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Assessment of the Economic Impact of Warfarin Substitution with Rivaroxaban

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Abstract

Objective: To evaluate the economic impact of substituting warfarin with rivaroxaban in geriatric patients undergoing anticoagulation therapy. **Methods:** A retrospective study conducted at the Central Institute of the Hospital das Clínicas, Faculty of Medicine, University of São Paulo. Micro-costing and macro-costing analyses were performed, considering direct costs related to the use of warfarin and rivaroxaban, including expenses for medications, INR tests, and medical interconsultations for dose adjustment. **Results:** The analysis included 21 patients, of whom 17 (81.0%) were considered eligible for substitution. The cost simulation indicated savings of approximately R$ 2,758.31 (R$ 162.25/patient) with the adoption of rivaroxaban, mainly due to the elimination of the need for INR tests and medical consultations for dose adjustment. **Conclusion:** Substituting warfarin with rivaroxaban can result in significant cost savings for the institution, in addition to providing clinical benefits to patients. However, the adoption of this strategy should be preceded by a careful assessment of contraindications to ensure treatment safety and effectiveness.

Keywords: rivaroxaban, warfarin, anticoagulants, costs and cost analysis, health technology assessment.

Avaliação do impacto econômico da substituição de varfarina por rivaroxabana

Resumo

Objetivo: Avaliar o impacto econômico da substituição da varfarina pela rivaroxabana em pacientes geriátricos em uso de anticoagulação. **Métodos:** Estudo retrospectivo conduzido no Instituto Central do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. Foram realizadas análises de microcusteio e macrocusteio considerando os custos diretos relacionados ao uso da varfarina e da rivaroxabana, incluindo gastos com medicamentos, exames de INR e interconsultas médicas para ajuste de dose. **Resultados:** A análise incluiu 21 pacientes, dos quais 17 (81,0%) foram considerados elegíveis para substituição. A simulação de custos indicou uma economia de aproximadamente R$ 2.758,31 (R$ 162,25/paciente) com a adoção da rivaroxabana, principalmente devido à eliminação da necessidade de exames de INR e consultas médicas para ajuste de dose. **Conclusão:** A substituição da varfarina pela rivaroxabana pode resultar em economia significativa para a instituição. No entanto, a adoção dessa estratégia deve ser precedida por uma avaliação criteriosa das contraindicações para garantir segurança e efetividade no tratamento.

Palavras-chave: rivaroxabana, varfarina, anticoagulantes, custos e análise de custo, avaliação de tecnologia em saúde.

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Introduction

The World Health Organization (WHO) defines the elderly population as those aged 65 years or older in developed countries and 60 years or older in developing countries. This definition aligns with the Elderly Statute, Law No. 10.741/2003, which regulates the rights guaranteed to individuals over 60 years of age in Brazil. Currently, Brazil has over 30.2 million elderly individuals, representing 14.6% of the population, with projections to reach 35% by 2070.[1]

Although increased life expectancy is a significant achievement, population aging is associated with physiological and functional changes resulting from senescence, which can progress to pathological conditions related to senility, such as neurodegenerative diseases and chronic conditions, including stroke.[2]

Elderly individuals require specific care, particularly in the hospital setting, due to the high prevalence of cardiovascular comorbidities and the increased risk of thromboembolic events, which often necessitate the use of anticoagulant therapies.[3]

Blood coagulation is a critical hemostatic process that culminates in the conversion of blood from its liquid state into a clot. This phenomenon is catalyzed by thrombin, which cleaves fibrinogen, converting it into fibrin.[3] The coagulation cascade functions as a serial enzymatic amplification mechanism. This accelerating enzymatic cascade must be controlled by inhibitors; otherwise, all blood in the body would solidify within minutes after the initiation of the hemostatic process.[3] In this context, coagulation pharmacology encompasses agents that modulate this enzymatic cascade. Such drugs are used both in the treatment of conditions associated with coagulation defects (procoagulants) and in the prevention and treatment of thromboembolic events related to unwanted coagulation (anticoagulants and antithrombotics).[3,5]

