0)
Incomplete first degree		44 (50.0)
Complete first degree		15 (17.0)
Incomplete second degree		8 (9.1)
Complete high school		11 (12.5)
Incomplete superior		2 (2.3)
Full Superior		1 (1.1)
Profession	84	
Farmer		15 (17.9)
Retired		31 (36.9)
House woman		10 (11.9)
Maid		4 (4.8)
Civil servant		4 (4.8)
Driver		3 (3.6)
Health professional		2 (2.4)
Other		15 (17.9)

Note. Data are mean ± SD or number (%) of patients.

Regarding the indication for anticoagulants, 43 (33.6%) used VKA due to the presence of AF. The other indications were mainly associated with aortic valve prosthesis in 40 patients (31.3%) and mitral valve prosthesis in 22 patients (17.2%), as detailed in Table 2.

Table 2. Reasons for indication of anticoagulant use in patients scheduled to attend the Anticoagulation Outpatient Clinic, during the pandemic period of *SARS-COV2*, from March to May 2020 (N=128)

Reasons for indication of anticoagulant therapy	N (%)
Atrial fibrillation	43 (33.6)
Aortic valve prosthesis	40 (31.3)
Mitral valve prosthesis	22 (17.2)
Thrombus in left ventricle	2 (1.6)
Deep vein thrombosis/Pulmonary thromboembolism	2 (1.6)
Triple mechanical prosthesis	1 (0.8)
Double prosthesis (mitral and aortic)	13 (10.2)
Uncompressed cardiomyopathy	2 (1.6)
Thrombus and/or Left Ventricular Aneurysm	3 (2.3)

Note. Data are number (%) of patients.

Regarding appointments scheduled during the initial phase of the pandemic by *SARS-COV2*, 63.7% attended the appointments during the analysis period, with 42.4% on the initially planned date. Of the remaining ones, 0.8% showed up late one month after the scheduled date and 20.5% between one and five months after the scheduled date. When questioned, the population reported adequate adherence to the recommended social isolation measures, followed by more than 90%. The presence of flu syndrome was reported in only 2 cases (4%) among those who attended the appointments on the initially planned date and in 2 patients (5.7%) among those absent (p = 0.999) (Table 3). Cases of SARS-COV2 infection have not been confirmed.

Table 3. Sociodemographic characteristics, the indication of anticoagulant therapy, and reasons for the attendance or not of patients scheduled at the Anticoagulation Outpatient Clinic, in the pandemic period of *SARS-COV2*, from March to May 2020 (N=132).

| Variables | Attendance to the consultation | | P |
	Yes N=56 N (%)	No N=76 N (%)	
Age in years	60.5±11.3	61.4±13.7	0.677[a]
Gender			0.090[b]
Male	31 (55.4)	53 (69.7)	
Schooling			0.505[c]
Illiterate	5 (10.4)	2 (5.0)	
Incomplete first degree	22 (45.8)	22 (55.0)	
Complete first degree	10 (20.8)	5 (12.5)	
Incomplete second degree	3 (6.3)	5 (12.5)	
Complete high school	6 (12.5)	5 (12.5)	
Incomplete superior	2 (4.2)	0 (0.0)	
Full Superior	0 (0.0)	1 (2.5)	
Profession			0.317[c]
Farmer	10 (21.7)	5 (13.2)	
Retired	12 (26.1)	19 (50.0)	
House woman	7 (15.2)	3 (7.9)	
Maid	3 (6.5)	1 (2.6)	
Civil servant	3 (6.5)	1 (2.6)	
Driver	2 (4.3)	1 (2.6)	
Health professional	2 (4.3)	0 (0.0)	
Other	7 (15.2)	8 (21.1)	
Indication of anticoagulant therapy			0.206
Atrial fibrillation	14 (25.0)	29 (38.2)	
Aortic valve prosthesis	17 (30.4)	23 (30.3)	
Mitral valve prosthesis	20 (35.7)	16 (21.1)	
Thrombus or Left Ventricular Aneurysm	3 (5.4)	2 (2.6)	
Other	2 (3.6)	6 (7.9)	
Reasons for non-attendance			
Influenza syndrome			0.999[c]
Yes	2 (4.0)	2 (5.7)	
No	48 (96.0)	33 (94.3)	

Social isolation			0.999[c]
Yes	41 (93.2)	31 (91.2)	
No	3 (6.8)	3 (8.8)	
Distance from the city of *Santa Maria*			0.857[c]
Local	28 (50.0)	33 (43.4)	
>100 km	3 (5.4)	5 (6.6)	
<50 km	4 (7.1)	8 (10.5)	
Between 50 and 100 km	21 (37.5)	30 (39.5)	

Note. P: (a) Student T-Test; (b) Pearson Chi-square test; (c) Fischer's Exact Test. Data are mean ± SD or number (%) of patients.

