



Cognitive function and adherence to anticoagulation treatment in patients with atrial fibrillation

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Abstract

Background Medication adherence is an integral part of the comprehensive care of patients with atrial fibrillation (AF) receiving oral anticoagulations (OACs) therapy. Many patients with AF are elderly and may suffer from some form of cognitive impairment. This study was conducted to investigate whether cognitive impairment affects the level of adherence to anticoagulation treatment in AF patients. **Methods** The study involved 111 AF patients (mean age, 73.5 ± 8.3 years) treated with OACs. Cognitive function was assessed using the Mini Mental State Examination (MMSE). The level of adherence was assessed by the 8-item Morisky Medication Adherence Scale (MMAS-8). Scores on the MMAS-8 range from 0 to 8, with scores < 6 reflecting low adherence, 6 to < 8 medium adherence, and 8 high adherence. **Results** 46.9% of AF patients had low adherence, 18.8% had moderate adherence, and 33.3% had high adherence to OACs. Patients with lower adherence were older than those with moderate or high adherence (76.6 ± 8.7 vs. 71.3 ± 6.4 vs. 71.1 ± 6.7 years) and obtained low MMSE scores, indicating cognitive disorders or dementia (MMSE = 22.3 ± 4.2). Patients with moderate or high adherence obtained high MMSE test results (27.5 ± 1.7 and 27.5 ± 3.6). According to Spearman's rank correlation, worse adherence to treatment with OACs was determined by older age ($r_s = -0.372$) and lower MMSE scores ($r_s = 0.717$). According to multivariate regression analysis, the level of cognitive function was a significant independent predictor of adherence ($b = 1.139$). **Conclusions** Cognitive impairment is an independent determinant of compliance with pharmacological therapy in elderly patients with AF. Lower adherence, beyond the assessment of cognitive function, is related to the age of patients.

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1 Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice, especially among elderly patients. Compared to recent years, the incidence of AF has doubled, but it also tends to increase with age. Arrhythmia affects approximately 4% of 60–70 year olds, with the highest incidence rate being observed among those over 80 years of age (10%–17%). In 50% of cases, patients suffer from permanent AF. It is estimated that, over the next twenty years, the

number of people affected by AF will double again due to ageing societies and greater life expectancy. By 2030, the number of patients with newly diagnosed AF is expected to reach 14–17 million people in Europe alone.^[1] The use of anticoagulant therapy has noticeably increased in the last decade. On one hand, it can reduce the risk of cardioembolic stroke, but on the other hand, it tends to increase the probability of hemorrhagic complications. The therapeutic effect of anticoagulants can only be achieved if patients adhere to a treatment schedule.^[2] Approximately 40%–60% of patients do not take their drugs as prescribed.^[3–5]

According to the available reports, 10%–26% of AF patients discontinued warfarin therapy after the first year.^[6,7] Gumbinger, *et al.*^[8] states that, during the first 15 months following the start of therapy, as many as 39% of patients receiving oral anticoagulants (OACs) do not adhere to the recommended pharmacological treatment.

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The European Heart Rhythm Association Practical Guide recommends educating patients to improve their adherence with therapy during every visit to a specialist. According to the Guide, patients should be given a special patient card with the therapy start-up scheme and instructions for the proper use of medications (including information on how to take the medicines, how often go for check-ups, and what may happen if the therapy is interrupted). It is worthwhile involving family members in the education process, so that they can understand the importance of adherence and help the patients persevere with treatment.^[9]

The most frequently mentioned causes of non-adherence to pharmacological therapy are the patients' lack of preparedness to follow the recommended therapeutic regimen and their poor understanding of the issues related to anticoagulant treatment.^[10–13] Other factors that contributed to worse adherence are age, level of education, drug-drug interactions, comorbidities, duration of treatment, cost of medicines, and the necessity for retaining constant control of the international normalized ratio (INR). A low level of adherence to pharmacological therapy may lead to frequent rehospitalization and a higher mortality rate.^[4]