The most widely used oral anticoagulant currently is warfarin, a vitamin K antagonist (VKA) belonging to the coumarin class. It acts by interfering with the γ-carboxylation of coagulation factors II, VII, IX, and X[3]. This class of medications requires frequent monitoring of prothrombin time (PT) and dose adjustment to maintain an international normalized ratio (INR) of 2 to 4 in adults and 2 to 3 in the elderly population. Among the adverse effects of warfarin, hemorrhage (especially intestinal or cerebral) stands out, which can be reversed by discontinuing the medication and/or administering vitamin K, fresh frozen plasma, or coagulation factor concentrates (for life-threatening bleeding).[3,4,5] The therapeutic use of warfarin is complex due to variability in individual response and interactions with other medications and foods rich in vitamin K, such as vegetables and organ meats.[3,4,5]

Treatment duration also varies, as, due to the aforementioned interactions, it is difficult for a patient to remain within the desired therapeutic range, thus leading to dose adjustments and prolonged treatment duration.[6] The difficulty in achieving therapeutic control and poor patient adherence led to the development of novel oral anticoagulants (NOACs), which act by directly inhibiting factor Xa in the coagulation cascade.[7] Among this class of anticoagulants, we can mention rivaroxaban, approved for the prevention of venous thromboembolism and stroke, as well as systemic embolism in atrial fibrillation.

Unlike warfarin, the use of rivaroxaban does not require routine laboratory monitoring to verify anticoagulation efficacy.[3,4] However, this class of medication has significant contraindications, such as: significant active bleeding, concomitant use of other anticoagulants, moderate to severe hepatic impairment (Child-Pugh B and C), presence of prosthetic heart valves, severe renal impairment, use of azole antifungals or human immunodeficiency virus (HIV) protease inhibitors, pregnant women, and nursing mothers. Its most common adverse effects are bleeding and anemia, which can be reversed with andexanet alfa, which acts by binding to factor Xa inhibitors, rapidly reducing their concentration and neutralizing their anticoagulant effect.[8,9]

When analyzing the existing therapeutic possibilities and a potential substitution for anticoagulation management, the most appropriate and economically advantageous choice for both the hospital and the patient must be verified.[10] In this scenario, Health Technology Assessment (HTA) becomes indispensable, as it is a systematic process that analyzes the clinical, economic, ethical, and social consequences of health technologies.[11] Economic analyses compare different alternatives, weighing costs and health consequences, considering the growing impact of costs associated with the adoption of health technologies and the increased demand from users for healthcare services.[12] While health technologies are defined as any health intervention, health economic evaluations are defined as formal analytical techniques to compare different courses of action, taking into account both costs and health consequences, both positive and negative.[12]

Costs are classified as direct, indirect, and intangible.[12] The Brazilian Ministry of Health (MS) defines direct costs as those resources that can be directly identified and consumed by patients, such as medications, laboratory tests, and medical consultations, i.e., all resources consumed during treatment, both medical and non-medical. In contrast, indirect costs are those resources that are not identified or clearly linked to the patient, including, for example, absenteeism, retirement, early pensions, and reduced or lost income. Intangible costs, although difficult to measure, affect the patient's quality of life, such as pain, suffering, among others.[12]

Regarding identification, costs can be estimated using gross-costing or microcosting methods. Regarding the assessment of cost components, methods can be performed using a top-down or bottom-up approach. According to the Ministry of Health (MS), microcosting is the method that seeks to evaluate costs as accurately as possible, in which all cost components are defined at the most detailed level based on individual patient treatment data, such as the cost of medications used, tests performed, medical fees resulting from the comorbidity, among others. Gross-costing, on the other hand, is the method that uses cost component data at an aggregated level; these costs are distributed among the various services and procedures performed but are not directly linked to the time spent on a specific procedure, such as estimating the average cost per patient. It is the easiest method to apply and, therefore, the most commonly used in studies aiming to generate generic cost information. The main disadvantage is its low precision.[12,13]

Although rivaroxaban offers clinical advantages, its adoption as a replacement for warfarin implies a higher unit acquisition cost. The lack of specific data on the offset of the drug's direct costs with the savings generated by the elimination of laboratory tests, dose-adjustment consultations, and management of complications associated with warfarin constitutes a fundamental gap in knowledge for evidence-based decision-making. Therefore, the present study aims to evaluate the economic impact of replacing warfarin with rivaroxaban in geriatric patients on anticoagulation therapy through a simulation of associated costs in a reference university hospital.

