Oral anticoagulation in patients with atrial fibrillation: from guidelines to practice

Paula Gonçalves Macedo[1*], Eustáquio Ferreira Neto[2], Bruno Toscani da Silva[3], José Roberto Barreto Filho[4], Henrique Maia[5], Clarissa Novakoski[6], André Zanatta[7], Edna Marques de Oliveira[8], Jairo Macedo da Rocha[8], Tamer Najar Seixas[9], Ayrton Klier Peres[10], Luiz Leite[11]

Study conducted at the Atrial Fibrillation Center, Brasília, DF, Brazil

ABSTRACT

Objective. Although oral anticoagulation (OAC) has proved beneficial for patients with atrial fibrillation (AF) and embolic risk factors, it is still underused. The objective of this study was to evaluate the adequacy of anticoagulation therapy in patients with AF followed up in a private clinic specialized in cardiology, in accordance with the American and European societies of cardiology guidelines/2006 and with the Sociedade Brasileira de Cardiologia (Brazilian Society of Cardiology - SBC) guidelines/2003.

Methods. Between November 2005 and August 2006, 7,486 electrocardiograms were evaluated and 53 patients with AF diagnosis and complete detailed information in medical records on embolic risk factors and oral anticoagulation treatment were selected.

Results. Among the 53 patients included (68±16 years; 29 men – 55%), 25 (48%) had hypertension, 20 (38%) heart failure and 3 (6%) diabetes mellitus. Among the 15 patients with high embolic risk, 13 (86%) were using OAC. In accordance with the American and European guidelines: 32 (60%) patients were Class I, 17 (32%) Class IIa, 1 (2%) Class IIb and 3 (6%) Class III. Treatment was adequate in 21 (66%) Class I patients and 13 (76%) Class IIa. In this subgroup, anticoagulation therapy was being used in 7/19 (37%) patients ≥ 75 years compared to 22/30 (73%) younger (p=0.016). Among the 3 patients within Class III, 1 was incorrectly on OAC. According to Brazilian guidelines, 33 (62%) were on correctly indicated antithrombotic therapy. There was no difference in the appropriate prescription of oral anticoagulants, comparing Brazilian and American/European guidelines (55% vs. 55%).

Conclusion. Anticoagulant therapy is being adequately prescribed for the majority of AF patients, although this index is still far from ideal, especially in a cardiology clinic. This is even more critical in the group of elder patients.

Key words: Atrial fibrillation. Anticoagulants. Clinical practice guideline

*Correspondência:
SQS 213 - Bloco A – apto. 106
Asa Sul
Brasília – DF, Brazil
CEP: 70292-010

INTRODUCTION

Atrial fibrillation (AF) prevalence is considerably increasing due to the population's aging and the increase in associated risk factors, such as obesity, systemic hypertension (SH) and diabetes mellitus (DM).[1,2] Atrial Fibrillation is a disease related to stroke, heart failure (HF) and mortality due to all the causes; currently it is seen as a public health problem.[3,4] Ischemic stroke index in non-valvular AF patients is around 5% per year, being 5 to 7 times higher than in patients without AF. In rheumatic valvular disease, Framingham's study has shown that the risk is 17 times higher.[1]

Oral anticoagulation is capable of preventing cerebral embolic events. A meta-analysis based on the 'intention-to-treat' principle concluded that this therapy is highly effective in preventing

