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Original Research

Effects of a Pharmacist-Led Educational Interventional Program on Electronic Monitoring–Assessed Adherence to Direct Oral Anticoagulants: A Randomized, Controlled Trial in Patients with Nonvalvular Atrial Fibrillation

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ABSTRACT

Purpose: Several landmark trials have reported that direct oral anticoagulants (DOACs) are more effective in preventing stroke and systemic embolism than vitamin K antagonists. However, nonadherence to DOACs worsens prognosis in patients with nonvalvular atrial fibrillation (NVAF) despite the effectiveness of the drugs. The purpose of this study was to evaluate the effects of a pharmacist-led educational interventional program involving motivational interviewing on medication adherence, as assessed by electronic monitoring, in patients receiving DOACs for the treatment of NVAF.

Methods: This prospective, randomized, interventional study was conducted at outpatient cardiology clinics at general hospitals and pharmacies in Japan. Patients with NVAF who were treated with a once-daily DOAC (edoxaban) or a twice-daily DOAC (apixaban) were randomized to receive either: (1) an educational interventional program involving motivational interviewing regarding adherence to anticoagulants; or (2) standard medication counseling. The primary end point was the change in the *medication adherence rate*, calculated as the number of days that patients appropriately took the drug, as assessed by an electronic monitoring device, divided by the total number of days that the drug was prescribed, from a 12-week observation period to a 12-week intervention period. The secondary end points were tolerability outcomes. The effect of the educational interventional program on the primary end point was analyzed in subgroups stratified by gender and type of DOAC received.

Findings: A total of 268 patients completed the observation period and were randomly assigned to one of the two study groups. The difference in the primary end point between the educational interventional program group and the standard medication counseling group was not significant (mean [SD], 2.9%

[8]Survey on Medication Adherence to Anticoagulant Drugs and Investigation of Improvement of Medication Adherence by an Educational Program in Nonvalvular Atrial Fibrillation.

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[7.5%] vs 3.4% [8.3%]). On multiple linear regression analysis, the difference in DOAC adherence between the two groups was not significant, but that adherence to apixaban was significantly improved among men in the educational interventional program ($\beta = 0.219$; $P = 0.012$). Two patients died of causes considered unrelated to treatment; no stroke/systemic embolism or major bleeding events were observed.

Implications: In this randomized, controlled study of the effects of a pharmacist-led educational interventional program using motivational interviewing on adherence to DOACs among patients with NVAF, adherence to DOACs, as assessed using an electronic monitoring device, was not improved with the educational interventional program compared to standard medication counseling . However, adherence to twice-daily apixaban was improved among men, but not among women, in the educational interventional program group. In this study, the selection of DOACs was not randomized, and the lack of assessment of the association between adherence to DOACs and clinical outcomes was a limitation. Japan Registry of Clinical Trials (jRCT) indentifier: jRCTs031180142. (*Clin Ther.* 2022;44:XXX–XXX)

Key words: adherence, atrial fibrillation, direct oral anticoagulant, electronic monitoring, motivational interviewing.

INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia that increases the risk for stroke due to thromboembolism.[1,2] Oral anticoagulants (OACs) such as vitamin K antagonists and direct (D)-OACs are recommended for use in the treatment of patients with nonvalvular (NV)-AF at an increased risk for stroke.[3,4] Several landmark trials have reported that DOACs are more effective in preventing stroke and systemic embolism than are vitamin K antagonists.[5–8] However, nonadherence to DOACs may worsen prognosis in patients with NVAF despite the effectiveness of the drugs. A recent meta-analysis reported that suboptimal adherence to DOACs was common and was associated with poor outcomes in patients with NVAF.[9] In the DOAC era, the characteristics of patients who are nonadherent to prescribed DOACs, and the educational methods that could effectively improve adherence in these patients, remain unclear. Several studies have reported the effects of educational programs—information booklets, reminder tools, access to virtual clinics, artificial-intelligence platforms, and telemonitoring systems—on adherence to DOACs, but the results have been controversial.[10–12]

