Patient Preference and Adherence

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ORIGINAL RESEARCH

A survey of reasons for continuing warfarin therapy in the era of direct oral anticoagulants in Japanese patients with atrial fibrillation: the SELECT study

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Purpose: Although warfarin has historically been the standard of care for preventing ischemic stroke in patients with nonvalvular atrial fibrillation (NVAF), the use of direct oral anticoagulants (DOACs) is rapidly increasing. In this study, we examined the demographic and clinical characteristics of patients continuing warfarin therapy and investigated reasons for warfarin continuation.

Patients and methods: Each study site consecutively registered 10 patients with NVAF who had been taking warfarin for at least 12 months. Demographic and clinical characteristics and international normalized ratio (INR) values were collected from medical records. Physicians responded to questionnaires exploring reasons for continuing warfarin therapy.

Results: Overall, 313 patients treated with warfarin were registered at 33 sites. Mean ± SD age was 76.4±9.6 years; 62.9% of patients were male. The proportion of patients with INR values in the therapeutic range was 74.6% and 48.8% among patients aged ≥70 years and <70 years, respectively. Over half of the patients (51.4%) had been advised to switch from warfarin to DOACs; the primary physician-reported reason for this recommendation was superior safety and effectiveness. However, patients reported continuing warfarin because of the high price of DOACs (47.2%) and long-term positive experiences with warfarin (31.7%). The remaining 48.6% of patients with NVAF had never been counseled by their physicians about DOACs as an alternative to warfarin. For 76% of these patients, physicians favored warfarin for medical reasons, such as impaired renal function and controlled INR, but in the remaining patients, medical reasons for continuing warfarin were lacking.

Conclusion: Approximately half of the patients in this study were informed of warfarin alternatives primarily for improved efficacy and safety, but elected not to change regimens because of the high price of DOACs and long-term positive experiences with warfarin. In the remaining half, physician preference or specific patient characteristics prevented a change in therapy.

Keywords: anticoagulant, physician preference, nonvalvular atrial fibrillation, patient satisfaction

Plain language summary

Although warfarin has historically been the standard of care for preventing ischemic stroke in patients with nonvalvular atrial fibrillation, the use of direct oral anticoagulants (DOACs) is rapidly increasing. We examined the demographic and clinical characteristics of patients continuing warfarin therapy and investigated reasons for warfarin continuation in the era of DOACs. More than half of the patients (51.4%) had been advised to switch from warfarin to DOACs; the primary physician-reported reason was "better safety and effectiveness profile of DOACs compared with warfarin". However, patients reported continuing warfarin because of the high price of DOACs (47.2%) and long-term positive experiences with warfarin (31.7%). The remaining 48.6% of patients had never been counseled by their physicians about DOACs

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as an alternative to warfarin. For 76% of these patients, physicians favored warfarin for medical reasons (eg, impaired renal function and controlled international normalized ratio), but in the remaining patients, medical reasons for continuing warfarin were lacking.

Introduction

Atrial fibrillation (AF) is a common arrhythmia in elderly populations and a major risk factor for cardioembolic stroke, which can lead to serious disability and diminished quality of life.[1–4] The incidence of AF is on the rise, and major cardiovascular risk factors, including age, male gender, hypertension, heart failure, and obesity, are known to increase the risk of developing AF.[5–7] Current AF treatment guidelines recommend the use of an oral anticoagulant (OAC) for prevention of cardioembolic stroke in patients with AF when additional risk factors are present.[8,9] Historically, warfarin has been the OAC of choice in AF. However, patients taking warfarin must monitor their anticoagulation status with regular measurements of international normalized ratio (INR) values. Even with routine testing, therapeutic INR values are difficult to maintain and are prone to fluctuations outside of the relatively narrow therapeutic range. Deviations in INR values may lead to serious outcomes including thrombosis and bleeding. In addition to regular monitoring, patients on warfarin must carefully regulate their diet and concomitant medications, avoiding antiplatelet drugs, nonsteroidal anti-inflammatory drugs, and other medications that may increase bleeding or interact with warfarin, thus imposing an additional burden on patients. Furthermore, it has been suggested that warfarin therapy may be associated with increased arterial stiffness.[10]

