CLINICAL SCIENCE

Warfarin doses for anticoagulation therapy in elderly patients with chronic atrial fibrillation

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OBJECTIVE: Anticoagulation is a challenge for the prophylaxis of thromboembolic events in elderly patients with chronic atrial fibrillation. Stable anticoagulation is defined as the time within >70% of the therapeutic range. However, the dosage required to achieve stable anticoagulation remains unknown. The aim of this study was to analyze the warfarin dose necessary for the maintenance of stable oral anticoagulation therapy in elderly patients.

METHODS: We analyzed 112 consecutive outpatients with atrial fibrillation who were ≥65 years of age, had received anticoagulation therapy with warfarin for more than 1 year and had a stable international normalized ratio between 2.0 and 3.0 for ≥6 months. The international normalized ratio was measured in the central laboratory using the traditional method.

RESULTS: The patients were stratified according to the following age groups: <75 or ≥75 years and <80 or ≥80 years. The mean daily doses of warfarin were similar for patients <75 or ≥75 years (3.34 ± 1.71 versus 3.26 ± 1.27 mg/day, $p = 0.794$) and <80 or ≥80 years (3.36 ± 1.49 versus 3.15 ± 1.23 mg/day, $p = 0.433$). In 88 (79%) patients, the daily warfarin dose was between 2 and 5 mg/day; in 13 (11%) patients, the daily warfarin dose was <2.0 mg/day; and in 11 (10%) patients, the daily warfarin dose was >5.0 mg/day. The correlation between the daily warfarin dose and the international normalized ratio was 0.22 ($p = 0.012$).

CONCLUSION: Stable anticoagulation was achieved in 80% of patients who received doses of 2 to 5 mg/day of warfarin, and the mean daily dose was similar across the age groups analyzed.

KEYWORDS: Warfarin; Anticoagulation; Elderly; Chronic Atrial Fibrillation.

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INTRODUCTION

Chronic atrial fibrillation (AF) is more prevalent in the elderly population and serves to increase the risk of thromboembolic events. Oral anticoagulation therapy with warfarin is highly effective for the prevention of thromboembolic events (1,2). However, only half of the patients with AF are within the therapeutic range of anticoagulation, whereas the other half does not use oral anticoagulants (3) or are inadequately anticoagulated (4). Currently, oral anticoagulation therapy with warfarin requires regular control of the levels of anticoagulation based on an international normalized ratio (INR) between 2 and 3 (INR2-3) (5). It is known that elderly patients are more likely to experience both thromboembolic events and bleeding, even when they are within the therapeutic range of anticoagulation (6). For example, intracranial bleeding occurs more frequently in very elderly patients (≥85 years) and those with an INR value >3.5 (7). According to this increased bleeding risk in the elderly, physicians may tolerate nontherapeutic INR levels or prescribe lower doses of warfarin than the nonelderly would receive, which leads to a bias that favors inadequate and ineffective anticoagulation (8). Previous studies have demonstrated the efficacy and safety of chronic oral anticoagulation with warfarin in elderly patients by adopting an INR range between 2 and 3 (INR2-3). Patients with AF who remained within the INR2-3 therapeutic range for more than 70% of the anticoagulation time had nearly an 80% reduction in the risk of stroke (9). However, the average warfarin dose used in these studies is unknown, especially the mean dose in patients with INRs within the ideal range. Therefore, the current study aimed to analyze the average warfarin dose for anticoagulation in patients with chronic, stable INR2-3 scores. By providing a definition of the appropriate dose for these patients, we aim to provide health professionals with the safest warfarin dose, thus reducing the risk of bleeding and adjusting the dynamics of the laboratory analysis for anticoagulation.

MATERIALS AND METHODS

From a population of 2,000 individuals undergoing chronic oral anticoagulation with warfarin, mostly to prevent

No potential conflict of interest was reported.

