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 205 (2021) 81–83

Contents lists available at ScienceDirect

Thrombosis Research

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

Letter to the Editors-in-Chief

Warfarin anticoagulation in the Covid-19 pandemic: Telephone-based management at a regional hematology outpatient center in Joinville, Brazil

ARTICLE INFO

Keywords
Oral anticoagulation
Warfarin
COVID-19
Remote warfarin management

Dear editors,

Oral anticoagulation (OA) is a well-established therapeutic approach for prevention of cardioembolic stroke and venous thromboembolism [1]. Adequate OA is a key element in reducing the high social burden, morbidity and mortality associated with cardiovascular diseases [2–4]. In January 2020, the World Health Organization (WHO) declared COVID-19 a public health emergency of international concern. Since then, the strategy of social distancing has been adopted in most countries, with varying degrees of restriction and compliance. Among various implications of this strategy, a negative impact in the management of chronic diseases is expected, due to reduced access to health-care facilities [2].

OA with warfarin demands regular prothrombin time (PT) with international normalized ratio (INR) testing, and medical follow-up for identifying factors that may increase risk of bleeding or poor INR control [3–5]. For most indications of OA, an INR between 2 and 3 is deemed adequate. The time in the therapeutic range (TTR) calculated by the Rosendaal method is an essential measure of quality of OA with warfarin, on both individual and populational levels [6].

In March 2020, COVID-19 cases were beginning to increase in Brazil, and local authorities restricted in-person non-urgent medical appointments. This compromised the OA follow-up at our treatment center, and a telephone-based model had to be implemented quickly. Since then, OA follow-up is based on a scheduled telephone call, in which the patient reports to the hematologist the INR result, occurrence of bleeding or other clinical event. Considering that most patients on OA are elderly, and with old age being a significant risk factor for severe COVID-19, this remote approach could prove favorable if OA quality is sustained [2,5].

To assess the impact of this unplanned shift from in-person to telephone-based OA with warfarin, we performed a retrospective analysis of patients seen at Centro de Hematologia e Hemoterapia de Santa Catarina (HEMOSC) in the city of Joinville, Brazil. All patients on OA seen between March and September 2019 (In-Person Cohort, IPC) and March and September 2020 (Telephone-based Cohort, TBC) had their electronic health charts reviewed. Inclusion criteria were age 18 years or older and warfarin anticoagulation with a target of 2.0 to 3.0 INR. Exclusion criteria were less than three visits in the study period or more than one missing INR value. All PT essays were performed after venipuncture. IPC patients received updated warfarin dosing by the hematologist after showing a new INR result. TBC patients informed a new INR result verbally, via e-mail or text message, and were verbally informed of any changes on warfarin dosing. A printed warfarin prescription and request for new INR were made available for all patients at each appointment. Warfarin dispensation at our site was available for all patients. Time in therapeutic range (TTR) was determined by the Rosendaal linear interpolation method [6]. Stable warfarin dose was defined as three or more consecutive prescriptions without change. Irregular attendance to clinical follow-up was defined as tardiness of 30 days or more in relation to expected return visit. This study was approved by the institutional review board and carried out in accordance with the Declaration of Helsinki. Statistical analyses were performed using R Studio version 1.4.1106.

Retrospective analysis of 358 patients in 2019 (IPC) and 411 patients in 2020 (TBC) was performed. In IPC, 1552 prothrombin time tests with INR were performed; in TBC, 1803. Main patient characteristics are featured in Table 1. Female patients were 50% ($n = 180$) in IPC and 49% ($n = 203$) in TBC ($p = 0.83$). Median age at first follow-up visit was 73 years (interquartile range, IQR: 65–80) in IPC and 71 years (IQR: 62–78) in TBC ($p = 0.015$). Main indications for OA were previous cardioembolic stroke (50% in IPC; 45% in TBC), atrial fibrillation (41% in IPC; 35% in TBC), and mechanical heart valve (5% in IPC; 11% in TBC).