1. Especialização em Arritmias Cardíacas e Médica Assistente do Hospital de Base do Distrito Federal, Brasília, DF
2. Especialização em Cardiologia - Médico Assistente do Hospital do Coração de Brasília, Brasília, DF
3. Estudante de Medicina Escola Superior de Ciências da Saúde/ESCS/FEPECS/SES/DF e Membro do Centro de Fibrilação Atrial/Hospital de Base do Distrito Federal, Brasília, DF
4. Especialização em Arritmias Cardíacas - Médico Assistente do Hospital de Base do Distrito Federal, Brasília, DF
5. Especialização em Eletrofisiologia - Médico Assistente do Hospital de Base do Distrito Federal – Brasília, DF
6. Curso Superior de Enfermagem - Membro do Centro de Fibrilação Atrial/Hospital de Base do Distrito Federal, Brasília, DF
7. Especialização em Arritmias Cardíacas - Médico assistente do Centro de Tratamento Cardiovascular, Brasília, DF
8. Especialização em Arritmias Cardíacas - Médica assistente da Clínica Biocárdios, Brasília, DF
9. Especialização em Eletrofisiologia - Médico assistente da Ritmocárdio, Brasília, DF
10. Pós-Doutorado pela University Of Limburg Academic Hospital Maastricht, Holanda - Presidente da Ritmocárdio, Brasília, DF
11. Pós-Doutorado pelo Mayo Clinic - Rochester MN - USA, Estados Unidos - Diretor do Centro de Fibrilação Atrial/Hospital de Base do Distrito Federal, Brasília, DF

stroke, presenting a relative risk reduction of 62%, absolute risk reduction of 2.7% per year for primary prevention and 8.4% per year for secondary prevention.[5] However, OAC use is associated to potentially lethal side effects, such as hemorrhagic stroke. The analysis of 5 clinical trials showed a rate of sever hemorrhagic events of 1.3% per year.[6]

Thus, anticoagulant therapy must be indicated when embolic risk is high and superposed to the risk of bleeding. In this sense, there are guidelines and consensuses on the theme that guide the antithrombotic therapy use.

The Brazilian guideline for AF, published in 2003 by the Brazilian Society of Cardiology, directs the OAC indication according to the patient's age and the presence of thromboembolic risk factors.[7] Recommendations are similar in the American and European societies of cardiology AF guidelines, published in 2006.[8] Despite the existence of specific publications on the theme, studies show that anticoagulation is underused even in reference centers in Brazil and in developed countries.[9-11]

The objective of this study is to evaluate the frequency and the adequacy of anticoagulant therapy in AF patients attended in a cardiology clinic in the Federal District.

METHODS

It is an observational retrospective study, conducted at Biocárdios – a private clinic that attends patients referred from all the Federal District to cardiologic treatment. ECGs performed in the period of November 2005 and August 2006 were evaluated by the clinic's arrhythmologists, selecting those who had AF diagnosis. Clinical data and from complementary exams were collected from medical records. No informed consent term was obtained from the patients.

The second phase was the analysis of collected data, and it was performed by another group of researchers, who did not know the identities of both patients and doctors, and had access only to the data bank. The variables analyzed were: sex, age, comorbidities, antithrombotic drugs use, and presence of factors that contraindicated anticoagulation (blood dyscrasias patients, aortic dissection, pregnancy, and others). The presence of contraindicating factors to antithrombotic therapy did not characterize a criterion of exclusion from the analysis.

AF guidelines

In this study, OAC prescription adequacy was assessed according to two AD guidelines: one published by the Brazilian Society of Cardiology (SBC) and the other by the North-American and European societies of cardiology. SBC has published in 2003 the AF Brazilian guideline, which orientates the more adequate conducts in face of a patient suffering from this arrhythmia. As for the indication of OAC use, the guideline recommends it to be indicated whenever one of the following embolic risk factors is present: patient over 75 years old, presence of congestive heart failure, left ventricular ejection fraction lower than 35%, SH, DM, thyrotoxicosis, previous embolic event, mitral valve stenosis, valve prosthesis, or persistent atrial thrombus. The use of acetylsalicylic acid is recommended to patients younger than 60 and who have no cardiopathies or embolic risk factors, and also for patients to whom OAC use contraindicated.

North-American/European guideline for AF patients care was published in 2006 by the American College of Cardiology, American Association of Cardiology, and by the European Society of Cardiology. In this text, diagnostic and therapeutic conducts were oriented according to the following classes of recommendations: Class I, Class IIa, Class IIb, and Class III. For antithrombotic therapy indication, embolic risk factors were classified as follows:

- Low risk: female, age between 65 and 74, and coronary artery disease;
- Intermediate risk: age ≥ 75, systemic hypertension, HF, depressed left ventricular function and DM;
- High risk: previous stroke or transitory ischemic attack or embolism, mitral stenosis or valve prosthesis.

