

## Barriers to Warfarin Use for Stroke Prevention in Patients With Atrial Fibrillation in Hong Kong

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### ABSTRACT

**Background:** Oral anticoagulation medications such as warfarin reduce the risk of stroke in atrial fibrillation (AF) but have been underutilized. This study aimed to investigate physicians' perceptions of stroke prevention management and patients' knowledge of AF and warfarin therapy in Hong Kong (HK).

**Hypothesis:** Both physician and patient's knowledge on warfarin use were the barriers for stroke prevention in patients with atrial fibrillation in Hong Kong.

**Methods:** This prospective survey-based study was conducted between February 2011 and April 2011 to assess physicians' perceptions of stroke prevention management, patients' knowledge of AF, and patients' knowledge of warfarin therapy. The results were scored and compared with those in foreign countries.

**Results:** Sixty-two physicians and 114 warfarin users were recruited in the study. The average score of HK physicians in the knowledge of stroke prevention therapy in AF patients was lower than that of Australian (AUS) family physicians (HK 2.48 vs AUS 4.02 out of 7). The mean scores of AF patients in Hong Kong regarding the knowledge of AF were lower than that of United Kingdom (UK) (HK 1.16 vs UK 2.24 out of 4) ( $P < 0.001$ ) and that of Finland (FIN) (HK 2.77 vs FIN 5.94 out of 8) ( $P < 0.001$ ), respectively. The mean score of AF patients in Hong Kong regarding the knowledge of warfarin therapy was lower than that of AF patients in the United States (US) (HK 2.39 vs US 3.92).

**Conclusions:** The barriers of warfarin use for AF patients in Hong Kong were related to both physicians and patients. Many Hong Kong physicians did not comply with international recommendations of stroke prevention in AF patients, and AF patients had a low knowledge level about the disease and warfarin therapy.

### Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice.<sup>1</sup> The prevalence of AF increases with age, with 5% of patients over 65 years and 10% over 80 years.<sup>1</sup> Nonvalvular AF (NVAF) greatly increases the risk of stroke and the severity of stroke episodes, with 60% of these stroke episodes leading to severe disability or premature death.<sup>2,3</sup> Oral anticoagulation therapy is the standard of care for stroke prevention in AF patients. Current therapeutic guidelines recommend warfarin as the first-line anticoagulation agent for stroke prevention in most AF patients with 1 or more risk factors for stroke. However,

warfarin is underutilized in AF patients in many countries.<sup>3-7</sup> About 56% to 85% of AF patients are not receiving warfarin in Western countries.<sup>3</sup> Another study revealed that only 21% to 67% of patients who should receive warfarin treatment actually receive the therapy.<sup>8</sup> Aspirin and other antiplatelet agents are the major substitutes of stroke-prophylactic drugs among these cases. The monotherapy of aspirin and other antiplatelet drugs is associated with a higher mortality rate and more disabling stroke events, with only minimal reduction in hemorrhagic events.<sup>2</sup>

Underutilization of warfarin for stroke prevention has also been found in Hong Kong (HK). A retrospective study of hospitalized AF patients reflected that only 41% of the AF patients with CHA<sub>2</sub>DS<sub>2</sub>VASc score  $\geq 2$  were receiving warfarin.<sup>9</sup> The CHA<sub>2</sub>DS<sub>2</sub>VASc score is a new risk factor-based approach extended the old CHADS<sub>2</sub> scheme by considering additional stroke risk factors that may impact on the decision of using anticoagulation therapy or not. CHA<sub>2</sub>DS<sub>2</sub>VASc is an acronym that stands for congestive heart failure, hypertension, age  $\geq 75$  years (doubled points),

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diabetes, prior stroke (doubled points), vascular disease, age 65 to 74 years, and sex category (female).<sup>2</sup> Warfarin-users had fewer cases of death and hospitalization due to ischemic stroke and had a similar bleeding rate as nonwarfarin users.<sup>9</sup> Another local study reported more than 30% of AF patients did not receive appropriate antithrombotic therapy; 34% of AF patients were treated with aspirin alone, and 22% of them were not receiving any antithrombotic therapy.<sup>10</sup> The aims of this study were to assess the knowledge of Hong Kong physicians in stroke prevention management for AF patients and the understanding of AF and warfarin therapy in Hong Kong Chinese AF patients, and to compare the knowledge levels of both physicians and patients with those in Western countries.