Motivational interviewing is a patient-centered counseling/communication method used for helping patients to make choices by finding internal motivation; it is commonly used for helping patients to change their health-related behaviors and outcomes.[13] Motivational interviewing has been applied in the treatment of substance abuse and chronic diseases, as well as in mental health programs.[14–16] This method has been adopted in an attempt to improve medication adherence in patients with diseases such as HIV infection, osteoporosis, hypertension, dyslipidemia, and asthma.[17–19] Therefore, this study aimed to evaluate the effects of an educational interventional program involving motivational interviewing by pharmacists on medication adherence, as assessed by electronic monitoring, in patients with NVAF being treated with a once-daily DOAC (edoxaban) or a twice-daily DOAC (apixaban).

PATIENTS AND METHODS

Study Design

The Survey on Medication Adherence to Anticoagulant Drugs and Investigation of Improvement of Medication Adherence by an Educational Program in NVAF (SMAAP-AF) was a multicenter, prospective, interventional study in patients with NVAF, with two periods: a 12-week observational period (stage 1), and a 12-week single-blind, randomized, parallel-group intervention period (stage 2). In stage 1, medication adherence in enrolled patients with NVAF who were treated with once-daily edoxaban or twice-daily apixaban was electronically monitored. Patients who completed stage 1 were randomized 1:1, using a minimization method, based on medication adherence in Stage 1 and demographic characteristics as assignment factors. Equal numbers of patients were randomly assigned to receive the medication educational interventional program and standard medication counseling, using a Web-based dynamic random-allocation system (see **Supplemental Figure 1** in the online version at doi:10.1016/j.clinthera.

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2022.09.011). The educational interventional program and standard medication counseling were delivered by pharmacists at participating pharmacies.

Study Patients

This study enrolled outpatients with NVAF who visited the cardiology clinics at Tokyo Women's Medical University Hospital (Tokyo, Japan), the National Hospital Organization Yokohama Medical Center (Yokohama, Japan), and Tokyo Women's Medical University Yachiyo Medical Center (Yachiyo, Japan), from May 15, 2018, through November 30, 2018.

The study participants were patients aged ≥20 years who had been diagnosed with NVAF and were undergoing treatment with edoxaban or apixaban, with the medication first being prescribed at least 4 weeks prior to enrollment into this study. The exclusion criteria included patients who may have had difficulty maintaining adherence, whose medications were managed by a person other than themselves, who were or would be hospitalized during the study period, and/or who were pregnant. A full list of inclusion and exclusion criteria is provided in **Supplemental Table I** (the online version at doi:10.1016/j.clinthera.2022.09.011).

During the trial, each patient received his or her prescribed medications, including the DOAC, from the same participating pharmacy. The study protocol was approved by the institutional review board at Tokyo Women's Medical University (approval number 180201) and the Certified Review Board of Hattori Clinic (Tokyo, Japan; approval number CRB3180027). Written informed consent was obtained from all study participants.

Study Procedures

In stage 1, patients were provided with standard medication counseling by a pharmacist at the time of drug dispensation. An electronic monitoring device—a card-type electronic device set into the press-through pack (PTP) of each DOAC—was provided in advance by the pharmacy or pharmacy department of the surveyed facility. After the pharmacist explained to the patient that the electronic device automatically records the date and time at which the drug is used, and that the patient should bring all of the electronic devices to the next visit, the electronic devices with the prescribed DOACs were provided to the patient. At the next visit, the pharmacy or pharmacy department at each facility collected the electronic devices that had been provided at the previous visit, and the data center collected the electronic devices from each pharmacy and obtained the electronic data. DOAC-adherence status during the first 8 weeks, which was blinded to the patients and physicians/pharmacists, was used as an adjustment factor for randomization.

In stage 2, patients who were allocated to the educational interventional program group participated in the motivational interviewing program, and patients who were allocated to the standard medication counseling group continued to receive standard medication counseling from pharmacists. Physicians, medical staff, outcomes assessors, and data analysts were blinded to group assignments. The use and collection of electronic monitoring devices were the same as those in stage 1.