thromboembolic events in patients with AF, we selected 112 ambulatory elderly patients (≥65 years) who had received consecutive anticoagulation therapy with warfarin for more than 1 year and who had been INR2-3 stable for ≥6 months. These patients were divided into two groups according to the following age categories: <75 or ≥75 years and <80 or ≥80 years. We included only patients with AF and excluded patients with renal disease (creatinine levels >2.0 mg/dL) and uncompensated hepatic cancer or known endocrine diseases. We also excluded patients who had bleeding or significant changes in their INR in the preceding six months. The tolerable INR range was 1.8 to 3.2. The control routine outpatient anticoagulation analysis consisted of periodic visits to the doctor every two months with concomitant INR analysis. The Ethics Committee of the Heart Institute (InCor) approved this study, and written informed consent was obtained from all participants. Coagulation measurements were made using an automated method in our clinical laboratory, and the INR value was calculated according to the plasma clotting time of the patient divided by the clotting time of a normal control, raised to the power of the International Sensitivity Index (ISI). The venous blood samples were collected in tubes containing sodium citrate 3.8%. The plasma was obtained by centrifugation at 3000 rpm for 15 minutes and then analyzed using the Tcoag Destiny Max^{TM} (Trinity Biotech, Ireland) automated equipment. Also, a specific kit (PT Tcoag TriniCLOT Excel S) containing thromboplastin extracted from rabbit brain tissue was used, and this method had an ISI of 1.2. Normal, abnormal, and normal pooled plasma internal controls (TRINICHECK CONTROL - Trinity Biotech) were prepared in the laboratory and tested daily to assess the reliability and efficiency of the laboratory procedures to generate valid results. The results were divided into the following three groups according to the INR value obtained: INR<2.0, insufficiently anticoagulated patients; INR≥2.0 but <3.5, appropriately anticoagulated patients; and INR≥3.5, excessively anticoagulated patients.

Statistical analysis

Sample size was calculated based on the differences between the 0.5 mg dose of warfarin and the average 1.5 mg standard deviation for patients <75 or ≥75 years, which resulted in 46 individuals for each group. The categorical variables were analyzed using the χ^2 test, and continuous variables were analyzed using the unpaired Student's *t*-test. A simple linear regression was used to analyze the correlation between the INR versus the daily warfarin dose. *p*-values<0.05 were considered statistically significant. The statistical software used was the ''Primer of Biostatistics'' version 4.02 (10).

RESULTS

The mean age of the selected patients was 79.3±5.57 years with a range from 65 to 98 years. Of these, 47 (42%) patients were male, and 65 (58%) were female. Regarding patient distribution by age, 27 patients were 65 to 75 years of age, 69 patients were 76 to 85 years of age, and 16 patients were ≥85 years of age. The average daily warfarin dose to maintain INR2-3 were similar for patients <75 or ≥75 years (3.34±1.71 versus 3.26±1.27 mg/day, $p=0.794$) and patients <80 or ≥80 years (3.36±1.49 versus 3.15±1.23 mg/day, $p=0.433$) (Table 1). To achieve INR2-3, 88 (79%) patients received daily warfarin doses of 2 to 5 mg; 13 (11%) patients received doses <2 mg/day, and 11 (10%) patients received doses >5 mg/day. The correlation between the daily warfarin dose and the INR value was 0.22 ($p=0.012$) (Figure 1).

Table 1 - Daily warfarin doses in 112 patients with atrial fibrillation undergoing oral anticoagulation.

Groups	Age	N	Dose mg/day (mean±SD)	Minimum dose (mg/day)	Maximum dose (mg/day)
<75 or ≥75 years	<75	27	3.34±1.71[a]	1	7.14
	≥75	85	3.26±1.27[a]	0.57	7.14
<80 or ≥80 years	<80	66	3.36±1.49[b]	1	7.14
	≥80	46	3.15±1.23[b]	0.57	7.14
	Total	112	3.28±1.39	0.57	7.14

SD = standard deviation; [a]< 75 vs. ≥75 years-old, $p=0.794$; [b] < 80 vs. ≥80 years-old, $p=0.433$.

DISCUSSION

This study demonstrates that 80% of patients had INRs within the optimal oral anticoagulation range (2.0 to 3.0) after receiving warfarin doses of 2-5 mg/day, and the mean dose was similar for both elderly age groups analyzed (<75 or ≥75 years and <80 or ≥80 years). Previous studies have demonstrated the importance of maintaining a stable INR value between 2.0 to 3.0 for reducing strokes and mortality in patients with AF. The INR value remained within the therapeutic range more than 70% of the time, and age has been shown not to prevent patients from maintaining INRs within the recommended anticoagulation range (9,11,12). The stability of the INR value resulting from these doses facilitated anticoagulation in elderly patients, as well as the frequency of laboratory control. Furthermore, these doses may result in a smaller number of patients with an inadequate INR value (<2.0) and, therefore, increased protection from thromboembolic events and major bleeding. A recent study on patients with stable anticoagulation, time within the therapeutic range >70%, and effective INR2-3 values demonstrated daily doses similar to those observed in our study (6). These authors also showed progressive reduction in the warfarin dose with increasing age, as 43 mg/week for patients aged 41 to 50 years was reduced to 24 mg/week for the 81- to 90-year-old age group. However, disconcordant with our study, this dose reduction was

