Management of anticoagulation with vitamin K antagonists in a tertiary hospital outpatient clinic

Fernando Pivatto Júnior, André Luis Ferreira da Silva, Bárbara Marina Simionato, Fernanda Fuzinatto, Jerônimo De Conto Oliveira, Leonardo Martins Pires, Roberta Cristina Petry, Rafael Selbach Scheffel, Luís Carlos Amon

Clin Biomed Res. 2014;34(2):139-144

Department of Internal Medicine, Hospital de Clínicas de Porto Alegre – Porto Alegre (RS), Brazil.

Corresponding author:
Fernando Pivatto Júnior
E-mail: fpivatto@gmail.com
Porto Alegre, RS, Brazil

ABSTRACT

INTRODUCTION: Atrial fibrillation (AF) is one of the main risk factors for stroke. Vitamin K antagonists (VKA) reduce this risk, and the effectiveness of this treatment is directly related to time in therapeutic range (TTR). This study aimed to report the TTR in patients with non-valvular AF at an anticoagulation outpatient clinic; and to describe the profile of this population of patients in terms of risk of stroke, as well as the occurrence of adverse events during the follow-up.

METHODS: Retrospective cohort study involving patients of the anticoagulation outpatient clinic of the Department of Internal Medicine at Hospital de Clínicas de Porto Alegre. We evaluated outpatient visits, hospital admissions, and emergency visits from January to December 2011. TTR was calculated using the Rosendaal method.

RESULTS: Sixty-three patients were investigated. Their mean age was 74.3±10.9 years. The $CHADS_2$ score was ≥ 4 in 44.5% of the patients; 63.5% of them had a CHA_2DS_2-VASc score ≥ 5. The TTR was 64.8%. During follow-up, the incidence of overall bleeding was 31.7%, with major and minor bleeding rates of 4.8% and 34.9%, respectively. There were no other complications related to AF or anticoagulation.

CONCLUSION: The patients achieved a TTR of 64.8% during follow-up, which is deemed appropriate and in agreement with the literature. Patients had high risk for stroke, and the incidence of minor bleeding was higher than the rate found in the literature, whereas the incidence of major bleeding was similar to the one found in previous studies.

Keywords: Anticoagulants; warfarin; phenprocoumon; atrial fibrillation; internship and residency

Atrial fibrillation (AF) is the most common clinically significant cardiac arrhythmia. Prevalence of AF is approximately 0.4% in the general population and may be up to 9% in individuals aged 80 years or more[1]. AF increases the risk of death and of systemic and brain thromboembolism, particularly ischemic stroke (relative risk of stroke is 2.4 to 3.0 compared with the overall population)[2,3].

Vitamin K antagonists, such as warfarin and phenprocoumon, reduce the risk of ischemic stroke in patients with AF by approximately 60%[4]. Effectiveness of treatment with vitamin K antagonists is directly related to time in optimal therapeutic range (percentage time with a prothrombin time/international normalized ratio [PT/INR] of 2.0-3.0)[5]. In a systematic review, the mean time in therapeutic range of randomized trials was 66.4%, with no statistically significant difference when compared to the mean time observed at outpatient anticoagulation clinics. This means even in large studies, for a significant percentage of time, patients do not get optimal benefits from these drugs[6].

Randomized studies have already shown that management of anticoagulation by anticoagulation clinics is at least as good as routine hospital follow-up[7], and marginally better than management by family physicians[8]. These clinics are usually managed by specialized professionals (hematologists, cardiologists, nurses specialized in anticoagulation). The primary objective of the present study was to report the time in therapeutic range on oral anticoagulant therapy with vitamin K antagonists in patients with non-valvular AF at an outpatient anticoagulation clinic from a Brazilian teaching hospital. The secondary objective of our study was to describe the profile of this patient population in terms of risk of ischemic stroke, as well as the occurrence of adverse events during the study period.

METHODS

We conducted a retrospective cohort study including patients with non-valvular AF on oral anticoagulation with vitamin K antagonists attending the outpatient anticoagulation clinic of the Department of Internal Medicine at Hospital de Clínicas de Porto Alegre (HCPA). This hospital is a tertiary care teaching hospital located in an upper-middle-class area in southern Brazil. However, most patients at the HCPA are from a low-income background.