Class I recommendation for OAC use is applied to patients with less than one high risk factor or two or more intermediate risk factors. Class IIa recommendation orientates OAC or ASA use in patients with only one intermediate risk factor and in those with only two low risk factors. In Class IIb, patients with coronary diseases submitted to myocardial revascularization treated with OAC, ASA, and clopidogrel are included, and also patients with age inferior to 60 years and no cardiopathy who do not receive any antithrombotic treatment. Class III is related to OAC use in patients with no risk factors.

Study definitions

After medical records review and analysis, the patients were classified according to adequacy of therapy used in conformity with the two guidelines recommendations. Considering the SBC guideline, patients were seen as adequate when they were using ASA or OAC or were not under antithrombotic therapy as oriented in accordance with the presence of the aforementioned risk factors.

In relation to American/European guideline, the patients were first divided in the recommendation Classes I, IIa, IIb or III, taking into consideration the presence of low, intermediate, and high risk factors. After this, the existing therapy was classified in adequate or inadequate, according to each Class orientation.

Finally, based in both consensuses, therapy used with each patient was subdivided in: correct or incorrect OAC use and correct and incorrect ASA use. The absence of antithrombotic therapy – OAC or ASA – was also classified as correct or incorrect.

Statistic analysis

Continuous variables were presented with average ± 1 standard deviation. Categorical variables were compared by the Chi square test. Confidence intervals were calculated with 95% probability and for rejection of the null hypothesis p values under 0.05 were considered.

RESULTS

In the period from November 2005 to August 2006, 7,486 electrocardiograms (ECG) were evaluated and those with AF diagnosis were selected, which represented 62 (0.83%) patients. Nine (15%) were excluded due to data insufficiency. Among the 53 patients included (68±16 years; 29 men - 55%), 20 (38%) were ≥ 75 years, 25 (48%) had hypertension, 20 (38%) had heart failure, 3 (6%) had diabetes mellitus and four (8%) ejection fraction ≤ 35%. Thirty-one (58%) patients were using OAC, 13 (25%) were using ASA and eight (15%) were not under

antithrombotic therapy (Table 1). In two patients anticoagulant therapy was considered inappropriate: the first, 90 years old, had metastatic prostate cancer, and the second lived in Goiás countryside, having no condition of keeping a serial control of INR. Both were using ASA.

According to the recommendation of the American/European antithrombotic therapy guideline, 32 (60%) patients had Class I indication; 17 (32%), Class IIa; one (2%), Class IIb; and 3 (6%), Class III. In relation to embolic risk factors characterized in the same guideline, 15 (28%) patients had at least one high risk factor, 33 (62%) intermediate risk factor and 2 (4%) only low risk factor. Three (6%) patients did not have any embolic risk factor. A relevant datum is that 8 (89%) out of the nine patients with previous brain embolism and nine (90%) of the 10 patients with valvulopathy were under anticoagulant therapy. Therefore, among the 15 patients with high embolic risk (four had valve diseases with previous stroke), 13 (86%) were using OAC.

Among the Class I patients, 21/32 (66%) were considered adequate (19 were using anticoagulant and two were using ASA due to showing contraindication to OAC). Among the Class IIa patients, 13/17 (76%) were being correctly treated, 10 of them with anticoagulant prescription and three with ASA prescription. One patient was characterized as Class IIb for using OAC, clopidogrel and ASA in a 200mg dosage, even after one year of percutaneous revascularization. From the 3 patients with Class III indication, only one (33%) was using OAC, that is, being incorrectly treated (Figure 1).

Considering all the patients with Class I and IIa indications, there was no difference in relation to the anticoagulation index between men and women (60% vs 58.3%, p=NS). Still analyzing this subgroup, only 7/19 (37%) of the patients aged ≥ 75 were receiving anticoagulation, against 22/30 (73%) of those aged younger (p=0.016).

