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Original Article

Long-term outcome and risk factors associated with events in patients with atrial fibrillation treated with oral anticoagulants: The ASSAF-K registry

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ABSTRACT

Background: Oral anticoagulant therapy for atrial fibrillation (AF) has changed dramatically. Direct oral anticoagulant (DOAC) therapy is administered by general practitioners and specialists. However, the beneficial long-term effects and safety of DOACs have not been well investigated in real-world clinical practice.
Methods: The ASSAF-K (a study of the safety and efficacy of OAC therapy in the treatment of AF in Kanagawa), a prospective, multi-center, observational study, was conducted to clarify patient characteristics, status of OAC treatment, long-term outcomes, and adverse events, including cerebrovascular disease, bleeding, and death.
Results: A total of 4014 patients were enrolled (hospital: 2500 cases; clinic: 1514 cases). The number of patients in the final dataset was 3367 (mean age, 72.6 ± 10.0 years; males, 66.3 %). CHA_2DS_2-VASc and HAS-BLED scores were 3.0 ± 1.6 and 2.2 ± 1.0, respectively. The risk factors of the primary composite outcome (all-cause death, serious bleeding events, cerebral hemorrhage, and stroke) were higher age, lower body mass index, lower diastolic blood pressure, lower creatine clearance, history of heart failure, history of stroke, and medication of anti-platelet agents. The event-free rates of the primary composite outcome with DOACs, warfarin, and without OACs were 92.7 %, 88.0 %, and 87.4 %, respectively. The event rate of DOACs was significantly lower than that of warfarin [HR 0.63 (95 % CI 0.48–0.81)], and similar results were observed after adjustment for AF stroke risk score [HR 0.70 (95 % CI 0.54–0.90)]. Serious bleeding events tended to occur less frequently with DOACs compared with warfarin [unadjusted HR 0.53 (95 % CI 0.31–0.91), adjusted HR 0.61 (95 % CI 0.33–1.11)].
Conclusions: This multi-center registry demonstrated the long-term outcome in patients with AF treated with and without OACs and suggests that DOAC therapy is safe and beneficial in hospitals and clinics.

Introduction

Previous studies have revealed that the incidence of atrial fibrillation (AF) tends to increase with age [1,2]. A large number of patients with AF and associated complications, including stroke and heart failure (HF), are a worldwide critical burden. Cardiogenic cerebral infarction can be fatal, but even if patients survive, cardiogenic cerebral infarction causes hemiplegia. Approximately 40 % of patients with AF have HF, which is a critical issue globally [3]. Almost half of patients with HF have AF [3], and such patients are known to be at a greater risk of stroke [4]. Therefore, how best to prevent complications due to AF is an important therapeutic goal. Anticoagulation therapy is one of the important treatment strategies. Recently, novel direct oral anticoagulants (DOACs) have been

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developed and are widely used in clinical practice. Meta-analyses have demonstrated that DOACs significantly reduce the likelihood of stroke, intracranial hemorrhage, and mortality with similar major bleeding rates as warfarin [5,6]. Based on this evidence, recent guidelines recommend DOACs according to the CHA_2DS_2-VASc score [7,8]. However, the effectiveness and safety of DOACs in a real-world setting have not been fully understood to date, although several Japanese studies have been reported [9–11]. Therefore, we conducted a prospective cohort study to examine the current situation of OAC therapy for patients with AF as prescribed by general physicians and cardiologists.

Methods

The ASSAF-K (a study of the safety and efficacy of OACs in the treatment of AF in Kanagawa) is a multi-center, prospective, observational study conducted to clarify the clinical features and long-term events of patients with AF in the era of DOACs.

