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ORIGINAL ARTICLE

Cost-effectiveness for prevention of thromboembolism by anticoagulants in non-valvular atrial fibrillation: additional analysis from the Hokuriku–Plus AF Registry

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Abstract

Although benefits of direct oral anticoagulants (DOAC) for treatment of non-valvular atrial fibrillation (AF) were well demonstrated, few data exist regarding cost-effectiveness between DOAC and warfarin uses in real-world clinical practice. Therefore, we estimated total cost of treatment for AF by authorized cardiologists in Japan. We studied consecutive 617 anticoagulated non-valvular AF patients (418 men, mean age 68.8, 54% warfarin) consulted by authorized cardiologists. The mean time in therapeutic range of warfarin was 71.8%. Under these conditions, we calculated the cost of anticoagulants, laboratory examination, and hospitalization due to thromboembolism or bleeding during follow-up for 3.1 years. Thromboembolism occurred in 26 patients (4.2%, 1.3/100 person-year) and hemorrhagic events in 20 patients (3.2%, 1.0/100 person-year). There was no significant difference in the occurrence rate of thromboembolism (log rank $P=0.16$) or hemorrhagic events (log rank $P=0.83$) between these two groups. Importantly, warfarin group showed lower cost than DOAC group (117,361 ± 743,710 yen/year vs. 310,436 ± 1,075,639 yen/person, $P=0.009$) in terms of cost including drug, medical check, and hospitalization. These results demonstrate that the total cost with warfarin can be lower than DOAC in treatment for AF by authorized cardiologists in Japan, although further prospective randomized cost calculation is necessary including post-discharge care fee.

Keywords Atrial fibrillation · Anticoagulation · Medical fee · Authorized cardiologist

Abbreviations

AF	Atrial fibrillation
BNP	Brain natriuretic peptide
DOAC	Direct oral anticoagulant
JCS	Japanese circulation society
TTR	Time in therapeutic range
PT-INR	Prothrombin time–international normalized ratio
TIA	Transient ischemic attack

Introduction

A line of evidence demonstrates that non-valvular atrial fibrillation (AF) should be treated with anticoagulation agents such as warfarin or direct oral anticoagulant (DOAC) [1–3]. The non-inferiority of DOACs compared to warfarin in prevention of thromboembolic events has been shown in clinical trials [4, 5]. In addition, non-inferiority to warfarin in terms of the absence of hemorrhagic complications was shown in studies using all DOACs [4–7]. Under these conditions, DOACs have been increasingly used because of rapid onset and reversal of action, absence of an effect of dietary vitamin K intake on activity, fewer drug interactions, and

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lack of need for routine coagulation monitoring. However, at the present time, the price of DOACs in Japan is approximately 17 times as high as that of warfarin, thus contributing to increasing total medical budget which is now total 42 trillion yen in 2015 [8].

Recently, some study demonstrated that there was no evidence of superiority of DOACs in terms of occurrence of thromboembolic and hemorrhagic events [9]. In that study, attending doctors consisted of not only authorized cardiologists but also of general physicians [10]. Therefore, the cost-effectiveness of DOACs versus warfarin in prevention of thromboembolic and hemorrhagic events when prescribed by authorized cardiologists or general physicians is still unclear.

The Hokuriku-plus AF Registry is a prospective and observational study which evaluates the occurrence of cardiovascular events in patients with non-valvular AF treated with DOACs or warfarin [11]. In the present study, we evaluate the cost-effectiveness of DOACs or warfarin from the Hokuriku-plus AF Registry and additional patients consulted by authorized cardiologists in Japan.

Materials and methods

Study population

This study observed the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee for Medical Research of Kanazawa University Graduate School of Medical Science.

The Hokuriku-plus AF Registry is a multicenter, population-based, prospective cohort study. We enrolled patients who had AF of all types on 12-lead ECG or Holter monitoring at any time. In brief, 1492 subjects aged 30–94 years were recruited from a total of 19 institutions in Hokuriku and Yokohama area. The baseline enrollment was performed from January 2013 to May 2014, and follow-up examinations were conducted after 2 years. All cardiologists for outpatient clinic were authorized by the Japanese Circulation Society.

Paroxysmal AF was defined as AF that lasted > 30 s and terminated spontaneously. Persistent AF was defined as AF that lasted > 7 days and required either pharmacological therapy or electrical cardioversion for termination. AF refractory to cardioversion or where cardioversion was not attempted was classified as permanent.