The patients at the outpatient anticoagulation clinic of the Department of Internal Medicine at HCPA are attended by first year Internal Medicine resident physicians. These healthcare professionals are supervised by attending physicians, specialized in Internal Medicine. The residents are guided during work at the clinic and attend a one-hour lecture at the beginning of the residence program. The clinic receives approximately 40 to 60 patients over 4 days a week. All decisions regarding management of anticoagulation are based on a protocol published by Kim et al.[9].

All patients who visited the clinic in three consecutive months (October to December 2010) were screened for inclusion in the study. We believe that screening this time range was adequate, since the patients attended the clinic at a maximum interval of two months. Patients with valvular AF, i.e., with mitral stenosis or previous heart valve surgery, were excluded because the ischemic stroke predictive scores ($CHADS_2$ and CHA_2DS_2-VASc) do not include these disorders in their analyses[10,11]. Patients who were lost to follow-up, who died or whose anticoagulation therapy was discontinued were included in our analysis, and the time in therapeutic range was measured until the last test available.

We performed a retrospective review of outpatient visits, emergency visits, and hospitalizations from January to December 2011 based on the patients' electronic medical records. Patients were evaluated for anticoagulation control (using PT/INR tests) and occurrence of adverse events (ischemic stroke, systemic embolism, or bleeding).

Presence of chronic dialysis or renal transplantation or serum creatinine $\geq$ 200 μmol/L (2.26 mg/dL) was classified as abnormal kidney function[12]. Abnormal liver function was defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin > 2x upper limit of normal, in association with AST/ALT/ALP >3 x upper limit of normal)[12]. Major bleeding was defined as any bleeding requiring hospitalization and/or causing a decrease in hemoglobin level > 2 g/dL and/or requiring blood transfusion[12].

The mean risk of ischemic stroke was calculated based on the risk factors included in the $CHADS_2$ and CHA_2DS_2-VASc scores. Thus, we assessed age, sex, left ventricular ejection fraction (LVEF), complex aortic plaque and history of transient ischemic attack (TIA), stroke, diabetes, peripheral

artery disease, hypertension, myocardial infarction, and heart failure. Previous systemic embolism, combined use of antiplatelet agents, oral anticoagulant (warfarin or phenprocoumon), and number of PT/INR tests were also investigated.

The $CHADS_2$ score was calculated based on the presence of cardiac failure, hypertension, age above 75 years, diabetes, and prior stroke or TIA, as previously described[10]. The CHA_2DS_2-VASc included ages 65-74, female gender and vascular disease, and age 75 and above also carries extra weight, with 2 points[11]. LVEF was obtained from the transthoracic echocardiogram, measured by the Simpson method in the presence of segmental changes or by the Teicholz method in the absence of segmental changes. Determination of the INR through prothrombin time was performed at the Haematology Laboratory of Hospital de Clínicas de Porto Alegre using a standard coagulometric method (Siemens BCS).

Time in therapeutic range was calculated based on the percentage of PT/INR tests in 2.0-3.0 range and Rosendaal's linear interpolation method[13], using the INR-Day 0.2.1 software. This method assumes that the PT/INR value between two measurements will vary linearly from the value of the first measurement to the value of the second measurement (Figure 1A). Therefore, the time between two measurements is divided into days, and small intervals of PT/INR are used over the range of the time interval. Subsequently, the person-time at each PT/INR value is added up over all measurements of all patients and then grouped into 0.5 PT/INR cells (Figure 1B). Descriptive data were reported as number (%) and mean ± standard deviation (SD). We used SPSS 15.0 for statistical analysis.

Using a 95% confidence level and a margin of error of 3.5, we calculated a sample size of 53 patients in order to estimate the stroke and/or systemic embolization outcomes (annual incidence 1.69%[14]), and 47 patients for major bleeding (annual incidence 1.5%[12]). For the minor bleeding outcome, the calculated sample was 47 patients, using a margin of error of 8% and a 95% confidence level (annual incidence of 9.6[15]). We used the WinPepi 11.32 software for this analysis.

This study was approved by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre.All authors complied with the recommendations of the Declaration of Helsinki.

