

# Warfarin Adherence and Its Associated Factors among Patients with Atrial Fibrillation\*

Varaporn Panichpathom<sup>1</sup>, Aurawamon Sriyuktasuth, RN, DSN<sup>1</sup>,

Doungrut Wattanakitkriear, RN, DNS<sup>1</sup>, Chatkanok Dumavibhat, MD<sup>2</sup>

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## Abstract

**Purpose:** To identify level of warfarin adherence and investigate factors associated with warfarin adherence in Thai patients with atrial fibrillation.

**Design:** Correlational predictive study.

**Methods:** This study was conducted at a university hospital in Thailand. One-hundred twenty patients with non-valvular atrial fibrillation receiving warfarin were recruited. Data were collected using Thai versions of Oral Anticoagulation Measurement of Treatment Adherence Scale, Medication Regimen Complexity Index, Health Literacy Scale, and Beliefs about Oral Anticoagulation Survey. Descriptive statistics, Spearman's correlation, and multiple linear regression analysis were applied to analyze the data.

**Main Findings:** The findings indicated that all participants in this study had high warfarin adherence ( $\bar{X} = 5.76$ ,  $SD = .25$ ). However, only 45.8% of them could maintain International Normalized Ratio (INR) within the therapeutic range. The complexity of a warfarin regimen, health literacy, perceived benefits and perceived barriers of taking warfarin jointly predicted 14% of the variance in warfarin adherence ( $R^2 = .140$ ,  $F_{(4,115)} = 4.664$ ,  $p = .002$ ). Participants with lower perceived barriers had better warfarin adherence ( $\beta = -.285$ ,  $p = .002$ ).

**Conclusion and recommendations:** Although all participants in this study adhered to warfarin, they still had risks of INR instability. Health care providers should pay more attention to decreasing barriers of taking warfarin to enhance warfarin adherence and maintain INR within the target range.

**Keywords:** atrial fibrillation, medication adherence, warfarin

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Corresponding Author: Associate Professor Aurawamon Sriyuktasuth, Faculty of Nursing, Mahidol University, Bangkok 10700, Thailand; e-mail: aurawamon.sri@mahidol.ac.th

\* Master's thesis, Master of Nursing Science Program (International Program), Faculty of Nursing and Faculty of Graduate Studies, Mahidol University

<sup>1</sup> Faculty of Nursing, Mahidol University, Bangkok, Thailand

<sup>2</sup> Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

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# ความร่วมมือในการรับประทานยารักษาเบาหวาน และปัจจัยที่เกี่ยวข้อง ในผู้ป่วยภาวะหัวใจเต้นไม่เป็นจังหวะชนิดหัวใจห้องบนสั่นพลิ้ว\*

วรารณ พานิชปฐม<sup>1</sup>, อรวมน ศรียุคศุภ, DSN<sup>1</sup> กวรัตน์ วัฒนกิจไกรเลิศ, พย.ก.<sup>1</sup>  
ฉัตรกนก กุมวิภาท, พ.บ.<sup>2</sup>

## บทคัดย่อ

**วัตถุประสงค์:** เพื่อศึกษาความสัมพันธ์ในการรับประทานยารักษาเบาหวาน และปัจจัยที่เกี่ยวข้องกับความร่วมมือในการรับประทานยารักษาเบาหวานในผู้ป่วยที่มีภาวะหัวใจเต้นไม่เป็นจังหวะชนิดหัวใจห้องบนสั่นพลิ้ว

