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Anticoagulation Adherence and Its Associated Factors in Patients with Atrial Fibrillation: A Cross-sectional Study

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1. Pei-Ti Chen: conception and design, acquisition of data, analysis and interpretation of data, revising the manuscript critically
2. Tsae-Jyy Wang: conception and design, analysis and interpretation of data, drafting and revising the manuscript
3. Ming-Hsiung Hsieh: conception and design, acquisition of data, analysis and interpretation of data, revising the manuscript critically
4. Ju-Chi, Liu: acquisition of data, analysis and interpretation of data
5. Chieh-Yu Liu: conception and design, analysis and interpretation of data, revising the manuscript critically
6. Kwua-Yun Wang: conception and design, revising the manuscript critically
7. Wen-Chun Laio: conception and design, revising the manuscript critically

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ABSTRACT

Objective: To investigate anticoagulant adherence and its associated factors, including demographics, clinical variables, AF severity, knowledge, satisfaction with services, perceived barriers, perceived benefits, symptom severity, and self-efficacy in AF patients.

Design: This is a cross sectional study.

Participants and setting: A convenient sample of AF patients was recruited from cardiology clinics of two teaching hospitals in Taiwan.

Measures: Data were collected using the study questionnaires, including the AF related symptom subscale of the AF Severity Scale, the Knowledge of Warfarin Anticoagulation Treatment Scale, the Satisfaction Scale about Service and Warfarin Treatment, the perceived benefits subscale of the Beliefs about Anticoagulation Survey, the Concerns about Anticoagulation Therapy Scale, The Self-efficacy for Appropriate Medication Use scale, and the short-form Adherence to Refills and Medications Scale

Results: A total of 151 AF patients participated in the study. The average medication adherence score was 8.83 (SD = 1.87). No significant difference was observed in medication adherence between patients on warfarin and patients on NOACs. Multiple linear regression analysis showed that perceived barriers (β =.181, t = 2.42*) and self-efficacy (β =-.479, t = -6.40***) were important predictors of anticoagulation adherence. These two variables explained 34.0% of the variation in adherence ($F_{(2,149)}$ = 38.11 , p <.001).

Conclusion: Patients with AF reported good adherence to anticoagulant therapy. Patients with greater self-efficacy for and perceived less barriers to appropriate anticoagulant use reported better adherence to anticoagulation therapy. Interventions focusing on

decreasing barriers and enhancing self-efficacy may help to promote anticoagulation adherence in AF populations.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first known study to compare medication adherence between patients taking warfarin and NOACs. We found no group difference in medication adherence. Patients in both groups reported good adherence to anticoagulant therapy.
- Patients with greater self-efficacy for and perceived less barriers to appropriate anticoagulant use reported better adherence to anticoagulation therapy. Patients with less symptoms, higher satisfaction, greater perceived benefits, and less perceived barriers reported greater self-efficacy for appropriate anticoagulant use. Strategies to address AF related symptoms, satisfaction with services, as well as perceived benefits and barriers of taking anticoagulants should be developed to increase self-efficacy and thereafter to enhance anticoagulant adherence.
- The cross-sectional nature of the study precluded an assessment of medication adherence change over time and did not permit us to determine causal relationships among the study variables. A self-report questionnaire was used to measure medication adherence, which was subject to recall and social desirability biases. Finally, the influences of anticoagulation adherence on patients' treatment outcomes were not examined.

INTRODUCTION

Atrial fibrillation (AF) is the most common type of arrhythmia.[1-3] AF associated hemodynamic changes and thrombosis increase risks of heart failure, stroke, and sudden death.[4] In Taiwan, patients with AF are 5-fold more likely to have a stroke than the general population, whereas one in five stroke patients has AF.[5] Moreover, 46.2% of patients with AF have ischemic stroke within three years of diagnosis.[6] Anticoagulation treatment is the most important measure for preventing stroke in AF patients.[1-3] However, inadequate anticoagulation use is a global problem.[7-8] In Taiwan, while 90% of AF patients meet the criteria for anticoagulation treatment, only 28.28% use it.[9] Correlation studies on AF and stroke show that 185,570 cases of stroke occur each year in AF patients with no anti-platelet or oral anticoagulation treatment.[10]

Vitamin K antagonists (VKAs) such as warfarin and novel oral anticoagulants (NOACs) are the two main types of anticoagulants currently used for patients with AF.[1-3] While using Warfarin, the international normalized ratio (INR) must be closely monitored as warfarin tends to interact with other drugs or foods, and it is difficult to maintain the percentage of time in the therapeutic range.[1,3] NOACs should be used if INR is difficult to maintain in the desirable therapeutic range while using warfarin.[2] Lin et al.[11] found that it is difficult to choose an optimal dose of warfarin in Asian populations because of substantial variation in the individual response to warfarin and the narrow therapeutic range. Chiang et al.[1] also found that warfarin significantly increases the risk of intracranial hemorrhage and recommended NOACs as the preferred treatment in Asian AF populations. However, warfarin is still the most common and widely used anticoagulant for patients with AF in Taiwan.[11]

Good anticoagulant adherence ensures medication safety and effective prevention of stroke. Low adherence is associated with higher mortality and morbidity of cardiovascular diseases.[12] Knowing factors that affect anticoagulant adherence will help identify the populations at risk for non-adherence and develop appropriate measures to improve medication adherence. Previous studies showed that low adherence was related to 1) concerns about adverse drug reactions; [13] 2) inadequate knowledge of AF associated risks for stroke;[13] 3) unawareness of the importance of medication adherence;[13] 4) symptom severity;[13] 5) fear of regular blood tests;[13] 6) inability to attend frequent clinical visits;[14] 7) undergoing invasive treatments or procedures;[13] and 8) comorbidities.[14] However, most of these studies were conducted in Western Caucasian populations and in patients taking warfarin. Whether patients from different culture backgrounds share similar factors deserve further investigations. Additionally, few studies have investigated the differences in medication adherence for taking NOACs versus warfarin in AF patients and have yielded inconsistent results. Yao et al.[15] conducted a retrospective cohort analysis to investigate adherence to oral anticoagulants in patients with AF, wherein proportion of days covered (PDC) ≥ 80% indicated good adherence. The overall PDC was 47.5% for NOACs (dabigatran, rivaroxaban, and apixaban) and 38.7% for warfarin (p <.001), indicating better adherence to NOACs than to warfarin. Choi et al.[16] analyzed 364 AF cases (warfarin: n = 204, dabigatran: n = 160) and assessed medication adherence with missed doses per month. The data showed that an average of 0.65 dabigatran tablets and an average of 0.63 warfarin tablets were missed per month (p =.916). The results from the above studies show that medication adherence varies with each NOACs, which is not always superior to that of warfarin.

Therefore, the purposes of this study were to 1) compare the differences in adherence between patients treated with warfarin and NOACs; 2) explore factors influencing anticoagulant adherence in patients with AF, including demographics, clinical variables (disease duration, stroke risk assessment, bleeding risk assessment, anticoagulation therapies, and adverse reactions), AF severity, anticoagulation treatment knowledge, satisfaction with services, beliefs about anticoagulation treatment, and self-efficacy for appropriate medication; and 3) investigate the important predictors of anticoagulant adherence in AF patients.

METHODS

Study design

This is a cross sectional study. Data were collected with self-reported questionnaires.

Participants and setting

AF patients who met the following eligibility criteria were recruited from cardiology outpatient clinics of two teaching hospitals in Taipei, Taiwan. The inclusion criteria were 1) ≥ 20 years of age; 2) fluent in Mandarin or Taiwanese; 3) diagnosed with AF; and 4) treated with warfarin or NOACs for anticoagulation. The exclusion criteria were 1) diagnosed with psychological diseases; 2) diagnosed with uncontrolled hypertension; 3) diagnosed with the New York Heart Association (NYHA) grade VI heart failure; 4) implanted with a cardiac pacemaker; 5) had a cardiac surgery in the past three months; or 6) hospitalized for AF in the past three months. The desired sample size was estimated by using the G power (v3.1) software. In consideration of the number of potential predictors (n =17) in this study, a sample size of 146 would have 80% power to

detect a medium effect size of $f^2 = 0.15$ with a 0.05 level of significance using a multiple linear regression fixed model.

Patient and public involvement

The development of the research hypothesis was informed by working closely with patients with AF. However, patients and public were not involved in the recruitment to and conduct of the study. An abstract of the study results will be mailed to the study participants.

Data collection

The investigator administered the study questionnaire after obtaining informed consent from each subject. The data collection took place at the waiting areas outside the outpatient clinics during the patients' visits to the clinics. For subjects who were unable to read the questionnaire due to vision or other problems, the investigator read each question to help them complete the questionnaire.

Variables and measurements

Socio-demographics were provided by the subjects, including age, sex, education level, marital status, and employment status. Data on clinical variables were extracted from the participants' medical records, including disease duration, CHA_2DS_2-VASc score for stroke risk assessment, HAS-BLED score for bleeding risk assessment, and anticoagulation therapies (name of medication and dosing frequency). The subjects were also asked to report anticoagulant-related adverse reactions, including bleeding events, hypersensitivity, gastrointestinal reactions, dizziness, headache, fainting, limb pain, and edema.

The AF related symptom subscale of the AF Severity Scale (AFSS)[17] was used to measure symptom severity. The 7-item subscale covers 7 AF related symptoms. For each item, the subjects indicated how often within the last month they experienced the symptom on a 6-point Likert scale (from 0_ I have not had this symptom in the past 4 weeks to 5_ a great deal). The total score of the 7 items represents the scale score, with a possible range of 0 to 35. Higher scores indicate higher levels of symptom severity. The scale has shown an acceptable level of reliability and validity in past studies involving AF patients.[18] In this study, Cronbach's α value was 0.80, indicating good internal consistency.

The Knowledge of Warfarin Anticoagulation Treatment Scale[19] was used to measure warfarin treatment knowledge. The 11-item scale covers four areas of warfarin treatment knowledge: administration (e.g., dose, color, and route of administration), interaction with foods, interaction with other drugs, and side effects. There are five choices for each item, and only one of the choices is correct (scored 1). The total score of the 11 items represents the scale score, with a possible range of 0 to 11. Higher scores indicate higher levels of understanding of warfarin treatment. The scale was also modified to measure the NOACs treatment knowledge. The item 1 (regarding anticoagulant dosage) in the original scale was revised into two items, one for dosage and one for name of the medication in the NOACs knowledge scale. The item 2 (regarding INR) in the original scale was deleted. The item 4 (regarding how to make up the missing dose) was revised into two items, one for missing a dose in taking NOACs once a day, and one for missing a dose in taking NOACs twice a day. The total score of the 13 items represents NOACs treatment knowledge. The potential scores range from 0 to 12, with

higher scores indicating higher levels of understanding of NOACs treatment. To facilitate analysis and comparison, the score of each scale was converted to a scale of 0 to 100 (actual score/possible maximum score x 100). The knowledge of warfarin anticoagulation treatment scale has shown good psychometric properties in a previous study involving patients treated with anticoagulants.[19] In the current study, Kuder–Richardson Formula 20 (KR-20) was 0.680 for warfarin treatment knowledge and 0.625 for NOACs treatment knowledge.

The Satisfaction Scale about Service and Warfarin Treatment (SSWT)[19] was used to measure subjects' satisfaction with services and anticoagulation treatment provided by the health care team. The original scale includes seven positive statements about the services and warfarin treatment. In the current study, the term of warfarin was replaced with anticoagulants. The item 5 (regarding INR monitoring) in the original scale was deleted as it only applies to patients treated with warfarin. Therefore, there were only six items used in the current study. For each item, the subjects indicated their levels of agreement on a 5-point Likert scale (from 0_ strongly disagree to 4_ strongly agree). The total score of the 6 items represents the scale score, with a possible range of 0 to 24. Higher scores indicate higher levels of satisfaction about service and warfarin treatment. The scale has shown good psychometric properties in a previous study involving patients treated with anticoagulants.[19] In this study, Cronbach's α was 0.867.

