

Comparing follow-up of patients with vitamin K antagonists in a health center: pre- and post-COVID-19 pandemic

Comparaç o do seguimento de doentes hipocoagulados com antagonistas da vitamina K numa unidade de sa de: pr  e p s pandemia COVID-19

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ABSTRACT

Introduction and objectives: During the COVID-19 pandemic, the follow-up of patients treated with vitamin K antagonists (VKAs) may have been affected. This study aims to compare how these patients were monitored pre- and post-COVID-19 pandemic and understand the impact of non-face-to-face appointments on their follow-up. **Methods:** We conducted a retrospective cohort study in a Portuguese Health Center. The study included patients treated with VKAs and followed at the Health Center for international normalized ratio (INR) monitoring between March 2019 and March 2021. **Data collected:** sex, age, type of VKA; INR; date of INR assessment, type of appointment (face-to-face or phone/e-mail). Rosendaal's method was used to calculate pre-COVID-19 and post-COVID-19 time in therapeutic range (TTR). Good TTR control was defined if values $\geq 70\%$. **Results:** 44 patients were included. The mean TTR in the pre-COVID-19 period was 64.55% (95% CI: 58.10 - 71.00%). The post-COVID-19 mean was slightly higher (+ 2.26%), 66.81% (95% CI: 59.66 - 73.97%), but the difference was not statistically significant ($p = 0.576$). The use of non-face-to-face appointments did not contribute to worsening post-pandemic TTR, showing no lower follow-up than during pre-pandemic period in which all contacts were face-to-face [CI (95%) -0.397 - 0.196 for a reference range -0.489 - 0.693]. **Conclusions:** The TTR value in both periods was similar and lower than the value defined for effective hypocoagulation. The use of non-face-to-face consultation in the post-COVID-19 period does not seem to have influenced the quality of hypocoagulation.

Keywords: Anticoagulants, Warfarin, International normalized Ratio, COVID-19, SARS-CoV-2.

RESUMO

Introduç o e objetivos: Durante a pandemia COVID-19 o acompanhamento de doentes medicados com antagonistas da vitamina K (AVKs) pode ter sido afetado. Este estudo pretende comparar a forma como estes doentes foram monitorizados antes e depois da pandemia COVID-19 e compreender o impacto da consulta n o presencial no seu seguimento. **M todos:** Estudo de coorte retrospectivo num Centro de Sa de em Portugal. O estudo incluiu doentes tratados com AVKs e seguidos no Centro de Sa de para monitorizaç o do *International Normalized Ratio* (INR) entre março de 2019 e março de 2021. **Dados recolhidos:** sexo, idade, tipo de AVK; INR; data da avaliaç o do INR, tipo de consulta (presencial ou por telefone/e-mail). Foi utilizado o m todo de interpolaç o linear de Rosendaal para calcular o tempo em intervalo terap utico (TTR) pr  e p s-COVID-19. Foi definido um bom controle se valores de TTR $\geq 70\%$. **Resultados:** Foram inclu dos 44 doentes. A m dia de TTR no per odo pr -COVID-19 foi de 64,55% (95% IC: 58,10 - 71,00%). A m dia p s-COVID-19 foi ligeiramente superior (+ 2,26%), 66,81% (95% IC: 59,66 - 73,97%), mas a diferença n o foi estatisticamente significativa ($p = 0,576$). A utilizaç o da consulta n o presencial n o contribuiu para o agravamento do TTR no per odo p s-pandemia, n o mostrando um seguimento inferior ao do per odo pr -pandemia em que todos os contatos foram presenciais [IC (95%) -0,397 - 0,196 para um intervalo de refer ncia -0,489 - 0,693]. **Conclus es:** O valor de TTR em ambos os per odos foi semelhante e inferior ao valor definido para hipocoagulaç o eficaz. A utilizaç o da consulta n o presencial no per odo p s-COVID-19 n o parece ter influenciado a qualidade da hipocoagulaç o.

Palavras-chave: Anticoagulantes, Varfarina, Coeficiente internacional normalizado, COVID-19, SARS-CoV-2.