Recently, direct oral anticoagulants (DOACs), also known as non–vitamin K antagonist OACs, have been introduced for stroke prevention in patients with AF. DOACs – dabigatran, rivaroxaban, apixaban, and edoxaban – have shown superior or noninferior safety and efficacy compared to warfarin in large randomized controlled trials[11–13] and in real-world settings.[14–20] Although many patients with nonvalvular AF (NVAF) have switched to DOAC therapy, a significant proportion of patients are still treated with warfarin. The AGAIN study[38] was a prospective observational study conducted in Japanese patients with NVAF that investigated patient-reported satisfaction with apixaban after switching from warfarin (UMIN000018970). In this study, most physicians switched patients to apixaban in compliance with treatment guidelines,[21] but many patients remained on warfarin for reasons unsubstantiated by scientific evidence, including higher prices of DOACs compared to warfarin, lack of pressing reasons to switch (INR stably controlled within the therapeutic range), and fear of the potential risks of bleeding or ischemic events during the transition, either due to an overlap or a gap between warfarin and DOAC coverage. A further analysis of these reasons, as well as the characteristics of patients who remained on warfarin, was not explored in the study.

Therefore, the aim of this study was to investigate the reasons for continuing warfarin rather than switching to DOACs. Additionally, we examined the demographic and clinical characteristics of patients who continued warfarin treatment compared with patients who switched to DOACs.

Methods

Statement of ethics

This multicenter, retrospective study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by each hospital's ethics committee or by a central ethics committee (Supplementary materials, Table S1). The study is registered with UMIN-CTR, a clinical trial registry in Japan (study ID: UMIN000024531).

Study design

This study consisted of retrospective data collection of the patient's medical record and a questionnaire on the physician's perception on warfarin use in general. Physicians and investigators made a contract involving provisions and usage of the data for this study. Patient-level data, including patients' clinical and demographic characteristics and INR values, were retrospectively collected from medical records. To obtain the reasons why patients chose to continue the use of warfarin though they were advised to switch to DOAC, physicians, not patients, completed a questionnaire retrospectively based on a medical chart of each patient. Data including evaluations of physicians' knowledge and beliefs of warfarin-based anticoagulant therapy and general treatment strategies for NVAF were also collected. All data provided from physicians were de-identified. In this study, as no primary data collection of patient data was conducted, written informed consent was not required for this study according to local regulations in Japan.

Study sites

In total, 33 sites (10 hospitals and 23 clinics) were randomly selected from the institutions participating in the AGAIN study. Of these 33 institutions, 28 specialized in cardiology. Ten or more patients were registered consecutively at each site.

Study population

Adult Japanese patients with NVAF who had been treated with warfarin for prevention of cardioembolic stroke and

systemic embolism for at least 12 months before the index date (defined as the date of contract execution between Pfizer Japan and the study site) and who had never been treated with DOACs were eligible for the study. At each institution, the first 10 consecutive patients to meet enrollment criteria were selected retrospectively from the index date to eliminate selection bias. A total of 313 patients were ultimately enrolled in the study.

Data collection

Patient demographic and clinical characteristics were retrospectively collected from the medical record to construct a dataset for the 1-year period preceding each patient's most recent hospital visit. Each patient's physician received a questionnaire regarding the reasons for recommending or not recommending switching from warfarin to a DOAC (Figure 1, Q2 and Q4) and the reasons the patient declined to comply with this recommendation (Figure 1, Q3). Additionally, with the assistance of a contract research organization (Mebix Inc., Tokyo Japan), we sent a second questionnaire to the same group of physicians that addressed their general (non–patient-specific) strategies and beliefs regarding anticoagulant therapy with warfarin and DOACs (Supplementary materials, Figure S1).