The advanced age of most AF patients entails the risk of cognitive disorders and frailty syndromes.^[4] The use of anticoagulant treatment in these patients may be particularly troublesome because of periodic changes in drug administration on the basis of monthly results of laboratory tests. Additionally, patients may not take their medicines according to the therapeutic schedule and may be unaware of their interactions with certain foods.^[14] The available studies suggest that assessing cognitive function at the onset of anticoagulant treatment may be essential for adherence to therapy and anticoagulation control (time in therapeutic range, TTR); this applies particularly to elderly patients who live alone.^[15]

The literature describes the controversy over the influence of cognitive disorders on adherence to OACs therapy. Horstmann, *et al.*^[16] who analyzed AF patients 12 months after stroke and transient ischemic attack (TIA), demonstrated that physical and functional disabilities had greater effects on the level of adherence to the prescribed therapy than did cognitive disorders. Gumbinger, *et al.*^[8] on the other hand, claimed that the most common cause of giving up therapy was the fear of bleeding and the necessity of INR monitoring, while dementia was associated with poorer adherence. Our study was undertaken to address the controversy over the impact of cognitive function on adherence. There are reports whose authors use the Morisky Medication Adherence Scale (MMAS) to measure adherence to

acenocumarol treatment, or the relation between self-reported adherence and the time in therapeutic INR range.^[7,17,18] Our study is the first to investigate the connection between cognitive function and the level of adherence to the prescribed treatment on the basis of the 8-item Morisky Medication Adherence Scale (MMAS-8).

2 Methods

2.1 Study design and sample

The aim of this study was to investigate whether cognitive impairment affects the level of adherence to anticoagulation treatment in AF patients. The study involved patients suffering from AF and being treated with oral anticoagulants. The following questions were posed in this study: (1) does age have an impact on adherence to medication? (2) Is there any correlation between cognitive impairment, patient age, and adherence to oral anticoagulant therapy in AF patients?

The study was conducted between January and September 2015 at the Cardiology Unit of the Voivodeship Lower-Silesian Specialist Hospital. It involved 142 patients consecutively admitted to the hospital and selected by the cardiologist on the basis of the inclusion and exclusion criteria. The inclusion criteria were age > 60 years, a diagnosis of AF (paroxysmal, persistent, or permanent), and anticoagulant treatment lasting for at least six months. The exclusion criteria were ischemic stroke in the last six months, severe renal or liver insufficiency, triple anticoagulant therapy for coronary angioplasty procedures, and a lack of consent to participate in the study. Ultimately, 31 patients were excluded. The study involved 111 patients who were over 60 years of age, were diagnosed with AF and used oral anticoagulant—either vitamin K antagonist (VKA) or a novel oral anticoagulants (NOACs)—for at least six months. The questionnaires were distributed by a cardiac nurse 1–2 days after admission to the clinic. The questions concerned the last six months of therapy and were answered directly by the patients. All patients were informed of the purpose and nature of our study and provided their written informed consent to be included in it. All patients completed all questionnaires. Information concerning the sociodemographic and clinical data come from the hospital registry files.

2.2 Ethical consideration

This study was approved by the Bioethical Committee of the Medical University of Wrocław (No. KB 53/2014). All qualified patients provided their informed and voluntary consent to participate in the study.