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INTRODUCTION

Anticoagulant therapy is crucial to prevent adverse thromboembolic events in some diseases¹. There are two types of anticoagulant drugs, vitamin K antagonists (VKAs) (warfarin and acenocoumarol) and direct oral anticoagulants (DOACs)¹. VKAs are widely used, low cost, and there is great evidence they prevent thromboembolic events². They have, however, a narrow therapeutic window, requiring frequent monitoring and dosage adjustment².

Atrial fibrillation (AF), the most common sustained supraventricular arrhythmia in adults³, requires chronic hypocoagulation to prevent thromboembolic events³. Even though the 2020 European Society of Cardiology (ESC) guidelines considered DOACs first-line anticoagulant in AF³, some patients are treated with VKAs. Furthermore, VKAs play an important role in some situations where there is a contraindication for DOACs, such as in patients implanted with a mechanical prosthetic heart valve³.

The international normalized ratio (INR) is used to monitor the effect of VKAs therapy⁴. However, to assess the quality of hypocoagulation in these patients over time, the calculation of the time in therapeutic range (TTR) has been proposed. TTR measures the time of INR within the desired range^{1,2,4}. According to the ESC guidelines, VKAs are safe and effective with TTR values greater than 70%³.

Rosendaal's linear interpolation method is a method of calculating TTR that assumes there is a linear increase or decrease between two consecutive INR determinations and assigns a specific INR value each day between tests^{4,5}.

With the emergence of the Covid-19 pandemic, there was a need to readjust healthcare activity, with many patients being followed remotely or even to the extension of the time interval between INR assessments⁶. Some studies suggest that TTR values of patients treated with VKAs have decreased since the beginning of the COVID-19 pandemic, which in turn makes these patients vulnerable to complications⁷.

This study aimed to assess the quality of monitoring of patients treated with VKAs, pre- and post-COVID-19 pandemic, by applying

Rosendaal's linear interpolation method. It is also intended to know the impact of non-face-to-face appointments on monitoring patients treated with VKAs.

MATERIALS AND METHODS

A retrospective cohort study was conducted in a Health Center in the central region of Portugal between March 2019 and March 2021.

A list of Health Center patients who had at least one VKAs prescription during this period (March 2019 to March 2021) was obtained. By consulting clinical records, a Microsoft Excel® database was created with the patients who met the inclusion criteria for the study. Patients aged 18 years or older, treated with VKAs (warfarin or acenocoumarol) throughout the study period, and followed at the studied Health Center for INR monitoring were included in this study. Patients who changed therapy to DOACs, patients with less than six INR assessments per year, and deaths during the studied period were excluded.

Clinical data were extracted from the medical record, including sex, age, INR value, date of INR assessment, type of consultation (face-to-face or non-face-to-face), and type of VKAs (warfarin or acenocoumarol). INR values were classified as infra-therapeutic, therapeutic, or supra-therapeutic, according to the INR target range recommended for each patient.

TTR values were calculated for each patient from March 2019 to February 2020 (pre-COVID-19 period) and from March 2020 to February 2021 (post-COVID-19 period), using Rosendaal's linear interpolation method⁵. TTR \geq 70% was considered a high-quality INR control, according to the ESC guidelines³. It was also defined that the patient had a non-face-to-face follow-up if most appointments for INR monitoring were remote (telephone or email). This type of appointment was only considered to have taken place when patients had no cognitive deficits or clinical conditions that implied difficulty in understanding the adjustment.

To ensure confidentiality, data access to each case file was performed by the physician

responsible for the patient. The data were transcribed to a database and a code was assigned to each patient. Data collection was performed by physicians not belonging to the research team. This ensured that the researchers only had access to anonymized data. The study was approved by the Ethics Committee of the Regional Health Authority of the Centre Region.