**รูปแบบการวิจัย:** การศึกษาความสัมพันธ์เชิงทำนาย

**วิธีดำเนินการวิจัย:** การวิจัยครั้งนี้ศึกษาที่โรงพยาบาลมหาวิทยาลัยแห่งหนึ่งในประเทศไทย เก็บข้อมูลในผู้ป่วยภาวะหัวใจเต้นไม่เป็นจังหวะชนิดหัวใจห้องบนสั่นพลิ้วที่ได้รับยารักษาเบาหวานจำนวน 120 ราย เก็บรวบรวมข้อมูลโดยใช้แบบสอบถามความร่วมมือในการรับประทานยาต้านการแข็งตัวของเลือด ดัชนีชี้วัดความซับซ้อนของแผนการใช้จ่ายแบบสอบถามความรู้เท่าทันทางสุขภาพ แบบสอบถามความเชื่อเกี่ยวกับการใช้ยาต้านการแข็งตัวของเลือด ฉบับภาษาไทย วิเคราะห์ข้อมูลโดยใช้สถิติพรรณนา สหสัมพันธ์แบบลำดับที่ของสเปียร์แมน และสถิติถดถอยพหุคูณ

**ผลการวิจัย:** ผู้เข้าร่วมการวิจัยทุกรายมีความร่วมมือในการรับประทานยารักษาเบาหวานอยู่ในระดับสูง ( $\bar{X} = 5.76$ ,  $SD = .25$ ) แต่มีเพียงร้อยละ 45.8 ที่มีค่าไอออนอาร์ (INR) อยู่ในช่วงที่เหมาะสม ความซับซ้อนของแผนการใช้จ่ายยารักษาเบาหวาน ความรู้เท่าทันทางสุขภาพ การรับรู้ประโยชน์และการรับรู้อุปสรรคในการรับประทานยารักษาเบาหวานสามารถร่วมกันทำนายความร่วมมือในการรับประทานยารักษาเบาหวานได้ ร้อยละ 14 ( $R^2 = .140$ ,  $F_{(4,115)} = 4.664$ ,  $p = .002$ ) และพบว่ากลุ่มตัวอย่างที่มีการรับรู้อุปสรรคในการรับประทานยารักษาเบาหวานน้อย มีความร่วมมือในการรับประทานยารักษาเบาหวานสูง ( $\beta = -.285$ ,  $p = .002$ )

**สรุปและข้อเสนอแนะ:** ถึงแม้ว่าผู้เข้าร่วมการวิจัยทุกคนมีความร่วมมือในการรับประทานยารักษาเบาหวานแต่ยังคงมีความเสี่ยงต่อความผันแปรของค่า INR บุคลากรสุขภาพควรให้ความสนใจในการลดอุปสรรคของการรับประทานยารักษาเบาหวาน เพื่อเพิ่มความร่วมมือในการรับประทานยาและคงค่าไอออนอาร์ (INR) ให้อยู่ในช่วงการรักษา

**คำสำคัญ:** ภาวะหัวใจเต้นไม่เป็นจังหวะชนิดหัวใจห้องบนสั่นพลิ้ว, ความร่วมมือในการรับประทานยา, ยารักษาเบาหวาน

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Corresponding Author: รองศาสตราจารย์อรวมน ศรียุคศุภ, คณะพยาบาลศาสตร์ มหาวิทยาลัยมหิดล บางกอกน้อย กรุงเทพฯ 10700, e-mail: aurawamon.sri@mahidol.ac.th

\* วิทยาลัยนวัตกรรมการพยาบาลศาสตรมหาบัณฑิต (หลักสูตรนานาชาติ) คณะพยาบาลศาสตร์ และบัณฑิตวิทยาลัย มหาวิทยาลัยมหิดล

<sup>1</sup> คณะพยาบาลศาสตร์ มหาวิทยาลัยมหิดล

<sup>2</sup> คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล

วันที่รับบทความ: 9 พ.ย. 2561 / วันที่แก้ไขบทความเสร็จ: 18 ธ.ค. 2561 / วันที่ตอบรับบทความ: 28 ธ.ค. 2561

## Background and Significance

Atrial fibrillation (AF) is the most common cardiac arrhythmia which can be found worldwide. Globally, the percentage of patients who suffered from AF has risen to advanced ages<sup>1</sup>. Recent estimates suggest that the prevalence of patients with AF would increase due to the snowballing effect of the elderly in the future. AF can cause severe complications especially stroke due to its pathophysiology. Thus, patients with AF need to receive anticoagulant medication for thromboembolism long-term prevention. However, to obtain the maximum medication effectiveness, adherence to medication is required for patients who received anticoagulant medication<sup>2</sup>.