## Methods

This prospective survey-based study was conducted between February 2011 and April 2011. The research protocol was approved by the Survey and Behavioral Research Ethics Committee, the Chinese University of Hong Kong. Two surveys were designed and conducted to assess the knowledge of AF and warfarin of physicians in English (Supplementary Appendix 1) and patients in Hong Kong in traditional Chinese. We adopted the original questionnaire by Gattellari et al. in English for the physicians.<sup>11</sup> The questionnaire for patients was designed based on 2 previously published surveys conducted in the United Kingdom<sup>12</sup> and Finland,<sup>13</sup> and translated into the traditional Chinese version and validated.

The questionnaires were distributed to physicians, including both usual medical specialties to treat AF patients (family medicine, geriatrics, general practitioner, internal medicine, and geriatrics) and specialties (accident and emergency department, anesthesia, gastrointestinal and hepatology, intensive care, oncology, ophthalmology, orthopedics, pediatrics, psychiatry, radiology surgery, and urology) not usually treating AF patients in 2 local public hospitals (Princess Margaret Hospital and Kwong Wah Hospital), and also at the Multispecialty Medical Mega Conference held on April 16–17, 2011 in Hong Kong. The total score of this part (8 case scenarios of self-reported management of NVAF) was 7. For each case in cases 1 to 7, a choice of warfarin monotherapy would be given 1 point (because warfarin is the correct answer for cases 1–7, all cases with benefits of reducing stroke risk from warfarin outweigh the increased risks of bleeding). For case 1, the choice of aspirin monotherapy would be given 0.5 point, because the AF management guidelines also recommend aspirin treatment in low-risk stroke patients, although warfarin is a more preferred option as stated in the guidelines. Case 8's treatment is still controversial, and was therefore not counted in this scoring system. The physician characteristics, including gender, years of practice, and medical specialty, were recorded.

For the patient's knowledge assessment, the inclusion criteria were: Chinese, with a documented diagnosis of AF; on current warfarin treatment; and attending the cardiac outpatient clinic/warfarin outpatient clinic/hypertension clinic at the Prince of Wales Hospital (PWH) between February 24, 2011 and March 31, 2011. The maximum

score in this assessment was 21. Patients' demographic and clinical data were collected from the clinical management system in the hospital. The patients provided written informed consent before participating in this study. Every participant was interviewed by the same research assistant in the outpatient clinic of the hospital. The questionnaire addressed the patients' knowledge of their heart condition and their awareness of the possible consequences, severity of AF, and the knowledge of warfarin.

The participants for the warfarin knowledge questionnaire were those who had already taken part in the questionnaire survey regarding patients' knowledge of AF, with the addition of other Chinese patients without AF, but with other indications of warfarin (currently on warfarin, attending the cardiac outpatient clinic/warfarin outpatient clinic/hypertension clinic in the PWH between February 24, 2011 and March 31, 2011) to compare their knowledge level of warfarin therapy with AF-patient participants. The maximum score was 10 points.

Data are presented as mean and standard deviation (SD), or absolute number and percentage, as appropriate.  $\chi^2$  test or Fisher exact test was carried out to compare categorical variables, whereas 1-sample *t* test, independent-sample *t* test, 1-way analysis of variance, or Pearson correlation were used for comparison among continuous variables, as appropriate. All statistical tests were 2-tailed, and statistical significance was defined as *P*value < 0.05. (SPSS version 16.0 for Windows; SPSS Inc., Chicago, IL)

## Results

A total of 62 physicians in different specialties, 70 AF patients with warfarin use, and 44 patients without AF but using warfarin for stroke prevention were recruited in this study.