The missing data were 44 for schooling, 48 for the profession; 47 for flu-like syndrome; and 54 for social isolation.

Regarding attendance at the ambulatory on the dates of consultations, there was low adherence of patients in the collection of INR on ambulatory dates related to the first weeks of the pandemic in Brazil (March 20th, 2020; March 27th, 2020; and April 17th, 2020; with attendance on the scheduled date of 52%, 50%, and 56.5%, respectively). On the other analysis days, blood collection attendance was above 70% (Table 4, Figure 1).

Table 4. Patients attending scheduled consultations with the Anticoagulation Outpatient Clinic during the *SARS-COV2* pandemic from March to May 2020 (N=132)

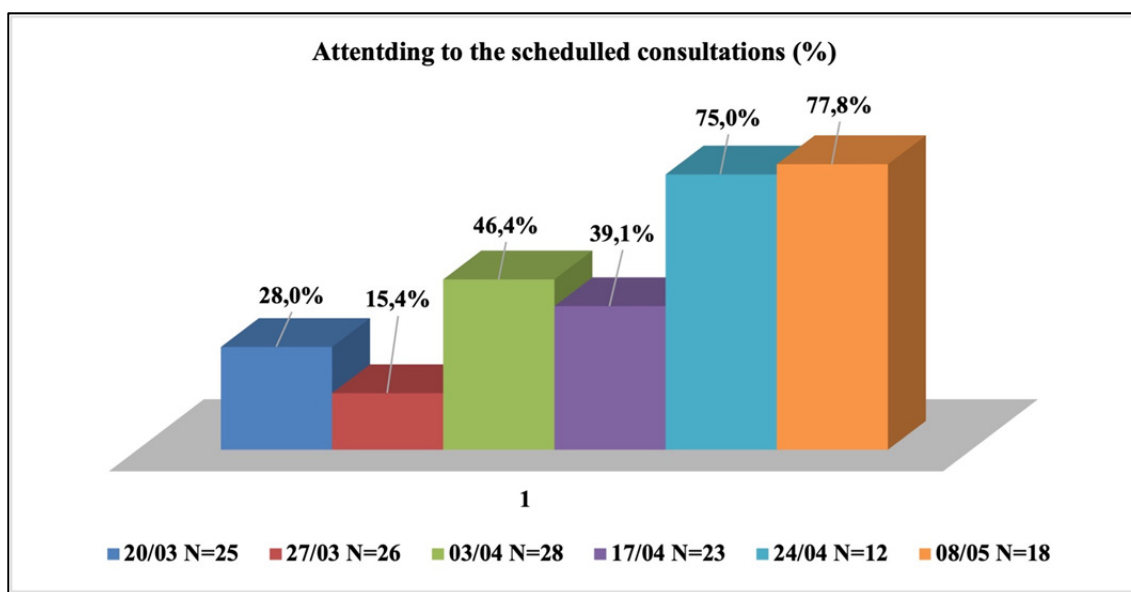|	Scheduling dates in 2020					
Attendance	March 20th N=25	March 27th N=26	April 3rd N=28	April 17th N=23	April 24th N=12	Mat 8th N=18
They did not show up	12 (48.0)	13 (50.0)	8 (28.6)	10 (43.5)	3 (25.0)	2 (11.0)
Attended						
On the scheduled date	7 (28.0)	4 (15.4)	13 (46.4)	9 (39.1)	9 (75.0)	14 (77.8)
Up to 2 months after	0 (0.0)	0 (0.0)	2 (7.2)	0 (0.0)	0 (0.0)	1 (5.6)
Between 2 to 5 months	6 (24.0)	9 (34.6)	5 (17.9)	4 (17.4)	0 (0.0)	1 (5.6)

Note. Data are number (%) of patients.

Figure 1. Patients attending consultations on the day of scheduling at the Anticoagulation Outpatient Clinic during the SARS-COV2 pandemic, from March to May 2020 (N=132)

Attendance to consultations registered the most significant drop on March 27th, 2020. On the other hand, on the last two dates analyzed (for the month of May 2020), the frequency of patients present was increased, reaching an adherence of 77.8% in the previous consultation analyzed. Attendance to consultations on May 8th, 2020, was higher than attendance to consultations on March 20th, 2020 (P<0.001); March 27th,2020 (P<0.001); April 3rd, 2020 (P=0.021); and April 17th, 2020 (P=0.006).