Intervention

The educational interventional program was conducted by board-certified pharmacists (Japan Pharmacists Education Center) who participated in a training program on motivational interviewing for patients taking DOACs that was conducted by the advisors of the medication education program in this study. As mentioned earlier, *motivational interviewing* is a method of providing medication guidance and support by exploring the reasons that patients do not want to take anticoagulants. The health care provider engages in a dialog that elicits positive statements by asking the patient to consider the role of anticoagulants rather than presenting a one-way solution. To prioritize the patient's motivation and self-determination toward behavior change (ie, taking the anticoagulant as prescribed), the methods were modified in this study.[13] The motivational interviewing conversation was based on four concepts—partnership, acceptance, compassion, and evocation[13]—as follows: (1) *partnership,* defined as the basic stance of working together with the patient to solve the problem (ie, nonadherence) rather than medical staff unilaterally suggesting a solution; (2) *acceptance,* defined as a pharmacist's suppression of the impulse to "correct" the patient with regard to the patient's adherence to DOAC treatment, and to instead listen to the patient's thoughts and opinions (during this process, the factors that prevent the patient from taking the DOAC become clear); (3) *compassion,* defined as a patient's welfare (ie, stroke prevention) as the central concern during

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motivational interviewing, rather than the convenience of the medical staff; and (4) *evocation,* defined as the pharmacist's seeking to evoke positive thoughts in the patient (to improve medication adherence) and the patient's self-determination to change (ie, taking the DOAC as prescribed). The pharmacist asked the patient several questions concerning the situation, based on the motivational interviewing sheet (see **Supplemental Figure 2** in the online version at doi:10.1016/j.clinthera.2022.09.011). During this process, the topic was discussed, and the patient's answers were recorded.

End Points

The primary end point was the change in the rate of adherence to DOAC treatment from stage 1 to stage 2 in patients who received the educational interventional program in stage 2 versus those who did not. *Medication adherence* during the study period was defined as the number of *days of adherence,* or the number of days on which the tablets in the PTP were accessed once daily (every 24 hours; edoxaban) or twice daily (every 12 hours; apixaban). The *medication adherence rate* was calculated as days of adherence divided by the total number of days that the drug was prescribed, as assessed using the electronic monitoring device. The secondary end points were tolerability outcomes, including major bleeding, stroke/systemic embolism, other serious adverse events, and adverse events associated with the discontinuation of the study intervention. The effect of the educational interventional program on the primary end point was also analyzed in subgroups stratified by gender and type of DOAC.

Assessment of Adherence

Medication adherence was measured using the Your Manager electronic monitoring device (Dai Nippon Printing Co Ltd, Tokyo, Japan), a card-type PTP electronic device that records the date and time when the packaging for each tablet in the PTP is opened.[20,21] Data were recorded in comma-separated value (.csv) format.

Adherence, as measured by the electronic monitoring device, was calculated as the percentage of days of adherence in the measurement period in each patient. *Days of adherence* was defined as the number of days on which tablets in the PTP were accessed once daily (one tablet every 24 hours, between 3 a.m. on a given day and 3 a.m. on the next day; edoxaban) or twice daily (one tablet every 12 hours, between 3 a.m. and 3 p.m. and between 3 p.m. on a given day and 3 a.m. on the next day; apixaban). *Days of nonadherence* was defined as the number of days with no record of access of a tablet within 24 hours (between 3 a.m. on a given day and 3 a.m. on the next day; edoxaban) or within 12 hours (between 3 a.m. and 3 p.m. on a given day or between 3 p.m. and 3 a.m. on the next day; apixaban) (ie, missed doses), or as more than one tablet accessed (edoxaban) or more than two tablets accessed (apixaban) within 24 hours (between 3 a.m. on a given day and 3 p.m. on the next day) (ie, extra doses). Any period during which DOAC therapy was temporarily discontinued by the investigator due to surgery or another invasive procedure during the measurement period was excluded.