The objectives and protocol of the ASSAF-K study have been described in detail previously [12]. Subjects were patients with AF, including persistent AF and continuous AF amenable to defibrillation, paroxysmal AF with and without valvular disease, and AF after valvular replacement. Subjects with a limited life expectancy because of cancer and subjects with senile cognitive impairment were excluded. The study started in 2013 and enrolment was concluded at the end of March 2015. The follow-up was finished at the end of March 2018. The goal of the present study was to clarify the outcome in AF patients with DOAC, warfarin, and without OACs. The primary composite outcome was all-cause mortality, serious bleeding events, cerebral hemorrhage, or stroke. The secondary outcomes were a composite outcome comprising death, cerebral hemorrhage, and stroke, and serious bleeding events. Criteria for serious bleeding events in patients not undergoing surgical treatment were defined as follows: fatal bleeding and/or symptomatic bleeding occurring at important sites or organs (cranial cavity, medullary cavity, eyes, posterior peritoneal cavity, joints, pericardium, or intramuscular bleeding associated with muscle compartment syndrome), bleeding associated with a decrease in hemoglobin concentration of ≥2.0 g/dL, bleeding requiring transfusion of 2 or more units of whole blood or red blood cells. This study was conducted in accordance with the principles of the Declaration of Helsinki. Institutional review board (IRB) approval was obtained representatively by the IRB committee of Kanagawa Prefecture Medical Association for clinics and at each participating hospital prior to commencement of the study.

Statistics

Continuous variables are expressed as mean and standard deviation and categorical variables as absolute values and percentages. Comparison among the three groups (without OACs, warfarin, and DOACs) was carried out using one-way ANOVA for continuous variables and the chi-square test for categorical variables. Cumulative event-free survival curves were constructed as time-to-event plots by Kaplan-Meier methods. Cox proportional-hazards regression was used to analyze the effect of OACs on survival in uni- and multivariable analyses. The primary outcome and the secondary composite outcome (death, cerebral hemorrhage, and stroke) were adjusted for the components of CHA_2DS_2-VASc score for AF stroke risk [13], and adjustment for the serious bleeding events was performed for the components of HAS-BLED score for major bleeding risk [14]. Statistical significance was accepted if the 95 % confidence interval (CI) excluded the value 1, or the p-value was <0.05. Statistical analyses were performed using R, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The ASSAF-K study comprised 4014 patients (hospital: $n = 2500$; clinic: $n = 1514$) from 105 institutes (26 hospitals and 79 clinics) in Kanagawa Prefecture, Japan. One hundred seventy-five patients were excluded because of missing data. The number of patients in the final data set excluding discontinuation or loss to follow up was 3367 (Fig. 1). The median follow-up was 37 months. The mean age of patients was 72.6 ± 10.0 years, and the proportion of male patients was 66.3 %. CHA2DS_2-VASc and HAS-BLED scores were 3.0 ± 1.6 and 2.2 ± 1.0, respectively. Of the total study population, 23.0 % had HF, 60.6 % had hypertension, and 20.7 % had diabetes mellitus. The mean age, CHA_2DS_2-VASc score, and HAS-BLED score at clinics were significantly higher compared with those at hospitals. Table 1 provides overall patient characteristics and characteristics according to OAC medication. Creatinine clearance was significantly different between groups, and it was highest in the DOAC group. The CHA_2DS_2-VASc score in the warfarin group was highest, and the CHA_2DS_2-VASc score was similar between the group without OACs and the group with DOACs. The HAS-BLED scores in the group without OACs, warfarin, and DOACs were 2.3 ± 1.1, 2.2 ± 1.0, and 2.1 ± 1.0, respectively.

Table 2 shows the results of the univariate Cox proportional hazards analyses for the primary composite outcome (all-cause death, serious bleeding events, cerebral hemorrhage, and stroke). The risk factors of the primary composite outcome were age [hazard ratio (HR) 1.08, 95 % confidence interval (CI) 1.07–1.10], body mass index (HR 0.90, 95 % CI 0.87–0.93), diastolic blood pressure (HR 0.98, 95 % CI 0.97–0.99), creatine clearance (HR 0.97, 95 % CI 0.97–0.98), history of heart failure (HR 1.66, 95 % CI 1.33–2.07), history of stroke (HR 1.18, 95 % CI 1.11–1.25), and medication of anti-platelet agents (HR 1.49, 95 % CI 1.18–1.87).