Statistical methods

For continuous variables, the mean ± SD, median, minimum, and maximum were calculated. Proportions are presented as percentages. Differences in patient characteristics between patients treated with warfarin in the current study and those who switched from warfarin to apixaban in the AGAIN study were compared using the paired *t*-test or chi-square test. Statistical analyses were conducted using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

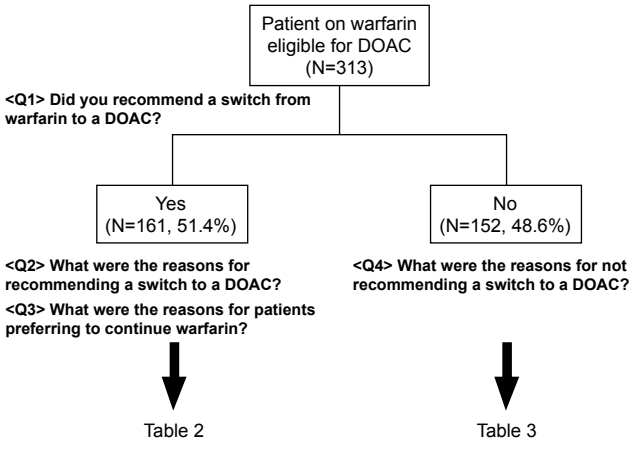

Figure 1 Flowchart of questions about physician recommendations to switch to DOACs or continue warfarin.

Notes: For each patient, physicians were asked Q1 to distinguish between patients who had received a recommendation to switch to DOACs and those who had not. For the former, physicians were then asked Q2 and Q3 to identify the underlying reason for the recommendation and the reason that the patient did not comply with the recommendation. For the latter, physicians were asked Q4 to identify the reason for not recommending switching from warfarin to DOACs.

Abbreviation: DOAC, direct oral anticoagulant.

Results

Patient characteristics

In total, 313 patients who met inclusion criteria were registered at 33 institutions. Patient demographic and clinical characteristics were collected retrospectively. Thirty-eight physicians answered questions regarding patient-specific reasons for continuing warfarin therapy, as well as additional questions addressing their knowledge and beliefs about anticoagulant therapy with warfarin and DOACs.

Patient demographic and clinical characteristics are shown in Table 1. Mean ± SD age was 76.4±9.6 years (73.5% of patients were ≥70 years old); 62.9% of patients were male. Mean ± SD $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores were 2.3±1.2, 4.1±1.8, and 2.6±1.2, respectively. Baseline INR values were within the recommended therapeutic range for 74.6% of patients aged ≥70 years and 48.8% of patients aged <70 years.

The mean ± SD annual number of INR measurements was 9.2±3.9 in patients aged ≥70 years and 8.2±3.6 in those aged <70 years; 43.0% and 36.1% of patients had changed warfarin dosages during the 52 weeks before the index date among patients aged ≥70 years and <70 years, respectively.

There was no significant difference in INR values between patients <70 years old and those ≥70 years old (2.0±0.5 and 2.0±0.4, respectively; P=1.000) (Table 1). Additionally, Figure 2 shows mean ± SD INR values at times when warfarin doses were increased (1.59±0.42 in patients aged ≥70 years and 1.82±0.43 in patients aged <70 years) and those at times when doses were decreased (2.60±0.77 in patients aged ≥70 years and 2.78±0.72 in patients aged <70 years). The timing of dose changes was similar between the two groups.

Reasons for switching to DOACs or continuing warfarin

Figure 1 shows a flowchart of the questions presented to physicians regarding switching from warfarin to DOACs and patients' reasons for continuing warfarin despite physician recommendations. Approximately half of all patients (51.4%) who continued warfarin treatment had been advised to switch from warfarin to a DOAC. The primary reason among physicians for recommending DOACs was "a better safety and effectiveness profile for DOACs compared with warfarin"