In Thailand, warfarin is widely used as an anticoagulant in AF patients. Patients undergoing warfarin therapy must be closely monitored International Normalized Ratio (INR) value to ensure that the level of warfarin remains in the effective range<sup>3</sup>. Warfarin dose is frequently adjusted based on the results of the INR. Furthermore, warfarin has many limitations which can cause difficulty to patient's daily life. For example, patients need to avoid high vitamin K consumption and take other medications with cautiousness because warfarin has many food and drug interactions resulting in INR instability<sup>3</sup>.

Moreover, warfarin causes bleeding tendency regarding its side effect. To lower the bleeding risk, patients who take warfarin need to perform daily activity with high precaution.

These limitations require the patients to change their daily behaviors to be appropriate with the treatment. Additionally, frequent blood tests are required while taking warfarin. This necessity influences patients to feel uncomfortable and annoyed<sup>4</sup>.

The aforementioned limitations of warfarin use might lead non-adherence to warfarin occurred resulting in INR instability and increasing risk for ischemic stroke. Previous studies reported that patients who had received warfarin exhibiting warfarin non-adherence in range between 22% and 68.2%<sup>5-6</sup>. However, these studies were conducted in other countries, where the social context and health care system are dramatically different from Thailand. A few studies examined anticoagulant adherence among Thai patients with other conditions, such as valvular replacement<sup>7</sup>, but status of warfarin adherence in Thai patients' particularly with non-valvular AF has never been identified.

Poor warfarin adherence is a crucial problem. To identify the factors associated with warfarin adherence is essential. The World Health Organization (WHO) recognized that medication adherence to long-term therapy is influenced by many factors; and those factors are categorized into five dimensions including social and economic factors, therapy-related factors, patient-related factors, condition-related factors, and health care team/health system-related factors, according to the Multidimensional Adherence Model (MAM)<sup>8</sup>.

The complexity of a warfarin regimen is considered as a therapy-related factor. Taking warfarin is more difficult and complicated than other medications such as antibiotics, because physician cannot prescribe warfarin with fixed dose. Warfarin dose adjustment to maintain INR stability is often required. In addition, many patients need to take warfarin with different daily doses according to the INR blood test results. Increasing complexity of warfarin regimen may result in decreased warfarin adherence. However, from literature review, the impact of complexity of warfarin regimen on adherence in AF patients was limited and no study surfaced regarding this issue earlier in Thailand.

Health literacy, as a patient-related factor, could possibly lead to nonadherence to warfarin. Patients with AF need to interpret their symptoms and participate in treatment evaluations and decision-makings. It is imperative that they are familiar with basic health information to care for themselves; otherwise, they may be faced with unpleasant conditions<sup>9</sup>. From a systematic review, mixed results of impact of health literacy on medication adherence were found among patients with chronic conditions including diabetes mellitus, glaucoma, HIV, and cardiovascular disease<sup>10</sup>. Thus, such results could not be used to conclude the association between health literacy and warfarin adherence in patients with AF.

Perceived benefits and perceived barriers of taking warfarin can be categorized in the patient-related factors. From a previous study conducted in patients with many conditions including atrial fibrillation, stroke, deep vein thrombosis, pulmonary embolism, and heart valve replacement undergoing warfarin as a treatment, results showed that warfarin adherence would increase when perceived benefits of taking warfarin increased and perceived barriers decreased; and the most important factor was perceived barriers of taking warfarin<sup>11</sup>. However, none of the studies related to these variables and conducted solely in patients with AF were found.