Under these conditions, we selected AF patients from Hokuriku-plus AF registry consulted to Kanazawa University Hospital because of simplifying to calculate total cost during follow-up period. All selected AF patients were prescribed the same oral anticoagulants during follow-up periods. Follow-up was terminated when anticoagulants were discontinued or changed to other medications because of thromboembolic/bleeding events or other reasons. AF patients at Kanazawa University Hospital other than those in the Hokuriku-plus AF registry were additionally enrolled in the present analysis. This additional AF cohort was enrolled starting in March 2011 (DOACs could be prescribed starting in March 2011 in Kanazawa University Hospital) and was also prescribed same oral anticoagulants during follow-up periods. Finally, we studied 617 anticoagulated non-valvular AF patients.

Evaluation of anticoagulation therapy

We measured the prothrombin time–international normalized ratio (PT–INR) and time in therapeutic range (TTR) as previously reported to evaluate the intensity of anticoagulation using warfarin [12]. As described in the JCS guidelines [1], we defined the optimal intensity of anticoagulation in terms of PT-INR: 1.6–2.6 for elderly patients (≥ 70 years) and 2.0–3.0 for younger patients (< 70 years). We also investigated whether DOACs were prescribed in appropriate dose at registration. We defined patients who received inappropriate low dose DOACs despite standard dose was recommended as "under-dosing of DOACs" and who received inappropriate high-dose DOACs despite low dose was recommended as "over-dosing DOACs" [13].

Evaluation of outcomes

The primary endpoint of this analysis was thromboembolic and major hemorrhagic events. Thromboembolic events (TEs) included the occurrence of ischemic stroke, transient ischemic attack (TIA), or systemic embolism. Stroke was defined as a sudden onset of focal deficit lasting > 24 h. Systemic embolism was defined as an acute vascular occlusion outside the brain [11]. Major hemorrhagic events were defined as intracranial hemorrhage including hemorrhagic stroke, hemorrhagic events requiring transfusion, and hemorrhagic events with reduction of hemoglobin by > 2 g/dL. We evaluated the risk for thromboembolism using $CHADS_2$ [14] and CHA_2DS_2-VASc [15] score at registration. The definitions of the components of these scoring systems are as follows: congestive heart failure was diagnosed if patients had a history of hospitalization due to heart failure (HF), had symptoms due to HF, or were treated for HF. Hypertension was diagnosed if peripheral blood pressure was > 140/90 mmHg or if the patient took anti-hypertensive medication. Diabetes was diagnosed if the fasting plasma glucose was > 126 mg/dL, random plasma glucose was > 200 mg/dL, glycated hemoglobin was > 6.5%, or if the patient was treated for diabetes mellitus. Vascular diseases were diagnosed if the patient had coronary artery disease, peripheral artery disease, or large-vessel disease. We also evaluated the risk for hemorrhage events using HAS-BLED score [16]. The definitions of the components of these

scoring systems are as follows: hypertension (systolic blood pressure > 160 mmHg), abnormal renal function (chronic dialysis or serum creatinine ≥ 200 mmol/L), abnormal liver function (aspartate aminotransferase or alanine aminotransferase threefold the upper limit of normal), stroke history, bleeding history, labile international normalized ratio (INR) data, elderly (age > 65 years), anti-platelet drug (APD), and excess alcohol (≥ 8 units alcohol/week).

Calculation of medical cost

Medical cost was calculated as three categories. The first one was drug cost (warfarin or Any DOACs) per year (yen/person-year). The second one was the sum of drug cost (yen/person-year) and medical examination fee (yen/person-year). Medical examination fee means the cost for medical fee in outpatient clinic (730 yen) in all patients and the cost for measurement of PT-INR (1830 yen) in warfarin group. The third was the sum of drug cost (yen/person-year), medical examination fee (yen/person-year), and the cost of hospitalization (yen/person-year) when the patient was hospitalized due to thromboembolic or hemorrhagic events. The calculation was based on Japanese medical expense in 2016.

