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Quality Assessment of Anticoagulation Dose Management: Comparative Evaluation of Measures of Time-in-Therapeutic Range

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Abstract. ***Background:*** **The results of clinical trials often hinge on the quality of oral anticoagulation management, yet the quality of such management is frequently not mentioned or measured. Time-in-therapeutic range (TTR) is one measure of quality of anticoagulation dose management, but various methodologies exist for measuring TTR.**

Objective: **This study was initiated to compare three commonly used methodologies for measuring TTR to see how they compare within the same cohort of patients.**

Patients/Methods: **Three common methodologies of calculating time-in-therapeutic range were analyzed retrospectively in a cohort of patients over six two-month intervals. Additional analysis was performed for three and six-month intervals. The methodologies included fraction of INRs in range; cross-section of the files; and linear interpolation.**

Results: **Fraction of the INRs in range and cross-section of the files methodologies gave similar results, while linear interpolation yielded significantly shorter time-in-range for the two-month, three-month, and six-month intervals measured. The advantages and disadvantages of each methodology are discussed.**

Conclusions: **The decision of which method to use should be based on clinic size, information desired, and clinic resources for ease of applying either of the methods in clinical practice. Each of these methodologies has their limitations and the question remains as to which method best reflects the quality of anticoagulation management. Regardless of these limitations, investigators are urged to employ at least one method of measuring the quality of oral anticoagulation management so as to better assess the validity of the clinical outcomes.**

Key Words. **oral anticoagulation, quality, prothrombin time, international normalized ratio**

Introduction

High quality dose management of oral anticoagulation is essential for achieving good outcomes in patients on warfarin therapy [1,2]. Evaluating the outcomes achieved in randomized controlled trials where warfarin therapy is employed in one treatment arm often hinges on the quality of anticoagulation management. Unfortunately, many randomized controlled trials do not assess or characterize how well warfarin therapy is managed. The same can be said when evaluating the quality of management of an anticoagulation clinic. One quality measure of anticoagulation management is assessing how well the patient's intensity of anticoagulation is maintained within the therapeutic range, since an increased time in therapeutic range (TTR) is associated with a reduction in hemorrhage and thromboembolism [1, 3–6]. Thus, TTR can be used as a surrogate marker to assess outcomes, but methods employed to measure TTR vary, making it difficult to compare results across trials [1]. This study was initiated to compare three commonly used methodologies for measuring TTR to see how they compare within the same cohort of patients.

Methods

Study patients

This study is a retrospective analysis of three methods of determining TTR for the same cohort of patients seen at a university hospital-based, pharmacist managed, anticoagulation clinic. All patients with varying indications for anticoagulation who were followed during the calendar year 2001, on warfarin therapy for at least 30 days, with a minimum of 4 International Normalized Ratio (INR) values recorded, and at least 2 INR values within 30 days of each other, were eligible for analysis. INRs from the first 30 days of therapy initiation in each patient were excluded from the analysis. INR values reported during temporary discontinuation of therapy i.e. hospitalization or medical procedure, were included in the analysis because this information was not documented consistently in the clinic records and was therefore difficult to exclude. Data were obtained from a software program (Coumacare®) used to track

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patient data. All three TTR methods were measured for six consecutive two-month time intervals. These small discrete time intervals were selected to determine if consistent differences were present thereby establishing more trust in the study results. Additional analyses were performed for three and six-month time intervals to increase confidence in results. Since the number of patient visits per month varied, 175 patients were randomly selected during each interval in order to have similar cohorts for analysis. Pre-defined target INR values were obtained from the Coumacare® database in order to determine if the INR value was within target range. The precise target range, rather than an expanded target range, was used for analysis.

Methodology for determining TTR

TTR was determined for each cohort of patients using the following three methodologies: the fraction of INR's in range; the cross-section-of-the-files methodology [7]; and the Rosendaal linear interpolation method [8]. The fraction of INR's in range was calculated by taking the number of INR's within target range for all patients divided by the total number of INR's during the selected time interval. The cross-section-of-the-files methodology was calculated by taking each patient whose INR value is in range at one point in time (the INR value that was closest to the midpoint of the selected interval ± 7 days) divided by the total number of INR's done on all patients at that point in time. The Rosendaal linear interpolation methodology was calculated using the INR-DAY software program (Dr. F.R. Rosendaal, Leiden, The Netherlands) that assumes a linear relationship exists between two INR values and allows one to allocate a specific INR value to each day for each patient [8]. An average time in range for all patients was determined. The study was approved by the Institutional Review Board of Boston University Medical Center.