Considering the Brazilian guideline, 47 patients had at least one risk factor and, thus, were eligible to OAC prescription. After analyzing the prescribed treatment, 33 (62%) patients were considered adequate, 29 using OAC correctly, three using ASA correctly, and one patient with no antithrombotic therapy.

Among all the patients, 29 (55%) were receiving OAC correctly indicated, both by the SBC guideline and by the America and European societies of cardiology guideline. Among the patients with anticoagulant therapy indication according to the Brazilian guideline (n=47/53), 29 (61.7%) were using OAC; while out of the 44/53 patients with indication according to the American/European guideline, 29 were using OAC (65.9%) Table 2.

There was difference only in the Class IIa subgroup (n=17/53), in which ASA use is considered correct by the American/European guideline and incorrect by the Brazilian guideline. Three patients (18%) were using ASA in this subgroup.

Table 1: Clinical characteristics of AF patients

Characteristics	N	%
Mean age	68 ± 16 years	---
Age ≥ 75 years	20	38
Male	29	55
Systemic hypertension	25	48
Diabetes mellitus	3	6
Heart failure	20	38
Ejection fraction ≤ 35%	4	8
Previous stroke/TIA	9	17
Mitral stenosis or valve prosthesis	10	19
ASA or Ticlopidine use	13	25
Oral anticoagulant use	27	50
ASA or anticoagulant use	4	8
No ASA or anticoagulant	8	15

Table 2: Correct use of anticoagulation in the population studied, according to the recommendations of the SBC guideline and American and European cardiology guideline

	Patients with OAC use indication			
Therapy used	SBC guideline N(%)	American/European guideline		
		Classe I N(%)	Classe IIa N(%)	SUBTOTAL N(%)
OAC use	29(61.7)	19(43.2)	10(22.7)	29(65.9)
No OAC	18(38.3)	11(25)	3	11(25)
No antithrombotic therapy	0	0	4(9.1)	4(9.1)
SUBTOTAL	47(100)	30(68.2)	14(31.8)	44(100)
TOTAL	47(100)		44(100)	

DISCUSSION

A literature review carried out in 2000, including approximately 6,500 patients, showed that warfarin was used only in 15 to 44% of the patients with no contraindication to anticoagulant therapy.[12] Further publications revealed that this index is increasing, but it is still very far from what is desired.[9-11,13] OAC use frequency in the sample presented here (55%) is similar to the one reported in the studies with the best results.[9-11] In a recent analysis of the UK data bank, that comprises 12,267 AF patients, 53% of the men and 40% of the women were using OAC, and only 56.5% of those who had high embolic risk received anticoagulant.[9] A group in the Heart Institute at the Universidade de São Paulo reported that, after a year of follow up in the division, 57.8% of the AF patients and only 60.4% of the patients with previous ischemic stroke were receiving OAC.[11] In this study, 86% of the patients with high embolic risk received anticoagulant prescription.

The aforementioned British study[9] reports a lower frequency of anticoagulation in female patients, which was not observed in our sample (60% of the men *vs* 58.3% of the women, p=NS).

Many studies show that old age is a factor associated to a lower anticoagulation rate,[9,12,14,15] which was confirmed in this study, with only 37% of the patients with age ≥ 75 years receiving anticoagulation, compared to 73% of those who were younger.

Patients with rheumatic valvular diseases are more frequently treated with OAC, probably for being younger, and thus, having a lower risk of bleeding, and for having a higher embolic risk.[16] This subgroup in general is excluded from randomized studies, because it is a known fact that they benefit from anticoagulation.[17] A study conducted in Japan showed that 81.6% of the rheumatic patients received anticoagulants, while in this study 90% of these patients were anticoagulated.[18]

