

SHORT EDITORIAL

Factors Associated with Variation in Time in Therapeutic Range (TTR)

Felipe Costa de Souza^{1,2} 

Universidade Federal Fluminense,¹ Niterói, RJ – Brazil

Hospital Universitário Gaffrée e Guinle,² Tijuca, RJ – Brazil

Short Editorial referring to the article: Factors Associated with Variation in Time in Therapeutic Range in Two Anticoagulation Clinics in Brazil

Anticoagulant therapy is recommended for several conditions, including atrial fibrillation (AF), venous thromboembolism, and after heart valve replacement.¹ While warfarin is commonly used to prevent ischemic stroke in patients with AF, direct oral anticoagulants (DOACs) and nonpharmacologic therapies may be equally or more effective than traditional warfarin.^{2,3} In addition, warfarin has a narrow therapeutic index and can interact with many drugs and foods, which poses a challenge to using it.⁴

A key strategy for reducing the risk of stroke or bleeding associated with warfarin is to maintain an optimal time in therapeutic range (TTR). TTR refers to the length of time a patient's international normalized ratio (INR) remains between 2 and 3, which is a widely accepted measure of effective warfarin management. While there is no universally accepted safe range for TTR, patients whose INR is in the therapeutic range more than 70% of the time have better outcomes in terms of stroke prevention. In addition, those with INR control greater than 40% of the time have improved survival.⁵

Current scientific literature identifies several factors associated with TTR variation (Figure 1). Costa et al. (2024) demonstrated that TTR variation is associated with sex at birth, dietary habits, anticoagulation indication, and most importantly, incorrect use of warfarin.⁶ Conversely, Luo et al. (2023) did not find significant differences related to sex at birth, clinical variables, or systemic diseases, but observed that patients with TTR < 65% had significantly lower weight compared to those with higher TTR values.⁷ Another

study of 182 patients with left ventricular assist devices found a 10.1% decrease in TTR in women compared to men and an 11.5% decrease in TTR associated with type 2 diabetes.⁸

Of all the issues related to poor TTR, the use of anticoagulant is the most frequently discussed and managed. Adherence to and satisfaction with therapy are critical factors influencing the quality of care. Patients switching from warfarin to DOACs report greater satisfaction, particularly among women and those who have been on warfarin for longer periods. However, the clinical correlation between this increased satisfaction and different TTR levels remains unproven.⁹

Drug dosage and oral bioavailability remain important considerations in anticoagulation therapy. Inadequate dosing is associated with a 3.5-fold greater likelihood of TTR falling outside the therapeutic range compared to patients receiving correct doses of warfarin. Warfarin treatment quality is comparable to that of drugs such as apixaban or dabigatran only when TTR approaches 80%, a goal that is often unattainable in the outpatient setting. In addition, warfarin is associated with a higher incidence of ischemic stroke, intracranial hemorrhage and mortality than these other oral anticoagulants.²

Adjusting warfarin doses based on INR measurements is a routine aspect of anticoagulant therapy. The initial dose of warfarin is critical to the time required to achieve a stable INR. Patients who do not achieve satisfactory INR values after multiple dose adjustments are at higher risk of poor TTR.⁷ Several studies have explored methods to improve warfarin management through dose adjustment tools. One successful case described by Kosum et al.¹⁰ compared two groups of patients at baseline, six months, and twelve months after implementation of a protocol for adjusting warfarin dosages. The study demonstrated

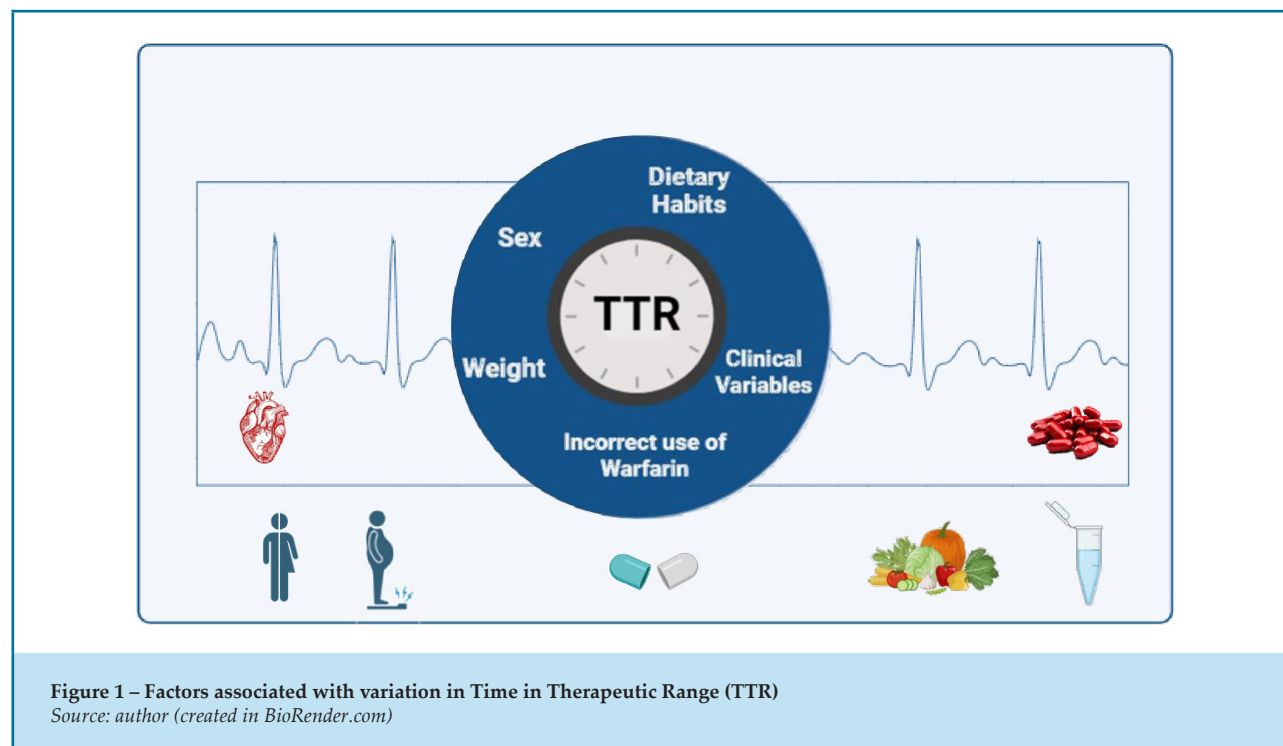
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Mailing Address: Felipe Costa Souza

Instituto Biomédico, Universidade Federal Fluminense. Rua Hernani Pires de Melo, 101. Postal code: 24210-130. São Domingos, Niterói, RJ – Brazil
E-mail: felipefarm@yahoo.com.br

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a significant increase in mean TTR from 65% at baseline to 70% at six months and 80% at twelve months.

The ongoing challenge of monitoring and maintaining TTR within a safe range remains for patients with AF treated with warfarin. Multiple factors, including patient characteristics, clinical conditions, and the affordability of DOACs, may influence the choice

of therapy.⁴ Maintaining an accessible approach for patients who require anticoagulant therapy is important, and warfarin remains the first option in many cases. However, managing the factors that directly affect TTR and using safer drug alternatives and nonpharmacological approaches whenever possible is critical.

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