Data Collection

At the time of enrollment, the patients' demographic information (age, gender, body weight, employment status, and whether they lived alone or with a partner/family); cognitive function, as assessed with the Japanese version of the Mini-Mental State Examination (MMSE)[22]; medical history; concurrent medications, including history of anticoagulant use; and score on the $CHADS_2$ score (congestive heart failure, hypertension, age ≥75 years, diabetes, stroke [doubled]) were recorded by the study coordinators. All adherence-related data from the electronic devices were evaluated by independent data assessors but were not made available to patients, physicians, clinic staff, or pharmacists until the last patient completed the study.

Sample-Size Estimation

According to a report by Shore et al,[23] the rates of nonadherence (<80% of days covered) were 34.8% (363/1042) among patients who did not receive any specific drug education and 19.7% (63/320) among those who received drug education in person or by telephone. In the study by Shore et al,[23] the relative risk adjusted for age, gender, and race was 1.26, whereas the crude odds ratio for noncompliance was 0.46. If the number of patients completing the intervention (stage 2) was 320 patients, and the significance level was 5%, then the power was 86.1%. Therefore, it was determined that 320 patients would be considered sufficient for the study purposes and that the target number of patients was 360.

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Statistical Analysis

The *full analysis set* comprised all patients who received at least one dose of study DOAC in the intervention period (stage 2) with sufficient records from the electronic monitoring device. The *per-protocol set* (PPS) included all patients who received consistent treatment with the same DOAC throughout stage 2 and whose data were recorded with the electronic monitoring device. In the full analysis set, the last observation carried forward method was used to impute missing values. Sensitivity analysis was performed using the PPS.

Continuous variables are presented as the means (SD) and were compared using the unpaired *t* test and the *U* test, as appropriate. Categorical variables were compared using the χ^2 test. A change in a variable was calculated as the value in stage 2 minus the baseline value in stage 1. Multiple linear regression analysis was performed to quantify the association of a change in adherence to DOAC therapy with the educational program administered during stage 2, adjusted for age, gender, type of DOAC, $CHADS_2$ score, living status, working status, antiplatelet/NSAID use, and stroke-related comorbidities. Subanalyses, stratified by gender and type of DOAC, were performed as described earlier. A *P* value of <0.05 was considered statistically significant. All data were handled and analyzed in full accordance with the analysis plan in the study protocol, using SPSS Statistics version 27.0 (IBM Co, Tokyo, Japan).

RESULTS

Patients

Of the 301 patients enrolled in the trial, 268 patients who completed stage 1 were randomly assigned to receive either the educational program or standard medication counseling (Figure 1). Among them, 77% had an indication for treatment with a DOAC as primary prevention. The baseline characteristics of the patients who were treated with edoxaban and apixaban are shown in Table I. There were no significant differences in age, gender, $CHADS_2$ score, MMSE score, living status, or work status between the groups.

Effect of the Educational Interventional Program

The educational interventional program and standard medication counseling groups had high adherence rates in the observational period (92.9% [12.3%] and 94.5% [11.0%] in the educational interventional program and standard medication counseling groups, respectively).

Although the adherence rates were increased from stage 1 to stage 2 in both the group receiving the educational program and the group receiving standard medication counseling (see **Supplemental Table II** in the online version at doi:10.1016/j.clinthera.2022.09.011), the difference between the two groups was not significant (Figure 2). Multiple linear regression analyses showed no significant difference in medication adherence between the two groups (Table II). However, adherence to apixaban was significantly improved among men (change, from 94.5% [5.9%] to 99.8% [1.0%]), but not among women (change, from 89.4% [14.2%] to 91.3% [15.7%]), in the educational interventional program (see **Supplemental Table II** in the online version at doi:10.1016/j.clinthera.2022.09.011 and Table II).