Table 1 Patient demographic and clinical characteristics

	Total (N=313)	<70 years old (N=83)	≥70 years old (N=230)	*P*-value[a]
Male gender	197 (62.9)	65 (78.3)	132 (57.4)	<0.001
Age (years)	76.4±9.6	64.3±4.9	80.8±6.6	<0.001
Weight (kg)	61.2±12.7 (N=252)	71.2±11.5 (N=63)	57.9±11.3 (N=189)	<0.001
Creatinine clearance (mL/min)	57.3±28.0 (N=250)	87.8±24.8 (N=62)	47.2±20.8 (N=188)	<0.001
Duration of warfarin therapy				
<5 years	85 (27.2)	22 (26.5)	63 (27.4)	0.876
≥5 years	228 (72.8)	61 (73.5)	167 (72.6)	
HAS-BLED score	2.6±1.2	2.1±1.2	2.7±1.1	<0.001
$CHADS_2$ score	2.3±1.2	1.5±0.8	2.6±1.1	<0.001
CHA_2DS_2-VASc score	4.1±1.8	2.7±1.4	4.6±1.7	<0.001
INR at baseline	2.0±0.4 (N=308)	2.0±0.5 (N=80)	2.0±0.4 (N=228)	1.000
FIR (%)	66.0±28.5 (N=309)	47.3±29.6 (N=81)	72.7±25.0 (N=228)	<0.001
Patients achieving therapeutic goals	209 (67.9) (N=308)	39 (48.8) (N=80)	170 (74.6) (N=228)	<0.001
Number of concomitant drugs	6.1±3.3	5.0±2.8	6.5±3.3	<0.001
Frequency of INR measurement (per year)	9.0±3.9 (N=309)	8.2±3.6 (N=81)	9.2±3.9 (N=228)	0.044
Percentage of patients whose warfarin dosages were changed in the past 1 year	41.2	36.1	43.0	0.274
Self-pay ratio to whole medical costs				
0%	25 (8.0)	3 (3.6)	22 (9.6)	<0.001
10%	165 (52.7)	2 (2.4)	163 (70.9)	
20%	19 (6.1)	1 (1.2)	18 (7.8)	
30%	102 (32.6)	76 (91.6)	26 (11.3)	
Others	2 (0.6)	1 (1.2)	1 (0.4)	

Notes: Data are presented as N (%) or mean ± SD. The number of patients used for the analysis was 313, 83, and 230 for total patients, patients aged <70 years, and patients aged ≥70 years, respectively, unless otherwise specified. In patients with NVAF, target INR level is within the following range according to Japanese treatment guidelines (Guidelines for Pharmacotherapy of Atrial Fibrillation [JCS 2013]): 2.0–3.0 for patients <70 years old and 1.6–2.6 for patients ≥70 years old.[21] $CHADS_2$ score was calculated based on age >75 years and the presence of congestive heart failure, hypertension, diabetes, and 2 points for stroke or transient ischemic attack. CHA_2DS_2-VASc score was calculated by allotting 1 point each for congestive heart failure/left ventricular dysfunction, hypertension, diabetes, vascular disease (prior myocardial infarction, peripheral arterial disease, or aortic plaque), age between 65 and 74 years, and female gender; 2 points each were allotted for age >75 years and prior stroke, or transient ischemic attack. HAS-BLED score was calculated based on the following components: hypertension, abnormal renal function, abnormal liver function, previous stroke, bleeding history or predisposition, labile INR, age >65 years, drugs predisposing patient to bleeding (antiplatelet agents or nonsteroidal anti-inflammatory drugs), and alcohol abuse. [a]Comparison between patients <70 years old and those ≥70 years old. An unpaired *t*-test and a chi-square test were used for continuous variables and categorical variables, respectively.

Abbreviations: FIR, frequency in therapeutic range; INR, international normalized ratio; NVAF, nonvalvular atrial fibrillation.

(55.3%), as shown in Table 2. However, although these patients had been advised to switch to DOACs, they chose to continue warfarin therapy primarily due to "much higher drug prices of DOACs" (47.2%) and their "long-term experience

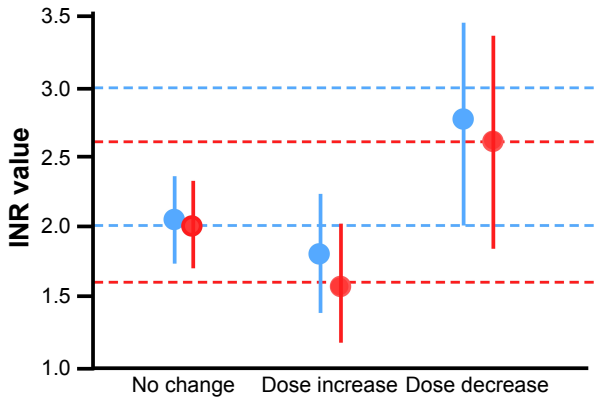

Figure 2 INR values when doses of warfarin were increased or decreased in patients <70 years old and ≥70 years old.