Statistical analyses were performed by using IBM Statistical Package for the Social Sciences (SPSS®), version 21.0. The population was divided into two groups according to a value of TTR \geq or $<$ 70%, respectively. The difference in TTR, number of appointments, and type of appointments/monitoring between the two groups was analyzed. We presented categorical variables as percentage and absolute frequency, and continuous variables as the mean \pm standard deviation (SD) or median with interquartile range. The normality of the distribution of continuous variables was analyzed using the Kolmogorov-Smirnov test. Student's t-test, ANOVA, Chi-square, Fisher's, and Mann-Whitney's tests were used to establish significant associations between the variables collected at the two moments of assessment and considering the non-face-to-face contacts. The non-inferiority assessment was calculated considering sample size, mean, and standard deviation. Descriptive and inferential analysis of the data was performed, with a 95% confidence interval. A *p*-value less than 0.05 was considered statistically significant.

RESULTS

Between March 2019 and March 2021, 78 patients were treated with VKAs in the Health Center. Of these, eight patients were excluded because they had suspended anticoagulant therapy, 12 were excluded because they had less than six INR assessments per year, and 14 were excluded because they had started DOACs. Forty-four patients were included in the study. The mean age of the patients included was 76.16 ± 11.47 years, and 14 (31.82%) were female (Table 1). Most were hypocoagulated by situations without contraindication for DOACs ($n = 31$; 70.45%). The

most used VKA was warfarin ($n = 43$; 97.73%) (Table 1).

Table 1

Cohort demographics and medical data.

Patient characteristics		
Patients, n	44	
Age, mean [IC 95%] (SD)	76.16 [72.63-79.69]	(11.47)
Female sex, n (%)	14	(31.82%)
Medical data		
Without contraindication for DOACs, n (%)	31	(70.45%)
With contraindication for DOACs, n (%)	13	(29.55%)
INR target range		
2.0 – 3.0 n (%)	32	(72.73%)
2.5 – 3.5 n (%)	12	(27.27%)
Number of INR measurements, median (Q1-Q3)	19	(17 – 22.25)
Type of VKA		
Warfarin	43	(97.73%)
Acenocoumarol	1	(2.27%)

AF: Atrial Fibrillation; VKA: vitamin K antagonist; INR: International Normalized Ratio; SD: standard deviation

The mean TTR in pre-COVID-19 period was 64.55% (95% CI: 58.10 – 71.00%). The post-COVID-19 mean was slightly higher (+2.26%), 66.81% (95% CI: 59.66 – 73.97%), but not statistically significant [$t(44) = -0.564$; $p = 0.576$] (Table 2; Figure 1).

Table 2

Follow-up of patients with vitamin K antagonists.

Type of follow-up		
Fully face-to-face, n (%)	17	(38.64%)
Partially face-to-face, face-to-face contacts, median (Q1-Q3)	80.00%	(67.95% – 90.19%)
TTR		
Days evaluated, median (Q1-Q3)	723.50	(701.25 – 735.50)
Mean Pre-COVID-19, mean TTR (95%IC)	64.55%	(58.10% – 71.00%)
Mean Post-COVID-19, mean TTR (95%IC)	66.81%	(59.66% – 73.97%)

TTR: Time in Therapeutic Range

In the subgroup analysis regarding the TTR value greater than 70%, there were 19 patients (43.18%) in the pre-COVID-19 period and 21 (47.73%) in the post-COVID-19 period (Table 3).

Considering the variation pre-COVID-19 and post-COVID-19, TTR improved in the post-COVID-19 period (n = 24; 54.55%) (Table 4). Analyzing the group with a TTR value lower than 70% in the pre-pandemic period (n = 25), it was found