### Questionnaire for Physicians

Most of the physicians were male (72.5%) and graduated from medical school within 10 years (58.5%). About 40% of respondents were in the specialties of family medicine (24.2%), internal medicine (8.1%), geriatrics (3.2%), and general practitioners (4.8%). Only 27% agreed or strongly agreed that they fully understood their patients' views on the benefits and risks of warfarin. The comparison between Hong Kong and Australian physicians<sup>11</sup> in the decisional conflicts is summarized in Table 1.

Over 45% of respondents said that they had patients with NVAF who experienced ischemic stroke without anticoagulation, and 41.9% responded that their patients experienced intracranial hemorrhage with anticoagulation. Over 25% and 11% of physicians felt that they were responsible for patients who experienced embolic stroke without anticoagulation and intracranial hemorrhage with anticoagulation, respectively. More than half (59.7%) thought that they were equally responsible for both adverse events.

Compared within different characteristics among respondents, specialty, gender, experience of adverse outcomes, and anticipated responsibility for adverse events in patients with NVAF were not found to be related to any significant differences in the self-reported management of NVAF. However, it was found that a physician with a practice of at

Table 1. Comparison of Decisional Conflicts Between Hong Kong Physicians and Australian Family Physicians

	Often I am unsure whether or not to prescribe warfarin		I feel I do not know enough about the benefits and risks of warfarin		It is hard to decide whether the benefits of warfarin outweigh the risks or vice versa		I fully understand my patients' views on both the benefits and risks of warfarin		Generally, patients fully understand the risks as well as the benefits of warfarin	
	% HK	% AUS	% HK	% AUS	% HK	% AUS	% HK	% AUS	% HK	% AUS
Strongly disagree/disagree	40.3	53.9	53.2	65.4	27.4	45.0	32.3	15.4	59.7	39.1
Neither	22.6	15.3	11.3	16.4	19.4	15.8	40.3	29.5	19.4	18.5
Strongly agree/agree	37.1	30.0	35.5	17.4	53.2	38.4	27.4	54.4	21.0	41.8

Abbreviations: AUS, Australian; HK, Hong Kong. Data source of Australian family physicians: Gattellari et al.<sup>10</sup>

Table 2. Self-Reported Management of Nonvalvular Atrial Fibrillation

Case Scenario	Case 1			Case 2			Case 3			Case 4			Case 5			Case 6			Case 7			Case 8		
	n	% HK	% AUS	n	% HK	% AUS	n	% HK	% AUS	n	% HK	% AUS	n	% HK	% AUS	n	% HK	% AUS	n	% HK	% AUS	n	% HK	% AUS
Aspirin	40	64.5	31.2	27	43.5	4.4	31	50.0	16.1	3	4.8	2.9	23	37.1	19.0	9	14.5	2.9	15	24.2	15.6	15	24.2	9.6
Warfarin	8	12.9	61.7	25	40.3	88.8	22	35.5	73.3	34	54.8	71.0	15	24.2	45.6	7	11.3	17.1	18	29.0	28.9	1	1.6	9.6
Clopidogrel	1	1.6	1.8	2	3.2	1.0	2	3.2	2.7	1	1.6	5.2	5	8.1	12.1	19	30.6	59.4	9	14.5	35.1	9	14.5	20.8
Aspirin and clopidogrel	1	1.6	2.7	1	1.6	1.5	2	3.2	4.9	6	9.7	9.1	8	12.9	15.9	5	8.1	2.0	5	8.1	5.9	5	8.1	4.5
Aspirin and warfarin	1	1.6	1.0	3	4.8	3.9	2	3.2	2.3	15	24.2	11.2	4	6.5	5.4	1	1.6	0.2	4	6.5	2.2	1	1.6	0.7
No antithrombotic treatment	9	14.5	1.3	2	3.2	0.3	0	0	0.3	0	0	0	2	3.2	1.0	19	30.6	17.4	9	14.5	11.2	29	46.8	52.3
Missing	2	3.2		2	3.2		3	4.8		3	4.8		5	8.1		2	3.2		2	3.2		2	3.2	

