Patient Preference and Adherence

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ORIGINAL RESEARCH

Warfarin Adherence Among Patients with Atrial Fibrillation in Rural Area of Dongyang, China: A Questionnaire-Based Study

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Introduction: Adherence to warfarin is associated with improved outcome in patients with atrial fibrillation (AF), but the adherence status of patients in rural areas of China is not known.

Methods: A questionnaire-based study evaluating warfarin adherence of rural residents with AF was carried out in Dongyang, China. Potentially eligible patients were screened and contacted by telephone, and their demographic characteristics were collected. Illness perception was assessed using the Brief Illness Perception Questionnaire (BIPQ), and warfarin adherence was assessed using a Chinese-version adherence scale. Univariate and multivariate analyses were conducted to identify factors associated with unsatisfactory adherence.

Results: A total of 201 patients (male, n=99; mean age, 70.3±8.12 years) were included, among whom 95 (47.3%) patients showed good adherence and 63 (31.3%) poor adherence. Number of co-dispensed drugs (multivariate analysis: odds ratio [OR]=3.64, 95% confidence interval [CI] 1.35–9.81, p=0.011) and BIPQ score (OR=1.25, 95% CI 1.17–1.33, p<0.001) were identified as factors associated with good adherence.

Conclusion: Medical adherence to warfarin needs to improve in rural patients with AF. Efforts that can reduce the number of co-dispensed drugs and increase illness perception may improve warfarin adherence. This study may benefit future management of warfarin administration to rural patients with AF.

Keywords: adherence, warfarin, illness perception, polypharmacy, rural

Introduction

Atrial fibrillation (AF) is the most common chronic arrhythmia, affecting more than 33 million people worldwide, and is associated with a more than 5-fold increased risk of stroke.[1] Based on the Chinese Ischemic Stroke Subclassification, one-third of ischemic strokes are cardiogenic, the primary cause of which is AF.[2] Oral anticoagulants (OACs) represent the primary strategy for the treatment of anticoagulation in AF patients.[3] Warfarin can reduce the risk of stroke by two-thirds compared with no antithrombotic therapy, and is used to be the gold-standard therapy for most AF patients.[4] Although novel OACs have offered some advantages including better adherence and the use of these drugs is increasing worldwide, warfarin is still administered to more than half of all outpatients in China because of its low price.[5] The narrow therapeutic index of warfarin and its association with an increased risk of bleeding necessitate frequent monitoring and dose adjustments according to the International Normalized Ratio (INR) to achieve the optimal dosage, which may be inconvenient for patients and requires them to attend healthcare facilities on a regular basis.[6,7]

Medication adherence is an important element in the success of any therapeutic plan.[8] Poor adherence is a main contributor to out-of-range INR, which influences patients either by subtherapeutic anticoagulation that increases the risk of stroke and thromboembolic events or over-anticoagulation that increases the risk of bleeding.[9–11] Previous reports

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have suggested that the quality of care and, subsequently, the outcomes of patients admitted for cardiovascular diseases including AF varies between urban and rural hospitals.[12] Canadian research showed that patients in rural settings were slightly more likely to fill a prescription for warfarin, probably because of the low price, but experienced stroke and major bleeding rates similar to those of their urban counterparts.[4] It is reported that residential location and educational attainment could influence warfarin adherence[13,14] Given the attention expected to be directed toward warfarin adherence in rural residents with AF, there are few data on this issue. Thus, we carried out a questionnaire-based study of adherence status among rural residents with AF in an area of Dongyang, China.

Materials and Methods

Ethical Approval and Informed Consent

This study was approved by Ethics Committee of Affiliated Dongyang Hospital of Wenzhou Medical University (2018-YX-073) and complied with the Declaration of Helsinki. The verbal form of informed consent to be obtained was also approved by Ethics Committee of Affiliated Dongyang Hospital of Wenzhou Medical University for the current study and was in accordance with local regulation. The researchers were approved to screen the medical records for potentially eligible patients. Informed consent was obtained verbally because the questionnaire was filled out via telephone and written informed consent was not obtainable. Researches explained the study to participants first and documented in the questionnaire if verbal informed consent was obtained.

Study Design and Patients

The study was designed as a questionnaire-based study. Patients who met the following criteria were invited to fill out the questionnaire: (1) has AF confirmed by electrocardiogram; (2) on anticoagulation therapy using warfarin for at least 6 months; (3) resides in the rural area of Dongyang, China. Patients who were at the end stage of any life-threatening disease or suffering from mental illness, cognitive despair, or communication difficulties were excluded.

Patients were recruited during Aug 2020 and Jun 2021. Researcher had access to information that could identify individual participants during and after data collection.