2.3 Instrument

We employed the Mini Mental State Examination (MMSE) developed by Folstein, *et al.*^[19] This is a widely used screening test for dementia, whose advantages include speed of administration and simple interpretation of its results. The MMSE measures cognitive functions such as sense of direction, memory, attention, linguistic function, and visual-spatial abilities, as well as the ability to count, recall things, repeat, and carry out orders.^[19] The possible score ranges from 0 to 30, with lower scores indicating more severe cognitive function disorders. Patients with scores < 23 are described as cognitively impaired.^[19]

Adherence to medication was measured using the Polish version of the MMAS-8—a self-reported instrument that is simple to administer, reliable, and economical for use in clinical practice. The MMAS-8 was designed to facilitate the identification of barriers to and behaviors associated with adherence to chronic medication, which consists of four items that assess intentional nonadherence and four items that assess unintentional nonadherence. The tool has been determined to be reliable and significantly associated with blood pressure control in individuals with hypertension, as well as with antihypertensive medication pharmacy fill rates. Total scores on the MMAS-8 range from 0 to 8, with scores < 6 reflecting low adherence, 6 to < 8 reflecting medium adherence, and 8 reflecting high adherence.^[20] This questionnaire has satisfactory psychometric properties and is also often used to assess adherence to anticoagulant treatment.^[7,17,18]

2.4 Statistical analysis

The normality of the empirical distribution of quantitative variables was verified using the Shapiro-Wilk test. The mean values and standard deviations for the quantitative variables were calculated. The mean values were compared in three groups of patients using the one-way analysis of variance (ANOVA). In case the null hypothesis on the lack of differences between the groups was rejected, *post hoc* tests were performed [multiple comparison tests and the least significant difference (LSD) test].

Qualitative and ordinal variables were grouped into contingency tables, the values for these variables were summed (n_i), and percentages were calculated. The independence of the qualitative variables was verified using Pearson's chi-square test. The strength of correlations among variables was determined by calculating Spearman's rank correlation coefficient (ρ) and its significance (P). The level of statistical significance was set at $P < 0.05$.

Multivariate linear regression analysis was employed to assess the influence of independent variables on the level of

adherence. The forward stepwise approach was used to select variables. Previously, the assumptions regarding the application of the least square method were verified, and analysis was conducted to check for the presence of outliers. The standardized coefficients β and regression coefficients b were calculated for explanatory variables (MMSE and age). Statistical significance of particular variables in the model was verified using Student's *t*-test. The quality of the proposed linear multivariate regression model was evaluated by means of standard error of estimation. The statistical analysis was carried out using Statistica v. 10.

3 Results

3.1 Sociodemographic and clinical characteristics

The study involved 111 AF patients (including 55 women) aged 60–93 years (mean \pm SD: 73.5 ± 8.3). The participants were categorized by level of adherence. According to the MMAS-8 results, 46.8% patients had low adherence, 19.8% had moderate adherence, and 33.4% had high adherence with the pharmacological therapy. The patients with low adherence were considerably older than those in the moderate- and high-adherence groups (76.6 ± 8.7 vs. 71.3 ± 6.4 vs. 71.1 ± 6.7 years; $P = 0.001$). The groups also differed in their levels of cognitive function: the low-adherence group had the lowest level of cognitive function (22.3 ± 4.2 ; $P < 0.001$), which suggests cognitive impairment (< 23 points). The levels of cognitive function in the moderate- and high-adherence groups were very similar and did not deviate from normal: 27.5 ± 1.7 vs. 27.5 ± 3.6 . In the group with low adherence, MMSE scores of less than 23 points were obtained by 48.1% of the patients; in the group with moderate adherence, this value was 22.7%; and in the group with high adherence, this was 10.8%. Table 1 shows basic statistics characterizing the patients. In all three groups, the duration of the disease was similar and the majority had been diagnosed less than five years ago. Only a small proportion of patients in the study sample were receiving new oral anticoagulants. In all three groups, the most common concomitant diseases were hypertension, diabetes, and heart failure, while the most common type of AF was paroxysmal AF; however, in the group with poor adherence, as many as 40.4% of the surveyed had permanent AF (Table 1).

3.2 Relationship between medication adherence and selected variables

3.2.1 Univariate regression analysis

Spearman's rank correlation coefficients (r_s) were calcu-

Table 1. Sociodemographic and clinical characteristics of AF patients with respect to treatment adherence.