In conclusion, the prevalence of Thai patients with AF would increase according to the future aging society. From literature review, many studies have identified and reported level of anticoagulant adherence and factors affecting the medication adherence in patients with different conditions<sup>7,11-13</sup>; and some inconsistent results were found. The studies regarding level of warfarin adherence in Thai patients with AF and factors influencing warfarin adherence in this population were limited. Hence, this study aimed to assess level of warfarin adherence and to examine its associated factors among Thai patients with AF. The findings of this study could fulfill this gap of knowledge and provided evidence to health care providers to tailor appropriate interventions to promote warfarin adherence of these patients.

## Objective

To identify level of warfarin adherence and investigate factors associated with warfarin adherence in Thai patients with atrial fibrillation.

## Methodology

This study was a correlational predictive study.

### *Population and Sample*

The population in this study was male and female patients aged 18 years and older who received warfarin treatment for non-valvular AF (NVAF). The participants were patients with NVAF who attended the medical out-patient unit of a university hospital in Thailand and met the following inclusion criteria: 1) had a diagnosis of NVAF with warfarin treatment for at least 3 months prior to the study; 2) had ability to read, write, and speak Thai language; and 3) be self-administer medication. In addition, those who had cognitive impairment screened by using the Mini Mental Screening Examination (MMSE)-Thai version<sup>14</sup>, were diagnosed with a psychiatric disorder, and had AF as a complication from cardiac surgery, were excluded from this study. The researchers calculated the sample size based on the predictive power of the independent variables (perceived benefits and perceived barriers) found in a similar study<sup>7</sup>. G Power software<sup>15</sup> was applied based on the effect size of .10,  $\alpha$  value of .05, the power of .80, and four independent variables. A total minimum

sample of 119 was required. Thus, in this study, 120 participants were included.

### *Ethical Considerations*

This project was approved by the Institutional Review Board of the study hospital, Thailand (COA. No. Si059/2018).

### *Data Collection*

After obtaining permission, the principle investigator met staff nurses at the clinic to explain the study. The staff nurses screened the potential participants for inclusion criteria. Patients who met the criteria were informed about the research. Written consents were obtained from interested and willing participants. Potential participants aged 60 and above were screened for cognitive impairment by using the MMSE-Thai version<sup>14</sup>. If they had no cognitive impairment, they were included in the study. While waiting for a visit with cardiologists, the researcher explained the participants how to respond the questionnaires and also asked their permission to collect the data from medical records.

### *Research Instruments*

1. Warfarin's regimen complexity: The Medication Regimen Complexity Index (MRCI) Thai version was used to measure complexity of warfarin regimen in this study. The original MRCI<sup>16</sup> was translated into a Thai version<sup>12</sup> by using back-translation method. The scale covers three sections including dosage forms, dosing frequencies, and additional directions. A total score of MRCI ranged from 3 to 9, in which the higher means the more regimen complexity.

2. Health literacy: The Health Literacy Scale Thai version was used to measure level of health literacy. The original scale<sup>17</sup> was developed to assess the three levels of health literacy which are functional, communicative, and critical health literacy. The back-translated Thai version was used in a study of Kumkrong, Maneesriwongul and Janpanich<sup>13</sup>. The scale consists of four subscales of functional (5 items), communicative (5 items), and critical health literacy (4 items). Each item was rated on 4-point scale ranging from “never” (1) to “always” (4). To calculate the scores of this scale, scores in functional health literacy subscale were reversed. Possible overall health literacy and each subscale score in the present study were calculated by averaging total scores. The higher score indicated higher health literacy.

3. Perceived benefits and perceived barriers of taking warfarin: The Beliefs about Oral Anticoagulation Survey (Thai version) translated by the researchers using back-translation method was used to measure perceived benefits and perceived barriers of taking warfarin in the study. Orensky and Holdford<sup>11</sup> modified the original version<sup>18</sup> into Beliefs about Oral Anticoagulation Survey and used in patients treated with anticoagulant medication. Total 12 items were divided into perceived benefits subscale (5 items) and perceived barriers subscale (7 items). The response options range from “strongly disagree” (1) to “strongly agree” (5). A possible total score for perceived benefits subscale is

5-25 points and 7-35 points for perceived barriers subscale. The higher score indicates higher perceived benefits or perceived barriers of taking warfarin.