Event-free rates of the primary composite outcome with DOACs, warfarin, and without OACs were 92.7 %, 88.0 %, and 87.4 %, respectively. The event rates of the primary composite outcome were estimated using the Kaplan–Meier method, which revealed that the event rate of DOACs was significantly lower than that of warfarin [HR 0.63 (95 % CI 0.48–0.81)] (Fig. 2A). Similar results were obtained when adjusted for the components of CHA_2DS_2-VASc score, a stroke risk score for patients with AF that also predict mortality risk [HR 0.70 (95 % CI 0.54–0.90)] (Table 3). Interestingly, the primary composite outcomes with warfarin were not different compared with those in the group without OACs. Patients treated with DOACs had a lower risk of death, cerebral hemorrhage, and stroke (secondary composite outcome) than those prescribed warfarin, even after adjustment [adjusted HR 0.75 (95 % CI 0.57–0.99)]. On the other hand, patients without OACs had a higher risk of the secondary composite outcome than those treated with warfarin after adjustment [adjusted HR 1.39 (95%CI 1.06–1.82)]. Serious bleeding events tended to occur less frequently in patients with DOACs and without anticoagulant compared with warfarin [DOAC: unadjusted HR 0.53 (95 % CI 0.31–0.91) and adjusted HR 0.61 (95 % CI 0.33–1.11); without OACs: unadjusted HR 0.50 (95 % CI 0.25–0.99) and adjusted HR 0.27 (95 % CI 0.11–0.69)] (Table 3).

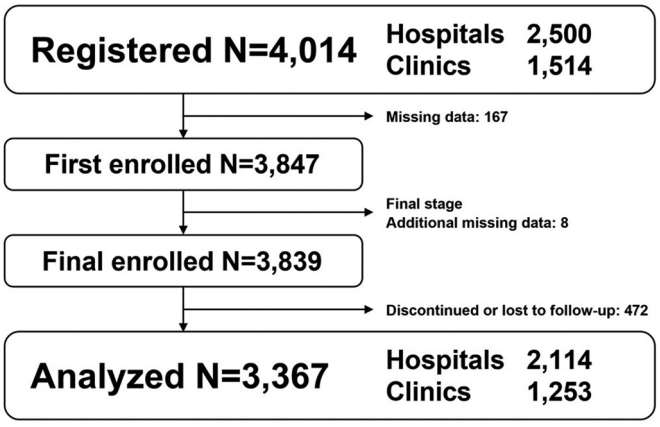

Fig. 1. Flow chart. Four thousand fourteen patients with atrial fibrillation were enrolled. The final number of patients was 3367.

Table 1
Patient characteristics.

	Total $n = 3367$	No anticoagulant $n = 688$	Warfarin $n = 1517$	DOAC $n = 1162$	p-Value
Age (years)	72.6 ± 10.0	72.6 ± 11.4	73.5 ± 9.2	71.5 ± 9.9	<0.001
Male gender, n (%)	2232 (66.3)	423 (61.5)	996 (65.7)	813 (70.0)	0.001
Body mass index (kg/m^2)	23.5 ± 3.6	23.1 ± 3.7	23.5 ± 3.7	23.7 ± 3.4	0.002
Systolic blood pressure (mmHg)	126.3 ± 16.2	128.6 ± 16.2	124.8 ± 16.5	127.1 ± 15.6	<0.001
Diastolic blood pressure (mmHg)	73.0 ± 11.4	72.5 ± 11.7	72.0 ± 11.2	74.7 ± 11.3	<0.001
Creatinine clearance (mL/min)	63.3 ± 27.9	60.8 ± 30.8	60.7 ± 27.2	68.3 ± 26.1	<0.001
History of heart failure, n (%)	774 (23.0)	103 (15.0)	471 (31.0)	200 (17.2)	<0.001
Hypertension, n (%)	2039 (60.6)	409 (59.4)	940 (62.0)	690 (59.4)	0.319
Diabetes mellitus, n (%)	697 (20.7)	120 (17.4)	332 (21.9)	245 (21.1)	0.054
Cerebral infarction, n (%)	467 (13.9)	65 (9.4)	226 (14.9)	176 (15.1)	0.001
Cerebral bleeding, n (%)	32 (1.0)	8 (1.2)	13 (0.9)	11 (0.9)	0.788
Beta-blocker, n (%)	1125 (33.4)	161 (23.4)	543 (35.8)	421 (36.2)	<0.001
Anti-platelet agents, n (%)	757 (22.5)	307 (44.6)	309 (20.4)	141 (12.1)	<0.001
$CHADS_2$ score	1.8 ± 1.3	1.7 ± 1.3	2.0 ± 1.3	1.7 ± 1.3	<0.001
CHA_2DS_2-VASc score	3.0 ± 1.6	2.9 ± 1.6	3.2 ± 1.5	2.8 ± 1.6	<0.001
HAS-BLED score	2.2 ± 1.1	2.4 ± 1.1	2.3 ± 1.1	2.1 ± 1.0	<0.001

