



Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: [www.elsevier.com/locate/jjcc](http://www.elsevier.com/locate/jjcc)



Original article

## Adherence to medication and characteristics of Japanese patients with non-valvular atrial fibrillation

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### ARTICLE INFO

#### Article history:

Received 14 August 2016

Received in revised form 7 November 2016

Accepted 21 November 2016

Available online xxx

#### Keywords:

Adherence

Anticoagulants

Atrial fibrillation

Japanese

### ABSTRACT

**Background:** Adherence to medication plays an important role in the prevention of morbidity and mortality in non-valvular atrial fibrillation (NVAF) patients. The aim of this study is to assess adherence to medication and risk factors for non-adherence in Japanese NVAF patients who are prescribed anticoagulants.

**Methods:** A total of 378 outpatients with NVAF who completed self-reported questionnaires were analyzed in this prospective study (mean age  $69 \pm 12$  years; 26% female). Self-reported adherence to cardiovascular drugs including anticoagulants was measured with a modified Siegal scale. Depression was defined as a Patient Health Questionnaire-9 score of  $\geq 10$ . Univariate and multivariate analyses were performed on several variables to analyze factors affecting non-adherence.

**Results:** In total, 291 (77%) of our patients received warfarin, and the remainder received direct oral anticoagulants. Fifty-two (14%) patients were defined as non-adherent. Univariate analyses showed that age  $< 65$  years,  $\geq 2$  times daily dosing of cardiovascular drugs and employment, but not depression, were significantly associated with non-adherence, 1.87 (95% CI: 1.01–3.42,  $p = 0.04$ ), 2.97 (95% CI: 1.64–5.49,  $p < 0.01$ ), 2.11 (95% CI: 1.16–3.93,  $p = 0.01$ ), and 0.74 (95% CI: 0.26–2.64), respectively. Multivariate analysis showed that only  $\geq 2$  times daily dosing was a significant independent risk factor (HR 3.06, 95% CI: 1.67–5.69,  $p < 0.01$ ).

**Conclusions:** Our study showed that the prevalence of non-adherence to medications was 14% in NVAF patients. Frequent daily dosing was an independent risk factor for non-adherence to medication (UMIN-CTR No. UMIN 000023514).

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### Introduction

Atrial fibrillation (AF) is a common form of tachyarrhythmia and is a risk factor for stroke [1–4]. Anticoagulant therapy reduces the risk of AF-related stroke [3,4] and is recommended to prevent thromboembolism for all patients with AF except for those who are at a truly low risk [5]. However, although anticoagulants are effective, adherence to anticoagulation therapy plays an important role in preventing stroke in at-risk AF patients. Previous reports have indicated several risk factors for poor adherence to warfarin

therapy [6–8]. Warfarin has a limited use because of its narrow therapeutic window [9] and several interactions with food, herbs, and concomitant drugs. Direct oral anticoagulants (DOACs) are useful for the prevention of stroke in patients with non-valvular AF (NVAF) [10], but it is not yet clear whether adherence to DOACs is improving in real-world settings. A recent national cohort of 5376 patients with NVAF who started taking dabigatran at all Veterans Affairs hospitals in the USA showed that lower adherence was associated with an increased risk of combined all-cause mortality and stroke [11]. In our experience, 2 patients who discontinued dabigatran by their own choice experienced ischemic stroke/transient ischemic attack (TIA) [12]. In Japanese patients, moreover, the persistence rate of warfarin was higher than in the US cohort studies, although the persistence rates of DOACs in our study are comparable to those results [12,13].

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<http://dx.doi.org/10.1016/j.jjcc.2016.11.009>

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Not only the drug itself but other factors, such as the patient's clinical background, socio-economic status, psycho-social status, the disease, and the patient–physician relationship, also affect adherence to medication [14–16]. The aim of this study is to assess adherence to medication and the risk factors for non-adherence in Japanese NVAF patients who are prescribed anticoagulants.

## Materials and methods

### Subjects

We conducted a substudy of a prospective observational study designed to evaluate depressed mood in outpatients with cardiovascular disease who visited outpatient cardiology clinics at Tokyo Women's Medical University Hospital (between March 2014 and May 2014), Tokyo Women's Medical University Medical Center East (between December 2014 and February 2015), and Tokyo Women's Medical University Aoyama Hospital (March 2015). This study was conducted in accordance with the Helsinki Declaration, and all patients provided written informed consent. After informed consent was obtained, the patients completed two self-reported questionnaires [the Patient Health Questionnaire-9 (PHQ-9) depression screening scale and a modified Siegal scale] on the same day. In total, of the 1544 patients who enrolled in this study, 1439 completed the two self-reported questionnaires. Of these, 480 patients received anticoagulation therapy. We then confirmed each patient's AF diagnosis and excluded patients with valvular heart disease, concurrent hyperthyroidism, deep vein thrombosis, pulmonary thromboembolism, other systemic thrombosis not associated with AF, reduced LV systolic function with no history of AF, and bypass graft surgery. Valvular heart disease was defined as moderate or severe mitral stenosis and mild rheumatic mitral stenosis according to angiographic, hemodynamic, or echocardiographic results or a history of valvular surgery, including valvular repair or replacement. The remaining 378 NVAF patients who received anticoagulants and completed the questionnaires were included in this study. The details of the study have been reported elsewhere [17]. The study protocol was approved by the institutional review board of Tokyo Women's Medical University (approval number: 2899, approval date: August 16, 2013).