4. Warfarin adherence: The Oral Anticoagulation Measurement of Treatment Adherence (MTA) (Thai version) was used to assess level of warfarin adherence in this study. Da Silva Carvalho, et al.<sup>19</sup> modified the original scale, Medication Treatment Adherence, which was used to measure medication adherence in Portuguese diabetics and hypertensive patients. They changed the word “medication” to “oral anticoagulant” and added some contents specific to oral anticoagulant medication. The modified scale namely the Oral Anticoagulation Measurement of Treatment Adherence was used to assess warfarin adherence in patients with heart valve replacement and AF<sup>19</sup>. To use in Thai patients with AF, the researchers used back-translation method to translate the scale into Thai language. The scale includes 7 items with a 6-point rating scale ranging from “always” (1) to “never” (6). An average mean score was used for the analysis in the present study with a score of 5 and above indicating the adherence to warfarin.

5. Participants’ characteristics and clinical information: Demographic and health information sheet developed by the researchers was used to collect the participant’s personal background and clinical information including diagnosis, comorbidity, medication, and INR levels.

### ***Validity and Reliability***

All questionnaires were well-developed and had been used in patients with chronic conditions. Consequently, researchers did not test their content validity. Researchers tested the reliability of all questionnaires with 30 participants who were similar to the sample in this study. The Cronbach's alpha coefficient of the instrument was .82 for MRCI, .60 for Health Literacy Scale, .76 for Beliefs about Anticoagulation Survey, and .70 for MTA. For each subscale of the Beliefs about Anticoagulation Survey, the Cronbach's alpha value of perceived benefits of taking warfarin subscale was .90; and perceived barriers of taking warfarin subscale was .65.

### ***Data Analysis***

Descriptive statistics including frequency, mean, percentage, standard deviation, and range were used to analyze participants' characteristics and the studied variables. To identify the correlations between the studied variables, Spearman's rank correlation was used due to unmet assumption of Pearson's product moment correlation. Multiple linear regression (enter method) was performed to identify the predictive power of the independent variables on warfarin adherence. Key assumptions of multiple regression analysis were tested and satisfactorily met.

### **Findings**

The mean age of the participants was 66.79 years old (SD = 9.70) with a range of 41 to 88 years. Fifty-six percent were male. Most of participants were married and unemployed; and forty-four percent received education at the primary school level. The highest percentage of comorbidity among participants was hypertension (68%). Almost a half of the sample (48%) had been diagnosed with AF for more than five years, and 46% had been using warfarin as a treatment for 1 to 5 years.

Table 1 shows self-reported warfarin adherence among the participants in this study. Overall self-reported warfarin adherence mean score was 5.76 (SD = .25) with a range of 5 to 6. This finding indicated that all participants in this study (100%) had high adherence to warfarin regimen (the MTA score  $\geq$  5). As displayed in Table 1, a mean score for each item ranged from 5.18 to 5.94. The item with the highest mean score of 5.94 (SD = .27) asked how often did you change the anticoagulant dose because you forgot to take it the day before; and that with the lowest mean score of 5.18 (SD = .85) asked how often did you forget to take the anticoagulant.

**Table 1:** Self-reported warfarin adherence among the participants (N = 120)

Item	Possible Range	Actual Range	$\bar{X}$	SD
Overall warfarin adherence	1-6	5-6	5.76	.25
- How often did you forget to take the anticoagulant?	1-6	3-6	5.18	.85
- How often did you not take the anticoagulant because you ran out of it?	1-6	4-6	5.70	.60
- How often did you take the anticoagulant out of scheduled time?	1-6	3-6	5.86	.47
- How often did you stop taking the anticoagulant because you felt better?	1-6	3-6	5.88	.50
- How often did you stop taking the anticoagulant because you felt worse?	1-6	4-6	5.89	.41
- How often did you not take the anticoagulant for reasons beyond your control?	1-6	4-6	5.90	.35
- How often did you change the anticoagulant dose because you forgot to take it the day before?	1-6	4-6	5.94	.27

In regard to correlations among the study variables, it was found that perceived barriers of taking warfarin had a significant negative correlation with warfarin adherence ( $r_s = -.383$ ,

$p < .01$ ). Perceived benefits of taking warfarin had a significant positive correlation with warfarin adherence ( $r_s = .274$ ,  $p < .01$ ), as illustrated in Table 2.