Questionnaire

The anonymous questionnaire contained 25 questions divided into three sections: (1) patient demographics; (2) illness perception; and (3) medical adherence.

Patient demographics included age, sex, history of drinking alcohol and smoking cigarettes, education level, employee and economic status, comorbidities, and number of co-dispensed drugs.

Illness perception was assessed using the Brief Illness Perception Questionnaire (BIPQ), which was designed to evaluate patients' cognitive and emotional representation of illness.[15] A higher BIPQ score indicates that the patient views the illness as more threatening. The questionnaire includes nine items. Items 1–8 reflect eight dimensions of ill perception: consequences, timeline, personal control, treatment control, identity, concerns, understanding, and emotional response. Each item is scored from 0 to 10 according to the degree of compliance. The overall score is calculated by adding up the score of items, with reversed scores for items 3, 4, and 7 applied. Item 9 of the BIPQ is an open question and was disregarded for the purposes of this study.

Medical adherence to warfarin was assessed using a Chinese-version scale similar to the eight-item Morisky Medication Adherence Scale (MMAS-8). The scale has proved to be suitable for evaluating adherence in patients receiving warfarin therapy.[16] Cronbach's alpha for internal consistency of the Chinese-version adherence scale was 0.81, the kappa coefficient for interobserver consistency was 0.92, and the test-retest reliability coefficient was 0.95. The scale consisted of eight items, each answered by yes (score 0 except item 5) or no (score 1 except item 5). A total score of 8 was defined as good adherence, a score of 6–7 was defined as moderate adherence, and a score lower than 6 was defined as poor adherence.

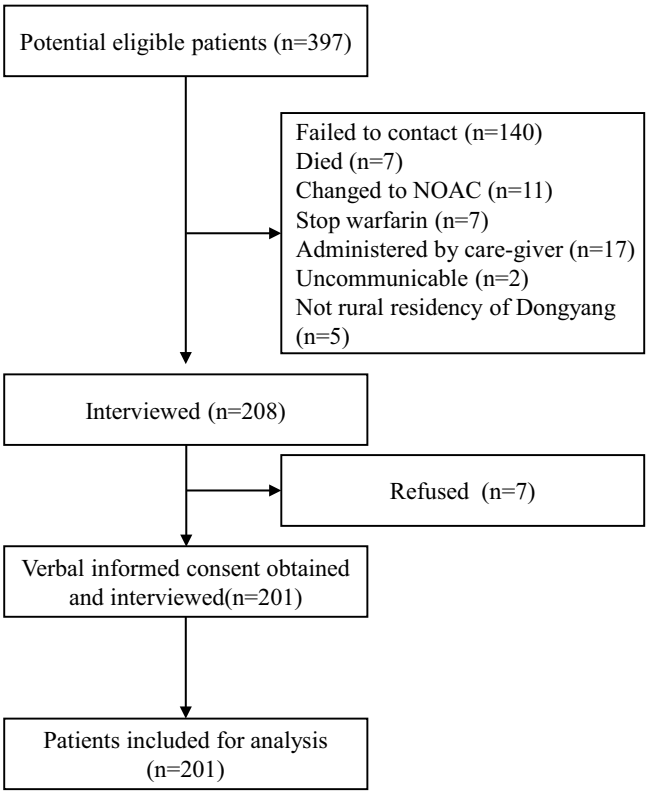

Figure 1 Flowchart of patient inclusion.

Data Collection

Staff contacted patients by telephone and explained the aim and details of the questionnaire. After verbal informed consent was obtained, staff checked whether the patient met inclusion criteria and did not meet exclusion criteria. If eligible, the patient was asked by staff to answer each item one by one and fill out the questionnaire. The staff would explained the items if patients were not understand, and there is no time limitation for the telephone interview to get the real idea.

Statistical Analysis

Categorical results were expressed as numbers and portions. Continuous results were expressed as means and standard deviations. To explore factors associated with adherence level, both moderate and poor adherence were classified as unsatisfactory adherence, and patients with co-dispensed drugs were divided into groups using ≤3 and >3 drugs. Univariate analysis was carried out by applying a chi-square test for portions and *t*-test for means. Multivariate logistic regression was performed to identify independent factors associated with good adherence. Factors with P<0.2 in univariate analysis were put into the multivariate logistic regression model. Minitab 14 software (Minitab, State College, PA, USA) was used for statistical analyses. A *p*-value of <0.05 was considered statistically significant.

Results

Demographics of Study Participants

Of the total 397 potentially eligible patients identified and contacted by telephone, 201 completed the questionnaire (Figure 1). The demographic characteristics of these patients are shown in Table 1.