Attendance to appointments scheduled for April 24th, 2020, was higher than attendance to appointments scheduled for March 20th,2020 (P<0.001); March 27th, 2020 (P<0.001); and April 17th, 2020 (P=0.026). Attendance to appointments scheduled for April 3rd, 2020, was higher than attendance to appointments scheduled for March 20th, 2020 (P=0.008); and March 27th, 2020 (P=0.008).

Table 3 describes the sociodemographic characteristics of the population, indications for anticoagulant therapy, clinical events, and reasons for the attendance or not of patients scheduled at the ambulatory during the study period. There was no statistically significant difference between sociodemographic characteristics of patients who attended the appointment and those who did not attend the appointment on the scheduled date, namely: age (p=0.677), gender (p=0.090), education (p=0.505), profession (0.317), and distance from the city where he lives to the ambulatory (p=0.857).

When analyzing the previous INR values of the studied patients in the collection before the scheduled appointment, most were within the desired INR range (56.6%). In the case of the INR collected in the index query, the adequacy was 50% in both groups. Therefore, there was no statistically significant difference in the INR between those who showed up on the scheduled date and those who did not. There was no significant difference between the INR values before and after the adoption of the adopted measures of social distancing (Table 5).

Table 5. Data from INR collection of patients scheduled at the Anticoagulation Outpatient Clinic, in the pandemic period of *SARS-COV2*, from March to May 2020 (N=132)

Variables	N (%)
Previous INR	2.73±0.85
Therapeutic target	
Within the desired range	73 (56.6)
Outside the desired range	56 (43.4)
INR collection in scheduled query	
Yes	56 (42.4)
No	76 (57.6)
INR collected	3.03±1.08
Therapeutic target	
Within the desired range	28 (50.0)
Outside the desired range	28 (50.0)
Post-consultation INR collection	
Yes	36 (47.4)
No	40 (52.6)
INR collected	2.57±0.85
Therapeutic target	
Within the desired range	18 (50.0)
Outside the desired range	18 (50.0)
Days between date consultation and INR collection	98 (70-119)

Note. Data are mean ± SD, number (%) and median of patients.

In telephone inquiries, the main reason for not attending the appointment on the scheduled date among those absent was social isolation guidelines and fear of contracting COVID-19 (p=0.999). The distance from the city of

residence to the clinic's location was not a significant factor in influencing attendance (p=0.857).

Regarding the presence of complications, there was no significant difference in the occurrence of bleeding or thromboembolic events between patients who attended and those who did not attend on the scheduled date. Four minor bleeding events were reported in the group that attended the planned date and seven that did not attend. Factors such as indication for anticoagulation (p=0.677), age (p=0.677), gender (p=0.090), education (=0.505), and profession (=0.317) also did not show a significant influence on the attendance to the appointment on the planned date.

4. Discussion

The present study demonstrated the profile of a population using VKA anticoagulation and their adherence to anticoagulant treatment in the initial period of the *SARS-COV2* pandemic in Brazil, encompassing the initial consultations between March 20th, 2020, and May 8th, 2020. This period corresponded to the moment of alarm and the initial fear of the new coronavirus infection, despite the low infectivity and lethality rates observed in this period in southern Brazil (Castro et al., 2021). The study population consisted of male individuals (63%) with a mean age of 61 years. It was also observed individuals with low education (76% had completed elementary school at most) and workers from rural areas, homemakers, or retired people. This sociodemographic profile finds some similarities with other populations of patients using anticoagulants in Brazil. The most common indications for the use of oral anticoagulation were AF (33.6%), followed by mechanical aortic valve prosthesis (31.3%) and mechanical mitral prosthesis (17.2%) (Pelegrino, Dantas, Corbi, & Carvalho, 2010).