Statistical methods

All INR values for patients meeting the inclusion criteria were obtained from Coumacare® software and were exported into a SAS statistical software program file for statistical analysis. The study null hypothesis was that the mean TTR difference for each pair of methods would be similar ($H_0 = 0$). A two-sided paired t-test was used to compare each pair of methods.

Results

The study included 633 patients who were managed by the anticoagulation clinic during the year of analysis. Table 1 summarizes patient-specific characteristics. Only 17% of the patients were newly started on warfarin therapy at some point during the study year. The majority of patients were on therapy for greater than one year before data analysis. Atrial fibrillation or flutter was the most common indication for anticoagulation. The target range for 78% of patients was 2.0–3.0.

Table 1. *Patient Characteristics*

	Characteristic	No.	Frequency (%)
Sex	Male	310	(48.9)
	Female	323	(51)
	Total	633	
Age	19–49	101	(15.9)
	50–69	288	(45.5)
	70–89	233	(36.9)
	≤18 or ≥90	11	(1.74)
Start date at clinic	1998 or before	154	(24.3)
	1999–2000	137	(21.7)
	2001	107	(16.9)
	before 2001, but not documented	235	(37.1)
Indication for AC	VTE (DVT, PE, Thrombophilia)	159	(25.2)
	Valvular heart disease	81	(12.9)
	CVA	89	(14.2)
	Atrial Fib/Flutter	250	(39.5)
	CAD or CHF	51	(8.2)
Target therapeutic range	2.0–3.0	495	(78.2)
	2.5–3.5	48	(7.6)
	Other	90	(14.2)

VTE: venous thromboembolism; DVT: deep venous thrombosis; PE: pulmonary embolism; CVA: cerebral vascular accident; CAD: coronary artery disease; CHF: congestive heart failure.

A total of 4,576 INR values were included in the study analysis. The mean TTR for each two month interval over the year for the fraction of INR's in range (0.81, SD = 0.03) was almost identical to the cross-sectional methodology (0.82, SD = 0.06), but both of these were different from the Rosendaal results (0.59, SD = 0.01). There was no statistically significant difference between the first two means ($p < 0.15$), but there was between the Rosendaal method and each of the others ($p < 0.001$ for each). When the same analysis was performed for three and six-month intervals the results were unchanged. Study results are summarized in Table 2.

Discussion

The quality of oral anticoagulation dose management is a central factor in determining the outcomes of care in studies of oral anticoagulation therapy [1]. Unfortunately, even well designed randomized clinical trials often fail to report on the quality of oral anticoagulation management [9,10]. When such data is available and compared, the methodology

Table 2. *Average Percent Time in Therapeutic Range (TTR) for Six Consecutive Two-Month, Three-Month and Six-Month Time Intervals Over the Year*

	Ave % TTR for two, three and six month time intervals		
Methodology	Two-Month Interval (SD)	Three-Month Interval (SD)	Six-Month Interval (SD)
Fraction of INR's	0.83 (0.03)[a]	0.82(0.02)[b]	0.81(0.02)[b]
Cross Sec	0.81 (0.06)[c]	0.84 (0.03)[c]	0.76 (0.03)[d]
Rosendaal	0.59 (0.02)[e]	0.58 (0.02)[e]	0.59 (0.06)[f]

[a,b]Fraction of INR's vs. Cross Sec: p-value $<0.15^{a}$ and p-value $<0.2^{b}$.
[c,d]Cross Sec vs. Rosendaal: p-value $<0.001^{c}$ and p-value $<0.025^{d}$.
[e,f]Fraction of INR's vs. Rosendaal: p-value $<0.001^{e}$ and p-value $<0.025^{f}$.

used for measuring quality often differs among trials making it difficult to compare results [1]. The same limitations apply to assessing the quality of dose management outside of clinical trials in anticoagulation clinics or usual care models of anticoagulation management [1,2].