Variable	Level of adherence			P
	Low n = 52	Medium n = 22	High n = 37	
Females	26 (50.0%)	10 (45.5%)	19 (51.4%)	0.905
Age, yrs	76.6 ± 8.7	71.3 ± 6.4	71.1 ± 6.7	0.001
City residence	41 (78.8%)	17 (77.3%)	31 (83.8%)	0.788
Duration of the disease, yrs				
Up to 5	31 (59.7%)	16 (72.7%)	22 (59.5%)	0.521
Over 5	21 (40.3%)	6 (27.3%)	15 (40.5%)	
Type of fibrillation				
Paroxysmal	23 (42.3%)	10 (50.1%)	18 (48.6%)	
Persistent	9 (17.3%)	4 (18.2%)	8 (21.6%)	0.726
Permanent	21 (40.4%)	7 (31.8%)	11 (29.7%)	
Concomitant diseases				
Hypertension	45 (86.5%)	16 (72.7%)	30 (81.1%)	0.902
Ischemic heart disease	7 (13.5%)	3 (13.6%)	4 (10.8%)	0.938
Diabetes	16 (30.8%)	10 (45.5%)	7 (18.9%)	0.287
Heart failure	22 (42.3%)	10 (45.5%)	11 (29.7%)	0.640
Hyperthyroidism	9 (17.3%)	3 (13.6%)	5 (13.5%)	0.896
Respiratory diseases	7 (13.5%)	2 (9.1%)	4 (10.8%)	0.878
Type of OACs				
VKA	44 (84.6%)	18 (81.8%)	30 (81.1%)	0.899
NOACs	8 (15.4%)	4 (18.2%)	7 (18.9%)	
MMSE score	22.3 ± 4.2	27.5 ± 1.7	27.5 ± 3.6	< 0.001
MMSE > 23	27 (51.9%)	17 (77.3%)	33 (89.2%)	< 0.001
MMSE < 23	25 (48.1%)	5 (22.7%)	4 (10.8%)	

Data are presented as mean ± SD or n (%). AF: atrial fibrillation; MMSE: Mini mental state examination; NOACs: novel oral anticoagulants; OACs: oral anticoagulants; VKA: vitamin K antagonist.

lated to assess the strength of the relationships between the level of adherence (expressed as a total MMAS-8 score) and the following variables: sociodemographic data, clinical data, and the level of cognitive impairment (expressed as a total MMSE score). Table 2 shows the results of the analysis, including the results of univariate regression analysis of adherence. The analysis demonstrated that the younger the patients ($r_s = -0.372$; $P < 0.001$) and the higher their scores on the MMSE ($r_s = 0.717$; $P < 0.001$), the higher the level of adherence they had.

In the further part of this study, a multiple stepwise regression model was used, where age and the level of cognitive function (according to the MMSE) were predictors, and the level of adherence according to the MMAS-8 was a dependent variable (Table 3). The model proved to be statistically significant [$F(2, 108) = 41.3$; $P < 0.0001$]. It explained 43.3% of variability of the results for the MMAS-8. Only one predictor was introduced to the model—namely, the level of cognitive function according to the MMSE. Age

Table 2. Univariate regression analysis of adherence (the total MMAS-8 score) with the variables analyzed.

	Correlation analysis		Univariate regression analysis	
	ρ	P	b	P
Females	0.057	0.549	0.251	0.501
Age	-0.372	< 0.001	-0.091	< 0.001
Place of residence city	0.031	0.664	0.114	0.808
Duration of the disease, yrs	-0.090	0.348	-0.200	0.276
Type of fibrillation	-0.065	0.497	-0.151	0.421
Hypertension	-0.061	0.520	-0.443	0.694
Diabetes	-0.122	0.200	-0.475	0.245
Heart failure	-0.138	0.148	-0.534	0.163
Number of concomitant diseases	-0.156	0.101	-0.303	0.087
MMSE	0.717	< 0.001	1.480	< 0.001