The perceived benefits subscale of the Beliefs about Anticoagulation Survey (BAAS)[20] was used to measure subjects' perceived benefits associated with taking anticoagulants. The subscale covers 5 potential benefits of taking anticoagulation, including lessening risk of having stroke, lowering chance of being hospitalized, feeling

healthier, improving quality of life, and worrying less about the disease. For each item, the subjects indicated their levels of agreement on a 5-point Likert scale (from 1_ strongly disagree to 5_ strongly agree). The potential scores range from 5 to 25, with higher scores indicating higher levels of perceived benefits associated with taking anticoagulation. The scale has shown reasonable psychometric properties in a previous study involving patients treated with anticoagulation.[20] In this study, Cronbach's α was 0.838.

The Concerns about Anticoagulation Therapy Scale[19] was used to measure perceived barriers regarding anticoagulation treatment. The scale lists ten potential concerns, including drug interactions, forgetting to take anticoagulants, side effects, hospital visits, diet interactions, activity restrictions, impact on work, not helpful, and difficulty of following instructions. The subjects were asked to indicate all concerns that apply to them. Each concern was scored 1. The potential scores range from 0 to 10, with higher scores indicating more concerns. The scale has shown acceptable psychometric properties in a previous study involving patients treated with anticoagulants.[19]

The Self-efficacy for Appropriate Medication Use scale (SEAMS)[21] was used to measure self-efficacy for appropriate anticoagulant use. The 13-item scale covers two dimensions of self-efficacy: for taking medications under difficult circumstances and for taking medications under uncertain or changing circumstances. For each item, the subjects indicated their level of confidence about taking medications correctly under a specific circumstance on a three-point response scale (1 _ not confident, 2 _ somewhat confident, and 3 _ very confident). The potential scores range from 13 to 39, with high scores indicating higher levels of self-efficacy for appropriate anticoagulant use. The

SEAMS has shown good psychometric properties for patients with coronary heart disease and other comorbid conditions. [21] In this study, Cronbach's α was 0.931.

The short-form Adherence to Refills and Medications Scale (ARMS)[22] was used to measure adherence to anticoagulation treatment. There are seven items in the scale. Subjects were asked to indicate how often they actually miss taking their anticoagulants in each item on a 4-point Likert scale (1_ none of the time to 4_ all of the time). The total score of the 7 items represents the scale score, with a possible range of 7 to 28. A higher score indicates worse adherence to anticoagulation treatment. The scale has shown good psychometric properties for patients with coronary heart diseases.[22] In this study, Cronbach's α was 0.70.

Statistical methods

Data were analyzed using the Statistical Package for Social Sciences 20.0 (SPSS, Inc., Chicago, IL, USA). Descriptive analyses were used to describe study variables. Independent t-tests and one-way analysis of variance (ANOVA) were performed to analyze the differences in anticoagulation adherence scores among different categorical study variables. Pearson product-moment correlations were performed to analyze the correlations among the continuous variables. Due to the large number of potential explanatory variables, stepwise linear regression was chosen for statistical model selection. All study variables were entered as dependent variables into stepwise linear regression models to find significant influencing factors of anticoagulant adherence. These included demographics (age, gender, educational level, marital status, and employment status), clinical variables (disease duration, CHA_2DS_2-VASc score, HAS-BLED score, anticoagulants, dosing frequency, and adverse reactions), symptom severity,

anticoagulation treatment knowledge, satisfaction with services, perceived benefits, perceived barriers, and self-efficacy for appropriate anticoagulant use. Categorical variables were dummy coded prior to analysis. The probability-of-F-to-enter ≦ .050 was used as the criterion for entering a variable into the model; the probability-of-F-to-remove ≧ .100 was used as the criterion for removing a variable from the model. Standardized residual plots and collinearity statistics of Variance Inflation Factor were used to examine the normality and independent assumptions of the regression. There was no violation in both assumptions.

RESULTS

The subjects were recruited from clinics associated with two hospitals, with 93(61.6%) and 58 (38.4%) subjects from each hospital. The demographics and values of study variables showed no significant differences between subjects recruited from the different hospitals (data not shown). The average age of the subjects was 71.98 (55 to 93; SD = 8.61) (Table 1). There were 95 (62.9%) males and 56 (37.1%) females in the study. The majority of the subjects were married (n = 125) and retired (n = 107) (Table 2). Subjects were diagnosed with an AF for 73.97 months (SD = 61.06) on average (Table 1). Of the 151 subjects, 98 (64.9%) received NOACs and 53 (35.1%) received warfarin. Most subjects (n=77, 51.0%) did not experience anticoagulation related side effects (Table 2).

The subjects reported good anticoagulation adherence, with an average score of 8.83 (SD: 1.87) on ARMS. They had few AF related symptoms, with an average score of 6.81 (SD = 5.41) on the symptom subscale of the AFSS. Shortness of breath during physical activity was the most common symptom experienced by these subjects. In

general, the subjects had poor understanding of anticoagulation treatment, with a mean score of 35.94 (0 to 92; SD = 19.32) on the anticoagulation treatment knowledge scale. Most subjects miss more than half of the treatment related questions, with most mistakes made in drug-food interactions, INR values, timing of taking anticoagulants, and how to prevent bleeding risks.

They reported moderate to high satisfaction with services and anticoagulation treatment, with a mean score of 19.06 (SD = 3.21) on the SSWT. In general, the subjects had high levels of agreement on the benefits of taking anticoagulants. Their average score on the perceived benefits subscale of the BAAS was 20.10 (SD = 2.46). They also reported few concerns regarding anticoagulation therapy, with an average score of 1.14 (SD = 1.32) on the concerns about anticoagulation therapy scale. The top three concerns indicated by the subjects were 1) side effects (n = 53, 63.1%); 2) drug interactions (n = 44, 52.4%); and 3) forgetting to take anticoagulants (n = 33, 39.3%). In general, the subjects had high levels of self-efficacy for appropriate anticoagulant use, with a mean score of 32.87 (SD = 6.07) on the SEAMS.

The difference in adherence between subjects treated with warfarin (mean = 8.62; SD = 1.63) and NOACs (mean = 8.94; SD = 1.99) was statistically insignificant. There was also no significant difference both in anticoagulant adherence and self-efficacy among subjects with different demographics and clinical variables (CHA_2DS_2-VASc score, HAS-BLED score, anticoagulants, dosing frequency, and adverse reactions) (see Table 2).

Results of Person correlation analyses showed that anticoagulation adherence was significantly associated with perceived barriers to ($r = .40$, $p < .001$) and self-efficacy for

appropriate anticoagulant use (r = -.56, p <.001). Other study variables (age, disease duration, symptom severity, knowledge, satisfaction, and perceived benefits) were not significantly associated with anticoagulation adherence (Table 3). The self-efficacy for anticoagulant use was significantly associated with symptom severity (r = -.23, p < .01), satisfaction (r = .29, p < .001), perceived benefits (r = .31, p < .001), and perceived barriers (r = -.45, p < .001). Age, disease duration, and knowledge were not related to self-efficacy.

The results of stepwise linear regression analyses showed that perceived barriers (ß =.181, t = 2.42*) and self-efficacy (ß =-.479, t = -6.40***) were significant predictors of adherence to anticoagulation therapy. These two variables collectively explained 34.0% of the variance in adherence to anticoagulation therapy [$F_{(2,149)}$ = 38.11, p < .001] (see Table 4). Other variables were excluded from the model. As for self-efficacy, satisfaction with services, perceived benefits, and perceived barriers were the significant predictors. These three variables together explained 29.0% of the variance in self-efficacy for anticoagulant use [$F_{(3,148)}$ = 19.997, p < .001] (see Table 4). Figure 1 presents the relationships among perceived benefits, perceived barriers, self-efficacy, and adherence to anticoagulation therapy with their respective standardized regression coefficients (β).

DISCUSSION

To the best of our knowledge, this is the first study to compare medication adherence between patients taking warfarin and NOACs. We found no group difference in medication adherence. Patients in both groups reported good adherence to anticoagulant therapy. It is difficult to compare our findings with previous studies, because most studies included only patients treated with warfarin[23] and used different

adherence measures.[23] Nevertheless, our sutdy subjects reported relativly good adherence to anticoagulant therapy with an average score of 8.83 (SD: 1.87) out of the possible range 7-28 in ARMS, comparing to 32.3% of non-adherent to warfarin therapy in a cross-sectional survey of 288 patients with AF.[23]

We found that perceived barriers and self-efficacy were significant predictors of anticoagulation adherence. Consistent with findings in previous studies of other populations,[24-25] patients with lower self-efficacy for and perceived greater barriers to appropriate anticoagulant use were at a higher risk for anticoagulation nonadherence. Therefore, interventions for enhancing anticoagulation adherence should address barriers and self-efficacy. Consistent with findings in a previous study,[23] concerns regarding side effects, drug interactions, and forgetting to take anticoagulants are the top barriers to appropriate anticoagulant use and should be addressed accordingly. As for self-efficacy, the subjects were also least confident about "taking anticoagulants properly should any adverse reaction occur". Therefore, addressing concerns regarding anticoagulant side effects should be the first priority in this population.

In addition, the study results showed that symptom severity, satisfaction, perceived benefits, and perceived barriers were significant predictors of self-efficacy for appropriate anticoagulant use. Patients with severer symptoms, lower satisfaction, less perceived benefits, and greater perceived barriers reported lower self-efficacy for appropriate anticoagulant use. Addressing AF related symptoms, satisfaction with services, perceived benefits, and barriers of taking anticoagulants may help increase self-efficacy and enhance anticoagulation adherence.

As for the AF related symptoms, we found that shortness of breath during physical activity was the most common symptom experienced by the subjects instead of mild dizziness/lightheadedness as reported in a previous study.[19] This may be explained by variations in AF associated symptom presentation.[1] As for professional support, the subjects were least satisfied with the time spent with a physician, nurse, or pharmacist during their visits at the hospital. This may be partially explained by the busy clinics in Taiwan. Physicians usually see many patients in a very short period of time.

Different from findings in previous studies,[23-24] we found that adherence to anticoagulation treatment was not significant related to knowledge of anticoagulation treatment. These may be due to most of these studies were conducted in different countries and only focused on patients treated with warfarin. Although our subjects showed poor understating of anticoagulation treatment, they reported good adherence to anticoagulation treatment. This may be partially explained by Taiwanese culture of obedience to a physician orders. In the hospitals where the study was conducted, anticoagulation treatment education was not routinely provided to patients treated with NOACs, but should be given to patients first treated with warfarin by a pharmacist according to the hospital routine. However, most of our subjects were unaware that they were taking anticoagulants and did not record receive any anticoagulation treatment education. The treatment knowledge scores were low in both warfarin and NOACs treatment groups, indicating the needs for strengthening anticoagulation treatment patient education. Special attentions should be paid to treatment related issues, such as drug-food interactions, INR values, timing of taking anticoagulants, and how to prevent bleeding risks. These are areas that most our subjects answered incorrectly. Additionally, teaching

strategies for patients with low health literacy may be warranted for better outcomes, as most of our subjects had only education levels of primary school or below.

This study had several limitations. First, the subjects were recruited from cardiology clinics of two teaching hospitals and may vary from those seen in other clinical settings. Thus, the results may not be generalizable outside this sample. Second, the cross-sectional nature of the study precluded an assessment of medication adherence change over time and did not permit us to determine causal relationships among the study variables. Third, a self-report questionnaire was used to measure medication adherence, which was subject to recall and social desirability biases. Finally, the influences of anticoagulation adherence on patients' treatment outcomes were not examined. Replication of the findings with a longitudinal study design, objective measures of medication adherence, and clinical outcome measures are warranted. Nevertheless, the study results present evidence for the importance of perceived barriers and self-efficacy on the adherence to anticoagulation therapy in patients with AF.