Notes: Mean ± SD is shown. Blue = patients aged <70 years; red = patients aged ≥70 years. Dotted lines show the therapeutic ranges recommended by the Japanese treatment guidelines for each age range.

Abbreviation: INR, international normalized ratio.

Table 2 Reasons physicians recommended switching to DOACs (N=161)

	n (%)
Medical reasons	
Unstable INR	19 (11.8)
Interaction with other drugs	1 (0.6)
High bleeding risk	11 (6.8)
Better safety and efficacy profile of DOACs	89 (55.3)
Concomitant disease	0 (0)
Reduction of overall risk accompanied with warfarin therapy	2 (1.2)
Bleeding during warfarin therapy	0 (0)
Timing of dental procedure	1 (0.6)
Timing of ablation	0 (0)
Timing of surgical procedure	0 (0)
Pregnancy	0 (0)
Other medical reasons	1 (0.6)
Nonmedical reasons	
To avoid regular INR measurement	21 (13)
To avoid food restrictions	13 (8.1)
Dose adjustment of warfarin is bothersome	2 (1.2)
To reduce total number of pills	0 (0)
Other nonmedical reasons	1 (0.6)

Note: Data are presented as n (%).

Abbreviations: DOAC, direct oral anticoagulant; INR, international normalized ratio.

Table 3 Reasons in favor of continued warfarin therapy (N=152)

	n (%)
Medical reasons	
INR stably controlled	57 (37.5)
Decreased renal function	39 (25.7)
No bleeding or ischemic events while taking warfarin	8 (5.3)
Concerns about bleeding and embolic events during switch	2 (1.3)
Frequent dose adjustments required	3 (2.0)
Other medical reasons	6 (3.9)
Nonmedical reasons	
Higher medical costs of DOACs compared to warfarin	11 (7.2)
Patients were satisfied with warfarin therapy	9 (5.9)
Patients had concerns about switching	13 (8.6)
INR measurement motivates patients to continue therapy	0 (0)
Other nonmedical reasons	2 (1.3)
Other reasons	2 (1.3)

Note: Data are presented as n (%).
Abbreviations: DOAC, direct oral anticoagulant; INR, international normalized ratio.

with warfarin without any trouble" (31.7%). Among the remaining half of the patients who were not advised to switch from warfarin to DOACs, leading reasons for continuing warfarin treatment were "INR stably controlled" (37.5%) and "decreased renal function" (25.7%) (Table 3).

Questionnaire results: physicians' insight into anticoagulation therapy

Tables 4 and 5 show physicians' responses to general questions of patient suitability for warfarin versus DOAC treatment (refer to Figure S1 for the questionnaire). In response to the question "Which patients do you think are suitable for warfarin treatment?", 81.6% of physicians selected "patients with decreased renal function", and 68.4% selected "patients who are satisfied with warfarin". A large majority of physicians responded that switching to DOACs is appropriate for patients with fluctuating INR levels (89.5%) and for patients with INR values consistently outside of the therapeutic range (76.3%).

Table 4 Physicians' perspective on patients suitable for warfarin treatment (N=38)

Characteristics	n (%)
Decreased renal function	31 (81.6)
Low body weight	16 (42.1)
INR within the recommended therapeutic range	20 (52.6)
No stroke events with INR below the therapeutic range	4 (10.5)
Patient satisfied with warfarin	26 (68.4)
Frequent dose adjustments required	10 (26.3)
Self-pay ratio of medical costs: 0%	0 (0.0)
Self-pay ratio of medical costs: 10%	0 (0.0)
Self-pay ratio of medical costs: 20%	1 (2.6)
Self-pay ratio of medical costs: 30%	16 (42.1)
NVAF patients with coronary artery disease	0 (0.0)
NVAF patients with mitral valve stenosis	22 (57.9)
NVAF patients with valvular disease	7 (18.4)
Other	3 (7.9)

Note: Data are presented as n (%).
Abbreviations: INR, international normalized ratio; NVAF, nonvalvular atrial fibrillation.