Table 1 Demographic Characteristics of Included Patients

Patient Characteristics	Total (n=201)	Adherence			*p*
		Good (n=95)	Moderate (n=43)	Poor (n=63)	
Male	99(49.3)	47(49.5)	26(60.5)	26(41.3)	0.953
Age	70.3±8.74	71.3±8.18	69±9.15	78.5±9.24	0.122
Smoking	15(7.5)	5(5.3)	2(4.7)	8(12.7)	0.295
Drinking	37(18.4)	15(15.8)	10(23.3)	12(19)	0.361
Low education	138(68.7)	72(75.8)	27(62.8)	39(61.9)	0.036
Physical labor	187(93.0)	88(92.6)	39(90.7)	60(95.2)	0.832
Co-incident disease					
Hypertension	96(47.8)	47(49.5)	18(41.9)	31(49.2)	0.645
Hyperlipidemia	23(11.4)	10(10.5)	5(11.6)	8(12.7)	0.698
Diabetes mellitus	29(14.4)	12(12.6)	6(14)	11(17.5)	0.49
Co-used drugs					
≤1	42(20.9)	21(22.1)	7(16.3)	14(22.2)	
2–3	95(47.3)	57(60)	16(37.2)	22(34.9)	
4–5	51(25.4)	15(15.8)	17(39.5)	19(30.2)	<0.001*
≥6	13(6.5)	2(2.1)	3(7)	8(12.7)	
Monthly income					
<2000 CNY or unstable income	185(92.0)	89(93.7)	37(86.0)	59(93.7)	-
>2000 CNY	16(8.0)	6(6.3)	6(14.0)	4(6.3)	
BIPQ score	41.1±9.8	47.8±8.4	32.6±6.0	36.8±6.4	<0.001

Notes: Data are presented as number (percentage) or mean standard±deviation. Adherence was defined as good (adherence score of 8), moderate (adherence score of 6–7), and poor (adherence score below 6). *p*-value was obtained by comparing patients with satisfactory (good) and unsatisfactory (moderate and poor) adherence. *Acquired by comparing patients with no more than 3 co-dispensed drugs versus more than 3 co-dispensed drugs.

Illness Perception and Warfarin Adherence

The mean BIPQ score was 40.1, and the scores for each item are shown in Table 2. As shown in Table 1, 95 patients had good adherence, 43 had moderate adherence, and 63 had poor adherence.

Factors Associated with Warfarin Adherence

Results of univariate factor analysis showed that education level, number of co-dispensed drugs, and BIPQ score may be factors associated with unsatisfactory adherence. As shown in Table 3, multivariate factor analysis showed that age, illness perception, and number of co-dispensed drugs are independent factors that are associated with good adherence to warfarin.

Table 2 Illness Perception Assessed by BIPQ Scale

Item	Total (n=201)		Good (n=95)		Moderate (n=43)		Poor (n=63)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Consequences	4.87	3.10	6.40	2.55	2.98	2.56	3.84	3.08
Timeline	9.18	1.26	9.80	0.69	8.28	1.03	8.86	1.55
Personal control	3.20	1.58	3.48	1.38	2.98	1.54	2.92	1.83
Treatment control	2.90	1.51	3.21	1.56	2.51	1.24	2.70	1.53
Identity	5.11	2.60	6.39	2.56	2.84	1.46	4.73	2.04
Concerns	7.21	2.00	6.45	2.20	7.58	1.42	8.10	1.54
Understanding	4.64	2.69	6.57	2.16	3.40	1.87	2.57	1.66
Emotional response	4.00	2.34	5.48	2.24	2.00	1.15	3.11	1.47

Table 3 Multivariable Logistic Analysis Showing Factors That are Associated with Good Warfarin Adherence

Variable	OR	95% CI	*p*
Co-dispensed drug ≤3	3.44	1.38–8.55	0.008
BIPQ score	1.25	1.17–1.33	<0.001
Age	1.07	1.02–1.12	0.003
Low educated	1.25	0.53–2.94	0.605

Discussion

To the best of our knowledge, this is the first study to evaluate the adherence to warfarin among patients in rural areas. Moreover, we established that the number of co-dispensed drugs and BIPQ score were associated with warfarin adherence. These findings should further benefit the management of rural patients taking warfarin.

The enrolled patients exhibited typical demographic characteristics of rural residency. Most of the patients were older and beyond retirement age, were mainly of low educational status, and had low or unstable income.[17] Moreover, most patients were physical workers, mainly farmers. Thus, the results of the study would be generally representative of rural AF patients. It is worth mentioning that a large portion of potentially eligible patients could not be contacted. Major reasons for this were that older rural patients were not familiar with mobile phones and moreover, as telecom fraud is increasing in China, people are advised not to answer unfamiliar telephone numbers.[18] Therefore, further face-to-face assessment of adherence is warranted.