MMAS-8: 8-item Morisky Medication Adherence Scale; MMSE: Mini mental state examination.

was not included in the model because of a strong correlation with the MMSE results ($r_s = -0.489$; $P < 0.0001$). Ultimately, the level of adherence can be estimated using the following model: $MMAS-8 = 0.655 + 0.272 \times MMSE$

3.2.2 Multivariate regression analysis

Since the results of multivariate regression analysis (Table 3) suggest that the constant value was insignificant in the model ($P = 0.751$), the analysis was conducted once again without the constant coefficient b_0 . The model proved to be statistically significant [$F(2, 109) = 938$, $P < 0.0001$]. The results obtained (Table 3) show that age is at the limit of statistical significance ($P = 0.064$). Ultimately, the level of adherence can be estimated using the following model: $MMAS-8 = 0.281 \times MMSE - 0.015 \times Age$

Multivariate analysis demonstrated that the level of cognitive function is a statistically significant independent determinant of adherence: the higher the level of cognitive function, the better the adherence to medication in AF patients ($\beta = 1.139$; $P < 0.0001$).

Table 3. Multivariate regression analysis of adherence with the variables analyzed with and without intercept (b_0).

Variable	β	SE_β	b	SE_b	P
Constant (b_0)	-	-	0.655	2.063	0.751
MMSE (b_1)	0.615	0.082	0.272	0.036	< 0.0001
Age (b_2)	-0.084	0.082	-0.020	0.020	0.3071
Constant (b_0)	-	-	0	-	-
MMSE (b_1)	1.139	0.093	0.281	0.023	< 0.0001
Age (b_2)	-0.173	0.093	-0.015	0.008	0.0645

MMSE: Mini mental state examination.

4 Discussion

An improved understanding of the determinants associated with adherence to medication and health behaviors has become an important outcome in management strategies for AF. The ability to identify indicators of low medication adherence is crucial for both improving clinical care and determining the targets of intervention for the prevention of complications in AF and for treatment of AF.

The incidence of AF increases with age. It affects 5% of patients over 70 years of age and 10% of those over 85. The average age of patients in our study was about 73 years. Elderly people also more often suffer from cognitive function disorders. In our study, 52 subjects with low levels of adherence obtained a mean MMSE score of 22.3 ± 4.2 , which points to cognitive disorders. The study of Crum *et al.*^[21] on community populations demonstrated that the average MMSE score was 27 points for ages 70–74 years, and 25 points for ages over 85 years. In the same study, 25% of the 70–74 year-olds surveyed had a score of only 24 on the MMSE, and the scores were inversely proportional to age. In the study conducted by Dublin, *et al.*^[22] on 65-year-old AF patients, as many as 11.1% were diagnosed with dementia, as compared to 5.9% of the general population of a similar age. Aside from stroke, AF patients are also at a 40%–50% higher risk of Alzheimer's disease and dementia. In the study of Flaker, *et al.*^[23] conducted on 71-year-old AF patients, 6.8% of the participants had MMSE scores below 24, suggesting dementia, while 7.7% had intermediate scores of 24–25 points. In another study on a group of 267 elderly patients, as many as 74% of the surveyed individuals obtained MMSE scores of 19.8 ± 6.8 , and 49.8% used blood-thinning drugs on a regular basis.^[24]

The efficient use of oral anticoagulant treatment requires from patients everyday adherence to the therapeutic regimen, periodic changes in drug administration, and an awareness of the possible interactions with certain foods. The available studies provide evidence for a significant association between adherence and anticoagulation control (TTR). In the study of Wang, *et al.*,^[25] patients with high adherence to warfarin therapy (MMAS-8 = 8) had good TTR control (< 80%). Poor adherence to oral anticoagulant therapy may be one of the reasons for a low TTR, which increases the risk of developing acute coronary syndrome and stroke, leading to a noticeable deterioration in cognitive function.^[23] The same studies show that even mild cognitive impairment at the onset of anticoagulant therapy correlates with poorer anticoagulation control during 1.3-year follow-ups.^[23] In the study of van Deelen, *et al.*,^[26] an MMSE score of less than 23 among AF patients receiving OACs therapy was an independent determinant of poor control of international nor-

malized ratio (INR). Similarly, in the study of Flaker, *et al.*^[23] low MMSE scores, indicating to cognitive impairment, correlated with a low TTR.