**Table 2:** Intercorrelations among the study variables (N = 120)

Studied Variables	1	2	3	4	5
1. Complexity of warfarin regimen	1				
2. Health literacy	.021	1			
3. Perceived benefits of taking warfarin	.031	.202*	1		
4. Perceived barriers of taking warfarin	-.025	-.070	-.309**	1	
5. Warfarin adherence	-.014	.118	.274**	-.383**	1

\* $p < .05$ , \*\* $p < .01$

As shown in Table 3, the findings of multiple linear regression analysis indicated that complexity of warfarin regimen, health literacy, perceived benefits, and perceived barriers of taking warfarin jointly predicted 14% of the variance in warfarin adherence ( $R^2 = .140$ ,  $F_{(4,115)} = 4.664$ ,  $p = .002$ ). However, only perceived barriers of taking warfarin significantly associated with warfarin adherence ( $\beta = -.285$ ,  $p = .002$ ).

**Table 3:** Multiple regression analysis for complexity of warfarin regimen, health literacy, perceived benefits, and perceived barriers of taking warfarin predicting warfarin adherence (N = 120)

Study Variables	B	SEB	$\beta$	t	p-value	95%CI
Constant	5.645	.243		23.251	<.001	5.164, 6.126
Complexity of warfarin regimen	-.005	.013	-.033	-.383	.703	-.030, .021
Health literacy	.068	.050	.120	1.366	.174	-.031, .167
Perceived benefits of taking warfarin	.010	.008	.123	1.326	.188	-.005, .260
Perceived barriers of taking warfarin	-.016	.005	-.285	-3.131	.002	-.025, -.006

$R = .374$ ,  $R^2 = .140$ ,  $\text{adj } R^2 = .110$ ,  $df = 4,115$ ,  $F_{(4,115)} = 4.664$

## Discussion

Level of warfarin adherence was measured by participants' self-report using Oral Anticoagulation Measurement of Treatment Adherence (MTA). Surprisingly, the average level of warfarin adherence in the present study was 5.76 (SD = .25) with a range of 5 to 6. This result indicated that 100 % of participants adhered to warfarin therapy at high level (the MTA score  $\geq 5$ ). These Thai participants reported higher warfarin adherence rate than participants in other previous studies. For example, a study of Japanese with AF reported 87% of participants adherent to their oral anticoagulants including warfarin<sup>5</sup>. Another previous study conducted in Saudi Arabia found that only 31.8% of participants

undergoing warfarin therapy were adherent<sup>6</sup>. Higher adherence rate in this study may be due to the characteristics of the participants and the study social contexts.

In Thailand, patients trust in medical expertise. Doctors are dominant and make treatment decisions, while patients are dependent and passive about their treatment. The participants in this study were middle-aged and older adults. Thus, they still were more likely to be passive about their treatments. In addition, during clinic visits, they were informed to strictly adhere to warfarin regimen as prescribed. Therefore, the participants were willing to follow the instruction and highly adhered to their warfarin treatment. Additionally, owing to the characteristics of

the participants, most of them had taken warfarin for several years. They might be used to this medication and took it as a part of their daily life.

Measurement might have been another possible issue. Even though all of mentioned studies used participants' self-report, different scales were applied to measure level of adherence. The Modified Siegal Scale<sup>5</sup>, and the Medication Adherence Questionnaire<sup>6</sup> were used among the previous studies, while the current study used MTA. It is possible that adherence to warfarin assessment causes the inconsistent finding across studies. However, only 45.8% had INR within the target range (INR 2-3). These results emphasized that the participants' warfarin doses need to be adjusted; and their INR need to be closely monitored although they all adhered to warfarin.