Table 5 Physicians' perspective on patients suitable for switching to DOACs (N=38)

Characteristics	n (%)
All patients for whom DOACs are indicated are suitable	9 (23.7)
INR consistently outside the therapeutic range	29 (76.3)
Fluctuations in INR	34 (89.5)
Inadequate dietary restriction	31 (81.6)
Dehydration	4 (10.5)
Patients aged <65 years	8 (21.1)
Patients aged ≥65 and <75 years	10 (26.3)
Patients aged ≥75 years	8 (21.1)
Diabetes mellitus	4 (10.5)
Concomitant treatment with NSAIDs	8 (21.1)
Concomitant treatment with antiplatelet drug	12 (31.6)
Patients requiring surgery	18 (47.4)
Patients scheduled for ablation treatment	16 (42.1)
Patients scheduled for dental procedure	6 (15.8)
Dementia	10 (26.3)
Depression	1 (2.6)
Self-pay ratio of medical costs: 0%	11 (28.9)
Self-pay ratio of medical costs: 10%	12 (31.6)
Self-pay ratio of medical costs: 20%	4 (10.5)
Self-pay ratio of medical costs: 30%	2 (5.3)
Other	0 (0.0)

Note: Data are presented as n (%).
Abbreviations: DOAC, direct oral anticoagulant; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug.

A comparison of patients on warfarin therapy (current study) versus patients who switched to apixaban (AGAIN study)

Table 6 shows the demographic and clinical characteristics of patients continuously treated with warfarin and those who switched from warfarin to a DOAC. There were significant differences between the two groups in the self-pay ratio of medical costs ($P<0.0001$), duration of warfarin treatment ($P<0.0001$), and the percentage of patients aged ≥70 years whose baseline INR values were within the therapeutic range ($P<0.0001$).

Discussion

This study surveyed patient characteristics, INR values, and physicians' and patients' reasons for continuing warfarin therapy rather than switching to DOACs in a population of patients with NVAF treated with warfarin. We found that ~50% of patients on warfarin were never counseled by

Table 6 Demographic and clinical characteristics of patients receiving continued warfarin therapy (current study) and patients who switched to apixaban (AGAIN study[38])

	SELECT (N=313)	AGAIN (N=697)	*P*-value
Male gender	197 (62.9)	433 (62.1)	0.8045
Age (years)	76.4±9.6	76.2±9.1	0.6816
Weight (kg)	61.2±12.7 (N=252)	60.6±12.6 (N=572)	0.5245
Creatinine clearance (mL/min)	57.3±28.0 (N=250)	60.8±43.0 (N=331)	0.2551
HAS-BLED score	2.6±1.2	2.6±1.1	1.000
$CHADS_2$ score	2.3±1.2	2.5±1.3	0.1171
CHA_2DS_2-VASc score	4.1±1.8	4.0±1.7	0.2877
INR at baseline	2.0±0.4 (N=308)	2.0±0.6 (N=672)	0.4718
FIR (%)	66.0±28.5 (N=309)	60.2±30.4 (N=672)	0.004
Patients achieving therapeutic goals			
<70 years	39 (48.8) (N=80)	55 (38.7) (N=142)	0.1477
≥70 years	170 (74.6) (N=228)	304 (57.4) (N=530)	<0.0001
Duration of warfarin therapy			
<5 years	85 (27.2)	261 (37.4)	<0.0001
≥5 years	228 (72.8)	326 (46.8)	
Self-pay ratio of total medical costs			
0%	25 (8.0)	104 (14.9)	<0.0001
10%	165 (52.7)	411 (59.0)	
20%	19 (6.1)	42 (6.0)	
30%	102 (32.6)	139 (19.9)	
Other	2 (0.6)	1 (0.1)	