The patients examined in our study were mainly treated with vitamin K antagonist (82.9%), and only 17.1% were taking the new oral anticoagulants. In the study of Castellucci, *et al.*,^[17] self-reported adherence to VKA and direct oral anticoagulants (DOACs) treatment was similar. However, as in our study, the group receiving NOACs was considerably smaller. In other studies, long-term adherence to DOACs therapy tended to be higher than VKA-adherence.^[16]

Using NOACs seems more favorable to patients, since they neither require regular coagulation monitoring nor interact with food. DOACs might represent a good alternative to VKA. In our study, the subjects with high adherence were more often those using NOACs; however, considering the small size of the group receiving this type of medications, we did not examine the type of oral anticoagulant agent as a factor contributing to adherence.

The available reports show that elderly age is related to both better and worse adherence to therapy.^[27] The oldest patients were those in the low-adherence group (76.1). This group had also the lowest average level of cognitive function (22.3), which was significantly lower than that reported by Crum, *et al.*^[21] In the study of Castellucci, *et al.*,^[17] age was associated with the level of adherence to anticoagulant therapy.

Our study demonstrated a significant relationship between the level of adherence to medication and the age of the surveyed individuals. The members of the low-adherence group were significantly older than their counterparts with moderate and high adherence levels. In univariate analysis, younger patients scored higher on the MMAS-8.

The connection between poor adherence to therapy and the level of cognitive function is not well documented in clinical practice. There are no studies assessing the influence of cognitive function on adherence to therapy among AF patients. The available reports focus on the assessment of anticoagulant therapy on the basis of the INR control. The efficient use of oral anticoagulant treatment requires from patients everyday adherence to the therapeutic regimen, periodic changes in drug administration, and an awareness of the possible interactions with foods. Effective AF management may be especially difficult for elderly patients with cognitive disorders. Hence, a low MMSE score may result in a low MMAS-8 score. The influence of cognitive impairment on medication adherence among elderly patients is discussed in the literature.^[27,28] Contradictory results may be caused by an insufficient representation of elderly patients with cognitive disorders in the majority of adherence stud-

ies.^[29,30] There is also a problem differentiating between normal forgetting and cognitive function disorders.^[27] Nevertheless, several studies confirm the relationship between the MMSE score < 24 and poorer adherence to the prescribed treatment among elderly patients.^[31–33]

In our study, the significant independent predictors of worse adherence to therapy were age and cognitive impairment in univariate analysis, and cognitive impairment alone in multivariate analysis.

The available studies suggest that patients with cognitive disorders less frequently receive oral anticoagulants and, even when they do, the therapy is less effective.^[23] Patients with cognitive disorders are at a higher risk of thromboembolic complications and bleeding. The low efficiency of therapy may be explained by poor adherence to treatment. In our study, as many as 46.8% of those surveyed with cognitive disorders had low levels of medication adherence. In the study of over-70-year-olds, Perera, *et al.*^[34] demonstrated that AF inpatients were significantly less likely to receive warfarin than their nonfrail counterparts. They were also more vulnerable to adverse clinical outcomes, regardless of antithrombotic therapy.

