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Time to Revisit the Time in the Therapeutic Range

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Abstract

In recent clinical trials, the "quality" of warfarin management has been characterized by the time in therapeutic range (TTR) – with the therapeutic range being an INR between 2.0 and 3.0. In many reviews of recent clinical trials, differences in the TTR have been used comparatively to critique and contrast the trials. However, TTR is a more complex measurement than is commonly appreciated, and many factors that underlie the TTR calculation, which can differ from trial to trial, have not been adequately addressed. This manuscript attempts to explain these issues so as to help the reader understand the factors that contribute to TTR and to understand the limitations of TTR so as to better understand anticoagulation trial results. It also addresses the issue of INRs below or above the therapeutic range, that can differ among trials, that are not provided simply by presenting a TTR value, but that can in a substantial way affect the bleeding risk and embolism-prevention likelihood of anticoagulation in a trial.

Introduction

Warfarin is a drug we love to hate. Despite the fact that we are extremely familiar with it (as it has been available to clinicians for over 60 years) and recognize that, when used properly, it is highly effective for reducing stroke and systemic embolism (SSE) [1] in at-risk patients with atrial fibrillation (AF) and/or mechanical heart valves as well as for treating and preventing venous thromboembolism (VTE), it is difficult to use. Patients and physicians alike find reasons to avoid it – too many doses to choose from, too many dietary interactions, too many drug and herbal interactions (both pharmacokinetic and pharmcodynamic), the risk of bleeding, and the need to monitor it closely because of these concerns. With respect to the latter, monitoring has taken the form of measuring the prothrombin time (PT), and reporting it as an international normalized ratio (INR) so that the results are consistently understandable regardless of the specific laboratory methodology. The target INR that appears to most effectively balance the risk of SSE or VTE versus the risk of bleeding is a range between 2.0 and 3.0 [2],[3] [except for a slightly higher range with mechanical valves and a slightly lower range in some Asian populations].

Rarely, however, does the INR remain stable in a given patient across time. More typically it varies, sometimes dramatically, in association with: dietary fluctuations; changes in the pharmacy-dispensed formulation; initiation, discontinuation, or change in dose of one or more concomitant medications, supplements, or over-the counter agents; changes in bowel flora or bowel function due to intercurrent or chronic diseases or the effect of drugs (such as antibiotics, NSAIDS, etc.[4]); and more [Table 1]. Thus, as a means of assessing the stability of warfarin anticoagulation (often used synonymously with the adequacy of anticoagulation), the Time in the Therapeutic Range (TTR)[5] has become a common reportable measure in clinical trials. TTR is presumed to represent the percent of time the INR remains in the target range across time.

While "on the surface" TTR should be an easily understandable and easily calculated number, this turns out not to be as straightforward as it may seem. Shouldn't the TTR simply be the number of INR values in the target range (numerator) over the total number of INR values measured (denominator)? At first glance, that might seem to be the case. Notably, this approach has been useful in assessing individual patients and has been the one most often used by practitioners [6] but it falls short when applied across patients in clinical trials [7] for multiple reasons: (1) How should one account for values measured in the first week or two before the warfarin effect is stabilized and the INR has had an opportunity to reach the target range? (2) How should one account for differences in frequency of INR measurements, such as daily or weekly versus monthly (and the non-measured fluctuations that might occur between measurements)? (3) How should one handle INR results during planned temporary discontinuations of warfarin, as, for example, due to surgery? (4) How should one assess the TTR as reported across clinical trials if the issues raised above are not handled identically from trial to trial or across geographical regions or types of practices within a single trial? A second approach that has been tried in clinical trials to deal in part with some of the above concerns is the cross-section-of-files method, where the INRs of all patients in a trial are sampled at a given point in time. [7] However, this approach also fails to successfully deal with all of the above issues. Patients will be missed if all subjects in a trial do not have an INR check in the same time frame/at the same frequency. And, variation due to changes in dose or diet will only be detected by chance. Accordingly, a third method was proposed by Rosendaal

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and colleagues. [8] It uses linear interpolation to assign an INR to each day in which an INR was not actually measured, based upon the prior and next actually measured INRs (see more below). Then the total number of measured or assigned INRs in the 2.0-3.0 range over the total number of combined measured and assigned INRs is used to determine the mean TTR. However, while this method is now the most common approach used in recent clinical trials, it, too, has major limitations.