Patients with AF usually require long-term use of anticoagulants to prevent strokes. In recent years, NOACs have been widely used in AF patients as NOACs do not require frequent monitoring (as for warfarin), have less interactions with foods or other drugs, and are fast-acting. However, few studies have compared medication adherence between warfarin and NOACs. This is the first study in Taiwan to compare medication adherence to warfarin and to NOACs as well as to explore factors associated with adherence to anticoagulation in patients with AF. The results showed that there was no significant difference in medication adherence between patients on warfarin and patients on NOACs. Patients with AF reported good adherence to anticoagulant therapy.

Perceived barriers and self-efficacy were significant predictors of medication adherence. Patients with greater self-efficacy for and perceived less barriers to appropriate anticoagulant use reported better adherence to anticoagulation therapy. Interventions focusing on decreasing barriers and enhancing self-efficacy may help to promote anticoagulation adherence in AF populations. Symptom severity, satisfaction, perceived benefits, and perceived barriers were significant predictors of self-efficacy for appropriate anticoagulant use. Patients with less symptoms, higher satisfaction, greater perceived benefits, and less perceived barriers reported greater self-efficacy for appropriate anticoagulant use. Strategies to address AF related symptoms, satisfaction with services, as well as perceived benefits and barriers of taking anticoagulants should be developed to increase self-efficacy and thereafter to enhance anticoagulant adherence.

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Table 1 Descriptive data of study variables (n = 151)

Variables	Mean	SD	Range
Age	71.98	8.61	55-93
Disease duration (month)	73.97	61.06	2-389
Symptom severity	6.81	5.41	0-22
Anticoagulation treatment knowledge	35.94	19.32	0-92
Warfarin	33.45	20.63	0-90.91
NOACs	38.42	19.08	0-91.67
Satisfaction with services and anticoagulation treatment	19.06	3.21	7-24
Perceived benefits of anticoagulation treatment	20.10	2.46	13-25
Perceived barriers to anticoagulation treatment	1.14	1.32	0-6
Self-efficacy for anticoagulant use	32.87	6.07	18-39
Anticoagulation adherence	8.83	1.87	7-15

SD, standard deviation

Table 2 Sample characteristics and comparisons of self-efficacy, and anticoagulation adherence among different characteristics of patients with atrial fibrillation (n = 151)

Variables	n	Self-efficacy			Adherence		
		$M \pm SD$	F / t	p	$M \pm SD$	F / t	p
Gender			-1.56	.121		1.50	.135
Female	56	31.88±6.75			9.13±2.05		
Male	95	33.46±5.58			8.65±1.74		
Educational level			.173	.915		0.37	.779
Primary school and below	51	32.88±6.24			8.80±1.93		
Middle school	21	33.48±7.10			8.76±2.21		
High school	33	33.12±5.82			8.61±1.90		
College and above	46	32.41±5.70			9.04±1.65		
Marital status			1.18	.238		-0.52	.604
Married	125	32.61±5.88			8.86±1.85		
Single, divorced or widowed	26	34.15±6.90			8.65±2.02		
Employment status			.540	.584		0.73	.482
Full time, part time	29	32.93±6.54			9.21±2.01		
Retired	107	33.07±5.72			8.74±1.82		
Unemployed	15	31.33±7.62			8.73±2.02		
CHA_2DS_2-VAS_C			.315	.731		-0.82	.416
Low-middle risk	9				8.33±1.58		
High risk	142	32.85±6.09			8.86±1.89		

Table 2 Sample characteristics comparisons of self-efficacy, and anticoagulation adherence among different characteristics of patients with atrial fibrillation (*continued*)

Variables	*n*	Self-efficacy			Adherence		
		M ± *SD*	*F* / *t*	*p*	*M* ± *SD*	*F* / *t*	*p*
HAS-BLED			.919	.360		-0.86	.392
Low risk	60	33.43±5.97			8.67±1.83		
High risk	91	32.50±6.14			8.93±1.90		
Anticoagulants			1.37	.172		-0.99	.324
Warfarin	53	33.79±4.90			8.62±1.63		
NOACs	98	32.38±6.59			8.94±1.99		
Dosing frequency			.081	.922		0.45	.641
Once a day	135	32.85±6.01			8.81±1.92		
Twice a day	11	33.45±6.86			9.27±1.56		
Once every two days	5	32.20±7.09			8.40±1.14		
Number of adverse reactions			1.18	.320		-2.15	.096
None	77	33.41±5.66			8.69±1.84		
One	51	33.02±6.28			8.76±1.74		
Two	14	30.93±6.74			8.69±1.88		
Three and more	9	30.44±7.02			10.33±2.45		

F: value of one-way analysis of variables; *t*: value of dependent t test

Table 3 Person product moment correlation coefficients among study variables (n = 151)

Variables	Age	Disease duration	Symptom severity	Knowledge	Satisfication	Perceived benefits	Perceived barriers	Self-efficacy	Adherence
Age	1								
Disease duration	.109	1							
Symptom severity	-.212**	-.164*	1						
Knowledge	-.154	-.007	.024	1					
Satisfication	-.052	-.006	-.025	.259**	1				
Perceived benefits	-.003	.032	-.082	.125	.393***	1			
Perceived barriers	-.030	-.122	.293***	-.048	-.086	-.171*	1		
Self-efficacy	.053	.059	-.234**	.056	.290***	.312***	-.450***	1	
Adherence	-.017	.056	.097	-.054	-.050	-.096	.397***	-.560***	1

*p < .05; **p < .01; ***p < .001

Table 4 Results of stepwise regressions on self-efficacy and anticoagulation adherence in patients with atrial fibrillation ($N = 151$)

Model	Dependent variables	Independent variables	ß	*t*	R^2	Adjusted R^2	*F*	VIF
1					.290	.275	19.997***	
	Self-efficacy	Perceived barriers	-.405	-5.74***				1.031
		Satisfication	.189	2.50*				1.183
		Perceived benefits	.168	2.20*				1.210
2					.340	.331	38.11***	
	Anticoagulation	Self-efficacy	-.479	-6.40***				1.254
	Adherence	Perceived barriers	.181	2.42*				1.254

* $p < .05$; *** $p < .001$

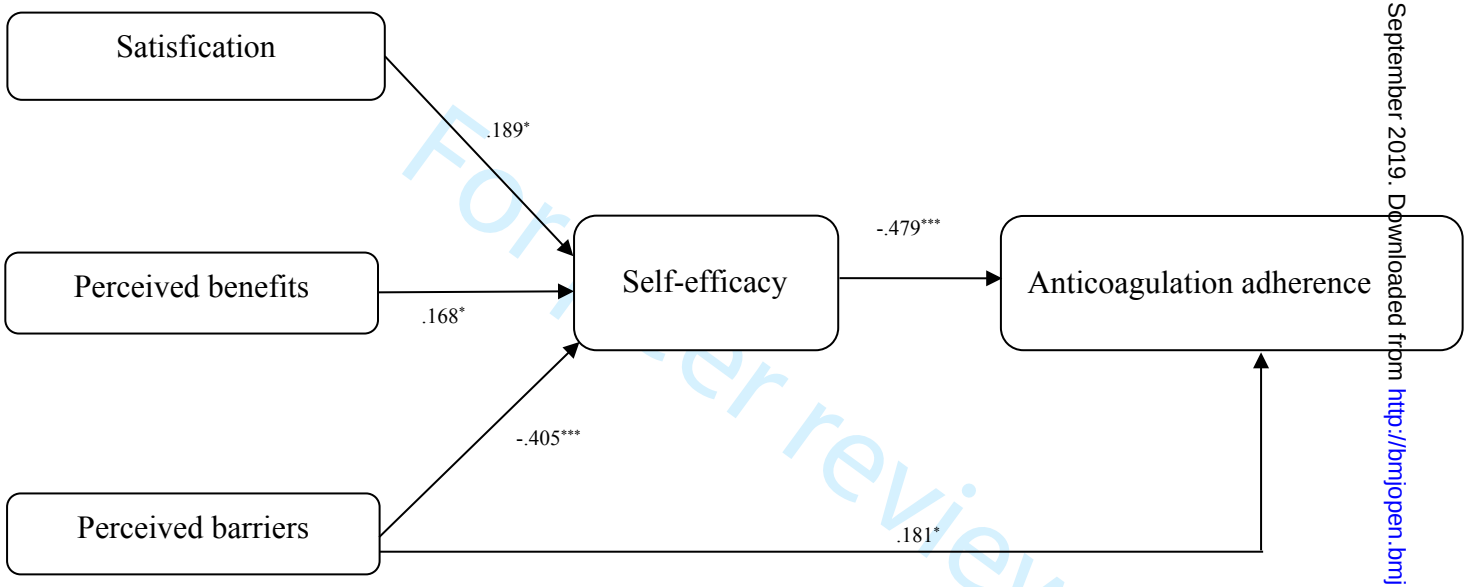

Figure 1. Relationships among symptom severity, satisfaction, perceived benefits, and perceived barriers in self-efficacy and adherence to anticoagulation therapy.

*$p < .05$; ***$p < .001$

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the STROBE cross sectional reporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3

Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	#3	State specific objectives, including any prespecified hypotheses	7
Study design	#4	Present key elements of study design early in the paper	7
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	7
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	8-9
Bias	#9	Describe any efforts to address potential sources of bias	8-12
Study size	#10	Explain how the study size was arrived at	7,10
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7,12-13

Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7,8
	#12b	Describe any methods used to examine subgroups and interactions	12
	#12c	Explain how missing data were addressed	n/a
	#12d	If applicable, describe analytical methods taking account of sampling strategy	n/a
	#12e	Describe any sensitivity analyses	n/a
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	10
	#13b	Give reasons for non-participation at each stage	n/a
	#13c	Consider use of a flow diagram	n/a
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	13
	#14b	Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	#15	Report numbers of outcome events or summary measures.	13-15

		Give information separately for exposed and unexposed groups if applicable.	
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13-15
	#16b	Report category boundaries when continuous variables were categorized	n/a
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a
Key results	#18	Summarise key results with reference to study objectives	14-15
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	18
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	15-17
Generalisability	#21	Discuss the generalisability (external validity) of the study results	18-19
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which	2

the present article is based

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Anticoagulation Adherence and Its Associated Factors in Patients with Atrial Fibrillation: A Cross-sectional Study

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2. Tsae-Jyy Wang: conception and design, analysis and interpretation of data, drafting and revising the manuscript
3. Ming-Hsiung Hsieh: conception and design, acquisition of data, analysis, and interpretation of data revising the manuscript critically
4. Ju-Chi, Liu: acquisition of data, analysis, and interpretation of data
5. Chieh-Yu Liu: conception and design, analysis and interpretation of data, revising the manuscript critically
6. Kwua-Yun Wang: conception and design, revising the manuscript critically
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ABSTRACT

Objective: To investigate anticoagulant adherence and its associated factors, including demographics, clinical variables, AF severity, knowledge, satisfaction with services, perceived barriers, perceived benefits, symptom severity, and self-efficacy in AF patients.

Design: This is a cross-sectional study.

Participants and setting: A convenient sample of AF patients were recruited from cardiology clinics of two teaching hospitals in Taiwan.

Measures: Data were collected using the study questionnaires, including the AF related symptom subscale of the AF Severity Scale, the Knowledge of Warfarin Anticoagulation Treatment Scale, the Satisfaction Scale about Service and Warfarin Treatment, the perceived benefits subscale of the Beliefs about Anticoagulation Survey, the Concerns about Anticoagulation Therapy Scale, The Self-efficacy for Appropriate Medication Use scale, and the short-form Adherence to Refills and Medications Scale

Results: A total of 151 AF patients participated in the study; 53 treated with warfarin and 98 treated with NOACs. The difference in adherence to warfarin (mean = 8.6; SD = 1.6) and NOACs (mean = 8.9; SD = 2.0) was statistically insignificant. Multiple linear regression analysis showed that perceived barriers (β =.18, p = .017) and self-efficacy (β =-.48, p < .001) were significant predictors of anticoagulation adherence. For every 1-unit increase in the perceived barriers, there will be a .18-unit increase in the adherence to anticoagulation therapy. For every 1-unit increase in the self-efficacy, there will be a .48-unit decrease in the adherence to anticoagulation therapy. Perceived barriers and self-efficacy collectively explained 34.0% of the variance in adherence to anticoagulation therapy [$F_{(2,149)}$ = 38.11, p < .001].