The overall adherence rate to warfarin in rural patients with AF was less than 50%, and more than 40% of patients had poor adherence. A meta-analysis showed that non-adherence to oral coagulants among AF patients approached 30%.[13] Although the assessment of adherence among different studies varied somewhat, the adherence status to warfarin in the study population generally was unsatisfactory. Numerous studies have concluded that poor adherence to warfarin is associated with poor outcome in AF patients.[10,11] Our findings draw special attention to the adherence status of warfarin in rural patients. Improvement in adherence to warfarin therapy is associated with better outcome, and the methods employed appear to be cost-effective.[19] Thus, the medical insurance system should be required to pay not only for the drugs but also the costs of the medical service that improves adherence to the drug regimen, and rural patients required special attention. It is reported that undertreatment of AF was among rural patients, and warfarin use and clinical event rates did not differ between rural and urban patients in a universal access publicly funded healthcare system.[20,21] Moreover, considering the efficacy, safety and adherence of NOACs, the medical insurance system should try best to cover the cost of these drugs.[22]

The number of co-dispensed drugs is an independent factor associated with warfarin adherence in rural patients with AF. However, older patients with AF often have complications such as hypertension and diabetes.[17] Nearly half of the patients in this study have hypertension and more than 30% are taking more than three drugs. A previous study also confirmed that polypharmacy is common among patients taking warfarin.[23] There are several ways to face the challenge of the polypharmacy issue. First, reducing the number of co-dispensed drugs and improving safety via medication reconciliation is potentially important in patients with chronic disease.[24] Second, thorough education regarding how to take these medications would be helpful.[24] Third, the results of this study also indicated that development of a compound preparation, which could reduce the number of co-dispensed drugs, would be a promising approach.

The other significant factor found in this study was the BIPQ score. Illness perception was reported to be a factor that influenced adherence in patients with chronic diseases such as hypertension and asthma.[25,26] Patients who experience stronger emotional reactions to their illness are more inclined to have greater concerns about their medication.[27] A recent study found that illness perception was associated with oral anticoagulants in AF patients.[28] Therefore, healthcare providers should identify and address patients' negative beliefs to improve adherence.[29]

Other factors may be associated with warfarin adherence, including age and lower education level. These factors are also identified in other patient populations.[14,30,31] It is interesting that increased age was associated with poor adherence

while young age is reported to be associated with poor adherence in some populations.[28] It is noteworthy that the education level among rural residents is generally lower in comparison with urban counterparts. Thus, rural patients carry an involuntary risk of low adherence. As these two factors are non-modifiable, physicians should be aware of adherence in relation to these factors when prescribing warfarin. It is reported that many patients failed anticoagulant usage due to doctor's incomplete inform of AF-related risk of stroke.[32] Appropriate education about warfarin therapy may also be helpful for rural patients.[33,34] Furthermore, it has been reported that doctor-patient relationship is fundamental in drug adherence, because when patients do not have the opportunity or if they do not trust the physician, they may not discuss their concerns about treatment.[35] Another important issue, which has been exasperated by COVID-19 outbreak, is represented by patients' embarrassment in revealing their financial situation, which may not allow them to afford high-cost medicine and, in certain situations, even the cheaper as they place other family members' needs before them.[35]

This study has some limitations. The questionnaire was filled out by telephone; thus, information bias may exist. The adherence status of patients who were not familiar with using a mobile phone had to be disregarded. The sample size of this study is small and selection bias may also exist. There may be confounding factors not be addressed. A direct comparison of adherence to warfarin between rural patients and urban patients was not obtained but is urgently required. Outcomes of patients with different adherence status should be evaluated further in future studies.

Conclusions

We found that adherence to warfarin in rural patients with AF was not satisfactory. As adherence may affect the outcome of warfarin treatment, efforts should be made to elevate the adherence level in patients. Moreover, the number of co-dispensed drugs, BIPQ score and age are associated with warfarin adherence. Any measure that can reduce the number of co-dispensed drugs or increase the BIPQ score would benefit the adherence to warfarin of rural AF patients.

Data Sharing Statement

Data are contained within the paper.

Institutional Review Board Statement

This work was approved by Ethical Committee of Affiliated Dongyang Hospital of Wenzhou Medical University (2018-YX-073).

Informed Consent Statement

Verbal informed consent was obtained from all subjects involved in the study.

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Disclosure

The authors declare no conflict of interest.

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