Data are presented as the mean ± SD or number (percentage).
DOAC, direct oral anticoagulant.

Table 2
Predictors of the primary composite outcome.

	HR	Lower CI	Upper CI	p-Value
Age	1.08	1.07	1.10	<0.001
Sex, male	0.89	0.71	1.10	0.28
Body mass index	0.90	0.87	0.93	<0.001
Systolic blood pressure	1.00	0.99	1.00	0.18
Diastolic blood pressure	0.98	0.97	0.99	<0.001
Creatinine clearance	0.97	0.97	0.98	<0.001
History of heart failure	1.66	1.33	2.07	<0.001
History of hypertension	1.04	0.93	1.16	0.47
History of diabetes mellitus	1.06	0.97	1.15	0.18
History of cerebral infarction	1.18	1.11	1.25	<0.001
History of cerebral bleeding	1.11	0.97	1.27	0.14
Beta-blocker	0.93	0.83	1.04	0.20
Anti-platelet agents	1.49	1.18	1.87	<0.001

CI, confidence interval; HR, hazard ratio.

Discussion

The ASSAF-K study was a prospective, multi-center study that examined patients at both clinics and hospitals. The registry demonstrated important data regarding real-world patient characteristics and long-term outcomes in patients with AF treated with DOACs, warfarin, or without OACs. The present study demonstrated that treatment with DOACs was more preventative compared with warfarin in a real-world clinical practice. American [7] and European [8] guidelines for the management of AF recommend DOACs over warfarin to prevent stroke in patients with AF and an elevated CHA_2DS_2-VASc score of ≥2 in males and ≥3 in females. However, the guidelines were based on a meta-analysis of previous randomized controlled studies [5,15]. In a real-world clinical setting, exclusion criteria, except contraindications to OACs in previous randomized controlled studies, were not indicated. Therefore, the guidelines should be confirmed in a real-world clinical setting. Recent real-world studies examined the efficacy and safety of DOACs compared with those of warfarin. A meta-analysis of observational studies demonstrated that the use of DOACs is associated with decreased rates of stroke or systemic embolism, ischemic stroke, myocardial infarction, all-cause death, major bleeding, intracranial bleeding, and gastrointestinal bleeding compared with warfarin [16]. However, real-world observational studies, except for two Japanese studies in the meta-analysis, were conducted retrospectively or using the national database or health insurance database [16]. A sub-analysis of the Fushimi study, which was a Japanese prospective cohort study, demonstrated no significant differences in stroke/systemic embolism events or major bleeding events between DOAC-treated and warfarin-treated patients with AF [17]. In this Fushimi study, the proportion of