Conclusion: We found no better adherence to NOACs compared to warfarin. Patients with greater self-efficacy and perceived fewer barriers showed better adherence to anticoagulation therapy.

Strengths and limitations of this study

- This is one of the few studies that compared medication adherence between patients taking warfarin and NOACs.
- The cross-sectional nature of the study precluded an assessment of medication adherence change over time and did not permit us to determine causal relationships among the study variables.
- A self-report questionnaire was used to measure medication adherence, which was subject to recall and social desirability biases.

INTRODUCTION

Atrial fibrillation (AF) is the most common type of arrhythmia.[1-3] AF associated hemodynamic changes and thrombosis increases risks of heart failure, stroke, and sudden death.[4] In Taiwan, patients with AF are 5-fold more likely to have a stroke than the general population, whereas one in five stroke patients has AF.[5] Moreover, 46.2% of patients with AF have an ischemic stroke within three years of diagnosis.[6] Anticoagulation treatment is the most important measure for preventing stroke in AF patients.[1-3] However, inadequate anticoagulation use is a global problem.[7-8] In Taiwan, while 90% of AF patients meet the criteria for anticoagulation treatment, only 28.28% use it.[9] Correlation studies on AF and stroke show that 185,570 cases of stroke occur each year in AF patients with no anti-platelet or oral anticoagulation treatment.[10]

Vitamin K antagonists (VKAs) such as warfarin and novel oral anticoagulants (NOACs) are the two main types of anticoagulants currently used for patients with AF.[1-3] While using warfarin, the international normalized ratio (INR) must be closely monitored as warfarin tends to interact with other drugs or foods, and it is difficult to maintain the percentage of time in the therapeutic range.[1,3] NOACs should be used if INR is difficult to maintain in the desired therapeutic range while using warfarin.[2] Lin et al.[11] found that it is difficult to choose an optimal dose of warfarin in Asian populations because of substantial variation in the individual response to warfarin and the narrow therapeutic range. Chiang et al.[1] also found that warfarin significantly increases the risk of intracranial hemorrhage and recommended NOACs as the preferred treatment in Asian AF populations. However, warfarin is still the most common and widely used anticoagulant for patients with AF in Taiwan.[11]

Good anticoagulant adherence ensures medication safety and effective prevention of stroke. Low adherence is associated with higher mortality and morbidity of cardiovascular diseases.[12] Knowing factors that affect anticoagulant adherence will help identify the populations at risk for non-adherence and allow for the development of appropriate measures to improve medication adherence. Previous studies showed that low adherence was related to 1) concerns about adverse drug reactions; [13] 2) inadequate knowledge of AF associated risks for stroke;[13] 3) unawareness of the importance of medication adherence;[13] 4) symptom severity;[13] 5) fear of regular blood tests;[13] 6) inability to attend frequent clinical visits;[14] 7) undergoing invasive treatments or procedures;[13] and 8) comorbidities.[14] However, most of these studies were conducted in Western Caucasian populations and in patients taking warfarin. Whether patients from different cultural backgrounds share similar factors deserve further investigations. Additionally, few studies have investigated the differences in medication adherence for taking NOACs versus warfarin in AF patients, and they have yielded inconsistent results. Yao et al.[15] conducted a retrospective cohort analysis to investigate adherence to oral anticoagulants in patients with AF, wherein the proportion of days covered (PDC) ≥ 80% indicated good adherence. The overall PDC was 47.5% for NOACs (dabigatran, rivaroxaban, and apixaban) and 38.7% for warfarin (p <.001), indicating better adherence to NOACs than to warfarin. Choi et al.[16] analyzed 364 AF cases (warfarin: n = 204, dabigatran: n = 160) and assessed medication adherence with missed doses per month. The data showed that an average of 0.65 dabigatran tablets and an average of 0.63 warfarin tablets were missed per month (p =.916). The results from the above studies

show that medication adherence varies with each NOACs, which is not always superior to that of warfarin.

Therefore, the purposes of this study were to 1) compare the differences in adherence between patients treated with warfarin and NOACs; 2) explore factors influencing anticoagulant adherence in patients with AF, including demographics, clinical variables (disease duration, stroke risk assessment, bleeding risk assessment, anticoagulation therapies, and adverse reactions), AF severity, anticoagulation treatment knowledge, satisfaction with services, beliefs about anticoagulation treatment, and self-efficacy for appropriate medication; and 3) investigate the important predictors of anticoagulant adherence in AF patients.

METHODS

Study design

This is a cross-sectional study. Data were collected with self-reported questionnaires.

Participants and setting

AF patients who met the following eligibility criteria were recruited from cardiology outpatient clinics of two teaching hospitals in Taipei, Taiwan. The inclusion criteria were 1) ≥ 20 years of age; 2) fluent in Mandarin or Taiwanese; 3) diagnosed with AF; 4) treated with warfarin or NOACs for anticoagulation. The exclusion criteria were 1) diagnosed with psychological diseases; 2) diagnosed with uncontrolled hypertension; 3) diagnosed with the New York Heart Association (NYHA) grade VI heart failure; 4) implanted with a cardiac pacemaker; 5) had a cardiac surgery in the past three months; 6) hospitalized for AF in the past three months. The desired sample size was estimated by

using the G power (v3.1) software. In consideration of the number of potential predictors (n =17) in this study, a sample size of 146 would have 80% power to detect a medium effect size of $f^2 = 0.15$ with a 0.05 level of significance using a multiple linear regression fixed model. The use of NOACs or warfarin was treated as a single variable for the sample size calculation.

Patient and public involvement

The development of the research hypothesis was informed by working closely with patients with AF. However, patients and the public were not involved in the recruitment process and conduct of the study. An abstract of the study results will be mailed to the study participants.

Data collection

The investigator administered the study questionnaire after obtaining informed consent from each subject. The data collection took place in the waiting areas outside the outpatient clinics during the patients' visits to the clinics. For subjects who were unable to read the questionnaire due to vision or other problems, the investigator read each question to help them complete the questionnaire.

Variables and measurements

Socio-demographics were provided by the subjects, including age, sex, education level, marital status, and employment status. Data on clinical variables were extracted from the participants' medical records, including disease duration, CHA_2DS_2-VASc score for stroke risk assessment, HAS-BLED score for bleeding risk assessment, and anticoagulation therapies (name of the medication and dosing frequency). The subjects were also asked to report anticoagulant-related adverse reactions, including bleeding

events, hypersensitivity, gastrointestinal reactions, dizziness, headache, fainting, limb pain, and edema.

The AF related symptom subscale of the AF Severity Scale (AFSS)[17] was used to measure symptom severity. The 7-item subscale covers 7 AF related symptoms. For each item, the subjects indicated how often within the last month they experienced the symptom on a 6-point Likert scale (from 0_ I have not had this symptom in the past 4 weeks to 5_ a great deal). The total score of the 7 items represents the scale score, with a possible range of 0 to 35. Higher scores indicate higher levels of symptom severity. The scale has shown an acceptable level of reliability and validity in past studies involving AF patients.[18] This English scale was translated into Chinese through the following steps: Chinese translation, synthesis, back translation, expert committee review, and pilot testing[19]. Its Content Validity Index (CVI) was greater than 0.9, indicating good expert validity[19]. In this study, Cronbach's α value was 0.80. A high Cronbach's α coefficient (e.g., > 0. 8) indicates good internal consistency reliability[20].

The Chinese version of Knowledge of Warfarin Anticoagulation Treatment Scale[21] was used to measure warfarin treatment knowledge. The 11-item scale covers four areas of warfarin treatment knowledge: administration (e.g., dose, color, and route of administration), interaction with foods, interaction with other drugs, and side effects. There are five choices for each item, and only one of the choices is correct (scored 1). The total score of the 11 items represents the scale score, with a possible range of 0 to 11. Higher scores indicate higher levels of understanding of warfarin treatment. The scale was also modified to measure NOACs treatment knowledge. The item 1 (regarding anticoagulant dosage) in the original scale was revised into two items, one for dosage and

one for the name of the medication in the NOACs knowledge scale. The item 2 (regarding INR) in the original scale was deleted. The item 4 (regarding how to make up the missing dose) was revised into two items, one for missing a dose in taking NOACs once a day, and one for missing a dose in taking NOACs twice a day. The total score of the 13 items represents NOACs treatment knowledge. The potential scores range from 0 to 12, with higher scores indicating higher levels of understanding of NOACs treatment. To facilitate analysis and comparison, the score of each scale was converted to a scale of 0 to 100 (actual score/possible maximum score x 100). The knowledge of warfarin anticoagulation treatment scale has shown good psychometric properties in a previous study involving patients treated with anticoagulants.[21] In the current study, Kuder–Richardson Formula 20 (KR-20) was 0.68 for warfarin treatment knowledge and 0.63 for NOACs treatment knowledge. The KR-20 is a measure of internal consistency reliability for dichotomous scale items.

The Chinese version of Satisfaction Scale about Service and Warfarin Treatment (SSWT)[19] was used to measure subjects' satisfaction with services and anticoagulation treatment provided by the health care team. The original scale includes seven positive statements about the services and warfarin treatment. In the current study, the term warfarin was replaced with anticoagulants. The item 5 (regarding INR monitoring) in the original scale was deleted as it only applies to patients treated with warfarin. Therefore, there were only six items used in the current study. For each item, the subjects indicated their levels of agreement on a 5-point Likert scale (from 0_ strongly disagree to 4_ strongly agree). The total score of the 6 items represents the scale score, with a possible range of 0 to 24. Higher scores indicate higher levels of satisfaction about service and

warfarin treatment. The scale has shown good psychometric properties in a previous study involving patients treated with anticoagulants.[21] In this study, Cronbach's α was 0.87.

The perceived benefits subscale of the Beliefs about Anticoagulation Survey (BAAS)[22] was used to measure subjects' perceived benefits associated with taking anticoagulants. The subscale covers 5 potential benefits of taking anticoagulation, including lessening the risk of having a stroke, lowering the chance of being hospitalized, feeling healthier, improving quality of life, and worrying less about the disease. For each item, the subjects indicated their levels of agreement on a 5-point Likert scale (from 1_ strongly disagree to 5_ strongly agree). The potential scores range from 5 to 25, with higher scores indicating higher levels of perceived benefits associated with taking anticoagulation. The scale has shown reasonable psychometric properties in a previous study involving patients treated with anticoagulation.[22] The scale was translated into Chinese by our research team following the same steps as described prior. Its CVI was 1.0 and Cronbach's α was 0.84.

The Chinese version of the Concerns about Anticoagulation Therapy Scale[19] was used to measure perceived barriers regarding anticoagulation treatment. The scale lists ten potential concerns, including drug interactions, forgetting to take anticoagulants, side effects, hospital visits, diet interactions, activity restrictions, impact on work, not helpful, and difficulty of following instructions. The subjects were asked to indicate all concerns that apply to them. Each concern was scored 1. The potential scores range from 0 to 10, with higher scores indicating more concerns. The scale has shown acceptable

psychometric properties in a previous study involving patients treated with anticoagulants.[22]

The Self-efficacy for Appropriate Medication Use scale (SEAMS)[23] was used to measure self-efficacy for appropriate anticoagulant use. The 13-item scale covers two dimensions of self-efficacy: for taking medications under difficult circumstances and for taking medications under uncertain or changing circumstances. For each item, the subjects indicated their level of confidence about taking medications correctly under a specific circumstance on a three-point response scale (1 _ not confident, 2 _ somewhat confident, and 3 _ very confident). The potential scores range from 13 to 39, with high scores indicating higher levels of self-efficacy for appropriate anticoagulant use. The SEAMS has shown good psychometric properties for patients with coronary heart disease and other comorbid conditions.[23] The scale was translated into Chinese by our research team with a CVI 1.0 and Cronbach's α 0.93.