Considering the indications of the 2003 Brazilian AF guideline and that of the American and European societies of cardiology, there was no difference in the OAC correct use (61.7% vs. 65.9%). However, the American/European guideline is more condescending in relation to ASA use in patients with only one intermediate risk factor (Class IIa). Besides that, there are some disparities related to risk factors considered in the aforementioned consensuses. The Brazilian guideline does not identify coronary artery disease as embolic risk marker while that one does not consider thyrotoxicosis. Nevertheless, for both variables there is no agreement in literature related to independent risk association.[17]

Some studies evaluated the causes of OAC underuse in AF patients.[12,14] Among others, it was observed that the physicians underestimated the benefit of the therapy; or were not aware of recent literature; or were aware, but did not accept the results; or, yet, did not believe that the characteristics of their patients matched the ones described in previous studies. Other causes pointed were: patients with old age, high risk of bleeding or physical or psychic incapacity, alcoholism, peptic ulcer disease, anemia, bad adherence to medication, ASA or non-steroid anti-inflammatories use, and difficulty of communication between patient and physician.[9,10,12,14] Another limitation for the institution of the therapy is the lack of physical structure and human resources that guarantee an adequate care, mainly in public hospitals.[19] Patients who receive anticoagulation must have the access to the health professional and to the laboratory facilitated, so that treatment efficacy and safety is assured. As this is not possible in many places, the physician prefers not to expose the patient to the risk of bleeding associated to medication.

The anticoagulant therapy adequacy, in conformity to the recommendations of guidelines, consensuses or embolic risk scores, was already published before, but not with the details presented here.[20,21] Such approach is important as it reflects not only the physicians' up-to-dating, but mainly the application of this knowledge in the clinical practice. This type of study might help in the detection and mapping of specific clinical practice in each place. With this knowledge it is possible to create orientation and lifelong learning programs and develop logistic conditions to facilitate the anticoagulation practice. The discrepancy between the guidelines' recommendations and the reality of clinical practice was observed here, even in the context of a private and specialized clinic, where theoretically the facility of access to the doctor would favor the use of this therapy. This distance between theory and practice was also reported in the ambit of prophylactic anticoagulation for thromboembolism. A national multicenter study showed that 29% of higher risk patients did not receive anticoagulant prescription.[22]

The limitations of this study were mainly the small size of the sample, the absence of analysis of the anticoagulation level – measured by the International Normalized Ratio (INR) – and the lack of active search for the motives that prevented doctors from using anticoagulant therapy. It was expected that the evaluation of 7,468 ECGs performed in a cardiology clinic could reveal a bigger proportion of AF patients. A possible explanation for this low index is the increasing number of self-referring to the cardiologist for check up, which results in the inclusion of many healthy individuals in this population. Another factor that may have contributed was the selection of only patients who presented AF at the ECG. Therefore, it is likely that patients with paroxystic AF were not included, who have the same OAC indications as patients with persistent or permanent AF. Perhaps a selection process which included, for instance, Holter evaluation, effort test and analysis of arrhythmias registered by implantable devices could broaden the number of patients included. In relation to the anticoagulation follow up, the lack of monthly records of the INR value in most of the medical records made the assessment of this datum impossible. Despite that, it was possible to evaluate the intention of the assistant doctor in 'anticoagulating' the patient, and thus analyze if the cardiologists are attentive to the need of preventing embolic events in AF patients. The last limitation pertains to the study design, which did not foresee the direct addressing of assistant doctors of the service for any kind of clarification.

CONCLUSION

Anticoagulant therapy is being correctly used in few more than half the AF patients studied in this sample, but this number is still very far from ideal, considering the indications of the current consensuses. In the patients with high embolic risk, the OAC treatment proportion was higher than the one reported in other studies, even if performed in reference centers. Finally, the patients over 75 years old are the ones receiving fewer anticoagulant prescriptions, despite the embolism risk directly increasing with aging.

No conflicts of interest declared concerning the publication of this article.