RESULTS

During the study period, 137 patients were attended at the outpatient anticoagulation clinic of the Department of Internal Medicine at HCPA. Out of these, 63 (46.0%) were receiving anticoagulation treatment for non-valvular AF and were included in the study. During the follow-up period, 8 patients did not complete the one-year follow-up: 5 discontinued the use of anticoagulants (7.9%), 2 were lost to follow-up (3.2%), and 1 died (1.6%) of a cause unrelated to anticoagulation. Thus, of the 63 patients included in the study, 55 completed the 365-day follow-up period (Figure 2), and the other 8 patients had a mean follow-up of 128.5 days. The demographic characteristics of the sample are shown in Table 1. There were no patients with abnormal kidney or liver function. The presence of complex aortic plaques was not included in Table 1 because only 4 patients (6.3%) underwent transesophageal echocardiogram.

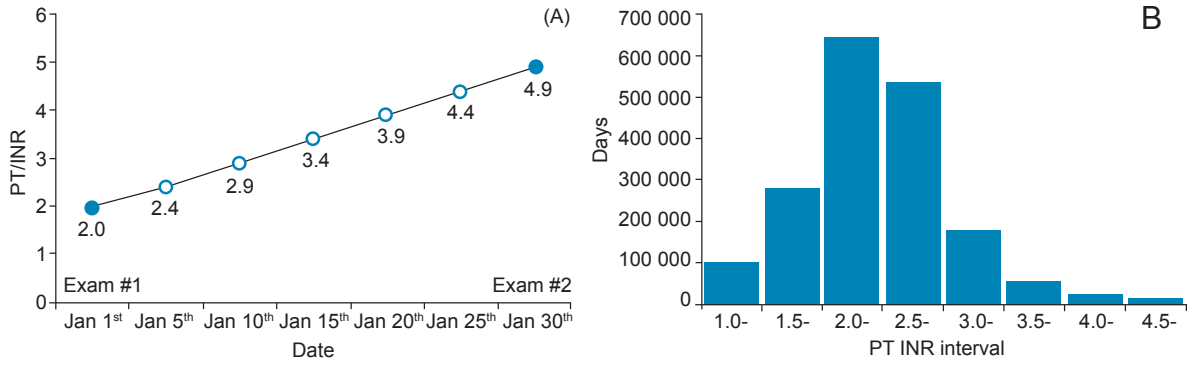

Figure 1: Rosendaal's linear interpolation method[13].

The 63 patients included in the present study underwent 738 PT/INR tests (mean 11.7±5.1 tests/patient). Of these, 395 tests (53.5%) showed INR between 2.0 and 3.0. As for time in therapeutic range, analyzed by Rosendaal's linear interpolation method, PT/INR remained between 2.0 and 2.9 in 64.8% of the follow-up period; and was between 1.5 and 3.4 in 89.9% of the follow-up period. The distribution of PT/INR ranges by follow-up days is presented in Figure 3.

Regarding risk of stroke, we found that our patients were at high risk for this outcome: 44.5% of them had a $CHADS_2$ score ≥ 4 (median of 3 points), and 63.5% had a CHA_2DS_2-VASc score ≥ 5 (median of 5 points). Since patients with a score ≥ 2 are considered to be at high risk, with an indication for anticoagulation according to the $CHADS_2$ and CHA_2DS_2-VASC scores, 95.2% and 100% of our patients, respectively, were included in this risk category.

During the follow-up period, 20 (31.7%) patients experienced at least one adverse event. As shown in Table 2, only bleeding was described, and no patient presented a thromboembolic event.

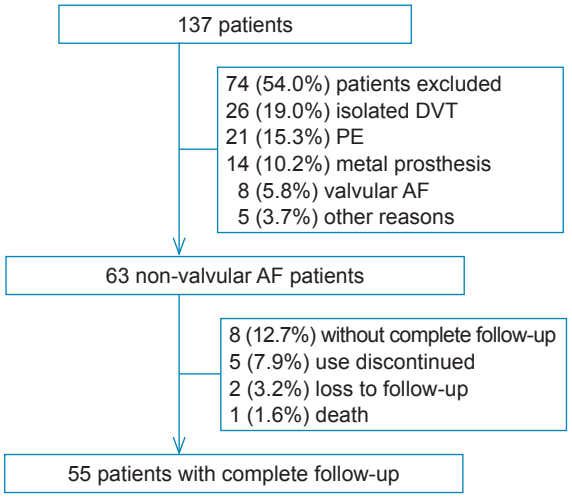

Figure 2: Enrollment and follow-up.

