International Normalized Ratio Variability: A Measure of Anticoagulation Quality or a Powerful Mortality Predictor

Gabriel Vanerio, MD*†

Background: As atrial fibrillation (AF) carries twice the mortality hazard when compared with a similar population without diagnosed AF, the importance of risk stratifying is obvious. Several variables are related to outcome: age, comorbidities, and use of several medications, particularly oral anticoagulants. The CHA_2DS_2VASc score is an extremely useful tool to predict thromboembolic events and also mortality. The international normalized ratio (INR) variability is a treatment efficacy variable also associated with morbidity in patients receiving warfarin. The objective of the study is to compare the prognostic value of the CHA_2DS_2VASc versus the INR variability or its combination to predict mortality. *Methods:* In this observational study, we analyzed 589 patients from our Atrial Fibrillation Cohort, all on warfarin for more than 1 year and had more than 5 INRs performed in the last 2 years.
The CHA_2DS_2VASc, HAS-BLED, and SAMe-TT_2R_2 scores were calculated as well as the INR variability using the time-in-therapeutic-range (TTR), the percentage of INRs (%INRs) within range, and the standard deviation of the INRs (SD_{INRs}). Kaplan–Meier survival curves were plotted via different cutoff points. *Results:* The mean TTR was 53 ± 23%; 34.6% of the patients had a TTR above 64%. The mean %INRs in range was 50.2 ± 20.2; 17.3% of the population had %INRs in range above 70%. The mean SD_{INRs} was .84 ± .54, and 38.4% had SD_{INRs} below .79.
Of 598, 139 (22%) discontinued warfarin treatment. Death was responsible for almost 50% of treatment discontinuation.
Of 598, 68 patients died during the study period (11.5 %); the most frequent causes of death were heart failure (30%), bleeding (17%), and ischemic stroke (15%).
Patient survival had a correlation with TTR, %INRs in range, SD_{INRs}, left ventricular ejection fraction, CHA_2DS_2VASc, and the combination of CHA_2DS_2VASc + SD_{INRs} (cutoff >1 and >.79, respectively). *Conclusions:* INR variability is an extremely useful tool to assess anticoagulation quality. Calculation of both CHA_2DS_2VASc and INR variability appears to be extremely useful to predict mortality in patients with AF receiving warfarin. The SD_{INRs} emerges as a strong mortality predictor compared to the other INR variability indexes. **Key Words:** Atrial fibrillation—warfarin—anticoagulants—therapeutics—mortality.

From the *CASMU Arrhythmia Service, Montevideo; and †Department of Cardiology, British Hospital, Montevideo, Uruguay.
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Address correspondence to Gabriel Vanerio, MD, CASMU Arrhythmia Service and the Department of Cardiology, British Hospital, 2420 Av., Italia, Montevideo 11600, Uruguay. E-mail: gabriel.vanerio@yahoo.com.
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Warfarin is the most common oral anticoagulant (OAC), and approximately 2% of adults in the developed world are receiving warfarin.[1]

The benefits of OAC in patients with atrial fibrillation (AF) are well known. In the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) trial, patients on warfarin had a significantly better survival after adjustment for other covariates.[2] Despite this key observation, there was no mention of the quality of anticoagulation. Useful measures to evaluate anticoagulation dose management are the time-in-therapeutic range

(TTR), the fraction of the international normalized ratios (INRs) in range, and other INR variability indexes.[3] Long periods with a TTR above 65% or a high percentage of INRs (%INRs) in range are associated with reduction in hemorrhage and thromboembolic events.[4-11] Therefore, monitoring INR variability to assess and correct warfarin treatment decreases complications.[1]

In our country and the rest of South America, there is no sufficient information regarding anticoagulation quality in patients receiving warfarin. There are data available with acenocumarol, a similar compound, but not warfarin.[12]

In the modern trials with non–vitamin K antagonists, regional data showed wide INR variation that could be explained by patient characteristics or country socioeconomic and health care standards. In Central and South America, the mean TTR on the RE-LY trial was 61%, and in the Rocket-AF trial Latin America, the mean i-TTR was 55.2 ± 20%.[13,14]

As AF carries twice the mortality hazard when compared with a similar population without diagnosed AF, the importance of risk stratifying is obvious. Several variables are associated with outcome: age, comorbidities, use of anticoagulants, and so forth. The CHA_2DS_2VASc score is an extremely useful tool to predict thromboembolic events and assess treatment efficacy.[15,16]

Objectives

To compare the prognostic value of the CHA_2DS_2VASc score versus different INR variability methods or its combination to predict mortality in patients receiving warfarin. We hypothesized that the combination of a risk score and a therapeutic evaluation variable has a clinically significant value.

Patients

The Montevideo-CASMU Atrial Fibrillation Cohort includes 3196 patients with AF. The registry started on April 1995 and ended in December 2012. In this observational study, we selected patients receiving warfarin with a minimum of 6 international normalized units performed from January 01, 2010, to July 31, 2012; all patients were followed until October 2013. All subjects included were receiving warfarin for more than 12 months before January 2010.

Methods

We utilized 3 methods to estimate INR variability: (1) standard deviation of INRs (SD_{INRs}) for each patient during the observation period, SD_{INRs}; (2) the fraction of INRs in range during the observation period for each patient, expressed in percentage as %INRs; and (3) percentage of TTR estimated by linear interpolation (Rosendaal method, worksheet template available at https://www.inrpro.com/article.asp?id=27)[3] Every INR-specific person-time was calculated by incorporating the frequency of INR measurements and their actual values and assuming that changes between consecutive INR measurements are linear over time.

We analyzed 9007 INRs, with a mean of 29 ± 5 INRs per patient (range, 6-48). When 3 consecutive INRs were performed with less than 20 days between tests, data were not included.

The CHA_2DS_2VASc, HAS-BLED[1], and SAMe-TT_2R_2[17] scores were calculated at the time the study started.

Target INR was 2-3 for 92% of the patients.

All patients were followed, and mortality was the primary end point, when possible; the cause of death was assessed.

AF Type Definitions

Paroxysmal AF: self-terminating AF, usually within 48 hours.

Persistent AF: when an AF episode either lasts longer than 7 days or requires termination by cardioversion, either with drugs or by direct current cardioversion.

Permanent AF: when the presence of the arrhythmia is accepted by the patient (and physician). Hence, rhythm control interventions are, by definition, not pursued in patients with permanent AF.

Outcome Definitions

Fatal bleeding that directly causes death with no other explainable cause directly observed (by either clinical specimen [blood, emesis, stool, and so forth] or imaging) or confirmed on autopsy.

Stroke

Definition of central nervous system (CNS) infarction: CNS infarction is brain cell death attributable to ischemia, based on pathological, imaging, or other objective evidence of cerebral focal ischemic injury in a defined vascular distribution. CNS infarction includes hemorrhagic infarctions.

Statistical Analysis

Categorical data are presented as absolute numbers and percentages, and continuous data as mean values and standard deviations. To compare variables, we utilized the Student *t* test, chi square and Fisher exact test, and one-way analysis of variance as appropriate. The effect of the presence of one or more mortality predictor was evaluated utilizing Kaplan–Meier survival curves (from January 2010 to October 2013). Factors were compared using the log-rank test, and a *P* value less than .01 was considered statistically significant. Multivariate Cox regression analysis with time-dependent covariate data was performed and presented as hazard ratios (HRs) with 95% confidence intervals (CI).