Abbreviations: AUS, Australian; HK, Hong Kong. Data source of Australian family physicians: Gattellari et al.<sup>10</sup>

least 20 years was more likely to choose warfarin in case 1 ( $P = 0.028$ ) and case 2 ( $P = 0.039$ ). The mean score of physicians in the case scenarios test was 2.84 (SD 1.59) out of 7. Number of years of practice, specialty, and gender were not found to be related to any significant differences in the scores of self-reported management. A comparison between Hong Kong physicians and Australian physicians is summarized in Table 2. Compared with Australian family physicians, fewer Hong Kong physicians chose warfarin for stroke prevention in most cases in the questionnaire.<sup>11</sup> They were more likely to choose aspirin rather than warfarin for stroke prevention management, whereas in Australia most of the family physicians chose warfarin for stroke prevention. Australian physicians knew more about stroke prevention management for AF patients than Hong Kong physicians.<sup>11</sup> This observation can be explained because of the different type of healthcare system in Hong Kong, where over 95% of patients are managed in the public sector by cardiologists. Therefore, physicians in other specialties do not manage as many AF patients and may not be familiar with the management of AF patients in Hong Kong.

### Questionnaire for Patients

**Patients' Knowledge of Atrial Fibrillation:** A total of 70 AF patients with warfarin use were interviewed in this part of questionnaire survey. The majority of the patient respondents were below 65 years old (56% male). Of the

patients, 15.7% had a history of congestive heart failure or left ventricular (LV) dysfunction, 17.1% had a history of vascular diseases, 32.9% had hypertension, 28.6% had diabetes, and 14.3% had a history of stroke, transient ischemic attack, or thromboembolic events. The study population had a CHA<sub>2</sub>DS<sub>2</sub>VASc score between 0 and 7, with a mean of 2.19. None of the patients were aware that their cardiac condition was AF. Only about 25% of the patients recognized AF as 1 type of cardiac arrhythmia, half did not know the symptoms of AF, and 74% did not know what underlying diseases triggered AF. Of the patients, 58.6% felt that AF was a serious condition, and 41% considered it not serious. One in 3 patients (32.9%) knew that AF could cause thrombus formation, and 10% knew that AF could potentially lead to heart failure. Over 70% of subjects did not know that AF patients have more than a 50% risk of recurrence.

The average score of AF patients in this assessment was 5.79 out of the maximum score of 21. The older the patient was, the lower the score in AF knowledge (Pearson correlation =  $-0.290$ ,  $P = 0.015$ ,  $R^2 = 0.084$ ). No other patient characteristic was found to be associated with a significant difference in the score. Hong Kong patients in general have a weaker understanding about AF. In the United Kingdom, 49% of patients with AF were aware that their heart condition was known as atrial fibrillation, whereas none of the Hong Kong patients with AF knew the exact name of their cardiac condition.<sup>12</sup> Fewer patients in this study knew the increased risk of stroke in AF than

in the United Kingdom (HK 33% vs UK 54%).<sup>12</sup> Compared to patients in Finland, more Hong Kong patients (70%) did exercise normally during AF than for patients in Finland (35%),<sup>13</sup> but fewer Hong Kong patients (<25%) knew the symptoms of AF than did patients in Finland (>80%).<sup>13</sup> When we compared the response from Hong Kong patients in questions from the UK survey (questions 1, 3, 6, and 7; maximum score of 4) and the Finland survey (questions 4, 9, 11, 12; maximum score of 8), the mean score of Hong Kong patient was 1.16 out of 4 and 2.77 out of 8, respectively.<sup>12,13</sup> The mean score in Hong Kong patients was much lower than UK patients (mean score 2.24 out of 4,  $P < 0.001$ )<sup>12</sup> and patients in Finland (mean score, 5.94 out of 8;  $P < 0.001$ ).<sup>13</sup>