Methods

This retrospective study evaluated the economic impact of replacing warfarin with rivaroxaban in geriatric patients, including a simulation of the associated costs.

The study was conducted at the Central Institute of the Hospital das Clínicas, Faculty of Medicine, University of São Paulo (ICHCFMUSP). The analyzed population included patients of both sexes who participated in the outpatient warfarin management protocol of the geriatrics service. All patients included in the protocol between May 11, 2021, and July 31, 2024, were considered. Patients whose identification (name or hospital registration number) or date of inclusion in the protocol were unavailable were excluded.

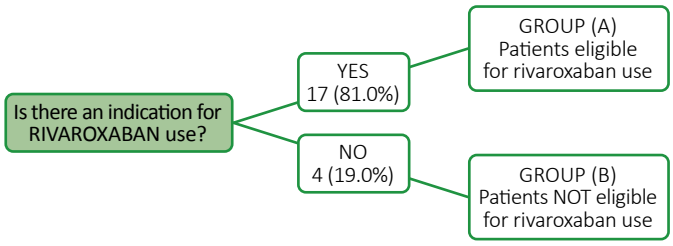
Data collection was performed using the following sources: the Hospital Information and Management System (SIGH), to identify patient prescriptions and quantify the warfarin tablets dispensed by the outpatient pharmacy, as well as the potential use of other medications contraindicated for concomitant use with rivaroxaban; the HCMED corporate system, to survey the number of INR tests performed for each patient and verify medical records regarding health conditions that contraindicate the use of rivaroxaban; and the corporate Excel spreadsheet Alerta COP, provided by the infrastructure and logistics department of Hospital das Clínicas, to identify the current price of warfarin 5 mg and rivaroxaban 10 mg at HCFMUSP during the study period (July 31, 2024).

The collected data were recorded in a Microsoft Excel spreadsheet containing the following information: name, hospital registration number (RGHC), date of birth, sex, date of enrollment in the protocol, date of last consultation, number of teleconsultations performed, contact phone number, and warfarin dosage adjustments.

Patient eligibility was determined by analyzing a data spreadsheet from the geriatrics service containing individuals previously enrolled in the warfarin management protocol. The inclusion criteria for patient selection in the study included: full name, hospital registration number (RGHC), date of inclusion in the warfarin protocol, and the ability to obtain a signed informed consent form (ICF).

After selection, patients were allocated into two distinct groups based on the assessment of contraindications to rivaroxaban: Group A (Candidates for Substitution): Patients who presented no contraindications for the use of rivaroxaban; Group B (Non-candidates for Substitution): Patients who exhibited at least one of the following exclusion criteria and/or contraindications for the use of rivaroxaban: moderate to severe hepatic impairment (Child-Pugh class B or C); presence of prosthetic heart valves; severe renal impairment; concomitant use of azole antifungals or human immunodeficiency virus (HIV) protease inhibitors. A decision tree was developed to determine the proportion of patients in each group and establish the decision criteria for replacing warfarin with rivaroxaban (Figure 1).

Figure 1. Clinical decision tree for patient eligibility for the substitution of warfarin with rivaroxaban.



Costs were analyzed using microcosting, including: unit cost of warfarin (R$ 0.13); cost of the INR test (R$ 13.34), as reported by the central laboratory division of ICHC; and the cost of medical labor related to teleconsultation, estimated at R$ 8.55 per 30-minute consultation. This value was calculated based on the monthly stipend of a medical resident at ICHC (R$ 4,106.90 for 240 hours/month), in accordance with Interministerial Ordinance No. 9 of October 13, 2021, which regulates resident stipends. Reimbursements from the Brazilian Unified Health System (SUS) to the institution were also considered, corresponding to the INR test at R$ 2.73 and the teleconsultation at R$ 10.00, according to the SUS Procedures, Medications, and OPM Table Management System (SIGTAP). A cost simulation was performed for the replacement of warfarin treatment with rivaroxaban.