Consider: is it possible to meaningfully compare the TTRs across the following examples?

(1)In trial A, a phase 2 study of a new oral anticoagulant versus warfarin, a 2-month run-in phase is followed by a 10-month maintenance phase. Warfarin is begun and INRs are checked per protocol on day 1, 3, 7, 11,14, 28, and then every 4 weeks. The INR exceeds 2.0 for the first time on day 14. Should the INR values on days 1, 3, 7, and 11 be included in the calculation of the TTR? If one uses the method of Rosendaal et al [8] they would be. Such was the case in the ROCKET-AF trial [9] of rivaroxaban vs warfarin in patients with AF. However, this was not the case in the ARISTOTLE [10] and RE-LY [11] trials of apixaban vs warfarin and dabigatran vs warfarin, in AF patients, in which values in the first week were not used (a modified Rosendaal method).

In trial B, which is identical to trial A in all respects, 20% of the patients required temporary discontinuation of anticoagulation during the trial because of surgery or an interventional procedure. Should any INRs obtained during the discontinuation periods be used in the TTR calculations for the trial? They will certainly be lower than in those patients in whom no interruption occurred, and will reduce the mean TTR reported for the trial. This has not commonly been discussed in clinical trial reports (though such days have been excluded in modified Rosendaal calculations).

(3)In trial C, which is identical to trial A except that the frequency of INR checks is left to the individual physician managing each patient. How should one compare the TTR in trial A, where values are checked only monthly to those in trial C, in which there is an average of 2.7 checks/month? If all of the monthly checks in trial A were in range the TTR would be 100%; however, if all the q4 week checks in trial C were in range but several of those checked during the month were not (and led to a change in warfarin dose), the TTR would be lower, despite the same values at the same 4-weekly checks. The Rosendaal approach to different frequency of INR checks, as per the above, uses linear interpolation of values for days between checks, such that an assumed value can be assigned to each day between actual checks. However, this cannot reflect the reality of the PT values when a low result leads to an increase in warfarin dose (and an increase in the PT in an average of 3 days) or a decrease in warfarin dose (and a decrease in PT in 3 days). In a representative patient in whom an INR of 1.5 leads to an increase in warfarin dose the day the low value is reported with a resultant rise in INR to 2.4 in 4 days, 2.6 at 2 weeks, and stability the rest of the month, the actual TTR would be higher in this patient than it would have been simply using the Rosendaal method and interpolating values from 1.5 to 2.6 four weeks. Interpolation will not increase the INR from 1.5 to 2.4 in 4 days, but rather, interpolated values would reach 2.4 in over 3 weeks and would be under 2.0 for almost 2 weeks.

(4)Trials D and E are both multinational studies of a new oral anticoagulant versus warfarin. Participating centers in trial D include: 40% U.S. and Canada, 30% western Europe, 15% eastern Europe, 10% Asian, and 5% south American. Participating centers in trial E include: 10% U.S. and Canada, 35% western Europe, 25% eastern Europe, 25% Asian, and 5% south American. In ROCKET-AF, INR rechecks averaged 8 days in North America if the INR was <1.5 and 14 days for an INR 1.5-1.9; however, it was 30 days in non-U.S., non-Western Europe centers. [12], [13] In ROCKET-AF, the mean TTR was 36% in India and 75% in Sweden. [11] If the same geographical differences in recheck frequency (often reflecting access to care, local traditions, source of payment for care, and more) occurred in trials D and E as occurred in ROCKET-AF, then could we truly compare the mean TTR values in trial D to those in trial E?

(5)In trial F, all patients receive all of their care from the physicians in the trial centers. In trial G, patients receive care from their trial physicians as well as from their individual primary care physicians. In the latter case, dietary changes and prescriptions for non-trial drugs are handled by the primary care physicians – often without the trial physician knowing until the patient's next study visit. Some of the primary care physicians rechecked INRs on their own when a dietary or drug change was made (some via an anticoagulation clinic, some not). Trial G has significant potential for alterations in the PTs between trial visits (and at the next trial INR measurement) whereas this is much less likely in trial F. So, again, how could one meaningfully compare the mean TTR between trials F and G?