Stable warfarin dose was observed in 168 (47%) IPC patients and 234 (57%) TBC patients ($p < 0.01$). Irregular attendance to clinical follow-up was seen in 12 (3%) IPC patients and 23 (6%) TBC patients ($p = 0.17$). Mean PT tests per patient was 4.33 (IQR: 3–5) in IPC and 4.38 (IQR: 3–5) in TBC ($p = 0.57$). Median interval in days between PT tests was 39 days (IQR: 31–44) in IPC and 37 days (IQR: 12–63) in TBC ($p = 0.02$).

The median TTR was 62% (IQR: 34–84) for IPC, and 63% (IQR: 40–88), with 52% of tests on target in IPC and 51% in TBC (Fig. 1). TTR equal to or above 65% was observed in 49% of TBC patients and 46% of IPC patients ($p = 0.56$). INR was close to target, considering target INR and values 1.80–1.99 or 3.01–3.50, in 71% of IPC PT tests and 72% of TBC PT tests. INR below 1.5 or above 5.0 were seen in 8% and 1.5% of IPC tests, and 7% and 2.3% of TBC tests.

While the shift in OA management at Hemosc - Joinville was carried out due to unforeseen circumstances, no detriment to warfarin control could be determined in our analysis. Comparable TTR, tests on target,

https://doi.org/10.1016/j.thromres.2021.07.006
Received 18 May 2021; Received in revised form 19 June 2021; Accepted 8 July 2021
Available online 9 July 2021

Table 1
Main features of OA patients using warfarin at Hemosc - Joinville.

	2019 (In-Person Cohort)	2020 (Telephone-Based Cohort)	*p*
Number of patients	358	411	–
Female gender (%)	180 (50%)	203 (49%)	0.83
Median age (years; IQR)	73 (65–80)	71 (62–78)	0.015*
Age ≥ 60 years	85%	79%	0.08
Indication for oral anticoagulation			
Atrial fibrillation (%)	149 (41%)	140 (35%)	0.036*
Cardioembolic stroke (%)	179 (50%)	186 (45%)	0.19
Mechanical heart valve (%)	16 (5%)	46 (11%)	<0.01*
Other (%)	14 (4%)	39 (9%)	<0.01*
Stable warfarin dosing (%)	168 (47%)	234 (57%)	<0.01*
Irregular attendance to clinical follow-up (%)	12 (3%)	23 (6%)	0.17
Mean number of PT tests (IQR)	4.33 (3–5)	4.38 (3–5)	0.57
Median interval in days between PT tests (IQR)	39 (31–44)	37 (12–63)	0.14
Number of performed PT tests	1552	1803	–
Median TTR (% of total days; IQR)	62% (34%–84%)	63% (40%–88%)	0.78
Patients with TTR ≥65%	46%	49%	0.56
Tests on target (%)	52%	51%	0.98
INR ≥1,80 and ≤3,50 (IQR)	1101 (71%)	1299 (72%)	0.49
INR <1,50 (%)	127 (8%)	128 (7%)	0.24
INR >5,00 (%)	23 (1,5%)	42 (2,3%)	0.08
INR >7,00 (%)	4 (0,3%)	10 (0,6%)	0.28

INR: international normalized ratio. IQR: interquartile range. PT: prothrombin time. TTR: time in therapeutic range.
* Statistically significant differences, considering *p* value below 0.05.

and number of tests per patient in each study period were observed in TBC and IPC. Using the Rosendaal linear interpolation method, effective cardiovascular prevention is associated with a TTR equal to or above 65% [6]. For a hematology treatment center, obtaining this standard collectively is an established measure of quality [1,7]. Median TTR for our patient population was just below this target in both cohorts. This reinforces that OA management at our institution needs further improvement, especially regarding patient adherence to treatment and follow-up. TTR below the target of 65% is not uncommon, both in clinical trials [8] and real world [1,4] scenarios. Considering the TTR (61.3%) for Central and South American treatment centers in the RE-LY study [8], observed quality of OA at our institution seems to be at least on par with regional standards. Also comparably, telephone-based oral anticoagulation due to COVID-19 has been recently reported as feasible in an anticoagulation clinic in the United States [9].