4.1 Limitations

We are well aware of the potential limitations of this study. The major is that the study sample was relatively small and was recruited from a single center. Furthermore, it is also the case that we did not calculate TTR for VKA, and we did not use HAS-BLED score (which is useful in predicting bleeding in patients taking anticoagulants: H-Hypertension, A-abnormal renal/liver function, S-stroke, B-bleeding, L-labile INRs, E-elderly > 65, D-drugs or alcohol) in the adherence analysis. Another limitation is that no other methods of adherence control were used besides the self-assessment questionnaire.

4.2 Conclusions

Even so, the results show that patients with worse adherence to medication are older and have lower levels of cognitive function. In univariate analysis, older age correlates with poorer medication adherence. In univariate and multivariate analysis, a lower MMSE score is a predictor of medication adherence. Cognitive impairment is an independent determinant of compliance with pharmacological therapy in elderly AF patients. Such findings may help to account for the elevated mortality risk in AF patients with cognitive impairment.

References

1 Zoni-Berisso M, Lercali F, Carazza L, *et al.* Epidemiology of

- atrial fibrillation: European perspective. *Clin Epidemiol* 2014; 6: 213–220.
- 2 Mahtani KR, Heneghan CJ, Nunan D, *et al.* Vitamin K for improved anticoagulation control in patients receiving warfarin. *Cochrane Database Syst Rev* 2014; CD009917.
- 3 Mahtani K, Heneghan C, Glasziou P, *et al.* Reminder packaging for improving adherence to self-administered long-term medications. *Cochrane Database Syst Rev* 2011; 9: 1–62.
- 4 Ferguson C, Inglis SC, Newton PJ, *et al.* The caregiver role in thromboprophylaxis management in atrial fibrillation: a literature review. *Eur J Cardiovasc Nurs* 2015; 14: 98–107.
- 5 Laliberté F, Nelson WW, Lefebvre P, *et al.* Impact of daily dosing frequency on adherence to chronic medications among nonvalvular atrial fibrillation patients. *Adv Ther* 2012; 29: 675–690.
- 6 Fang MC, Go AS, Chang Y, *et al.* Warfarin discontinuation after starting warfarin for atrial fibrillation. *Circ Cardiovasc Qual Outcomes* 2010; 3: 624–631.
- 7 Precioso Costa FJ, Larré Muñoz MJ, Navarro Ros FM, *et al.* [Level of control and treatment adherence of anticoagulation with acenocoumarol in primary care]. *Semergen* 2015; S1138–3593(15)00304-4. [Article in Spanish].
- 8 Gumbinger C, Holstein T, Stock C, *et al.* Reasons underlying nonadherence and discontinuation of anticoagulation in secondary stroke prevention among patients with atrial fibrillation. *Eur Neurol* 2015; 73: 184–191.
- 9 Heidbuchel H, Verhamme P, Alings P, *et al.* Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2015; 17: 1467–1507.
- 10 Zeolla MM, Brodeur RR, Dominelli A, *et al.* Development and validation of an instrument to determine patient knowledge: the oral anticoagulation knowledge test. *Ann Pharmacother* 2006; 40: 633–638.
- 11 Briggs AL, Jackson TR, Bruce S, *et al.* The development and performance validation of a tool to assess patient anticoagulation knowledge. *Res Social Adm Pharm* 2005; 1: 40–59.
- 12 Van Damme S, Van Deyk K, Moons P, *et al.* Instruments to assess patient's knowledge regarding oral anticoagulation therapy: a systematic review. *Eur J Cardiovasc Nurs* 2008; 7: 21–22.
- 13 Avila ChW, Aliti GB, Feijo MKF, *et al.* Pharmacological adherence to oral anticoagulant and factors that influence the international normalized ratio stability. *Rev Latino-Am. Enfermagem* 2011; 19: 18–25.
- 14 Marzona I, O'Donnell M, Koon T, *et al.* Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. *CMAJ* 2012; 184: E329–E336.
- 15 Campbell NL, Boustani MA, Skopelja EN, *et al.* Medication adherence in older adults with cognitive impairment: a systematic evidence-based review. *Am J Geriatr Pharmacother* 2012; 10: 165–177.
- 16 Horstmann S, Rizos T, Saribas M, *et al.* Cognitive impairment is not a predictor of failure to adhere to anticoagulation