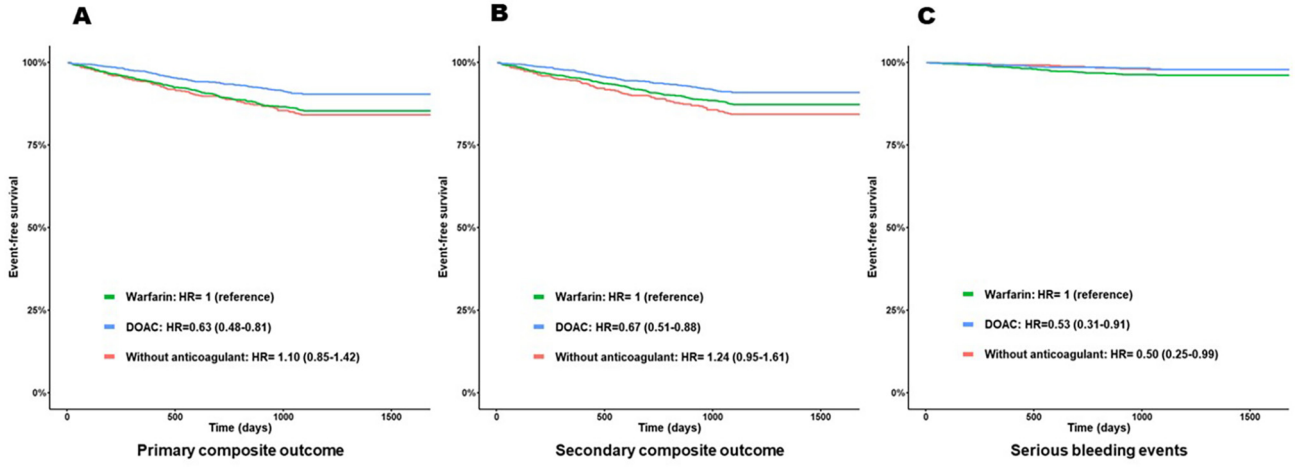

Fig. 2. Long-term outcomes. Kaplan–Meier estimates of (A) the primary composite outcome (all-cause death, serious bleeding events, and cerebral hemorrhage/stroke), (B) secondary composite outcome (all-cause death and cerebral hemorrhage/stroke), and (C) serious bleeding events in patients with atrial fibrillation.
DOAC, direct oral anti-coagulant.

Table 3
Unadjusted and adjusted hazard ratios for outcomes.

	Unadjusted HR (95 % CI)	*p*-Value	Adjusted HR (95 % CI)	*p*-Value
Primary composite outcome				
Warfarin	1 (reference)		1 (reference)	
DOAC	0.63 (0.48-0.81)	<0.001	0.70 (0.54-0.90)	0.006
Without anticoagulant	1.10 (0.85-1.42)	0.47	1.22 (0.94-1.58)	0.14
Death, cerebral hemorrhage, and stroke				
Warfarin	1 (reference)		1 (reference)	
DOAC	0.67 (0.51-0.88)	0.004	0.75 (0.57-0.99)	0.043
Without anticoagulant	1.24 (0.95-1.61)	0.12	1.39 (1.06-1.82)	0.017
Serious bleeding events				
Warfarin	1 (reference)		1 (reference)	
DOAC	0.53 (0.31-0.91)	0.021	0.61 (0.33-1.11)	0.11
Without anticoagulant	0.50 (0.25-0.99)	0.048	0.27 (0.11-0.69)	0.006

The primary composite outcome was all-cause mortality, serious bleeding events, cerebral hemorrhage, and stroke. The primary outcome and the secondary composite outcome (death, cerebral hemorrhage, and stroke) were adjusted for the components of CHA_2DS_2-VASc score for atrial fibrillation stroke risk, and adjustment for the serious bleeding events was performed for the components of HAS-BLED score for major bleeding risk.
CI, confidence interval; DOAC, direct oral anticoagulant; HR, hazard ratio.