References

1. Wolf PA, Dawber TR, Thomas HE Jr, Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. Neurology. 1978; 28: 973-7.
2. Abhayaratna WP, Seward JB, Tsang TSM, Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006;114:119-25.
3. 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.
4. Stewart S, Hart CL, Hole DJ, McMurray JJV. A population-based study of the long-term risks with atrial fibrillation: 20-year follow-up study of the Renfrew/Paisley study. Am J Med. 2002;113:359-64.
5. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med. 1999;131:492-501.
6. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomized controlled trials. Arch Intern Med. 1994;154:1449-57.
7. Sociedade Brasileira de Cardiologia. Diretriz de fibrilação atrial. Arq Bras Cardiol. 2003; 81(Suppl 6):1-24.
8. American College of Cardiology, American Heart Association, European Society of Cardiology. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). J Am Coll Cardiol. 2006;48:e149 -246.
9. De Wilde S, Carey IM, Richards N, Cook DG. Trends in the prevalence of diagnosed atrial fibrillation, its treatment with anticoagulation and predictors of such treatment in UK primary care. Heart. 2006;92:1064-70.
10. Waldo AL, Becker RC, Tapson VF, Colgan KJ. Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. J Am Coll Cardiol. 2005;46:1729-36.
11. Fornari L, Calderaro D, Nassar I, Lauretti C, Nakamura L, Bagnatori R, et al. Misuse of antithrombotic therapy in atrial fibrillation patients: frequent, pervasive and persistent. J Thromb Thrombolysis. 2007;23:65-71.
12. Bungard TJ, Ghali WA, Teo KK, McAlister FA, Tsuyuki RT. Why do patients with atrial fibrillation not receive warfarin? Arch Intern Med. 2000;160: 41-6.
13. Cabral NL, Volpato D, Ogata TR, Ramirez T, Moro C, Gouveia S. Fibrilação atrial crônica, AVC e anticoagulação: sub-uso de warfarina? Arq Neuropsiquiatr. 2004; 62(4):1016-21.
14. Cohen N, Almoznino-Sarafian D, Alon I, Gorelik O, Koopfer M, Chachashvily S, et al. Warfarin for stroke prevention still underused in atrial fibrillation: patterns of omission. Stroke. 2000;31:1217-22.
15. FALSTAF Study Group. Influence of age on the prescription of vitamin K antagonists in outpatients with permanent atrial fibrillation in France [Abstract]. Pharmacoepidemiol Drug Saf. 2007;16:32-8.
16. Salem DN, Stein PD, Al-Ahmad A, Bussey HI, Horstkotte D, Miller N, et al. Antithrombotic therapy in valvular heart disease-native and prosthetic: the seventh CCP conference on antithrombotic and thrombolytic therapy. Chest 2004; 126; 457-82.
17. Singer DE, Albers GW, Dalen JE, Go AS, Halperin JL, Manning J. Antithrombotic therapy in atrial fibrillation: the seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004; 126: 429-456.
18. Guo GB, Chang HW, Chen MC, Yang CH. Underutilization of anticoagulation therapy in chronic atrial fibrillation. Jpn Heart J. 2001; 42(1): 55-65.
19. Grinberg M. Entendo & aceito & faço. Estratégia pró-adesão à anticoagulação oral. Arq Bras Cardiol. 2004; 82(4): 9-12.
20. Nieuwlaat R, Capucci A, Lip GYH, Olsson SB, Prins MH, Nieman FH, et al. Antithrombotic treatment in real-life atrial fibrillation patients: a report from the Euro Heart Survey on Atrial Fibrillation. Eur Heart J. 2006; 27: 3018-26.
21. McBride D, Brüggenjürgen B, Roll S, Willich SN. Anticoagulation treatment for the reduction of stroke in atrial fibrillation: a cohort study to examine the gap between guidelines and routine medical practice. J Thromb Thrombolysis. 2007; 24(1): 65-72.
22. Deheinzelin D, Braga AL, Martins LC, Martins MA, Hernandez A, Yoshida WA, et al. Incorrect use of thromboprophylaxis for venous thromboembolism in medical and surgical patients: results of a multicentric, observational and cross-sectional study in Brazil.J Thromb Haemost. 2006; 4(6):1266-70.