The study's time horizon encompassed the cost analysis of the 17 patients eligible for the study, from their date of inclusion in the warfarin protocol on May 11, 2021, until July 31, 2024, with no costs considered beyond this period. Cost comparison was performed exclusively for patients in Group A (candidates for rivaroxaban use), simulating the replacement of warfarin with rivaroxaban. The cost of INR testing and healthcare team time for monitoring (teleconsultation) were considered only for patients on warfarin, as rivaroxaban does not require this monitoring.

Descriptive statistical analyses were performed to characterize the study sample and compare costs using cost-minimization analysis methods, where the amount spent on warfarin consumption was deducted from the amount that would be used with rivaroxaban. Cost-minimization analysis was chosen because the compared anticoagulants (warfarin and rivaroxaban) demonstrate comparable clinical efficacy and safety in preventing thromboembolic events when used for approved indications, as shown in clinical trials and real-world practice studies. In this situation, when therapeutic alternatives produce equivalent outcomes, the economic evaluation can focus exclusively on comparing the costs associated with the interventions. Assessment of warfarin treatment consumption was performed by collecting data from electronic medical records and laboratory test databases, with data analyzed in aggregate. The study was approved by the Ethics Committee (CAAE: 1974624.5.0000.0068, Opinion No.: 7,024,161, issued on September 24, 2024) and conducted in accordance with established ethical principles. All participants or their legal guardians signed the informed consent form.

Results

The initial evaluated population consisted of 28 patients followed by the geriatrics service. Of these, seven were excluded due to the absence of complete information in the spreadsheet, such as name, date of enrollment in the protocol, or hospital registration number (RGHC). Thus, 21 patients remained eligible to participate in the study. Of these, 17 (81.0%) were classified as Group A (patients eligible for rivaroxaban use), while 4 (19.0%) were allocated to Group B (patients not eligible for rivaroxaban use) (Figure 2).

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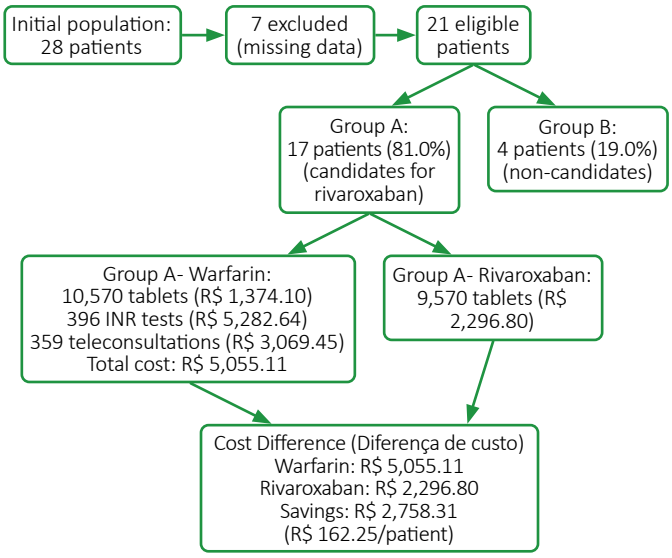
Figure 2. Distribution of patients according to eligibility for rivaroxaban use.



Patients in Group A consumed a total of 10,570 warfarin 5 mg tablets, resulting in a cost of R$ 1,374.10. Additionally, 396 INR tests were performed, with a total cost of R$ 5,282.64 (Table 1). In the same group, 359 medical teleconsultations were conducted, each lasting 30 minutes, totaling R$ 3,069.45 in medical professional fees. In the substitution simulation, the consumption of 9,570 rivaroxaban 10 mg tablets was estimated, with a total cost of R$ 2,296.80, considering a daily dose of 10 mg.

Table 1. Micro-costing: Consumption and costs of medications (warfarin and rivaroxaban), laboratory tests (INR test), and healthcare professional fee (teleconsultation).

Item	Unit Cost (R$)	Quantity Consumed/Performed	Total Cost (R$)
Warfarin 5 mg	0.13[1]	10,570	1,374.10
INR Test	13.34[2]	396	5,282.64
Rivaroxaban 10 mg	0.24[1]	9,570	2,296.80
Medical fee for teleconsultation[3]	8.55[4]	359	3,069.45

[1] Value extracted from purchase records (COP Alert Spreadsheet) of ICHC, 2024.
[2] Value provided by the Central Laboratory Division (DLC) team of ICHC.
[3] Each teleconsultation was assumed to last an average of 30 minutes.
[4] A value of R$ 4,106.90 for 240 hours/month was considered for the medical resident fee at ICHC.