Table 1: Demographic characteristics of the sample.

Characteristics	n = 63
Age, years	74.3 ± 10.9
Age ≥ 75 years	39 (61.9)
Female gender	31 (49.2)
Use of warfarin	62 (98.4)
Hypertension	62 (98.4)
Heart failure	42 (66.7)
LVEF (%)	56.1 ± 12.3
LVEF < 40%	7 (11.1)
Diabetes	32 (50.8)
Associated use of ASA	21 (33.3)
Prior stroke	20 (31.7)
Previous AMI	10 (15.9)
Peripheral arterial disease	10 (15.9)
Previous systemic embolism	4 (6.3)
Previous TIA	1 (1.6)

Data presented as number (%), mean ± standard-deviation. LVEF: left ventricular ejection fraction, ASA: acetylsalicylic acid, AMI: acute myocardial infarction, TIA: transient ischemic attack.

DISCUSSION

In the present study, we showed that patients followed up at our anticoagulation clinic have a time in therapeutic range of 64.8%. Moreover, this group of patients is at high risk for ischemic stroke (demonstrated by high scores on the $CHADS_2$ and CHA_2DS_2-VASc scores). The incidence of minor bleeding is higher than the one found in the literature, whereas the incidence of major bleeding was similar to the one described in previous studies.

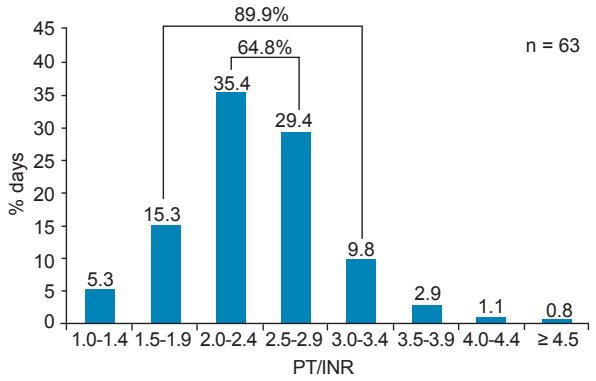

Figure 3: Time in therapeutic range.

Table 2: Adverse events during follow-up.

Adverse event*	n (%)
Major bleeding	3 (4.8)
Severe anemia**	1 (1.6)
Skin bruise	1 (1.6)
Hemothorax caused by fall	1 (1.6)
Minor bleeding	22 (34.9)
Genitourinary	7 (11.1)
Cutaneous	4 (6.3)
Epistaxis	4 (6.3)
Bleeding gums	3 (4.8)
Gastrointestinal	2 (3.2)
Hemoptysis	2 (3.2)

*Some patients had more than one type of bleeding; **Hb 5.8 g/L, requiring blood transfusion and hospitalization without exteriorization.

The percentage of time in therapeutic range is strongly associated with risk of bleeding and occurrence of thromboembolic events in patients receiving oral anticoagulant therapy with vitamin K antagonists[6]. Wallentim et al.[16] divided the time in therapeutic range of 5,791 patients with AF on warfarin into quartiles (< 53.6, 53.6-67.2, 67.2-78.4, and > 78.4%) and found a significant inverse association between the quartiles and the rate of stroke/systemic embolism (2.34, 1.72, 1.42, and 1.25%; p = 0.001), major bleeding (4.95, 3.71, 2.98, and 2.65%; p < 0.0001), total mortality (7.48, 3.30, 2.27, and 2.65%; p < 0.0001), and composite outcome of stroke, systemic embolism, pulmonary embolism, major bleeding and death (12.32, 7.35, 5.55, and 5.4%; p < 0.0001).

Walraven et al.[6], in a systematic review of the literature, analyzed anticoagulated patients from anticoagulation clinics and described a mean time in therapeutic range of 65.6% (95%CI 63.7-67.6%), without a significant difference when compared to the patients included in randomized clinical trials. It is worth mentioning that, even in recent large randomized clinical trials, using strict protocols, the percentage found is not really very different, and it may be even lower: the mean of the ROCKET AF study was 55%[17], the mean of the RE-LY study was 64%[14], and the mean of the ARISTOTLE study was 66%[18].