- of stroke patients with atrial fibrillation. *Cerebrovasc Dis* 2015; 39: 325–331.
- 17 Castellucci LA, Shaw J, van der Salm K, et al. Self-reported adherence to anticoagulation and its determinants using the Morisky medication adherence scale. *Thromb Res* 2015; 136: 727–731.
- 18 Mayet AY. Patient adherence to warfarin therapy and its impact on anticoagulation. *Saudi Pharm J* 2016; 24: 29–34.
- 19 Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; 12: 189–198.
- 20 Morisky DE, Ang A, Krousel-Wood M, et al. Predictive validity of a medication adherence measure in an outpatient setting. *J Clin Hypertens* 2008; 10: 348–354.
- 21 Crum RM, Anthony JC, Bassett SS, et al. Population-based norms for the mini-mental state examination by age and educational level. *J Am Med Assoc* 1993; 269: 2386–2391.
- 22 Dublin S, Anderson ML, Haneuse SJ, et al. Atrial fibrillation and risk of dementia: a prospective cohort study. *J Am Geriatr Soc* 2011; 59: 1369–1375.
- 23 Flaker GC, Pogue J, Yusuf S, et al. Cognitive function and anticoagulation control in patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes* 2010; 3: 277–283.
- 24 Annweiler C, Ferland G, Barberger-Gateau P, et al. Vitamin K antagonists and cognitive impairment: results from a cross-sectional pilot study among geriatric patients. *J Gerontol A Biol Sci Med Sci* 2015; 70: 97–101.
- 25 Wang Y, Kong MC, Lee LH, et al. Knowledge, satisfaction, and concerns regarding warfarin therapy and their association with warfarin adherence and anticoagulation control. *Thromb Res* 2014; 133: 550–554.
- 26 van Deelen BA, van den Bemt PM, Egberts TC, et al. Cognitive impairment as determinant for sub-optimal control of oral anticoagulation treatment in elderly patients with atrial fibrillation. *Drugs Aging* 2005; 22: 353–360.
- 27 Arlt S, Lindner R, Rosler A, et al. Adherence to medication in patients with dementia: predictors and strategies for improvement. *Drugs Aging* 2008; 25: 1033–1047.
- 28 Insel K, Morrow D, Brewer B, et al. Executive function, working memory, and medication adherence among older adults. *J Gerontol B Psychol Sci Soc Sci* 2006; 61: P102–P107.
- 29 Okuno J, Yanagi H, Tomura S. Is cognitive impairment a risk factor for poor compliance among Japanese elderly in the community? *Eur J Clin Pharmacol* 2001; 57: 589–594.
- 30 Rauch G, Veltkamp R. Cognitive impairment is not a predictor of failure to adhere to anticoagulation of stroke patients with atrial fibrillation. *Cerebrovasc Dis* 2015; 39: 325–331.
- 31 Gray SL, Mahoney JE, Blough DK. Medication adherence in elderly patients receiving home health services following hospital discharge. *Ann Pharmacother* 2001; 35: 539–545.
- 32 Salas M, In't Veld BA, van der Linden PD, et al. Impaired cognitive function and compliance with antihypertensive drugs in elderly: The Rotterdam Study. *Clin Pharmacol Ther* 2001; 70: 561–566.
- 33 Barat I, Andreasen F, Damsagaard EMS. Drug therapy in the elderly: what doctors believe and patients actually do. *Br J Clin Pharmacol* 2001; 51: 615–622.
- 34 Perera V, Bajorek BV, Matthews S, et al. The impact of frailty on the utilisation of antithrombotic therapy in older patients with atrial fibrillation. *Age Ageing* 2009; 38: 156–162.