The short-form Adherence to Refills and Medications Scale (ARMS)[24] was used to measure adherence to anticoagulation treatment. There are seven items on the scale. Subjects were asked to indicate how often they actually miss taking their anticoagulants in each item on a 4-point Likert scale (1_ none of the time to 4_ all of the time). The total score of the 7 items represents the scale score, with a possible range of 7 to 28. A higher score indicates worse adherence to anticoagulation treatment. The scale has shown good psychometric properties for patients with coronary heart diseases (n = 435).[24] The scale correlated strongly both with the Morisky adherence scale[25] (Spearman's rho =-.598, P < 0.01), and the cumulative medication gap[26] during the previous 6 months (Spearman's rho =.339, P < 0.01).[24] Patients with low ARMS scores were significantly more likely to

have controlled blood pressure (81.3% vs. 73.2%, $P < 0.05$). The scale also had good internal consistency (Cronbach's a = 0.814) and test-retest reliability (Spearman's rho = 0.693, $P < 0.001$).[24] In this study, Cronbach's α was 0.70.

Statistical methods

Data were analyzed using the Statistical Package for Social Sciences 20.0 (SPSS, Inc., Chicago, IL, USA). Descriptive analyses were used to describe study variables. Independent t-tests and one-way analysis of variance (ANOVA) were performed to analyze the differences in anticoagulation adherence scores among different categorical study variables. Pearson product-moment correlations were performed to analyze the correlations among the continuous variables. Due to a large number of potential explanatory variables, stepwise linear regression was chosen for statistical model selection. All study variables were entered as dependent variables into stepwise linear regression models to find significant influencing factors of anticoagulant adherence. These included demographics (age, gender, educational level, marital status, and employment status), clinical variables (disease duration, CHA_2DS_2-VASc score, HAS-BLED score, anticoagulants, dosing frequency, and adverse reactions), symptom severity, anticoagulation treatment knowledge, satisfaction with services, perceived benefits, perceived barriers, and self-efficacy for appropriate anticoagulant use. Categorical variables were dummy coded prior to analysis. The probability-of-F-to-enter $\leqq .050$ was used as the criterion for entering a variable into the model; the probability-of-F-to-remove $\geqq .100$ was used as the criterion for removing a variable from the model. Standardized residual plots and collinearity statistics of Variance Inflation Factor were

used to examine the normality and independent assumptions of the regression. There was no violation in both assumptions.

RESULTS

One of the researchers approached 156 eligible patients; 6 of them declined to participate. This left 151 eligible patients to take part in the study. All of them completed the study questionnaires and their data were included in the final analysis. Every subject filled out all the questionnaires except the knowledge scale. Fifty-three (35.1 %) subjects receiving warfarin answered The Knowledge of Warfarin Anticoagulation Treatment Scale; 98 (64.9%) subjects receiving NOACs filled out The Knowledge of NOACs Treatment Scale.

These subjects were recruited from clinics associated with two hospitals, with 93 and 58 subjects from each hospital, respectively. There was no significant difference in demographics or values of study variables between subjects recruited from the different hospitals (data not shown). The average age of the subjects was 72.0 (SD = 8.6) (Table 1). There were 95 males and 56 females in the study. The majority of the subjects were married (n = 125) and retired (n = 107) (Table 2). Subjects were diagnosed with an AF for 73.97 months (SD = 61.06) on average (Table 1). Of the 151 subjects, 98 received NOACs and 53 received warfarin. Most subjects (n = 77) did not experience anticoagulation-related side effects (Table 2).

The subjects reported an average score of 8.8 (SD = 1.9) on ARMS. The average score on the symptom subscale of the AFSS was 6.8 (SD = 5.4). Shortness of breath during physical activity was the most common symptom experienced by these subjects. The subjects had a mean score of 35.9 (SD = 19.3) on the anticoagulation treatment

knowledge scale. Most subjects miss more than half of the treatment-related questions, with most mistakes made in drug-food interactions, INR values, the timing of taking anticoagulants, and how to prevent bleeding risks. They reported a mean score of 19.06 (SD = 3.21) on the SSWT. Their average score on the perceived benefits subscale of the BAAS was 20.10 (SD = 2.5). They reported an average score of 1.14 (SD = 1.3) on the concerns about anticoagulation therapy scale. The top three concerns indicated by the subjects were 1) side effects (n = 53); 2) drug interactions (n = 44); and 3) forgetting to take anticoagulants (n = 33). The subjects had a mean score of 32.9 (SD = 6.1) on the SEAMS.

The difference in medication adherence between warfarin (mean = 8.6; SD = 1.6) and NOACs (mean = 8.9; SD = 2.0) was statistically insignificant. There was also no significant difference both in anticoagulant adherence and self-efficacy among subjects with different demographics and clinical variables (CHA_2DS_2-VASc score, HAS-BLED score, anticoagulants, dosing frequency, and adverse reactions) (Table 2). Results of Pearson correlation analyses showed that anticoagulation adherence was significantly associated with perceived barriers to ($r = .40$, $p < .001$) and self-efficacy for appropriate anticoagulant use ($r = -.56$, $p < .001$). Other study variables (age, disease duration, symptom severity, knowledge, satisfaction, and perceived benefits) were not significantly associated with anticoagulation adherence (Table 3). The self-efficacy for anticoagulant use was significantly associated with symptom severity ($r = -.23$, $p = .02$), satisfaction ($r = .29$, $p < .001$), perceived benefits ($r = .31$, $p < .001$), and perceived barriers ($r = -.45$, $p < .001$). Age, disease duration, and knowledge were not related to self-efficacy.

Results of stepwise linear regression analyses showed that perceived barriers (ß =.18, $p = .017$) and self-efficacy (ß =-.48, $p < .001$) were significant predictors of adherence to anticoagulation therapy. For every 1-unit increase in the perceived barriers score, there will be a .18-unit increase in the adherence to anticoagulation therapy score. In addition, for every 1-unit increase in the self-efficacy score, there will be a .48-unit decrease in the adherence to anticoagulation therapy score. Perceived barriers and self-efficacy collectively explained 34.0% of the variance in adherence to anticoagulation therapy [$F_{(2,149)} = 38.11$, $p < .001$] (see Table 4). Other variables were excluded from the model. As for self-efficacy, the satisfaction with services, perceived benefits, and perceived barriers were the significant predictors. These three variables together explained 29.0% of the variance in self-efficacy for anticoagulant use [$F_{(3,148)} = 20.00$, $p < .001$] (see Table 4). Figure 1 presents the relationships among perceived benefits, perceived barriers, self-efficacy, and adherence to anticoagulation therapy with their respective standardized regression coefficients (β).

DISCUSSION

This is one of the few studies that compared differences in medication adherence between warfarin and NOACs among patients with AF. We found no better adherence to NOACs compared to warfarin. It is difficult to compare our findings with other studies because most studies included only patients treated with warfarin[27] and used different adherence measures.[27] Nevertheless, our study subjects reported relatively good adherence to anticoagulant therapy with an average score of 8.8(SD = 1.9) out of the possible range 7-28 in ARMS, compared to 32.3% of non-adherent to warfarin therapy in a cross-sectional survey of 288 patients with AF.[27]

Perceived barriers and self-efficacy were found to be significant predictors of medication adherence. Consistent with findings in previous studies of other populations,[28-29] patients with greater self-efficacy and perceived fewer barriers reported better adherence to anticoagulation therapy. Concerns about side effects, drug interactions, and forgetting to take anticoagulants were the top barriers to appropriate anticoagulant use[27]. Symptom severity, satisfaction, perceived benefits, and perceived barriers were significant predictors of self-efficacy for appropriate anticoagulant use. Patients with severer symptoms, lower satisfaction, perceived less benefit and perceived greater barriers reported lower self-efficacy for appropriate anticoagulant use. Addressing AF related symptoms, satisfaction with services, perceived benefits, and barriers of taking anticoagulants may help increase self-efficacy and lead to enhanced anticoagulation adherence.

Different from findings in previous studies,[25-26] we found that medication adherence was not significantly related to anticoagulation treatment knowledge. This may be because most of these studies were conducted in different countries and only focused on patients treated with warfarin. Although our subjects showed poor understating of anticoagulation treatment, they reported good adherence to anticoagulation treatment. This may be partially explained by the Taiwanese culture of obedience to a physician's orders. The treatment knowledge scores were low in both warfarin and NOACs treatment groups, indicating the need for strengthening anticoagulation treatment patient education. Special attention should be paid to treatment-related issues, such as drug-food interactions, INR values, the timing of taking anticoagulants, and how to prevent bleeding risks. These are areas that most of our subjects answered incorrectly.

This study had several limitations. First, the subjects were recruited from cardiology clinics of two teaching hospitals and may vary from those seen in other clinical settings. Thus, the results may not be generalizable outside this sample. Second, the cross-sectional nature of the study precluded an assessment of medication adherence change over time and did not permit us to determine causal relationships among the study variables. Third, a self-report questionnaire was used to measure medication adherence, which was subject to recall and social desirability biases. Finally, the influences of anticoagulation adherence on patients' treatment outcomes were not examined. Replication of the findings with longitudinal study design, objective measures of medication adherence, and clinical outcome measures are warranted. Nevertheless, the study results showed no better adherence to NOACs compared to warfarin and present evidence for the importance of perceived barriers and self-efficacy-on the adherence to anticoagulation therapy in patients with AF. Strategies to address perceived barriers and self-efficacy may be more likely to be translated to other population groups, as the influence of these factors on medication adherence has also been reported in studies with other populations[28-29].

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Table 1 Descriptive data of study variables (n = 151)

Variables	Mean	SD	Range
Age	72.0	8.6	55-93
Disease duration (month)	74.0	61.1	2-389
Symptom severity	6.8	5.4	0-22
Anticoagulation treatment knowledge	35.9	19.3	0-92
Warfarin (n = 53)	33.5	20.6	0-90.9
NOACs (n = 98)	38.4	19.1	0-91.7
Satisfaction with services and anticoagulation treatment	19.1	3.2	7-24
Perceived benefits of anticoagulation treatment	20.1	2.5	13-25
Perceived barriers to anticoagulation treatment	1.1	1.3	0-6
Self-efficacy for anticoagulant use	32.9	6.1	18-39
Anticoagulation adherence	8.8	1.9	7-15

SD, standard deviation

Table 2 Sample characteristics and comparisons of self-efficacy, and anticoagulation adherence among different characteristics of patients with atrial fibrillation (n = 151)

Variables	n	Self-efficacy			Adherence		
		$M \pm SD$	F / t	p	$M \pm SD$	F / t	p
Gender			-1.56	.121		1.50	.135
Female	56	31.9±6.8			9.13±2.05		
Male	95	33.5±5.6			8.65±1.74		
Educational level			.17	.915		.37	.779
Primary school and below	51	32.9±6.2			8.80±1.93		
Middle school	21	33.5±7.1			8.76±2.21		
High school	33	33.1±5.8			8.61±1.90		
College and above	46	32.4±5.7			9.04±1.65		
Marital status			1.18	.238		-.52	.604
Married	125	32.6±5.9			8.86±1.85		
Single, divorced or widowed	26	34.2±6.9			8.65±2.02		
Employment status			.54	.584		.73	.482
Full time, part-time	29	32.9±6.5			9.21±2.01		
Retired	107	33.1±5.7			8.74±1.82		
Unemployed	15	31.3±7.6			8.73±2.02		
CHA_2DS_2-VAS_C			.32	.731		-.82	.416
Low-middle risk	9				8.33±1.58		
High risk	142	32.9±6.1			8.86±1.89		

Table 2 Sample characteristics comparisons of self-efficacy, and anticoagulation adherence among different characteristics of patients with atrial fibrillation (*continued*)