A slight increase in our patient population, with more patients on OA due to mechanical heart valves is mostly due to a cardiology outpatient center ceasing to follow-up OA in the COVID-19 pandemic. For this reason, the TBC patient population was slightly younger than in IPC. While an increase in stable warfarin dose was observed in TBC, whether this translates to better management needs to be evaluated with a longer follow-up period. The continuation of TBC may confirm if adherence to follow-up is not hindered by this remote approach.

Warfarin dispensing at Hemosc - Joinville consisted of approximately 116.000 pills in 2019 and 86.000 in 2020. While this 26% reduction, in face of a larger population in regular OA (411 versus 358), could impair OA, we expect that many patients chose to buy the medication close to home or online, thus reducing even further their need to exit their homes. Even before the pandemic, this preference was already reported by some patients. A well-structured health economics analysis of costs attributed to warfarin purchasing, PT testing, transportation to and from medical appointments and laboratory facilities is in order in the continuation of this study to compare our population with published data [4–10]. This is especially necessary considering the clinical possibility for many patients (about 80% of our patient population) of switching from warfarin to direct oral anticoagulants (DOAC). Recently, switching to DOAC due to COVID-19 restrictions has been reported with favorable outcomes [10]. In Brazil, warfarin is offered in the public health system and, should a patient decide to purchase it, its monthly out-of-pocket cost is approximately twenty times less expensive than a DOAC. No DOAC is currently dispensed in the public health system in Brazil [1], and its monthly cost is approximately one quarter of the national minimum wage.

Limitations of this study include its retrospective nature, the lack of patient-reported quality of life outcomes, and the sudden need to switch our OA follow-up, which precluded the elaboration of a clinical study protocol, validated in a small cohort before being applied to the whole population. Direct access to INR results via our laboratory providers is currently being pursued. We plan on offering patients the choice of returning to in-person OA management or staying in the remote approach as soon as COVID-19 restrictions begin to be eased. Considering the comparable OA management observed, telephone-based OA is feasible and safe in our patient population. Further studies are needed to confirm possible favorable effects on health economics and quality of life of patients.