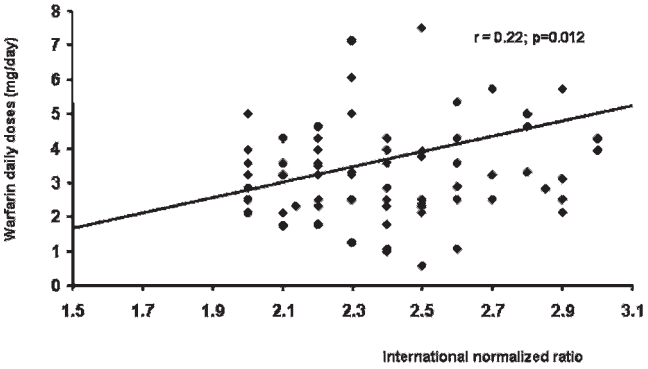

Figure 1 - A simple linear regression analysis comparing the daily warfarin dose and the international normalized ratio is presented.

statistically significant for the ten-year difference in the age group >40 years. In our study, the mean warfarin dose was similar between the groups of elderly individuals (≥65 years) for the threshold ages of 75 years or 80 years. Inadequate anticoagulation is frequent (13), and one recent study that presented a systematic review of several other studies showed that many patients with AF are either inadequately anticoagulated or do not receive anticoagulation therapy (14). In a previous study, patients with INRs between 1.5 and 1.9 had a higher recurrence of venous thromboembolism compared to patients with INRs between 2.0 to 3.0, and this range of INR values was also not associated with a reduced risk of clinically significant bleeding over a follow-up period of 2.4 years (15). As compared to the optimal range of anticoagulation (INR2-3), we observed a significantly increased risk of ischemic stroke in patients with INRs <1.8 as well as a risk of hemorrhagic stroke in patients with INRs >3.5, regardless of age or a high CHADS2 score (16). These results confirm the lack of an effect of age on complications related to inadequate anticoagulation (17). Other studies have also shown that the stability of INR2-3 was independently linked to elderly patients (>70 years) (18,19), and other independent variables identified in these studies included the absence of heart failure, clinically significant associated diseases, and diabetes. The absence of a significant relationship between the INR value and warfarin dose stresses the importance of individual variability, and, therefore, the need to develop a safe, therapeutic treatment window for elderly patients. In our study, the correlation between the INR value and the daily dose of warfarin was statistically significant but low ($r = 0.22$, $p = 0.012$), and the therapeutic window consisted of a daily dose from 2 to 5 mg. The definition of a warfarin dose that results in stable anticoagulation could also be used to promote patient adherence to this treatment process. The consensus statement of the *American Heart Association/American College of Cardiology/European Society of Cardiology* recommends a monthly laboratory analysis of patients on oral anticoagulation with warfarin with stable INRs between 2 and 3 (20). However, laboratory analyses are typically conducted over longer periods, e.g., every two months for patients with stable anticoagulation. Thus, additional studies are needed to determine the appropriate frequency of control laboratory analysis for this group of patients, but in the absence of significant changes in feeding routines, medications, and complications related to new diseases, the period for control analysis may be further extended. Similarly, in stable patients, anticoagulation control can be performed by other health professionals, such as nurses and pharmacists, who are involved in medical supervision. This would likely further reduce the costs of anticoagulation, and the effectiveness of these procedures has been documented (21,22). Cost reduction while maintaining the efficacy of anticoagulation could also be obtained by caring for patients receiving anticoagulation in groups, instead of seeing each patient individually (23). Another option for patients with stable anticoagulation is self-control of the INR value for adjusting the warfarin dose (24).

INR2-3 was obtained in 80% of AF patients aged ≥65 years with stable chronic anticoagulation when these patients were given warfarin doses of 2 to 5 mg/day. The mean daily dose of warfarin was similar for the elderly age groups studied. Moreover, the doses of warfarin mentioned above can be used to provide safe anticoagulation for most patients, and stable anticoagulation will likely provide a significant cost reduction.

AUTHOR CONTRIBUTIONS

Mansur AP designed the study and was responsible for the patient data collection and manuscript writing. Takada JY designed the study and was responsible for the patient data collection and statistical analysis. Avakian SD designed the study and was responsible for the patient data collection and manuscript revision. Strunz CM designed the study and was responsible for manuscript revision.

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