Sensitivity analyses in the PPS (see **Supplemental Figure 3** in the online version at doi:10.1016/j.clinthera.2022.09.011) showed that the use of the educational interventional program was not associated with improved medication adherence; but was associated with a numerically but not significantly improved rate of adherence to apixaban among men in the PPS (see **Supplemental Table III** in the online version at doi:10.1016/j.clinthera.2022.09.011).

Characteristics of the Patients Who Withdrew

The clinical characteristics of the 30 patients who withdrew from the study were compared with those of the patients who completed stage 2 (see **Supplemental Table IV** in the online version at doi:10.1016/j.clinthera.2022.09.011). The percentage of women was higher in the group that withdrew, and the adherence rate in stage 1 was lower in the group that withdrew than in the group that completed stage 2. Among the patients who withdrew, the percentage of women was higher in the educational interventional program group than that in the standard medication counseling group (13/14 [92.9%] vs 8/16 [50.0%]; $P = 0.01$). The percentage of patients who withdrew was numerically, but not significantly, higher in the apixaban group than in the edoxaban group (17/110 [15.5%] vs 13/158 [8.2%]; $P = 0.065$).

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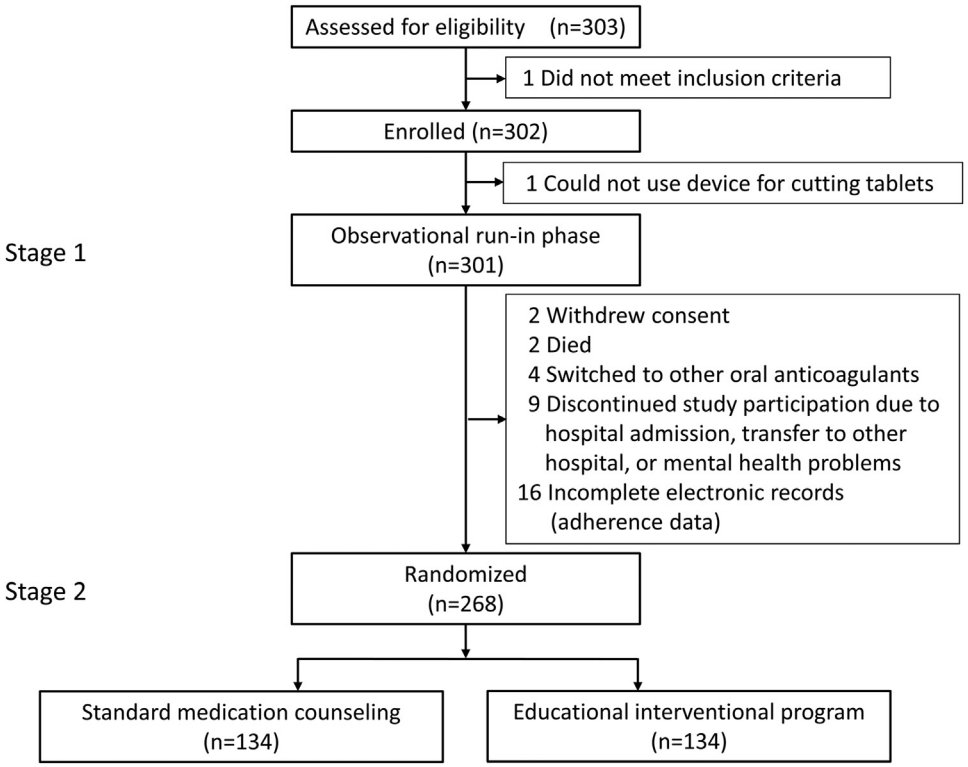

Figure 1. Participant flow chart.