The participants' behaviors may be a possible reason to explain ineffectiveness of warfarin treatment in this study. As advised, most of participants only focused on taking warfarin dose exactly as prescribed. However, consuming alcohol and food rich in vitamin K found in green and leafy vegetables, taking other medications such as NSAIDs and antibiotics, having underlying diseases (e.g. liver disease) or health conditions (e.g. fever or diarrhea), and genetics can alter effectiveness of warfarin<sup>3</sup>. It was found that many participants in this study reported unaware of food, alcohol, and drug interactions while taking warfarin. Some of them did not

manage their daily life appropriately to warfarin treatment. Some had taken over counter medications and supplements without consulting health care providers. Therefore, more than a half of the participants had INR out of the target.

Complexity of a warfarin regimen, health literacy, perceived benefits, and perceived barriers of taking warfarin contribute to 14% of the variance in warfarin adherence ( $R^2 = .140$ ,  $F_{(4,115)} = 4.664$ ,  $p = .002$ ). Perceived barriers of taking warfarin was the most imperative factor associated with warfarin adherence in patients with AF ( $\beta = -.285$ ,  $p = .002$ ). Perceived barriers of taking warfarin had negative effects on warfarin adherence in the current study. This can be interpreted as participants who had lower perception of barriers in taking warfarin were more likely to had better warfarin adherence. The result is also supported by the study of Han, Hong and Tiraphat<sup>20</sup> which reported that the higher perceived barriers represented, the less adherence to medication in Burmese hypertensive patients (adj OR = 2.55, 95%CI 1.27, 5.09).

In this study, complexity of a warfarin regimen ( $\beta = -.033$ ,  $p = .703$ ) was not significantly associated with warfarin adherence in patients with AF. It is possible that the results of warfarin complexity in each participant were quite similar, thus the MRCI might not be sensitive enough to capture the complexity of warfarin. Moreover, health literacy did not show association with warfarin

adherence ( $\beta = .120$ ,  $p = .174$ ). The result from a systematic review and meta-analysis supported the result of the current study in that the impact of health literacy on medication adherence was weak<sup>10</sup>. In this study, most of the participants especially older adults reported that their children or other family members helped to find and convey important health-related information to them. Additionally, their health care providers regarding importance of taking warfarin informed them. These might be a reason why health literacy was not associated with warfarin adherence in this study.

Finally, perceived benefits of taking warfarin had a small relationship with warfarin adherence ( $r_s = .274$ ,  $p < .05$ ). However, in multiple regression analysis, the perceived benefits of taking warfarin was insignificant associated with warfarin adherence ( $\beta = .123$ ,  $p = .188$ ). It can be explained as a negative relationship between perceived benefits and perceived barriers of taking warfarin ( $r_s = -.309$ ,  $p < .01$ ). A possibility exists, perceived barriers were beyond remarkable than perceived benefits. Thus, the result of the perceived benefits of taking warfarin was insignificant.

### Conclusion and Recommendations

The result of this study can satisfy a gap of knowledge and offer evidence to shape future interventions for warfarin adherence in AF patients. Recognized warfarin barriers, under patient-related factors, were reliable forecasters of warfarin adherence in AF

patients. The recommendations from this study are as follows;

1. Health care providers need to focus not only on warfarin adherence behavior, but also on patient's behaviors while taking warfarin by providing specific medical information especially how to maintain INR within the therapeutic range to increase the treatment effectiveness and safety.

2. Researchers may use the study's results to further develop health counselling interventions to support AF patients who have faced with barriers of taking warfarin to increase warfarin adherence and maintain INR within therapeutic ranges.

3. According to the reliability coefficient of the Health Literacy Scale was lower than .7 in this study, future research should explore health literacy measurement in Thai older adults with low to medium level of education to find a reliable and valid tool to assess health literacy in this population.

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