Notes: Data are presented as N (%) or mean ± SD. The number of the patients used for the analysis was 313 for the SELECT study (current study) and 697 for the AGAIN study, unless otherwise specified. In patients with NVAF, INR levels should be maintained within the following ranges according to Japanese treatment guidelines (Guidelines for Pharmacotherapy of Atrial Fibrillation [JCS 2013]): 2.0–3.0 for patients <70 years old and 1.6–2.6 for patients ≥70 years old.[21] $CHADS_2$ score was calculated based on age >75 years and the presence of congestive heart failure, hypertension, diabetes, and 2 points for stroke or transient ischemic attack. CHA_2DS_2-VASc score was calculated by allotting 1 point each for congestive heart failure/left ventricular dysfunction, hypertension, diabetes, vascular disease (prior myocardial infarction, peripheral arterial disease, or aortic plaque), age between 65 and 74 years, and female gender; 2 points each were allotted for age >75 years and prior stroke, transient ischemic attack, or thromboembolism. HAS-BLED score was calculated based on the following components: hypertension, abnormal renal function, abnormal liver function, previous stroke, bleeding history or predisposition, labile INR, age >65, drugs predisposing to bleeding (antiplatelet agents or nonsteroidal anti-inflammatory drugs), and alcohol abuse.
Abbreviations: FIR, frequency in therapeutic range; INR, international normalized ratio; NVAF, nonvalvular atrial fibrillation.

their physician about DOACs as an alternative treatment option, and therefore continued warfarin therapy primarily as a result of physicians' medical judgment. Additionally, we found that the percentage of patients with therapeutic INR values was notably high among patients aged ≥70 years.

In our investigation into the reasons for continuing warfarin rather than switching to DOACs, we found that about half of the patients remaining on warfarin therapy had never been advised by their physicians to switch therapies, nor had they been informed about DOACs as a potential alternative to warfarin. Medical rationales for continuing warfarin outweighed reasons related to patient convenience, including "INR stably controlled by warfarin", as reported by 37.5% of physicians (Table 3). When asked in general terms about which patients are suitable for continuing warfarin treatment, 52.6% of physicians responded, "patients whose INR is controlled within the recommended therapeutic range" (Table 4). In contrast, 76.3% of physicians stated that patients should be switched to DOACs "when INR values are not consistently within the therapeutic range of warfarin recommended by the guidelines". Correspondingly, 89.5% of physicians replied that "patients with fluctuations in INR" are appropriate for DOACs (Table 5).

Physicians reported that patients with large visit-to-visit INR fluctuations may carry a higher risk of bleeding and ischemic stroke. However, the opposite may not always be true, as patients receive the maximum benefit of stable INR only when INR is maintained within the optimal therapeutic range. Furthermore, results from previous randomized controlled trials suggest that patients treated with DOACs may experience fewer bleeding and/or ischemic events compared to patients on warfarin with INR levels stably maintained inside the therapeutic range. Hemorrhage has also been observed in patients with INR <3.0 in real-world settings.[22,23] Therefore, stably controlled INR may not always be a logical reason to forgo transitioning to DOACs, although many physicians reportedly believe that control status of INR is the most critical factor for deciding to continue warfarin therapy.

The second most common reason for not recommending DOACs was "reduced renal function", reported by 25.7%

of physicians (Table 3). Warfarin is metabolized in the liver, whereas all DOACs have some degree of renal excretion; dabigatran is the highest at 80%, followed by edoxaban (50%), rivaroxaban (33%), and apixaban (27%).[24–28] Therefore, warfarin can be expected to provide more stable anticoagulation than DOACs in patients with reduced renal function. However, patients with impaired renal function were excluded from the large-scale randomized Phase III trials that investigated the efficacy and safety of DOACs in comparison to warfarin.[11–13,29] In one study comparing apixaban and warfarin, apixaban reduced the rate of stroke, death, and major bleeding, regardless of renal function.[30] Further studies are needed to evaluate the efficacy and safety of DOACs compared with warfarin in patients with impaired renal function.