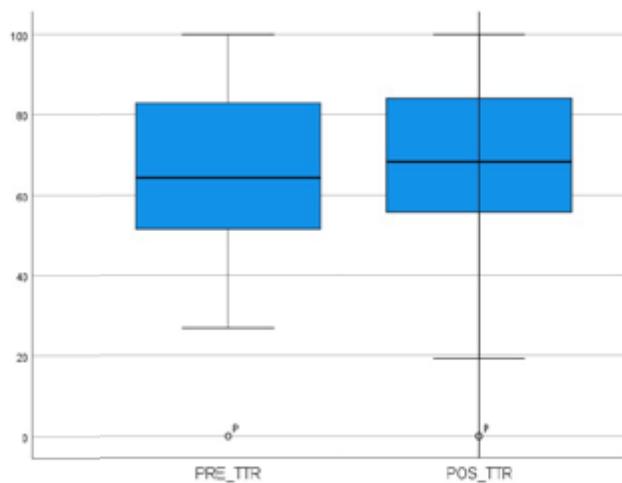


Figure 1: Box-in-Plot of the Minimum-Q1-Median-Q3-Maximum of TTR Pre- and Post-COVID-19.

Table 3
Anticoagulation control pre- and post-COVID-19.

Pre-COVID-19 TTR<70% n, (%)	Pre-COVID-19 TTR≥70% n, (%)	Post-COVID-19 TTR<70% n, (%)	Post-COVID-19 TTR≥70% n, (%)
25 (56.82%)	19 (43.18%)	23 (52.27%)	21 (47.73%)

TTR: Time in Therapeutic Range

Table 4
Comparison of anticoagulation variation, pre- and post-COVID-19.

Pre-COVID TTR<70% (n=25)		Pre-COVID TTR≥70% (n=19)		TTR variation (Pre and Post)	
Post-Covid TTR<70%	Post-Covid TTR≥70%	Post-Covid TTR<70%	Post-Covid TTR≥70%	Worse	Better
15 (60.00)	10 (40.00%)	8 (42.11%)	11 (57.89%)	20 (45.45%)	24 (54.55%)

TTR: Time in Therapeutic Range

that the majority 60% (n = 15) maintained a TTR value below 70%. While of the 19 patients with a pre-pandemic TTR ≥ 70%, the majority, 57.89% (n = 11), maintained good TTR value. (Table 4)

In the pre-COVID-19 period, all INR assessments were face-to-face. In the post-COVID-19 period, there were in-person and non-in-person assessments. The use of non-face-to-face assessments in the post-COVID-19 period did not interfere with the INR, with a TTR value no lower than in the pre-COVID-19 period (95% CI - 0.397 - 0.196 for a reference interval - 0.489 - 0.693).

Table 5
Comparison of anticoagulation control in patient subgroups.

	Mean	IC 95%	Test	p Value
Mean Differences, mean TTR (95%IC)	-2.26	(-10.35 - 5.83)	t -0.564	0.576
Worsening (post-pre < 0) according to the number of non-face-to-face contacts	--	--	Z 1.099	0.548
Mean (subgroup 31), mean TTR (95%IC)	-4.55	(-14.32 - 5.22)	t -0.951	0.349
Non-face-to-face contacts vs Worsening (post-pre < 0)			X ² 1.997	0.218
Non-face-to-face contacts vs good/bad TTR (>70%)			X ² 0.302	0.758

TTR: Time in Therapeutic Range

The variation in each group (TTR < and \geq 70%) pre- and post-COVID-19 was not associated with the use of non-face-to-face appointments (telephone or email) (X^2 0.302; $p = 0.758$) (Table 5).

DISCUSSION

It is known that INR outside the recommended therapeutic range predisposes patients to bleeding or thromboembolic complications⁸. During the COVID-19 pandemic, patients treated with VKAs may have avoided seeking health-care appointments, leading to lower TTR values and poorer follow-up⁷. According to Emren et al., it was found that during the pandemic, about 60% of patients did not seek medical help in case of bleeding complications, and about 6% reduced the dose of warfarin without medical indication⁷.

However, in this study, similar TTR values were found in the pre- and post-COVID-19 pandemic period; the pandemic does not seem to have affected the quality of follow-up of patients medicated with VKAs. Despite this, the TTR value in both periods (pre- and post-COVID-19) was < 70%, which is lower than recommended.