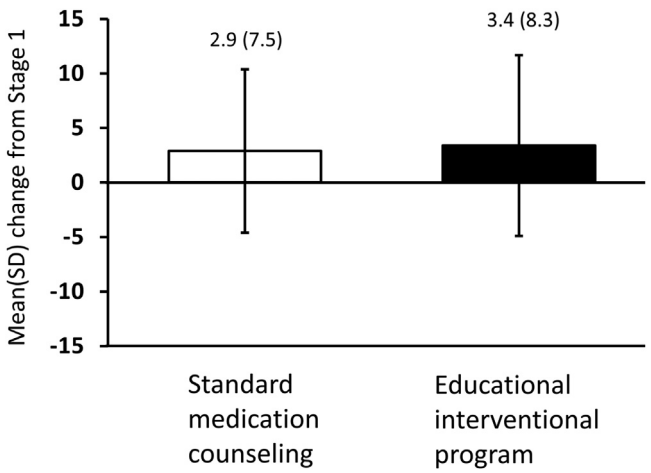

Figure 2. Mean (SD) changes in adherence rate (%) from stage 1 to stage 2 in the group receiving standard medication counseling versus the educational interventional program.

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Table I. Baseline characteristics.

Characteristic	Standard Medication Counseling (n = 134)	Educational Interventional Program (n = 134)	*P*
Age, mean (SD), y	73 (10)	73 (9)	0.773
Men, no. (%)	83 (62)	81 (60)	0.802
Body weight, mean (SD), kg	62 (12)	62 (12)	0.88
Creatinine clearance, mean (SD), mL/min	61 (23)	59 (22)	0.368
$CHADS_2$ score, mean (SD)	2.1 (1.5)	2.2 (1.4)	0.735
Stroke-related comorbidities, no. (%)			
Heart failure	58 (43)	55 (41)	0.711
Coronary heart disease	19 (14)	20 (15)	0.863
Hypertension	83 (62)	86 (64)	0.704
Diabetes	53 (40)	56 (42)	0.709
Previous stroke/TIA	13 (10)	18 (13)	0.34
Peripheral artery disease	12 (9)	17 (13)	0.326
Antiplatelet/NSAID use, no. (%)	11 (8)	8 (6)	0.475
MMSE ≤23, no. (%)	0	0	–
Living alone, no. (%)	26 (19)	28 (21)	0.761
Work status: working, no. (%)	51 (38)	50 (37)	0.9
Edoxaban/apixaban, n/n	78/56	80/54	0.804
Adherence rate in stage 1, mean (SD), %	94.5 (11.0)	92.9 (12.3)	0.259

$CHADS_2$ = cardiac failure, hypertension, age ≥75 years, diabetes, previous stroke or TIA (doubled); MMSE = Mini-Mental State Examination; NSAID = nonsteroidal anti-inflammatory drug; TIA = transient ischemic attack.

Table II. Multiple linear regression analysis of DOAC adherence with standard medication counseling (ref = 1) versus educational intervention.

Analysis Subgroup	B	SE	β	*P*
Overall	0.014	0.85	0.001	0.987
Men	1.27	0.65	0.113	0.052
Women	−1.16	1.94	−0.055	0.55
Edoxaban	−0.48	1.05	−0.457	0.65
Apixaban	0.96	1.38	0.066	0.49
Men				
Edoxaban	0.57	0.8	0.054	0.48
Apixaban	2.6	1	0.219	0.012
Women				
Edoxaban	−1.5	2.46	−0.065	0.55
Apixaban	−0.83	3.1	−0.047	0.79

B = regression coefficient; β = standardized regression coefficient.

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Table III. Tolerability outcomes. Data are given as numbers of patients.

Event	Standard Medication Counseling		Educational Interventional Program	
	Stage 1	Stage 2	Stage 1	Stage 2
Death				
Sudden death	–	1	–	0
Non-cardiovascular death	–	1	–	0
Hospitalization				
Heart failure	1	0	0	0
Cather ablation for AF	1	4	1	0
DC cardioversion of AF	0	1	0	0
Pacemaker implantation	0	1	0	0
Hyperparathyroidism	1	0	0	0
Urinary tract infection	0	0	1	0
Cataract surgery	1	0	0	0
Colonic polypectomy	0	0	0	1
Malignancy	0	1	0	1

AF = atrial fibrillation; DC = direct current.