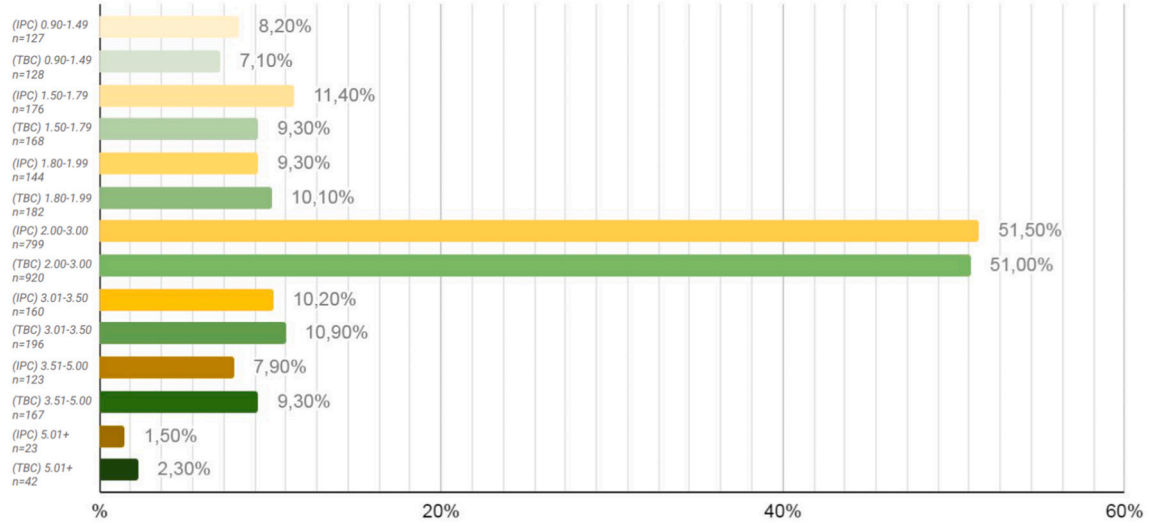

Fig. 1. All prothrombin time INR tests performed at in-person (IPC, $n = 1552$; yellow) and telephone-based (TBC, $n = 1803$; green) cohorts, according to categorized test results. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

KLCM and TA were supported for this work by UNIEDU Research Support Fund at Universidade da Região de Joinville (Univille).

References

[1] P.M.G.B. Silva, et al., Terapia de Anticoagulação em pacientes com Fibrilação atrial não valvar em ambiente de cuidado de Saúde privado no brasil: um estudo de mundo real, Arq. Bras. Cardiol. 114 (3) (2020) 457–466.
[2] D. Poli, et al., Managing anticoagulation in the COVID-19 era between lockdown and reopening phases, Intern. Emerg. Med. 15 (5) (2020) 783–786.
[3] N.L. Cabral, et al., Fibrilação atrial crônica, AVC e anticoagulação: sub-uso de warfarina? Arq. Neuropsiquiatr. 62 (4) (2004) 1016–1021.
[4] J.C. Mwita, et al., Quality of anticoagulation with warfarin at a tertiary Hospital in Botswana, Clin. Appl. Thromb. Hemost. 24 (4) (2018) 596–601.
[5] E. Alhmoud, et al., Anticoagulation clinic drive-up service during COVID-19 pandemic in Qatar, J. Thromb. Thrombolysis (2020) 1–4.
[6] F.R. Rosendaal, et al., A method to determine the optimal intensity of oral anticoagulant therapy, Thromb. Haemost. 69 (1993) 236–239.
[7] S. Liu, et al., Quality of warfarin management in primary care: determining the stability of international normalized ratios using a nationally representative prospective cohort, Can. Fam. Physician 65 (6) (2019) 416–425.
[8] H.G.C Van Spall, et al. Variation in warfarin dose adjustment practice is responsible for differences in the quality of anticoagulation control between centers and countries: an analysis of patients receiving warfarin in the randomized evaluation of long-term anticoagulation therapy (RE-LY) trial. Circulation 126:19 (2012) 2309-16.
[9] R. Cope, et al. Outpatient management of chronic warfarin therapy at a pharmacist-run anticoagulation clinic during the COVID-19 pandemic. J Thromb Thrombolysis (2021) 1-5.
[10] R. Patel, et al., Switching warfarin patients to a direct oral anticoagulant during the coronavirus Disease-19 pandemic, Thromb. Res. 197 (2021) 192–194.

Kendra Lys Calixto Machado[a], Suzana Tanquella da Rosa[b], Soraya Dobner[b], Ivan Schneider Boettcher[b], Gilberto Comaru Pasqualotto[b], Adelina Elisabeth Lehmkuhl Lopes[b], Tainá de Araújo[a], Lysandra Patricia Luchtenberg Bolduan[b], Maria Daniela Holthausen Perico Colombo[b], Marcelo Pitombeira de Lacerda[a,b,*]

[a] *Universidade da Região de Joinville (UNIVILLE), Brazil*

[b] *Centro de Hematologia e Hemoterapia de Santa Catarina (HEMOSC), Brazil*

[*] Corresponding author at: Universidade da Região de Joinville (UNIVILLE), Brazil.
E-mail address: marcelolacerda001@gmail.com (M.P. Lacerda).