**Patients' Knowledge of Warfarin Therapy:** A total of 114 patients were recruited in this part of questionnaire, including the 70 patients who participated in the previous AF knowledge questionnaire and 44 patients without AF but who were using warfarin for stroke prevention. The demographics of patients are summarized in Table 3. The mean CHA<sub>2</sub>DS<sub>2</sub>VASc score of the 114 recruited patients was 2.11, with a range of 0 to 7. Only 36% of subjects knew what their therapeutic international normalized ration (INR) level was, less than half (48%) of the patients understood that dietary changes could affect warfarin therapy, and more than 60% of patients did not know the importance of regulating their daily intake of vitamin K during warfarin therapy. Patients were not aware that other medications (58%), vitamins, grapefruit juice (42%), and traditional Chinese medicine (>70%) could interact with warfarin.

The average score was 4.67 of the maximum of 10 points. There was no statistically significant difference between AF patients and non-AF patients ( $P = 0.384$ ). A majority of subjects (99%) reported that they used warfarin as directed by their physicians. Thirty-six percent of subjects reported skipping a dose in the past year, and the most common reason for not taking warfarin was forgetfulness (95%). One in 10 patients (11.4%) admitted that they had doubled their warfarin dose. More than 2 in 3 patients (68%) could not recall their last or current INR level, and over 70% of subjects did not meet their target INR goal in at least 1 medical follow-up in the past 12 months. Thirty-one percent of patients had experienced blood loss in their stool or urine, and <10% required a blood transfusion. Regarding warfarin knowledge, more US patients understood what a therapeutic INR was (US 78% vs HK 37%), and that dietary changes can affect warfarin anticoagulation (US 68% vs HK 47%).<sup>5</sup> Fewer US patients did not know the importance of controlling their daily intake of vitamin K during warfarin therapy (US 9% vs HK 66%).<sup>5</sup> More US patients were aware that medications interact with warfarin (US 72% vs HK 37%), although slightly more Hong Kong patients were aware of the interactions of warfarin with vitamins (US 35% vs HK 44%).<sup>5</sup>

## Discussion

In the current study, both the prescribers and the patients underutilized warfarin in AF patients. The physicians' knowledge of stroke prophylaxis management in AF patients affected their decisions on prescribing oral anticoagulation

Table 3. Demographics of Patients in Warfarin Knowledge

	n All	% All	n AF	% AF
<b>Age, y</b>				
<65	78	68.4	47	67.1
65–74	17	14.9	10	14.3
≥ 75	19	16.7	13	18.6
<b>Gender</b>				
Male	62	54.4	39	55.7
Female	52	45.6	31	44.3
<b>Reason for warfarin therapy</b>				
AF	70	61.4		
Non-AF	44	38.6		
Prosthetic valve replacement	28	24.6		
Intravenous thrombosis	7	6.1		
Rheumatic heart disease	5	4.4		
Protein C deficiency	1	0.9		
Secondary MI prevention	1	0.9		
Allergy to multiple antiplatelets	1	0.9		
Others	1	0.9		
<b>Risk factors of stroke</b>				
With CHF/LV dysfunction	14	12.3	11	15.7
With vascular disease	18	15.8	12	17.1
With HT	35	30.7	23	32.9
With DM	24	21.1	20	28.6
With stroke/TIA/thromboembolism history	21	18.4	10	14.3
<b>Duration of warfarin use</b>				
<1 year	5	4.4	1	1.4
1–5 years	27	23.7	19	27.1
5–10 years	41	36.0	23	32.9
>10 years	33	28.9	21	30.0
Not sure/missing	8	7.0	6	8.6
<b>Frequency of INR checks</b>				
Once a week	2	1.75	1	1.4
Twice a month	3	2.63	3	4.3
Once a month	4	3.50	1	1.4
Once every 2 months	5	4.39	3	4.3
Once every 3 months	39	34.21	22	31.4
Once every 4 months	42	36.84	30	42.9
Once every 5 months	6	5.26	4	5.7