Both the medical teleconsultation and the INR tests are outpatient procedures that qualify for reimbursement from the Brazilian Unified Health System (SUS), as established in the SIGTAP system. The reimbursement for performing INR tests is R$ 2.73 per test, while medical teleconsultation is reimbursed at R$ 10.00 per session (Table 2).

Table 2. Transfers from the Brazilian Unified Health System (SUS)

SUS Transfer	Unit Cost (R$)	Quantity	Total Cost (R$)
INR Tests[1]	2.73[1]	396	1,081.08
Medical teleconsultation[2]	10.00[2]	359	3,590.00

[1] Source: SIGTAP – Prothrombin Time Activity Determination (PT) – Outpatient service value: R$ 2.73.
[2] Source: SIGTAP – Clinical consultation by a medical professional in specialized care, performed remotely using information and communication technology – Outpatient service value: R$ 10.00.

The final cost according to the values in effect in 2024, considering all expenses and reimbursements received, was R$ 5,055.11 for warfarin treatment. In contrast, when simulating replacement with rivaroxaban 10 mg, the final cost was R$ 2,296.80, resulting in a difference of R$ 2,758.31 (R$ 162.25/patient) between the two treatments (Table 3).

Discussion

The present study revealed that 81.0% of patients undergoing warfarin management follow-up in the geriatrics service were eligible for replacement with rivaroxaban, demonstrating significant potential for implementing this change in clinical practice. Among the main advantages of rivaroxaban are dosing convenience and the absence of dose adjustment requirements based on age, body weight, or renal function.[3,4] However, in patients with severe renal disease, especially those with creatinine clearance below 15 mL/min, the decision to use it must carefully consider the risk-benefit ratio. Clinical studies indicate that significant elevation of rivaroxaban plasma levels may increase the risk of bleeding[3,4]. In this context, Li et al. (2024) demonstrated that rivaroxaban was significantly more effective and safer than warfarin in patients with chronic kidney disease associated with atrial fibrillation, reducing both the incidence of stroke (RR = 0.75, 95% CI 0.67-0.84) and all-cause mortality (RR = 0.84, 95% CI 0.75-0.93).[7] Salcedo et al. (2019) also demonstrated that rivaroxaban is likely a dominant treatment over warfarin in elderly male patients with non-valvular atrial fibrillation and worsening renal function, providing an increase in QALYs at an overall reduced cost (rivaroxaban: 5.69 QALYs at a cost of R$ 66,075 per patient vs. warfarin: 5.22 QALYs with costs of $78,504 per patient).[14]

The cost simulation demonstrated that replacing warfarin with rivaroxaban is economically advantageous for the institution. This saving results from reduced expenditures on medical professional fees and INR tests (coagulation monitoring), as rivaroxaban eliminates the need for frequent laboratory tests, as well as teleconsultations for individualized dose adjustment. Previous studies also point to the cost-effectiveness of rivaroxaban compared to warfarin in certain scenarios[10]. They demonstrated that the annual outpatient cost was significantly higher in the warfarin group due to the greater need for outpatient visits (US$ 147.09 ± 78 vs. US$ 62.32 ± 19.79, $p < 0.001$), as well as costs associated with bleeding complications per patient (US$ 119.41 ± 61.8 vs. US$ 48.74 ± 14.63, $p < 0.001$). However, the annual medication cost was higher in the rivaroxaban group (US$ 71.55 ± 31.0 vs. US$ 362.6, $p < 0.001$). Despite this, when considering non-drug and hospital costs, warfarin was not shown to be cost-effective, reinforcing the economic viability of adopting rivaroxaban[10].