Variables	*n*	Self-efficacy			Adherence		
		M ± *SD*	*F* / *t*	*p*	*M* ± *SD*	*F* / *t*	*p*
HAS-BLED			.92	.360		-0.86	.392
Low risk	60	33.4±6.0			8.67±1.83		
High risk	91	32.5±6.14			8.93±1.90		
Anticoagulants			1.37	.172		-0.99	.324
Warfarin	53	33.8±4.9			8.62±1.63		
NOACs	98	32.4±6.6			8.94±1.99		
Dosing frequency			.08	.922		0.45	.641
Once a day	135	32.9±6.0			8.81±1.92		
Twice a day	11	33. 5±6.9			9.27±1.56		
Once every two days	5	32.2±7.1			8.40±1.14		
Number of adverse reactions			1.18	.320		-2.15	.096
None	77	33.4±5.7			8.69±1.84		
One	51	33.0±6.3			8.76±1.74		
Two	14	30.9±6.7			8.69±1.88		
Three and more	9	30.4±7.0			10.33±2.45		

F: the value of one-way analysis of variables; *t*: the value of dependent t-test

Table 3 Person product-moment correlation coefficients among study variables (n = 151)

Variables	Age	Disease duration	Symptom severity	Knowledge	Satisfaction	Perceived benefits	Perceived barriers	Self-efficacy	Adherence
Age	1								
Disease duration	.109	1							
Symptom severity	-.212**	-.164*	1						
Knowledge	-.154	-.007	.024	1					
Satisfication	-.052	-.006	-.025	.259**	1				
Perceived benefits	-.003	.032	-.082	.125	.393***	1			
Perceived barriers	-.030	-.122	.293***	-.048	-.086	-.171*	1		
Self-efficacy	.053	.059	-.234**	.056	.290***	.312***	-.450***	1	
Adherence	-.017	.056	.097	-.054	-.050	-.096	.397***	-.560***	1

*p < .05; **p < .01; ***p < .001

Table 4 Results of stepwise regressions on self-efficacy and anticoagulation adherence in patients with atrial fibrillation ($N = 151$)

Model	Dependent variables	Independent variables	ß	*t*	R^2	Adjusted R^2	*F*	VIF
1					.29	.28	20.00***	
	Self-efficacy	Perceived barriers	-.41	-5.74***				1.03
		Satisfication	.19	2.50*				1.18
		Perceived benefits	.17	2.20*				1.21
2					.34	.33	38.11***	
	Adherence	Self-efficacy	-.48	-6.40***				1.25
		Perceived barriers	.18	2.42*				1.25

* $p < .05$; *** $p < .001$; Adjusted R^2 a modified version of R^2 for the number of predictors in a model.

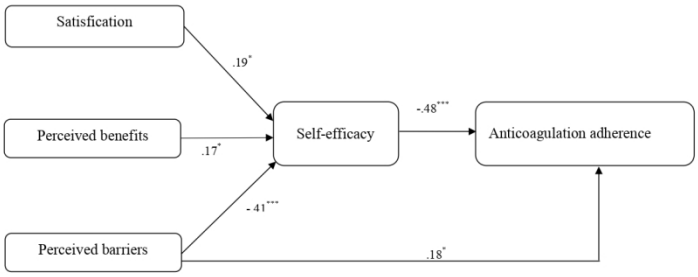

Figure 1. Relationships among symptom severity, satisfaction, perceived benefits, and perceived barriers in self-efficacy and adherence to anticoagulation therapy.

*$p < .05$; ***$p < .001$

1

Relationships among symptom severity, satisfaction, perceived benefits, and perceived barriers in self-efficacy and adherence to anticoagulation therapy

279x215mm (150 x 150 DPI)

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3

Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	#3	State specific objectives, including any prespecified hypotheses	7
Study design	#4	Present key elements of study design early in the paper	7
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	7
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	8-12
Bias	#9	Describe any efforts to address potential sources of bias	8-12
Study size	#10	Explain how the study size was arrived at	7,10
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7,12-13

Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	13
	#12b	Describe any methods used to examine subgroups and interactions	13
	#12c	Explain how missing data were addressed	n/a
	#12d	If applicable, describe analytical methods taking account of sampling strategy	n/a
	#12e	Describe any sensitivity analyses	n/a
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for exposed and unexposed groups if applicable.	14
	#13b	Give reasons for non-participation at each stage	n/a
	#13c	Consider use of a flow diagram	n/a
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	14
	#14b	Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	#15	Report numbers of outcome events or summary measures.	13-15

		Give information separately for exposed and unexposed groups if applicable.	
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15-16
	#16b	Report category boundaries when continuous variables were categorized	n/a
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a
Key results	#18	Summarise key results with reference to study objectives	14-16
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	18
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	17
Generalisability	#21	Discuss the generalisability (external validity) of the study results	18
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which	2

the present article is based

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Anticoagulation Adherence and Its Associated Factors in Patients with Atrial Fibrillation: A Cross-sectional Study

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ABSTRACT

Objective: To investigate anticoagulant adherence and its associated factors, including demographics, clinical variables, AF severity, knowledge, satisfaction with services, perceived barriers, perceived benefits, symptom severity, and self-efficacy in AF patients.

Design: This is a cross-sectional study.

Participants and setting: A convenient sample of AF patients were recruited from cardiology clinics of two teaching hospitals in Taiwan.

Measures: Data were collected using the study questionnaires, including the AF related symptom subscale of the AF Severity Scale, the Knowledge of Warfarin Anticoagulation Treatment Scale, the Satisfaction Scale about Service and Warfarin Treatment, the perceived benefits subscale of the Beliefs about Anticoagulation Survey, the Concerns about Anticoagulation Therapy Scale, The Self-efficacy for Appropriate Medication Use scale, and the short-form Adherence to Refills and Medications Scale

Results: A total of 151 AF patients participated in the study; 53 treated with warfarin and 98 treated with NOACs. The difference in adherence to warfarin (mean = 8.6; SD = 1.6) and NOACs (mean = 8.9; SD = 2.0) was statistically insignificant. Multiple linear regression analysis showed that perceived barriers (β =0.18, p = 0.017) and self-efficacy (β =-0.48, $p < 0.001$) were significant predictors of anticoagulation adherence. For every 1-unit increase in the perceived barriers, there will be a .18-unit increase in the adherence to anticoagulation therapy. For every 1-unit increase in the self-efficacy, there will be a .48-unit decrease in the adherence to anticoagulation therapy. Perceived barriers and self-efficacy collectively explained 34.0% of the variance in adherence to anticoagulation therapy [$F_{(2,149)} = 38.11$, $p < 0.001$].

Conclusion: We found no better adherence to NOACs compared to warfarin. Patients with greater self-efficacy and perceived fewer barriers showed better adherence to anticoagulation therapy.

Strengths and limitations of this study

- This is one of the few studies that compared medication adherence between patients taking warfarin and NOACs.
- The cross-sectional nature of the study precluded an assessment of medication adherence change over time and did not permit us to determine causal relationships among the study variables.
- A self-report questionnaire was used to measure medication adherence, which was subject to recall and social desirability biases.

INTRODUCTION

Atrial fibrillation (AF) is the most common type of arrhythmia.[1-3] AF associated hemodynamic changes and thrombosis increases risks of heart failure, stroke, and sudden death.[4] In Taiwan, patients with AF are 5-fold more likely to have a stroke than the general population, whereas one in five stroke patients has AF.[5] Moreover, 46.2% of patients with AF have an ischemic stroke within three years of diagnosis.[6] Anticoagulation treatment is the most important measure for preventing stroke in AF patients.[1-3] However, inadequate anticoagulation use is a global problem.[7-8] In Taiwan, while 90% of AF patients meet the criteria for anticoagulation treatment, only 28.28% use it.[9] Correlation studies on AF and stroke show that 185,570 cases of stroke occur each year in AF patients with no anti-platelet or oral anticoagulation treatment.[10]

Vitamin K antagonists (VKAs) such as warfarin and novel oral anticoagulants (NOACs) are the two main types of anticoagulants currently used for patients with AF.[1-3] While using warfarin, the international normalized ratio (INR) must be closely monitored as warfarin tends to interact with other drugs or foods, and it is difficult to maintain the percentage of time in the therapeutic range.[1,3] NOACs should be used if INR is difficult to maintain in the desired therapeutic range while using warfarin.[2] Lin et al.[11] found that it is difficult to choose an optimal dose of warfarin in Asian populations because of substantial variation in the individual response to warfarin and the narrow therapeutic range. Chiang et al.[1] also found that warfarin significantly increases the risk of intracranial hemorrhage and recommended NOACs as the preferred treatment in Asian AF populations. However, warfarin is still the most common and widely used anticoagulant for patients with AF in Taiwan.[11]

Good anticoagulant adherence ensures medication safety and effective prevention of stroke. Low adherence is associated with higher mortality and morbidity of cardiovascular diseases.[12] Knowing factors that affect anticoagulant adherence will help identify the populations at risk for non-adherence and allow for the development of appropriate measures to improve medication adherence. Previous studies showed that low adherence was related to 1) concerns about adverse drug reactions; [13] 2) inadequate knowledge of AF associated risks for stroke;[13] 3) unawareness of the importance of medication adherence;[13] 4) symptom severity;[13] 5) fear of regular blood tests;[13] 6) inability to attend frequent clinical visits;[14] 7) undergoing invasive treatments or procedures;[13] and 8) comorbidities.[14] However, most of these studies were conducted in Western Caucasian populations and in patients taking warfarin. Whether patients from different cultural backgrounds share similar factors deserve further investigations. Additionally, few studies have investigated the differences in medication adherence for taking NOACs versus warfarin in AF patients, and they have yielded inconsistent results. Yao et al.[15] conducted a retrospective cohort analysis to investigate adherence to oral anticoagulants in patients with AF, wherein the proportion of days covered (PDC) ≥ 80% indicated good adherence. The overall PDC was 47.5% for NOACs (dabigatran, rivaroxaban, and apixaban) and 38.7% for warfarin (p <0.001), indicating better adherence to NOACs than to warfarin. Choi et al.[16] analyzed 364 AF cases (warfarin: n = 204, dabigatran: n = 160) and assessed medication adherence with missed doses per month. The data showed that an average of 0.65 dabigatran tablets and an average of 0.63 warfarin tablets were missed per month (p = 0.916). The results from the above studies

show that medication adherence varies with each NOACs, which is not always superior to that of warfarin.

Therefore, the purposes of this study were to 1) compare the differences in adherence between patients treated with warfarin and NOACs; 2) explore factors influencing anticoagulant adherence in patients with AF, including demographics, clinical variables (disease duration, stroke risk assessment, bleeding risk assessment, anticoagulation therapies, and adverse reactions), AF severity, anticoagulation treatment knowledge, satisfaction with services, beliefs about anticoagulation treatment, and self-efficacy for appropriate medication; and 3) investigate the important predictors of anticoagulant adherence in AF patients.

METHODS

Study design

This is a cross-sectional study. Data were collected with self-reported questionnaires.

Participants and setting

AF patients who met the following eligibility criteria were recruited from cardiology outpatient clinics of two teaching hospitals in Taipei, Taiwan. The inclusion criteria were 1) ≥ 20 years of age; 2) fluent in Mandarin or Taiwanese; 3) diagnosed with AF; 4) treated with warfarin or NOACs for anticoagulation. The exclusion criteria were 1) diagnosed with psychological diseases; 2) diagnosed with uncontrolled hypertension; 3) diagnosed with the New York Heart Association (NYHA) grade VI heart failure; 4) implanted with a cardiac pacemaker; 5) had a cardiac surgery in the past three months; 6) hospitalized for AF in the past three months. The desired sample size was estimated by

using the G power (v3.1) software. In consideration of the number of potential predictors (n =17) in this study, a sample size of 146 would have 80% power to detect a medium effect size of $f^2 = 0.15$ with a 0.05 level of significance using a multiple linear regression fixed model. The use of NOACs or warfarin was treated as a single variable for the sample size calculation.