The above examples illustrate some of the complexities in the assessment and use of TTR values to make comparative judgements about the quality of warfarin treatment across centers, populations, or trials. These complexities seem to me to have been under-considered by some critics when trials of the new direct oral anticoagulants have been reviewed and compared, one against the other, and even in the FDA approved wording in the package inserts of these new agents. Going forward, I believe we should attempt to "use a level playing field" when utilizing the concept of TTR in trial assessment.

Finally, we also need to consider two important numbers that the TTR does not tell us. That is, the percent of INRs that are below 2.0 (low) and above 3.0 (high). Each of two trials could have a mean TTR of 68%, but in one, 30% of INRs are low and 2% are high, while the opposite is true in the other. In the former, the concern would be an increased risk of thromboembolism while in the latter, the concern would be an increased risk of bleeding. Might such account for differences in NOAC vs warfarin bleeding rates among the recent pivotal trials? We cannot know since such information has not been uniformly provided. Accordingly, a more meaningful although more complex measure might be TTR-F, M%, N, R, X%/X%, where F=average time between INR checks, M=mean of all INRs, N=number of INR measurements, R = range of INR values, and X%/X% = the percent of INRs 2.0/3.0. This approach would provide not only the mean TTR but information regarding important variables that affected its calculation plus important information regarding risks that the TTR does not detail. However, this suggestion has not yet been tested clinically. If significant differences exist among these numbers across trials, despite similar TTRs, they could be important in understanding and comparing the reported efficacy and bleeding rates in the trials, such as those of the recent pivotal NOAC versus warfarin trials in atrial fibrillation.

Thus, in sum: assessing and understanding TTR is a complex issue. Simple numerical averaging in a given patient is simple to calculate, but this approach is not truly suitable to clinical trials or even to inter-patient comparisons, though it can be of importance in the

Table 1: Some factors that can affect the INR and that relate to the interpretation of TTR

A.Common factors that can affect the INR:
Dietary fluctuations;
Changes in the pharmacy-dispensed formulation;
Initiation, discontinuation, or change in dose of one or more concomitant medications, supplements, or over-the counter agents;
Changes in bowel flora or bowel function due to intercurrent or chronic diseases or the effect of drugs (such as antibiotics, NSAIDS, etc.);
Patient's compliance with medication and dietary instructions, and monitoring.
B.Important factors that can affect the TTR:
Method used for TTR calculation;
Frequency of INR rechecks;
Geography and local traditions regarding INR recheck frequency;
Handling of periods of temporary discontinuation of anticoagulation;
Access to care and payment for care;
Totality of care-givers involved in a patient's care, and their location and data-sharing and timing of data-sharing.
C.Clinically important values that the TTR does not provide:
The percent of time that the INR is below 2.0 (risk for thromboembolism) and that it is above 3.0 (risk for bleeding).

management of individual patients. The cross-section-of-files method has been used in some older clinical trials, but fails to adequately account for the variations in INR that occur in given patients with changes in dose, drugs, diet, frequency of INR checks, and more. It is the least frequently used approach. [6] The Rosendaal approach (or modifications of it) has been used in the most recent large clinical trials. However, it requires a computerized data set and algorithm to calculate; it is not adequately flexible to account for real changes in INR that occur between actual INR measurements if factors that can alter the INR have occurred or if the frequency of INR rechecks varies significantly among patients or centers, and more. Accordingly, even it is imperfect (and when tested against the other two methods discussed above, it has given lower values [7]). Therefore, while TTRs will undoubtedly continue to be used in assessing vitamin K antagonist therapy, being better than any alternative way to quantitatively and qualitatively assess the adequacy of the regimen being used, its limitations and biases will need to be kept in mind when the values obtained are used in patient management or trial design, interpretation, and comparison.

Conflict Of Interests

None.

Disclosures

Dr. Reiffel has been an investigator in, a consultant for, and/or served on a speaker's bureau for: Boehringer Ingelheim, BMS, Daiichi Sankyo, Janssen, Pfizer, Portola pharmaceutical companies.

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