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Table 3. Cost Comparison between Warfarin and Rivaroxaban

Medication	Drug Cost (R$)	INR Cost (R$)	Medical Fee Cost (R$)	INR Reimbursement (R$)	Teleconsultation Reimbursement (R$)	Final Cost (R$)
Warfarin	1,374.10	5,282.64	3,069.45	1,081.08	3,590.00	5,055.11[1]
Rivaroxaban	2,296.80	-	-	-	-	2,296.80[2]

[1] Final cost (R$) = (Drug Cost + INR Cost + Medical Fee Cost) – (INR Reimbursement + Teleconsultation Reimbursement)
[2] Final cost (R$) = Drug Cost

The transition from warfarin to rivaroxaban in the Brazilian clinical setting is strongly influenced by pharmaceutical assistance policies and economic viability. Within the scope of the Brazilian Unified Health System (SUS), warfarin remains the main therapeutic alternative, being consolidated in the National List of Essential Medicines (RENAME). Its wide availability in the Basic Component of Pharmaceutical Assistance justifies its large-scale use, despite the logistical and clinical costs associated with frequent laboratory monitoring and the risk of adverse events resulting from its narrow therapeutic window. In contrast, access to direct oral anticoagulants (DOACs), such as rivaroxaban, still faces significant barriers in the public system; their distribution is not universal across all primary care units, often being restricted to specific state protocols.

In the specific context of the Geriatrics Outpatient Clinic of the Central Institute of Hospital das Clínicas (ICHCFMUSP), where this research was conducted, access to rivaroxaban reflects the complexity of technology management in a high-complexity university hospital. The prescription of this drug often depends on the patient's ability to pay out-of-pocket or on institutional dispensing protocols that prioritize cases with difficult management using warfarin.

A determining factor for expanded access was the expiration of the patent in Brazil for the drug Xarelto, whose active ingredient is rivaroxaban, which occurred in 2021 following judicial decisions related to the Industrial Property Law, allowing the registration and marketing of generic versions by the National Health Surveillance Agency (ANVISA). The entry of generics into the national market resulted in a substantial reduction in the unit acquisition price, mitigating the financial impact for institutions and patients, and strengthening the argument for its definitive incorporation into hospital therapeutic formularies and SUS reimbursement guidelines.

The results of this study should be interpreted with caution, considering its exploratory nature and the retrospective design adopted. The main limitation lies in the small sample size (17 patients), which compromises external validity and the generalizability of the findings to broader populations. Additionally, the retrospective design of the study introduces potential susceptibility to selection bias. The absence of a sensitivity analysis constitutes another methodological limitation, preventing verification of the robustness of the economic results against variation in key parameters, such as drug prices or test frequency.

Another limiting factor is the exclusion of indirect costs, such as those arising from serious adverse events or hospitalizations. The omission of these factors may underestimate the true economic impact of the substitution and should be addressed in future analyses. Finally, the study did not evaluate relevant subjective factors, such as patient perceptions and preferences regarding the use of warfarin versus rivaroxaban. The present study constitutes a cost-minimization analysis from an institutional perspective and does not aim to conduct a formal cost-effectiveness evaluation.

Conclusion

The results suggest that rivaroxaban may be a viable alternative from a cost-minimization perspective compared to warfarin for geriatric outpatients who do not present contraindications to its use. However, the substitution decision should be individualized and based on careful clinical evaluation.

The microcosting and gross-costing analysis of warfarin versus rivaroxaban use revealed that the reduction in costs associated with INR tests (coagulation monitoring) and medical professional fees, combined with the greater dosing convenience of rivaroxaban, may bring benefits to both patients and healthcare professionals. The reduced need for monitoring and dose adjustments allows professionals to direct their efforts toward other activities, in addition to generating significant financial savings for the institution.

It is important to note that future studies with larger and more diverse samples are needed, including the assessment of indirect costs and the impact on patients' quality of life. Such research could provide more robust evidence on the cost-effectiveness of rivaroxaban and contribute to clinical and administrative decision-making.

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Collaborators

Pereira ES and Souza RA performed data collection, analysis, and interpretation. All authors participated in the conception and research design. Pereira ES drafted the article. Sforsin AP and Pinto VB provided scientific supervision and critical revision of the article content. All authors approved the final version of the article.

Conflict of Interest Statement

The authors declare no conflicts of interest regarding this article.

Artificial Intelligence (AI) Systems

ChatGPT (OpenAI) was used to assist in the linguistic revision of the text. All generated suggestions were evaluated by the authors for approval of the final version of the article.

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