DOAC-treated patients was only 7 % (DOACs: $n = 270$; warfarin: $n = 1728$), which limited the interpretation of the effects of DOACs on outcomes. Another prospective observational AF study, the SAKURA registry, revealed that warfarin and DOACs equivalently prevented stroke and all-cause mortality rates for 3 years, but DOACs seemed to reduce the risk of major bleeding [10]. The SAKURA registry enrolled 3266 patients with AF treated with OACs between 2013 and 2015 at hospitals (76.8 %) and clinics (23.1 %) [18]. Our study was conducted between 2013 and 2018 at hospitals (62 %) and clinics (38 %) and enrolled 4014 patients with AF, including OAC untreated and OAC treated patients. Furthermore, the CHA_2DS_2-VASc score in the present study (3.0 ± 1.6) was higher compared with that of the SAKURA registry (2.74 ± 1.38). Thus, the inconsistent results between the present study and another two prospective studies might be due, in part, to the study length, proportion of clinics, and risk score points. Although patients taking warfarin were at a higher risk of poor outcome (because of higher age and higher CHA_2DS_2-VASc score) compared with patients in the DOAC group, in this study even after adjustment for the components of CHA_2DS_2-VASc score, DOACs had better outcomes than warfarin with respect to the primary and secondary composite outcomes. The CHA_2DS_2-VASc score is useful to predict stroke or thromboembolism 1 year before OAC therapy [19]. The guidelines recommend evaluating the risk of stroke and thromboembolism in patients with AF using the CHA_2DS_2-VASc score [7,8]. Risk stratification after OAC therapy is also important to manage patients with AF. The present study revealed that the risk factors for the primary composite outcome, including all-cause death, stroke, and major bleeding, were higher age, lower body mass index, lower diastolic blood pressure, lower creatine clearance, history of heart failure, history of cerebral infarction, and medication of anti-platelet agents. The PREFER in AF study demonstrated that abnormal liver function, labile international normalized ratio (INR), antiplatelet or non-steroidal anti-inflammatory drug use, prior stroke/transient ischemic attack/thromboembolic events, HF, and age ≥75 years are risk factors for 1-year thromboembolic events. Furthermore, the PREFER in AF study revealed that the risk factors associated with major bleeding were bleeding predisposition, age ≥75 years, vascular disease, abnormal renal function, labile INR, excessive alcohol consumption, and antiplatelet or non-steroidal anti-inflammatory drug use [19]. However, only 7.4 % of patients enrolled in the PREFER in AF study were treated with DOACs; therefore, these risk factors can be used mainly for warfarin-treated patients with AF [19]. Recently, data of five Japanese AF registries were analyzed. The data demonstrated that previous stroke, age, hypertension, persistent or permanent AF, and low body mass index were independent risk factors for ischemic stroke, but not for other major events; however, the independent risk factors for both stroke/thromboembolic events and major adverse events remain unknown in patients with AF treated with DOACs [11]. Thus, in previous studies, thrombosis risk factors and bleeding risk factors were analyzed separately, but it is significant that these risk factors were analyzed together in our study.

Limitations

The present study analyzed risk factors, but this analysis was performed using epidemiological information, current treatment status, and outcomes. This is because general physicians were included, and these physicians could not obtain electrocardiographic data and cardiac function data. Thus, although the present study is limited in that it did not include specialized cardiovascular factors, it can be used in a clinical setting even by non-cardiologists. The present study demonstrated that DOACs might be recommended for patients with AF as opposed to warfarin, but the design of the present study was not randomized, suggesting that the evidence level might be lower. However, guidelines based on randomized controlled trials have already recommend DOACs for patients with AF. The present real-world study confirmed this recommendation. The present study also demonstrated the long-term outcomes of efficacy and safety and identified risk factors for death, serious bleeding events, cerebral hemorrhage, and stroke.

Conclusion

The present study demonstrated real-world patient characteristics, long-term outcomes, and risk factors associated with death and stroke/major bleeding in patients with AF treated with DOACs, warfarin, or without OACs, suggesting that treatment with DOACs for real-world patients with AF was safe and beneficial in hospitals and clinics.

Declaration of competing interest

The authors declare that there are no conflicts of interests regarding the present study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jjcc.2022.08.012.

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