Non-adherence to oral anticoagulation appears more prevalent in younger patients, those of lower socioeconomic status, those less well informed about their disease and medications, cognitive impairment, frailty and risk of falling, comorbidity burden, lack of social support, alcohol, and drug abuse. We did not observe significant differences in the groups regarding adherence to INR collection and missing doses of VKA during the study period. Regarding adherence to blood collection in the period scheduled for INR control, there was low adherence to INR collection on the scheduled dates, particularly in the initial weeks of pandemic declaration, with adherence below 50% by April 17th, 2020. There was a substantial improvement in adherence in the following two weeks, with rates above 70%. Several factors can explain such behavior. First, the initial fear of contamination by *SARS-CoV2*, associated with the "Stay at Home" policy advocated by the Ministry of Health, may have significantly contributed to low adherence numbers (Caetano et al., 2020) (Croda & Garcia, 2020). The significant improvement observed in the following weeks was possibly due to the gradual loss of this initial fear, associated with the proactive work of the team members of the anticoagulation ambulatory. They started to contact the missing patients and reinforce the guidelines on the importance of adequate anticoagulation control. Such multidisciplinary and initiative-taking behavior is of fundamental importance, as demonstrated in several studies (Barbosa, Mafei, & Marin, 2004). The *IMPACT-AF* study for example demonstrated that a multifaceted and multilevel educational intervention aimed to improve the use of oral anticoagulation with VKA in patients with atrial fibrillation and at risk for stroke, resulting in a significant increase in the proportion of patients treated with oral anticoagulants in five middle-income countries (Vinereanu et al., 2017). In this sense, the nursing team is an essential part of the interdisciplinary care strategy for patients using oral anticoagulants, acting in educational actions that optimize the orientation and adherence of these individuals. The investigation of the individual needs of patients and their difficulties related to adherence to pharmacological treatment can allow the development of coping strategies (Ahmed et al., 2021). Regarding direct oral anticoagulation (DAOC), the adherence is considered better. In a recent systematic review and meta-analysis on real-world adherence and persistence to direct oral anticoagulation in patients with AF, the overall mean adherence was 77%, the overall proportion of patients with good adherence was 66%, and the overall proportion of persistence for all follow-up durations was 69%. The pooled persistence with any DOAC was shown to be higher than for VKAs [odds ratio (OR) 1.44, 95% confidence interval (CI) 1.12–1.86] (Ozaki et al., 2020).

However, the present study draws attention by demonstrating that, even before social distancing measures were adopted in Brazil, the INR adequacy rate of patients followed up at the anticoagulation clinic was just over half of the patients (56.6 %). As shown by the *RE-LY* registry, worldwide anticoagulation was used only in 58% of patients (Oldgren et al., 2014). Although our numbers only reflect the last INR collected and not the time in therapeutic range (TTR) of the patients, it is suggested that there is room for improvement in the control of the INR of the ambulatory patients, which not only improves control rates but reduces complications and improves clinical outcomes (Vinereanu et al., 2017). These results are in accordance with previous studies that supported a deficit in knowledge about oral anticoagulation and interactions with VKA with a correctness rate of less than 50% (Praxedes et al., 2016) (Alphonsa, Sharma, Sharma, & Bhatia, 2015).

5. Conclusion

Adherence to an anticoagulation ambulatory was low in the initial period of the SARS-CoV-2 pandemic in Brazil, with a gradual improvement in the following weeks. Determining the clinical characteristics and epidemiological profile of patients helps to determine the local needs of this population and implement active search strategies to improve adherence rates and reduce unfavorable outcomes. Controlled prospective studies are needed to determine which regional approach can best use our community.

Main messages

•　　To prevent thromboembolic events, vitamin K antagonists are the treatment of choice for many indications.

•　　COVID-19 emerged as a challenge for the management of patients undergoing anticoagulation.

•　　Determining patients' clinical characteristics and profiles helps implement active search strategies to improve adherence rates.

Current research questions

•　　What additional strategies could have improved patient adherence?

•　　Could the findings be different if the data were collected at the current moment of the pandemic?

•　　Could prospective studies bring more favorable results?

Contributors

SFH and DC participated in the study design. SFH, LCCP, LLS, GVP, MALS, and DC collected data. SFH and DC performed the statistical analyses. All authors contributed to interpreting results, drafted the manuscript, and approved the final manuscript.

Protection of Humans and Animals

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declara- tion of the World Medical Association updated in 2013.

Data Confidentiality

The authors declare having followed the protocols in use at their working centre regarding patients' data publication.

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Competing Interests Statement

The authors declare that there are no competing or potential conflicts of interest.

Figure Legend (colors)

- o　20/03 N=25 (blue)
- o　27/03 N=26 (red)
- o　03/04 N=28 (green)
- o　17/04 N=23 (purple)
- o　24/4 N=12 (gray)
- o　08/5 N=18 (orange)

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