Maintaining a patient's INR within the therapeutic range is a well established predictor of adverse events such as major hemorrhage or thromboembolism [1,3–6], and time-in-therapeutic-range (TTR) is a recommended quality measure for oral anticoagulation management [1,6]. However, TTR can be determined by a variety of methodologies making comparisons difficult, and a number of other variables will further influence the results. These additional variables include whether an exact or an expanded therapeutic range is used [11]; whether patients just beginning therapy are included or only patients who are already on established therapy are included [12,13]; whether INRs obtained during invasive procedures when warfarin therapy might be interrupted are included; and whether different oral anticoagulant preparations are included (warfarin, phenprocouman, acenocoumarol) [14–16].

The TTR results observed in our study are similar to TTR results previously reported [1,14,16,18–20]. The reason for the lower rate of TTR obtained using the Rosendaal method compared to other methodologies is not clear. It has been argued that extreme out-of-range INR values could lower the TTR obtained using this methodology [8], but in our study, an average 22% of patients had an INR <2.0 and only 4% had an INR >3.5. Hence, the lower TTR observed with the Rosendaal method cannot be explained by extreme INR values. Other studies reporting TTR have used wide target ranges (i.e. 2.8–4.8) which would increase the likelihood of patients achieving the desired TTR. Since this study used the narrower recommended target INR range, it is reasonable that we would observe lower TTR results than if we used a wider range, but this should have occurred across all methodologies.

In order to recommend one methodology over another, one must understand which method best reflects the outcomes of concern when one is over or under anticoagulated, i.e. hemorrhage or thromboembolism. No systematic studies of this nature have been performed, although Barbui et al. [20], in a review of outcomes from their anticoagulation clinic, found no difference between TTR calculated by either the fraction of INRs in range or the linear interpolation method in patients who experienced bleeding or thrombosis.

The advantages and disadvantages of the three methodologies compared in this study have been discussed in the literature [8,17–20] and are summarized in Table 3. The fraction of INR's in range methodology is simple to calculate and requires only one INR value per patient. This method becomes more precise as the number of patients increases. van

Table 3. *Advantages and Disadvantages of Methods to Obtain Time-in-Therapeutic Range (TTR)*

Methodology	Advantage	Disadvantage
Fraction of INR's	• Simple to calculate • Requires only one INR value per patient in clinic population • Not influenced by extent of INR out-of-range	• More frequent testing in unstable patients may bias overall results (will under-estimate TTR of group) • Does not take into account actual days within target range • Does not consider individual patients
Cross-section-of-the-files	• Simple to calculate • Considers individual patients • Not influenced by extent of INR out-of-range	• Does not take into account actual days within target range • Only considers one point in time
Rosendaal linear interpolation	• Takes into account actual days in target range • Allows one to calculate INR specific incidence rates of adverse events	• Calculation more difficult • Makes assumptions about INR between actual tests • Does not consider individual patients • Extreme out-of-range INR values may bias overall results

den Besselaar et al. [18] have suggested that a random sample of 70 patients should yield a precise level of overall therapeutic control. However, this method should underestimate TTR for a group if unstable patients are tested more frequently. The cross-section-of-the-files methodology is also simple to perform, and provides a snap shot of how individual patients are managed at a particular point in time. A single result, however, does not suggest how well patients are managed over time. Neither of these two methods can be used to calculate incidence rates at different INR values, which can be done with the Rosendaal method. Even so, the Rosendaal method is a more complicated calculation. It also makes assumptions that may not be true, and extreme values of out-of-range INRs may have an overall impact on the TTR for the entire group. This methodology does not assess the adequacy of anticoagulation of individual patients.

This is the only study comparing the three most common methodologies used for measuring TTR while on warfarin therapy, using the recommended narrower target ranges, over similar time intervals. The fraction of INR's in range and cross sectional methodology give similar TTR results in the same clinic population, but the Rosendaal method does not, at least when examining short time intervals. We are unable to recommend one methodology over another, since each methodology has specific attributes. The decision of which of these methods to use should be based on clinic size, information desired, and clinic resources for ease of applying either of the methods in clinical practice. Each of these methodologies has their limitations and the question still remains as to which method best reflects the quality of anticoagulation management. Regardless of these limitations, a clinic or clinical study should still use TTR as a guide to assess how well patients are being managed. All investigators are urged to employ at least one method of measuring the quality of oral anticoagulation management so as to better assess the validity of the clinical outcomes.

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