Tolerability Outcomes

No stroke/systemic embolism or major bleeding events were reported in either group throughout the trial. There were 17 serious adverse events reported among the 268 patients (Table III). Two patients (1%) had serious adverse events (deaths) unrelated to treatment. The other patients continued the same DOAC therapy during the trial. The most serious adverse events were related to AF treatment, such as hospitalization for catheter ablation and cardioversion and comorbidities other than cardiovascular disease. During the trial, there were few drug-related adverse events.

DISCUSSION

This study on electronically monitored DOAC adherence in Japanese patients with NVAF showed the following results: (1) the pharmacist-led educational interventional program involving motivational interviewing was not associated with significantly improved adherence to DOACs compared to standard medication counseling (primary end point); (2) the pharmacist-led educational interventional program improved adherence to twice-daily apixaban among men but not women; and (3) among the patients who withdrew, the percentage of women was higher in the educational interventional program group than in the standard medication counseling group.

In this study, there was no difference in adherence (threshold ≥80%) between the DOAC subgroups (edoxaban, 95% vs apixaban, 91%; $P = 0.2$) during stage 1 (observational period), but the percentage of patients with strict adherence (threshold ≥90%) was greater among edoxaban users than among apixaban users (87% vs 76%; $P = 0.01$). Multivariate analysis showed a negative relationship between apixaban use and an adherence rate of ≥90% (odds ratio = 0.49; 95% CI, 0.25–0.94).[21] In the DOAC era, a strict adherence threshold of >90%, which was based on the higher adherence rate (Proportion of Days Covered ≥90%) associated with the lowest risk,[24] will be needed to ensure the greater effectiveness of DOACs compared to that of warfarin. Therefore, a specific educational program will need to be provided to nonadherent patients taking DOACs, especially twice-daily DOACs, to further improve their adherence.

Few randomized trials have evaluated the effect of educational interventional programs on adherence to DOACs. The AEGEAN study (Assessment of an Education and Guidance Program for Eliquis Adherence in NVAF)[10] showed no effect of the educational program, which consisted of an informational booklet,

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reminder tools, and virtual clinic access, on adherence to apixaban in patients with NVAF. A feasibility study reported that a visual intervention using an artificial-intelligence platform could alter patient behavior and demonstrated a 67% improvement in adherence to DOACs.[11] A study using a telemonitoring system reported that electronic monitoring was associated with improved adherence to DOACs, and that telemonitoring combined with feedback was associated with further improved adherence.[12] These new technologies have the potential to motivate patients, including elderly patients.[12] Although interventional methods differ, increasing patient motivation leads to improvements in adherence to DOACs.

In general, patients with NVAF who are eligible for primary prevention but who have no symptoms or disorders may resist taking anticoagulants more than those receiving secondary prevention for stroke/systemic embolism. Systematic reviews and meta-analyses have shown that motivational interviewing was associated with improved lifestyle behaviors and health outcomes in health care settings.[14,15] However, there have been no reports on motivational interviewing as an educational interventional program used for improving adherence to DOACs in patients with NVAF. Recently some reports showed that pharmacist-led interventions were associated with significantly improved medication adherence in patients with bronchial asthma.[25,26] This is the first study to evaluate the effect of an educational interventional program involving motivational interviewing by pharmacists on adherence to DOACs in patients with NVAF.

In this study, the educational interventional program involving motivational interviewing was not effective in improving the adherence rate in all patients with NVAF. The reasons for this may include the high baseline adherence rates among the randomized patients (92.9% [12.3%] and 94.5% [11.0%] in the educational interventional program and standard medication counseling groups, respectively). Moreover, patients were aware of the purpose of this study (adherence to DOACs), the electronic monitoring method itself can improve medication adherence,[27] and only selected patients who met the inclusion/exclusion criteria were included in this study. These factors and other, unrecognized factors may have offset the effect of the educational interventional program. The precise motivational interviewing methods that are best suited for a clinical setting, especially with regard to anticoagulant therapy for NVAF, have not yet been established.