Patient and public involvement

The development of the research hypothesis was informed by working closely with patients with AF. However, patients and the public were not involved in the recruitment process and conduct of the study. An abstract of the study results will be mailed to the study participants.

Data collection

The investigator administered the study questionnaire after obtaining informed consent from each subject. The data collection took place in the waiting areas outside the outpatient clinics during the patients' visits to the clinics. For subjects who were unable to read the questionnaire due to vision or other problems, the investigator read each question to help them complete the questionnaire.

Variables and measurements

Socio-demographics were provided by the subjects, including age, sex, education level, marital status, and employment status. Data on clinical variables were extracted from the participants' medical records, including disease duration, CHA_2DS_2-VASc score for stroke risk assessment, HAS-BLED score for bleeding risk assessment, and anticoagulation therapies (name of the medication and dosing frequency). The subjects were also asked to report anticoagulant-related adverse reactions, including bleeding

events, hypersensitivity, gastrointestinal reactions, dizziness, headache, fainting, limb pain, and edema.

The AF related symptom subscale of the AF Severity Scale (AFSS)[17] was used to measure symptom severity. The 7-item subscale covers 7 AF related symptoms. For each item, the subjects indicated how often within the last month they experienced the symptom on a 6-point Likert scale (from 0_ I have not had this symptom in the past 4 weeks to 5_ a great deal). The total score of the 7 items represents the scale score, with a possible range of 0 to 35. Higher scores indicate higher levels of symptom severity. The scale has shown an acceptable level of reliability and validity in past studies involving AF patients.[18] This English scale was translated into Chinese through the following steps: Chinese translation, synthesis, back translation, expert committee review, and pilot testing[19]. Its Content Validity Index (CVI) was greater than 0.9, indicating good expert validity[19]. In this study, Cronbach's α value was 0.80. A high Cronbach's α coefficient (e.g., > 0. 8) indicates good internal consistency reliability[20].

The Chinese version of Knowledge of Warfarin Anticoagulation Treatment Scale[21] was used to measure warfarin treatment knowledge. The 11-item scale covers four areas of warfarin treatment knowledge: administration (e.g., dose, color, and route of administration), interaction with foods, interaction with other drugs, and side effects. There are five choices for each item, and only one of the choices is correct (scored 1). The total score of the 11 items represents the scale score, with a possible range of 0 to 11. Higher scores indicate higher levels of understanding of warfarin treatment. The scale was also modified to measure NOACs treatment knowledge. The item 1 (regarding anticoagulant dosage) in the original scale was revised into two items, one for dosage and

one for the name of the medication in the NOACs knowledge scale. The item 2 (regarding INR) in the original scale was deleted. The item 4 (regarding how to make up the missing dose) was revised into two items, one for missing a dose in taking NOACs once a day, and one for missing a dose in taking NOACs twice a day. The total score of the 13 items represents NOACs treatment knowledge. The potential scores range from 0 to 12, with higher scores indicating higher levels of understanding of NOACs treatment. To facilitate analysis and comparison, the score of each scale was converted to a scale of 0 to 100 (actual score/possible maximum score x 100). The knowledge of warfarin anticoagulation treatment scale has shown good psychometric properties in a previous study involving patients treated with anticoagulants.[21] In the current study, Kuder–Richardson Formula 20 (KR-20) was 0.68 for warfarin treatment knowledge and 0.63 for NOACs treatment knowledge. The KR-20 is a measure of internal consistency reliability for dichotomous scale items.

The Chinese version of Satisfaction Scale about Service and Warfarin Treatment (SSWT)[19] was used to measure subjects' satisfaction with services and anticoagulation treatment provided by the health care team. The original scale includes seven positive statements about the services and warfarin treatment. In the current study, the term warfarin was replaced with anticoagulants. The item 5 (regarding INR monitoring) in the original scale was deleted as it only applies to patients treated with warfarin. Therefore, there were only six items used in the current study. For each item, the subjects indicated their levels of agreement on a 5-point Likert scale (from 0_ strongly disagree to 4_ strongly agree). The total score of the 6 items represents the scale score, with a possible range of 0 to 24. Higher scores indicate higher levels of satisfaction about service and

warfarin treatment. The scale has shown good psychometric properties in a previous study involving patients treated with anticoagulants.[21] In this study, Cronbach's α was 0.87.

The perceived benefits subscale of the Beliefs about Anticoagulation Survey (BAAS)[22] was used to measure subjects' perceived benefits associated with taking anticoagulants. The subscale covers 5 potential benefits of taking anticoagulation, including lessening the risk of having a stroke, lowering the chance of being hospitalized, feeling healthier, improving quality of life, and worrying less about the disease. For each item, the subjects indicated their levels of agreement on a 5-point Likert scale (from 1_ strongly disagree to 5_ strongly agree). The potential scores range from 5 to 25, with higher scores indicating higher levels of perceived benefits associated with taking anticoagulation. The scale has shown reasonable psychometric properties in a previous study involving patients treated with anticoagulation.[22] The scale was translated into Chinese by our research team following the same steps as described prior. Its CVI was 1.0 and Cronbach's α was 0.84.

The Chinese version of the Concerns about Anticoagulation Therapy Scale[19] was used to measure perceived barriers regarding anticoagulation treatment. The scale lists ten potential concerns, including drug interactions, forgetting to take anticoagulants, side effects, hospital visits, diet interactions, activity restrictions, impact on work, not helpful, and difficulty of following instructions. The subjects were asked to indicate all concerns that apply to them. Each concern was scored 1. The potential scores range from 0 to 10, with higher scores indicating more concerns. The scale has shown acceptable

psychometric properties in a previous study involving patients treated with anticoagulants.[22]

The Self-efficacy for Appropriate Medication Use scale (SEAMS)[23] was used to measure self-efficacy for appropriate anticoagulant use. The 13-item scale covers two dimensions of self-efficacy: for taking medications under difficult circumstances and for taking medications under uncertain or changing circumstances. For each item, the subjects indicated their level of confidence about taking medications correctly under a specific circumstance on a three-point response scale (1 _ not confident, 2 _ somewhat confident, and 3 _ very confident). The potential scores range from 13 to 39, with high scores indicating higher levels of self-efficacy for appropriate anticoagulant use. The SEAMS has shown good psychometric properties for patients with coronary heart disease and other comorbid conditions.[23] The scale was translated into Chinese by our research team with a CVI 1.0 and Cronbach's α 0.93.

The short-form Adherence to Refills and Medications Scale (ARMS)[24] was used to measure adherence to anticoagulation treatment. There are seven items on the scale. Subjects were asked to indicate how often they actually miss taking their anticoagulants in each item on a 4-point Likert scale (1_ none of the time to 4_ all of the time). The total score of the 7 items represents the scale score, with a possible range of 7 to 28. A higher score indicates worse adherence to anticoagulation treatment. The scale has shown good psychometric properties for patients with coronary heart diseases (n = 435).[24] The scale correlated strongly both with the Morisky adherence scale[25] (Spearman's rho = -0.598, P < 0.01), and the cumulative medication gap[26] during the previous 6 months (Spearman's rho = 0.339, P < 0.01).[24] Patients with low ARMS scores were significantly more likely

to have controlled blood pressure (81.3% vs. 73.2%, $p < 0.05$). The scale also had good internal consistency (Cronbach's $\alpha = 0.814$) and test-retest reliability (Spearman's rho = 0.693, $p < 0.001$).[24] In this study, Cronbach's α was 0.70.

Statistical methods

Data were analyzed using the Statistical Package for Social Sciences 20.0 (SPSS, Inc., Chicago, IL, USA). Descriptive analyses were used to describe study variables. Independent t-tests and one-way analysis of variance (ANOVA) were performed to analyze the differences in anticoagulation adherence scores among different categorical study variables. Pearson product-moment correlations were performed to analyze the correlations among the continuous variables. Due to a large number of potential explanatory variables, stepwise linear regression was chosen for statistical model selection. All study variables were entered as dependent variables into stepwise linear regression models to find significant influencing factors of anticoagulant adherence. These included demographics (age, gender, educational level, marital status, and employment status), clinical variables (disease duration, CHA_2DS_2-VASc score, HAS-BLED score, anticoagulants, dosing frequency, and adverse reactions), symptom severity, anticoagulation treatment knowledge, satisfaction with services, perceived benefits, perceived barriers, and self-efficacy for appropriate anticoagulant use. Categorical variables were dummy coded prior to analysis. The probability-of-F-to-enter $\leqq 0.05$ was used as the criterion for entering a variable into the model; the probability-of-F-to-remove $\geqq 0.10$ was used as the criterion for removing a variable from the model. Standardized residual plots and collinearity statistics of Variance Inflation Factor were

used to examine the normality and independent assumptions of the regression. There was no violation in both assumptions.

RESULTS

One of the researchers approached 156 eligible patients; 6 of them declined to participate. This left 151 eligible patients to take part in the study. All of them completed the study questionnaires and their data were included in the final analysis. Every subject filled out all the questionnaires except the knowledge scale. Fifty-three (35.1 %) subjects receiving warfarin answered The Knowledge of Warfarin Anticoagulation Treatment Scale; 98 (64.9%) subjects receiving NOACs filled out The Knowledge of NOACs Treatment Scale.

These subjects were recruited from clinics associated with two hospitals, with 93 and 58 subjects from each hospital, respectively. There was no significant difference in demographics or values of study variables between subjects recruited from the different hospitals (data not shown). The average age of the subjects was 72.0 (SD = 8.6) (Table 1). There were 95 males and 56 females in the study. The majority of the subjects were married (n = 125) and retired (n = 107) (Table 2). Subjects were diagnosed with an AF for 74.0 months (SD = 61.1) on average (Table 1). Of the 151 subjects, 98 received NOACs and 53 received warfarin. Most subjects (n = 77) did not experience anticoagulation-related side effects (Table 2).

The subjects reported an average score of 8.8 (SD = 1.9) on ARMS. The average score on the symptom subscale of the AFSS was 6.8 (SD = 5.4). Shortness of breath during physical activity was the most common symptom experienced by these subjects. The subjects had a mean score of 35.9 (SD = 19.3) on the anticoagulation treatment

knowledge scale. Most subjects miss more than half of the treatment-related questions, with most mistakes made in drug-food interactions, INR values, the timing of taking anticoagulants, and how to prevent bleeding risks. They reported a mean score of 19.1 (SD = 3.2) on the SSWT. Their average score on the perceived benefits subscale of the BAAS was 20.1 (SD = 2.5). They reported an average score of 1.1 (SD = 1.3) on the concerns about anticoagulation therapy scale. The top three concerns indicated by the subjects were 1) side effects (n = 53); 2) drug interactions (n = 44); and 3) forgetting to take anticoagulants (n = 33). The subjects had a mean score of 32.9 (SD = 6.1) on the SEAMS.

The difference in medication adherence between warfarin (mean = 8.6; SD = 1.6) and NOACs (mean = 8.9; SD = 2.0) was statistically insignificant. There was also no significant difference both in anticoagulant adherence and self-efficacy among subjects with different demographics and clinical variables (CHA_2DS_2-VASc score, HAS-BLED score, anticoagulants, dosing frequency, and adverse reactions) (Table 2). Results of Pearson correlation analyses showed that anticoagulation adherence was significantly associated with perceived barriers to ($r = 0.40$, $p < 0.001$) and self-efficacy for appropriate anticoagulant use ($r = -0.56$, $p < 0.001$). Other study variables (age, disease duration, symptom severity, knowledge, satisfaction, and perceived benefits) were not significantly associated with anticoagulation adherence (Table 3). The self-efficacy for anticoagulant use was significantly associated with symptom severity ($r = -0.23$, $p = 0.02$), satisfaction ($r = 0.29$, $p < 0.001$), perceived benefits ($r = 0.31$, $p < 0.001$), and perceived barriers ($r = -0.45$, $p < 0.001$). Age, disease duration, and knowledge were not related to self-efficacy.