Several studies indicate that patients on VKAs often have INR values outside the recommended therapeutic range^{2,9,10,11,12} and are often under-anticoagulated¹³. Studies carried out exclusively in primary health care have also revealed suboptimal TTR values^{8,14}. In HIPOGAIA, a study developed in primary health care in Portugal, a mean TTR of $67.4 \pm 6.5\%$ was observed, i.e., close to the value found in our study¹. However, the TTR reference values defined for effective hypocoagulation vary from study to study.

On the other hand, the SAIL Warfarin Out of Range Descriptors Study warns that the exclusive use of TTR for monitoring the effectiveness of hypocoagulation may be insufficient since even with adequate TTR, there may occasionally be INR values far outside the reference range, leading to a risk of haemorrhage or thromboembolic events¹⁰.

Several factors that affect the TTR value have not been considered in this study. Patients with mechanical prosthetic heart valves under

VKAs¹⁵ and patients at high bleeding risk seem to have lower TTR values¹⁴, conditioning possible complications. Age, sex, and the frequency of INR assessment are also factors that appear to affect TTR values⁸. In addition, excessive alcohol consumption, comorbidities, non-adherence to therapy, dosage errors, changes in usual medication, and variations in dietary vitamin K intake seem to have an impact on INR control^{14,16}.

Several ways of monitoring anticoagulated patients with VKAs, such as remote INR monitoring, have been described^{1,7,17}. Management of the disease at home seems to improve patients' quality of life and could be an appropriate solution for their follow-up during the pandemic¹⁷.

In this study, non-face-to-face assessments (email or telephone) in the post-COVID-19 period did not interfere with the INR, with a TTR value no lower than in the pre-COVID-19 period. Virtual monitoring of patients under VKAs has proven effective in therapy control and management. Thus, our study may inform the development of new strategies for remote monitoring of patients with VKAs.

In addition, patient education on therapy management may increase their confidence in controlling the disease¹⁷. According to Lale Dinç Asarcıklı et al., only 30.2% of patients seem to be aware of their target INR values¹². Thus, health education for patients under VKAs could be an important area of future intervention. We are also alert to the possibility of future replacement of VKAs by DOACs in cases where these are not contraindicated.

The main limitation of this study is the small sample size, partly explained by the increasing use of DOACs. In addition, this was a study conducted in a single Health Center. Thus, in the future, it would be interesting to study several Portuguese Healthcare units. Variables such as age, gender, socio-economic level, comorbidities, or polymedication may affect the TTR, so they may constitute bias. The fact that there are different methods to calculate TTR and different reference values for effective hypocoagulation may also constitute a limitation in interpreting the results and comparing them with other existing studies. Finally, the potential lack of records in the patient's clinical files may affect the results.

CONCLUSIONS

We have concluded that the TTR value in both periods (pre- and post-COVID-19) was similar and lower than the value defined for effective hypocoagulation. Thus, transition to DOACs may be an alternative for eligible patients. Health education and closer monitoring of these patients may also improve the management of treatment and associated cardiovascular risks.

The use of non-face-to-face appointments in the post-COVID-19 period does not seem to have influenced the quality of control of hypocoagulation. In the future, new non-face-to-face monitoring strategies for hypocoagulated patients with VKAs may be an added value by reducing costs and associated constraints.