As previously mentioned, 51.4% of patients taking warfarin had been advised by their physician to switch to a DOAC. Although it is not entirely clear why warfarin therapy was continued in these patients, patient preference likely affected this decision. Our results revealed that patients elected to continue warfarin therapy primarily due to the "much higher drug prices of DOACs" (reported by 47.2% of patients) and a "long-term experience of warfarin without any trouble" (31.7%). AF commonly occurs in the elderly, as reflected in this survey population (73.5% of patients were ≥70 years old). Consequently, many patients with AF have a limited income – often solely pension – and may not be able to afford more expensive medications. This may explain why drug price was the leading reason for continuing warfarin, the least expensive OAC.

As shown in Table 6, there were minimal differences in clinical and demographic background between patients on warfarin (from the current study) and patients who switched to apixaban (from the AGAIN study). Only three significant differences in background were observed between the two groups: 1) duration of warfarin treatment, 2) percentage of patients aged ≥70 years with therapeutic INR levels, and 3) self-pay ratio of medical costs. Not coincidentally, these differences between warfarin users and apixaban users correspond with the reasons that patients reported a preference for continuing warfarin therapy, namely, that patients on long-term warfarin have had positive experiences, that patients have been able to maintain stable INR with warfarin, and that patients with higher self-pay ratios tend to choose the more affordable OAC.

The aim of this study was to explore the reasons for continued warfarin use from the perspective of both physicians and patients. However, the most critical element in this scenario, regardless of the type of OAC, is patient compliance with medications as prescribed by physicians. Patient satisfaction with and preference for a given pharmaceutical regimen may have a significant impact on medication adherence.[31] The importance of patient adherence to anticoagulant therapy for prevention of stroke cannot be overstated; a single missed dose may lead to stroke.[32,33] Therefore, patient preference for anticoagulation therapy should be taken into consideration to maintain optimal medication adherence. Equally important is a healthy doctor–patient relationship that includes discussion of all treatment options and frequent communication about patient satisfaction with anticoagulation therapy.

As shown in Table 1, mean INR values were comparable between patients aged <70 years and ≥70 years, indicating that physicians are not always strictly adherent to the Japanese Circulation Society's 2013 Guidelines for Pharmacotherapy of Atrial Fibrillation; these guidelines recommend that INR levels in patients with NVAF should be maintained between 2.0 and 3.0 in patients aged <70 years old, and between 1.6 and 2.6 in patients aged ≥70 years old.[21] As shown in Figure 2, physicians may be targeting the INR range of 1.6–2.6 even in younger patients, despite Japanese guideline recommendations for a therapeutic range of 2.0–3.0. Similar results have been reported by investigators from the Fushimi Registry, a community-based survey of patients with AF in Japan that primarily consists of private clinics of general practitioners,[34,35] and the J-RHYTHM Registry, a nationwide registry of patients with AF recruited from hospitals and clinics specializing in cardiology.[36,37] This finding implies that physicians may treat patients of all ages with relatively low doses of warfarin to maintain INR values between 1.6 and 2.6 regardless of guideline recommendations, likely out of concern related to the development of bleeding events. Taken together, these results suggest that INR is suboptimally controlled in patients aged <70 years, regardless of the specialty of the physician managing care.

Limitations

This study has several limitations because of its design and methodology. The study was conducted at a limited number of institutions that were chosen at random from the AGAIN study; therefore, the results may not be suitable for extrapolation to general practice in Japan or other countries. Additionally, the questionnaires used in this study have not been validated linguistically and psychometrically, and methods for using them have not been standardized.

Conclusion

Approximately half of the patients in this study received a recommendation from their physician to switch from warfarin to a DOAC, primarily on the basis of improved efficacy and safety, but elected not to change regimens because of the high price of DOACs. In the remaining half of the study population, physician preference or specific patient characteristics prevented a change of therapy. From the physician's perspective, stable INR control was the most important reason to continue warfarin, even if INR values were below the therapeutic range. For patients, lower cost and long-term positive experiences with warfarin constituted the rationale for warfarin preference. Ultimately, a healthy doctor–patient relationship that includes discussion of all treatment options and frequent communication about patient satisfaction with anticoagulation therapy is crucial for achieving medication adherence.

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Author contributions

All authors contributed toward study design, data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

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