Results of stepwise linear regression analyses showed that perceived barriers (ß = 0.18, $p = 0.017$) and self-efficacy (ß = -0.48, $p < 0.001$) were significant predictors of adherence to anticoagulation therapy. For every 1-unit increase in the perceived barriers score, there will be a 0.18-unit increase in the adherence to anticoagulation therapy score. In addition, for every 1-unit increase in the self-efficacy score, there will be a 0.48-unit decrease in the adherence to anticoagulation therapy score. Perceived barriers and self-efficacy collectively explained 34.0% of the variance in adherence to anticoagulation therapy [$F_{(2,149)} = 38.1$, $p < 0.001$] (see Table 4). Other variables were excluded from the model. As for self-efficacy, the satisfaction with services, perceived benefits, and perceived barriers were the significant predictors. These three variables together explained 29.0% of the variance in self-efficacy for anticoagulant use [$F_{(3,148)} = 20.0$, $p < 0.001$] (see Table 4). Figure 1 presents the relationships among perceived benefits, perceived barriers, self-efficacy, and adherence to anticoagulation therapy with their respective standardized regression coefficients (β).

DISCUSSION

This is one of the few studies that compared differences in medication adherence between warfarin and NOACs among patients with AF. We found no better adherence to NOACs compared to warfarin. It is difficult to compare our findings with other studies because most studies included only patients treated with warfarin[27] and used different adherence measures.[27] Nevertheless, our study subjects reported relatively good adherence to anticoagulant therapy with an average score of 8.8 (SD = 1.9) out of the possible range 7-28 in ARMS, compared to 32.3% of non-adherent to warfarin therapy in a cross-sectional survey of 288 patients with AF.[27]

Perceived barriers and self-efficacy were found to be significant predictors of medication adherence. Consistent with findings in previous studies of other populations,[28-29] patients with greater self-efficacy and perceived fewer barriers reported better adherence to anticoagulation therapy. When considering the pharmacokinetics of these anticoagulants, the effect of the adherence on clinical outcomes may be different. It may be better to show their results separately. Therefore, we further analyzed warfarin and NOACs users separately and found that the independent predictors of perceived barriers and self-efficacy for adherence were persistent. Concerns about side effects, drug interactions, and forgetting to take anticoagulants were the top barriers to appropriate anticoagulant use[27]. Symptom severity, satisfaction, perceived benefits, and perceived barriers were significant predictors of self-efficacy for appropriate anticoagulant use. Patients with severer symptoms, lower satisfaction, perceived less benefit and perceived greater barriers reported lower self-efficacy for appropriate anticoagulant use. Addressing AF related symptoms, satisfaction with services, perceived benefits, and barriers of taking anticoagulants may help increase self-efficacy and lead to enhanced anticoagulation adherence.

Different from findings in previous studies,[25-26] we found that medication adherence was not significantly related to anticoagulation treatment knowledge. This may be because most of these studies were conducted in different countries and only focused on patients treated with warfarin. Although our subjects showed poor understating of anticoagulation treatment, they reported good adherence to anticoagulation treatment. This may be partially explained by the Taiwanese culture of obedience to a physician's orders. The treatment knowledge scores were low in both warfarin and NOACs treatment

groups, indicating the need for strengthening anticoagulation treatment patient education. Special attention should be paid to treatment-related issues, such as drug-food interactions, INR values, the timing of taking anticoagulants, and how to prevent bleeding risks. These are areas that most of our subjects answered incorrectly.

This study had several limitations. First, the subjects were recruited from cardiology clinics of two teaching hospitals and may vary from those seen in other clinical settings. Thus, the results may not be generalizable outside this sample. Second, the cross-sectional nature of the study precluded an assessment of medication adherence change over time and did not permit us to determine causal relationships among the study variables. Third, a self-report questionnaire was used to measure medication adherence, which was subject to recall and social desirability biases. Finally, the influences of anticoagulation adherence on patients' treatment outcomes were not examined. Replication of the findings with longitudinal study design, objective measures of medication adherence, and clinical outcome measures are warranted. Nevertheless, the study results showed no better adherence to NOACs compared to warfarin and present evidence for the importance of perceived barriers and self-efficacy-on the adherence to anticoagulation therapy in patients with AF. Strategies to address perceived barriers and self-efficacy may be more likely to be translated to other population groups, as the influence of these factors on medication adherence has also been reported in studies with other populations[28-29].

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Table 1 Descriptive data of study variables (n = 151)

Variables	Mean	SD	Range
Age	72.0	8.6	55-93
Disease duration (month)	74.0	61.1	2-389
Symptom severity	6.8	5.4	0-22
Anticoagulation treatment knowledge	35.9	19.3	0-92
Warfarin (n = 53)	33.5	20.6	0-90.9
NOACs (n = 98)	38.4	19.1	0-91.7
Satisfaction with services and anticoagulation treatment	19.1	3.2	7-24
Perceived benefits of anticoagulation treatment	20.1	2.5	13-25
Perceived barriers to anticoagulation treatment	1.1	1.3	0-6
Self-efficacy for anticoagulant use	32.9	6.1	18-39
Anticoagulation adherence	8.8	1.9	7-15

SD, standard deviation

Table 2 Sample characteristics and comparisons of self-efficacy, and anticoagulation adherence among different characteristics of patients with atrial fibrillation (n = 151)

Variables	n	Self-efficacy			Adherence		
		$M \pm SD$	F / t	p	$M \pm SD$	F / t	p
Gender			- 1.56	0.121		1.50	0.135
Female	56	31.9 ± 6.8			9.1 ± 2.1		
Male	95	33.5 ± 5.6			8.7 ± 1.7		
Educational level			0.17	0.915		0.37	0.779
Primary school and below	51	32.9 ± 6.2			8.8 ± 1.9		
Middle school	21	33.5 ± 7.1			8.8 ± 2.2		
High school	33	33.1 ± 5.8			8.6 ± 1.9		
College and above	46	32.4 ± 5.7			9.0 ± 1.7		
Marital status			1.18	0.238		-0.52	0.604
Married	125	32.6 ± 5.9			8.9 ±1.9		
Single, divorced or widowed	26	34.2 ± 6.9			8.7 ± 2.0		
Employment status			0.54	0.584		0.73	0.482
Full time, part-time	29	32.9 ± 6.5			9.2 ± 2.0		
Retired	107	33.1 ± 5.7			8.7 ± 1.8		
Unemployed	15	31.3 ± 7.6			8.7 ± 2.0		
CHA_2DS_2-VAS_C			0.18	0.86		-0.82	0.416
Low-middle risk	9	33.2 ± 6.1			8.3 ± 1.6		
High risk	142	32.9 ± 6.1			8.9 ± 1.9		

Table 2 Sample characteristics comparisons of self-efficacy, and anticoagulation adherence among different characteristics of patients with atrial fibrillation (*continued*)

Variables	*n*	Self-efficacy			Adherence		
		M ± *SD*	*F* / *t*	*p*	*M* ± *SD*	*F* / *t*	*p*
HAS-BLED			0.92	0.360		-0.86	0.392
Low risk	60	33.4 ± 6.0			8.7 ± 1.8		
High risk	91	32.5 ± 6.14			8.9 ± 1.9		
Anticoagulants			1.37	.172		-0.99	0.324
Warfarin	53	33.8 ± 4.9			8.6 ± 1.6		
NOACs	98	32.4 ± 6.6			8.9 ± 2.0		
Dosing frequency			0.08	0.922		0.45	0.641
Once a day	135	32.9 ± 6.0			8.8 ± 1.9		
Twice a day	11	33.5 ± 6.9			9.3 ± 1.6		
Once every two days	5	32.2 ± 7.1			8.4 ± 1.4		
Number of adverse reactions			1.18	0.320		- 2.15	0.096
None	77	33.4 ± 5.7			8.7 ± 1.8		
One	51	33.0 ± 6.3			8.8 ± 1.7		
Two	14	30.9 ± 6.7			8.7 ± 1.9		
Three and more	9	30.4 ± 7.0			10.3 ± 2.5		

F: the value of one-way analysis of variables; *t*: the value of dependent t-test

Table 3 Person product-moment correlation coefficients among study variables (n = 151)

Variables	Age	Disease duration	Symptom severity	Knowledge	Satisfaction	Perceived benefits	Perceived barriers	Self-efficacy	Adherence
Age	1								
Disease duration	0.11	1							
Symptom severity	-0.21**	-0.16*	1						
Knowledge	-0.15	-0.01	0.02	1					
Satisfication	-0.05	-0.01	-0.03	0.26**	1				
Perceived benefits	-0.00	0.03	-0.08	0.13	0.39***	1			
Perceived barriers	-0.03	-0.12	0.29***	-0.05	-0.09	-.17*	1		
Self-efficacy	0.05	0.06	-0.23**	0.06	0.29***	0.31***	-0.45***	1	
Adherence	-0.02	0.06	0.09	-0.05	-0.05	-0.10	0 .40***	-0.56***	1

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

Table 4 Results of stepwise regressions on self-efficacy and anticoagulation adherence in patients with atrial fibrillation ($N = 151$)

Model	Dependent variables	Independent variables	ß	*t*	R^2	Adjusted R^2	*F*	VIF
1					0.29	0.28	20.00***	
	Self-efficacy	Perceived barriers	-0.41	-5.74***				1.03
		Satisfication	0.19	2.50*				1.18
		Perceived benefits	0.17	2.20*				1.21
2					0.34	0.33	38.11***	
	Adherence	Self-efficacy	-0.48	-6.40***				1.25
		Perceived barriers	0.18	2.42*				1.25

* $p < 0.05$; *** $p < 0.001$; Adjusted R^2 a modified version of R^2 for the number of predictors in a model.

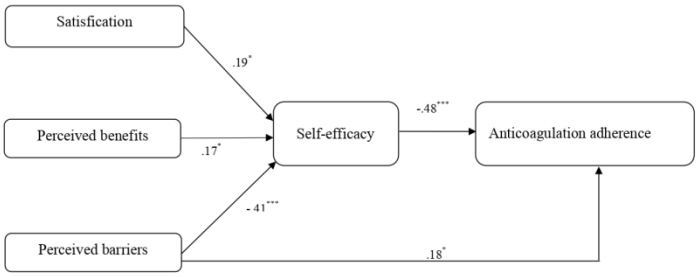

Figure 1. Relationships among symptom severity, satisfaction, perceived benefits, and perceived barriers in self-efficacy and adherence to anticoagulation therapy.

*$p < .05$; ***$p < .001$

1

Relationships among symptom severity, satisfaction, perceived benefits, and perceived barriers in self-efficacy and adherence to anticoagulation therapy

279x215mm (150 x 150 DPI)

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3

Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	#3	State specific objectives, including any prespecified hypotheses	7
Study design	#4	Present key elements of study design early in the paper	7
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	7
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	8-12
Bias	#9	Describe any efforts to address potential sources of bias	8-12
Study size	#10	Explain how the study size was arrived at	7,10
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7,12-13

Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	13
	#12b	Describe any methods used to examine subgroups and interactions	13
	#12c	Explain how missing data were addressed	n/a
	#12d	If applicable, describe analytical methods taking account of sampling strategy	n/a
	#12e	Describe any sensitivity analyses	n/a
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for exposed and unexposed groups if applicable.	14
	#13b	Give reasons for non-participation at each stage	n/a
	#13c	Consider use of a flow diagram	n/a
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	14
	#14b	Indicate number of participants with missing data for each variable of interest	n/a
Outcome data	#15	Report numbers of outcome events or summary measures.	13-15

		Give information separately for exposed and unexposed groups if applicable.	
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15-16
	#16b	Report category boundaries when continuous variables were categorized	n/a
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	n/a
Key results	#18	Summarise key results with reference to study objectives	14-16
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	18
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	17
Generalisability	#21	Discuss the generalisability (external validity) of the study results	18
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which	2

the present article is based