### Self-reported adherence

We measured self-reported adherence to cardiovascular drugs, including anticoagulants, using a modified Siegal scale for kidney transplant recipients [18,19] because there are no specific self-reported adherence assessment scales for specific pharmacotherapies in AF patients.

First, we asked the patients, "In the last 4 weeks, how often have you not taken your cardiovascular drugs?". The patients could answer the items with never (corresponding to adherence), once a month, every 2 weeks, every week, every 3–4 days, every other day, or every day. Second, if the patients reported not taking cardiovascular drugs, they answered a question about the reason for their non-adherence and chose one of the following options: they had not taken them because they forgot, because they believed they did not need them, and/or because they believed they did not need as much of them as their doctors thought. Although no validity data have been provided for this modified questionnaire, any answer other than "never" was defined as non-adherence according to a cut-off criterion described in previous reports [19].

### Depression

Depressive symptoms were assessed using the Japanese version of the PHQ-9. The PHQ-9 is a self-reported scale containing

9 symptoms that reflect the diagnostic criteria for depression and is an established tool for depression screening in patients with cardiovascular disease [20]. Depression was defined as a PHQ-9 score  $\geq 10$ .

### Statistical analysis

The summary data are presented either as the mean and standard deviation (SD) or as the numbers of patients. Baseline clinical data were compared between adherent and non-adherent patients using Student's *t* test and Mann–Whitney *U* test. Categorical variables were subjected to chi-square analysis. Univariate and multivariate analyses using the Cox proportional hazards model were performed to assess the relationship between non-adherence and the following baseline characteristics: age <65 years, female gender, left ventricular ejection fraction <40%, hypertension, diabetes mellitus, New York Heart Association (NYHA) functional class III, history of TIA/stroke, estimated glomerular filtration rate (eGFR) based on the Modification of Diet in Renal Disease formula [21] <60 ml/min/1.73 m<sup>2</sup>, CHA<sub>2</sub>DS<sub>2</sub>-VASc score [5] of 0–1, implantation of pacemaker/implantable cardioverter-defibrillator, polypharmacy ( $\geq 4$  medications),  $\geq 2$  times daily dosing [22], depression, living status, and employment status. The forward stepwise method was used for the multivariate analyses with entry or removal on the basis of *p*-values set at 0.05. Values *p* < 0.05 were considered statistically significant. Data analyses were performed with SPSS software (version 11.01, SPSS Inc., Chicago, IL, USA).

## Results

The patients' baseline characteristics are shown in Table 1. Of our study patients, 59% had heart failure with an NYHA functional class of II or III, and 9% had depression as defined by the PHQ-9. Anticoagulants were indicated in most patients with NVAF for the prevention of stroke and thromboembolism; 98% of the patients had a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of  $\geq 1$  [5], and the remainders received anticoagulants at their physician's discretion because of atherosclerotic risk factors such as hyperlipidemia and hyperuricemia or venous disease. A total of 291 (77%) patients were prescribed warfarin, and the remainder were prescribed DOACs.

Fifty-two (14%) out of 378 patients reported not having taken their medication at least once in the 4 weeks prior to completing the questionnaire. A comparison of patients' clinical characteristics according to adherence and non-adherence is shown in Table 1. The mean age of non-adherent patients was lower than that in adherent patients, although there were no significant differences in gender, underlying cardiovascular disease, coexisting conditions, implanted devices, CHA<sub>2</sub>DS<sub>2</sub>-VASc score or concomitant medications between the groups. Compared with adherent patients, more non-adherent patients had a 2 and  $\geq 3$  times daily dosing frequency and were employed.

There was no difference between warfarin and DOACs in terms of the distribution of non-adherence according to the modified Siegal scale (Table 2). The major reason patients reported for not taking their medication was forgetting. However, some patients believed that their drugs were not always necessary for their cardiac disease (Table 3). Univariate analyses showed that younger age (<65 years),  $\geq 2$  times daily dosing, and employment were significantly associated with non-adherence (Table 4). Multivariate analysis showed that only  $\geq 2$  times daily dosing was a significant independent risk factor (HR 3.06, 95% CI 1.67–5.69, *p* < 0.01) (Table 4).

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