Interestingly, in the subgroup analyses in the present study, the educational interventional program was associated with improved adherence to twice-daily apixaban among men. A systematic review found that medication adherence decreased as the number of daily doses increased.[28] We previously reported that a regimen of frequent (≥2) daily doses was significantly associated with self-reported nonadherence to medications, including DOACs, in patients with NVAF.[29] In patients who were nonadherent due to the need for multiple daily doses, this educational interventional program involving motivational interviewing may be useful for improving adherence to DOACs. However, the educational interventional program was not effective in women taking apixaban, in whom a relatively low mean adherence rate was observed in stage 1 (89.0% [16.7%]). Moreover, the percentage of women who withdrew from the educational interventional program group was high. It has been reported that medication adherence is lower in women than in men.[30–33] In particular, adherence to treatments for diabetes and cardiovascular disease is known to be consistently lower among women than among men.[32] The reasons for these differences are still speculative. It is possible that women prioritize their families over themselves, have a negative image of medications, and/or discontinue medications more frequently due to side effects compared with men.[32] Depressive symptoms and dissatisfaction with communication with the health care provider have also been reported as factors associated with low adherence among women.[34] The reason for gender differences in the response to the educational interventional program involving motivational interviewing remains unclear. There has been no evidence of gender differences in the benefits of motivational interviewing. However, it is possible that there are gender differences in the effect of the educational interventional program on the behavior response or outcomes. Choudhry et al[35] reported that the effect of interventional telephone counseling by pharmacists was significantly greater in men than in women. In the present study, the pharmacists involved in the educational interventional program were predominantly women, which might have partially contributed to the gender difference in the effect of pharmacist-led intervention. It is possible that men and women benefit from different

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types of interventions.[36] Because the obstacles to taking DOACs vary among individual patients, it is understandable that the effects of a standardized educational intervention may not be equal across subgroups. Further studies are needed to evaluate this issue.

Limitations

This study had several limitations. The selection of DOACs was not randomized. This selection bias might have partially resulted from physician and patient preferences, associated comorbidities, and concurrent medications.[21] The number of medication counseling sessions in each patient was not standardized. Most of the patients received medication counseling or the educational interventional program twice in stage 2, but some received it three times because the number of visits depended on usual medical care and was not specified in the study protocol. Because this study was a short-term evaluation in a small number of patients, the effect of adherence on the clinical outcome could not be evaluated. In addition, due to the lack of appropriate previous studies and the paucity of studies on DOAC adherence in Japanese patients with AF prior to the start of this study, power and sample-size calculations, including feasibility, were performed with reference to an observational study from the United States. As a result, the actual number of patients enrolled during the planned recruitment period was 301, but many of them were well adherent. Even if the estimated target number of patients was reached, the results of this study would not have changed. Studies in nonadherent patients may be needed to better clarify the effects of educational interventions. There might be a gender bias in educational interventional program delivery: The pharmacists involved in the program in the present study were predominantly women. However, to prevent bias regarding the quality of program implementation, the educational interventional program was conducted by pharmacists who had received prior motivational interviewing training. In this study, appropriate personality tests were not performed as part of the patient background, and it has been reported that personality may be a factor related to adherence.[37]

CONCLUSIONS

In this study in patients with NVAF, adherence to DOACs, as assessed with electronic monitoring, was not significantly improved with a pharmacist-led educational interventional program involving motivational interviewing compared to standard medication counseling. However, among men, but not women, adherence to twice-daily apixaban was improved with the educational interventional program.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

T.S. and N.H. organized the study. T.S., T.K., and Y.Y. designed the protocol. K.I., F.M., Y.A., S.H., Y.Y., and N.H. were involved in the conceptual design. T.S., K.I., F.M., Y.A., S.H., Y.Y., and N.H. contributed to data acquisition. N.F. and E.S. contributed to data validation and analysis. T.S. wrote the manuscript. All of the authors reviewed the manuscript and approved the final version for submission.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clinthera.2022.09.011.

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