Table 3. Continued

	n All	% All	n AF	% AF
Twice a year	8	7.02	4	5.7
Not sure	5	4.39	2	2.9
Whether INR met target in the past 12 months (2.0–3.0; 2.0–3.5 for patients with valve replacement)				
Yes	31	27.2	20	28.6
No	82	71.9	50	71.4
Missing	1	0.9	0	0

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; DM, diabetes mellitus; HT, hypertension; INR, international normalized ratio; LV, left ventricular; MI, myocardial infarction; TIA, transient ischemic attack.

therapy. A lack of knowledge of, or the noncompliance to therapeutic guidelines on stroke prophylaxis management and the overestimation of the bleeding risk associated with warfarin therapy, may prevent physicians from prescribing warfarin for AF patients, as reflected by different studies.<sup>7,11,14,15</sup> Patients' knowledge of AF and warfarin can affect their utilization of warfarin. A deficiency in understanding of their own disease and warfarin may mean that the patients do not know the necessity of treatment, which may lead to noncompliance of warfarin therapy, and in turn influence both physicians' and patients' preference on antithrombotic agent for stroke prevention therapy.<sup>12</sup> Patients' lack of knowledge of warfarin and AF may be due to limited consultation time during medical appointments in Hong Kong. The number of doctors relative to population of Hong Kong is much lower than those of Australia, the United Kingdom, and Finland (2010 figures: HK, 17.8 doctors per 10,000 population<sup>16</sup> vs 30, Australia; UK, 27; Finland, 29<sup>17</sup>) that doctors in Hong Kong cannot spend much time with patients to educate them of their diseases and medications.

Warfarin therapy is challenging for both physicians and patients due to frequent blood monitoring, narrow therapeutic index, and drug-drug and drug-food interactions. Recently, newer class of warfarin alternatives called direct thrombin inhibitors and factor Xa inhibitors are available with few side effects and less blood monitoring.<sup>18,19</sup> Dabigatran has shown to be superior to warfarin based on the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial.<sup>19</sup> In addition, nonpharmacological management using left atrial appendage (LAA) occlusion devices can also be considered as an alternative management of AF without the need of long-term warfarin management. Recently, our group has demonstrated the LAA occlusion device was considered more cost-effective as compared to all oral pharmacological regimens in the management of AF.<sup>20</sup>

The current study is limited by the small sample size in both physician and patient groups. The current study was conducted based on self-reported responses from patients, which may lead to errors. Future studies are necessary to validate and confirm our findings in this pilot study. In

addition, the educational levels of the patients were not collected in the survey.

The exact vitamin K consumption was not assessed in patients. In our previous finding, vitamin K consumption was 1 of the factors affecting the INR levels of warfarin therapy.<sup>21</sup> The need for vitamin K intake control for warfarin therapy may prevent patients from taking warfarin for stroke prophylaxis and also lead to noncompliance problems. Future studies may investigate how this factor may influence patients when choosing stroke prophylaxis therapy.

## Conclusion

This study concluded that the barriers of warfarin use for AF patients in Hong Kong were related to both physicians and patients. Our results reflected that many Hong Kong physicians did not comply with international recommendations of stroke prophylaxis therapy in AF patients, and AF patients in Hong Kong had a low knowledge level of AF and warfarin therapy. Patients with AF in Hong Kong were generally not knowledgeable in the disease and warfarin therapy compared to AF patients in Western countries. Education and interventions should be conducted to improve knowledge of both physicians and patients in the management of AF.

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