REFERENCES

- Guedes M, Rego C. Estudo HIPOGAIA: monitorização da hipocoagulação oral com dicumarínicos no conelho de Gaia. 2016;35(9).
- Gateman D, Trojnar ME, Agarwal G. Time in therapeutic range: Warfarin anticoagulation for atrial fibrillation in a community-based practice. *Can Fam Physician*. 2017;63(10):e425-e431.
- Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2021;42(5):373-498. doi:10.1093/eurheartj/ehaa612
- SIDDIQUI S, DEREMER C, WALLER J, GUJRAL J. Variability in the Calculation of Time in Therapeutic Range for the Quality Control Measurement of Warfarin. *J Innov Card Rhythm Manag*. 2018;9(12):3428-3434. doi:10.19102/icrm.2018.091203
- Rosendaal FR, Cannegieter SC, Van der Meer FJM, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost*. 1993;69(3):236-239. doi:10.1055/s-0038-1651587
- Cope R, Fischetti B, Eladghm N, Elaskandrany M, Karam N. Outpatient management of chronic warfarin therapy at a pharmacist-run anticoagulation clinic during the COVID-19 pandemic. *J Thromb Thrombolysis*. Published online 2021:3-7. doi:10.1007/s11239-021-02410-w
- Emren ZY, Şenöz O, Erseçgin A, Emren SV. Evaluation of Bleeding Rate and Time in Therapeutic Range in Patients Using Warfarin Before and During the COVID-19 Pandemic—Warfarin Treatment in COVID-19. *Clin Appl Thromb*. 2021;27. doi:10.1177/10760296211021495
- Sawicka-Powierza J, Buczkowski K, Chlabicz S, Gugnowski Z, Powierza K, Ołtarzewska AM. Quality control of oral anticoagulation with Vitamin K antagonists in primary care patients in Poland: A multi-centre study. *Kardiol Pol*. 2018;76(4):764-769. doi:10.5603/KP.2018.0011
- Kim Y, Park ES, Kang DW, Kim TJ, Lee SH. Maintenance dose of warfarin beyond time in therapeutic range for preventing vascular events. *J Neurol Sci*. 2019;398(November 2018):69-74. doi:10.1016/j.jns.2019.01.031
- Harris DE, Thayer D, Wang T, et al. An observational study of international normalized ratio control according to NICE criteria in patients with non-valvular atrial fibrillation: The SAIL Warfarin out of Range Descriptors Study (SWORDS). *Eur Hear J - Cardiovasc Pharmacother*. 2021;7(1):40-49. doi:10.1093/ehjcvp/pvz071
- Albaltain MA, Alharthi MM, Dagriri K, et al. Assessment of the quality of anticoagulation management with warfarin in a tertiary care center. *Saudi Med J*. 2020;41(11):1245-1251. doi:10.15537/smj.2020.11.25456
- Asarcıklı LD, Kafes H, Şen T, et al. Time in therapeutic range values of patients using warfarin and factors that influence time in therapeutic range. *Turk Kardiyol Dern Ars*. 2021;49(6):463-473. doi:10.5543/tkda.2021.21015
- Mearns ES, White CM, Kohn CG, et al. Quality of vitamin K antagonist control and outcomes in atrial fibrillation patients: A meta-analysis and meta-regression. *Thromb J*. 2014;12(1):1-20. doi:10.1186/1477-9560-12-14
- Urbanas G, Valius L, Šakalytė G, Petniūnas K, Petniūnienė I. The quality of anticoagulation therapy among warfarin-treated patients with atrial fibrillation in a primary health care setting. *Med*. 2019;55(1):1-11. doi:10.3390/medicina55010015
- Pastori D, Lip GYH, Poli D, et al. Determinants of low-quality warfarin anticoagulation in patients with mechanical prosthetic heart valves. The nationwide PLECTRUM study. *Br J Haematol*. 2020;190(4):588-593. doi:10.1111/bjh.16528
- Björck F, Kadhim H, Sjölander A. Predictors for INR-control in a well-managed warfarin treatment setting. *J Thromb Thrombolysis*. 2019;47(2):227-232. doi:10.1007/s11239-018-1765-4
- Ng DLC, Malik NMBA, Chai CS, et al. Time in therapeutic range, quality of life and treatment satisfaction of patients on long-term warfarin for non-valvular atrial fibrillation: a cross-sectional study. *Health Qual Life Outcomes*. 2020;18(1):1-9. doi:10.1186/s12955-020-01600-z
- Price EL, Ansell J. Virtual Education for Patient Self-Testing for Warfarin Therapy Is Effective During the COVID-19 Pandemic. *Jt Comm J Qual Patient Saf*. 2022;48(4):214-221. doi:10.1016/j.jcjq.2022.01.001

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AA: conception of the work, data acquisition, literature review, draft of the manuscript.

VV: conception of the work, data analysis, critical review of the paper.

SR: conception of the work, literature review, critical review of the paper.

TP: conception of the work, literature review, data acquisition, critical review of the paper.

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