Connolly et al.[19] suggested that there is a target time in therapeutic range, which is estimated between 58-65%. This target has been suggested as the cutoff for patients to actually derive benefit from oral anticoagulants when compared to the use of dual antiplatelet therapy. This study showed that patients with TTR < 58-65% had similar adverse event rates when compared to subjects treated with acetylsalicylic acid (ASA) plus clopidogrel. Notably, the mean overall TTR for Brazilian sites in this study was 47.1% and 64.8% in this report. This highlights the potential benefit of using our clinic model/protocol in the context of the public health care system.

Pisters et al.[12], in a large recent study including 3,456 ambulatory and hospitalized AF patients from teaching, non-teaching, and specialized hospitals in European countries, using the same definitions of major bleeding used in this analysis, described an annual incidence of major bleeding of 1.5%. In a previous meta-analysis, the mean annual frequency of major/minor bleeding with use of anticoagulants was 3.0% and 9.6%, respectively[15]. Thus, the rate of major bleeding found in the present study (4.8%) is similar to that described in the literature, whereas the rate of minor bleeding (34.9%) was higher. Possible explanations for this discrepancy include: small sample size, different definitions of bleeding used in different studies, and possible increased predisposition to bleeding in our sample due to a high prevalence of elderly patients and patients with multiple comorbidities.

There are some limitations in our study. First, the retrospective design may have influenced the quality and consistency of the data collected. Besides, the chart review of the patients could only identify events (cardiovascular and bleeding) that occurred at HCPA or that were reported by the patients in clinical care. Second, the relative small sample size associated with the short follow-up period may have underestimated the occurrence of adverse events, especially events related to AF, which have a longer latency period. Finally, the fact that the study was conducted at a single center can also be considered a limitation.

The patients with non-valvular AF on oral anticoagulant therapy managed at an outpatient clinic at a teaching hospital achieve an optimal time in therapeutic range of 64.8% during the 12-month follow-up period, which is deemed appropriate and in agreement with the literature. These data are important because they show that this strategy is a feasible approach for patients treated within the context of the Brazilian public health system at a teaching hospital and could expand the coverage for patients who need this therapy.

ACKNOWLEDGEMENTS

The authors would like to thank Professor Frits Rosendaal from the Department of Clinical Epidemiology, Leiden University Hospital (Netherlands), who kindly provided the software used in this study (INR Day). This study was supported by the Research Incentive Fund of the Hospital de Clínicas de Porto Alegre (FIPE), Brazil.

REFERENCES

1. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001;285:2370-5.
2. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation. 1998;98:946-52.
3. Frost L, Engholm G, Johnsen S, Moller H, Husted S. Incident stroke after discharge from the hospital with a diagnosis of atrial fibrillation. Am J Med. 2000;108:36-40.
4. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146:857-67.
5. White HD, Gruber M, Feyzi J, Kaatz S, Tse HF, Husted S, et al. Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: results from SPORTIF III and V. Arch Intern Med. 2007;167:239-45.
6. Van Walraven C, Jennings A, Oake N, Fergusson D, Forster AJ. Effect of study setting on anticoagulation control: a systematic review and metaregression. Chest. 2006;129:1155-66.
7. Fitzmaurice DA, Hobbs FD, Murray ET, Holder RL, Allan TF, Rose PE. Oral anticoagulation management in primary care with the use of computerized decision support and near-patient testing: a randomized, controlled trial. Arch Intern Med. 2000;160:2343-8.
8. Wilson SJ, Wells PS, Kovacs MJ, Lewis GM, Martin J, Burton E, et al. Comparing the quality of oral anticoagulant management by anticoagulation clinics and by family physicians: a randomized controlled trial. CMAJ. 2003;169:293-8.
9. Kim YK, Nieuwlaat R, Connolly SJ, Schulman S, Meijer K, Raju N, et al. Effect of a simple two-step warfarin dosing algorithm on anticoagulant control as measured by time in therapeutic range: a pilot study. J Thromb Haemost. 2010;8:101-6.
10. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285:2864-70.
11. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137:263-72.
12. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138:1093-100.
13. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993;69:236-9.
14. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139-51.
15. Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: clinical epidemiology, prediction, and prevention. Am J Med. 1993;95:315-28.
16. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet. 2010;376:975-83.
17. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883-91.
18. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981-92.
19. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation. 2008;118:2029-37.

Received: 25/01/14
Accepted: 13/04/14