Statistical analysis

Continuous variables are presented as mean ± SD, and categorical variables are presented as percentage. Continuous variables were compared using Student's *t* test for paired data, and categorical variables were compared using Fisher's exact test. To investigate differences between groups in the cumulative ratio for cardiac events, the occurrence of cardiac events is presented using Kaplan–Meier cumulative survival curves and compared using the log-rank test. Adjusted hazard ratios (HR) and corresponding 95% confidence intervals (CI) of each variable associated with cardiac events were calculated by Cox-proportional hazard model. All statistical analyses were performed using JMP Pro version 11 (SAS Institute, Cary, NC, USA).

Results

Of the 1492 patients with AF who had been enrolled in the Hokuriku-plus AF registry, 144 were registered in the Kanazawa University Hospital. Among them, 18 were excluded for mitral stenosis and/or mechanical prosthetic valve and 45 were excluded because of their anticoagulants were changed or discontinued during follow-up. Therefore, a total of 81 patients with non-valvular AF were included in this analysis. Additional 536 patients were enrolled from those being consulted in outpatient clinic of Kanazawa University Hospital. Therefore, there were 617 patients (67.7% male, mean age 68.8 ± 10.7 years) were included for analysis in the present study.

Warfarin was prescribed to 333 patients (54%), and DOACs were prescribed to 284 patients (46%) at the time of enrollment. In DOAC group, dabigatran was prescribed in 63 (10.2%), rivaroxaban was 121 (19.6%), apixaban was 80 (12.9%), and edoxaban was 20 (3.4%) patients.

During follow-up, the frequency of PT-INR measurement was 1.2 ± 1.2/month. Under this condition, the average values of the TTR of warfarin treated patients were 71.8 ± 18.4%. Baseline characteristics of patients with warfarin and those with DOACs are listed in Table 1. Compared with patients with DOACs, those with warfarin had significantly high incidence of persistent or permanent type of AF, heart failure, and previous stroke/TIA. $CHADS_2$ score, CHA_2DS_2–VASc score, HAS-BLED score, plasma BNP level, and left atrial diameter were significantly greater in patients treated with warfarin than those with DOACs. Renal function was worse in warfarin treating patients than those with DOAC. The total observation time was 1933 person-years, and the median observation time was 3.0 years (interquartile range 1.3–4.9 years).

During follow-up period, thromboembolic events occurred in 26 patients (4.2%, 1.3/100 person-year) and hemorrhagic events in 20 (3.2%, 1.0/100 person-year). Importantly, in Kaplan–Meier analysis, there were no significant differences in the occurrence of thromboembolic (log rank $P = 0.16$) and hemorrhagic (log lank $P = 0.83$) events between patients treated with warfarin and DOACs (Fig. 1). In regard to the contents of hemorrhagic events, there was no significant difference in the occurrence rate of intracranial hemorrhage and gastrointestinal hemorrhage between warfarin and DOAC group (1.20% vs. 0.35%, $P = 0.38$, 1.80% vs. 1.06%, $P = 0.52$, respectively). We evaluated the predictors for the occurrence of thromboembolic events or hemorrhagic events using Cox-proportional hazard model (Table 2). In both thromboembolic and hemorrhagic events, warfarin use was not associated with the occurrence of these events (HR 1.35; 95% CI 0.47–4.88, $P = 0.60$, HR 0.35; 95% CI 0.12–1.06, $P = 0.06$, respectively).

When we calculated drug cost in warfarin group vs. DOAC group (10,278 ± 7355 yen/person-year vs. 194,448 ± 7964 yen/person-year, $P < 0.0001$), drug cost with medical fee in outpatient clinic (45,617 ± 36,605 yen/person-year vs. 201,900 ± 201,696 yen/person-year, $P < 0.0001$) and those with hospitalization fee (117,361 ± 743,710 yen/year vs. 310,436 ± 1,075,639 yen/person, $P = 0.009$), these were significantly lower in patients treated with warfarin than those with DOACs (Fig. 2). The cost for hospitalization (yen/person-year) in patients treated with warfarin was comparable to that in patients treated with DOAC (71,744 ± 49,140 yen/person-year vs. 108,535 ± 53,211 yen/person-year, $P = 0.61$, Fig. 3). The mean cost of hospitalization due

Table 1 Clinical and echocardiographic characteristics of the entire AF patient and warfarin or DOAC user groups

Variables	All ($n=617$)	Warfarin ($n=333$)	DOAC (n=284)	P value†
Age, years	68.8 ± 10.7	69.7 ± 10.4	67.6 ± 11.0	0.01
Male sex, *n* (%)	418 (67.7)	229 (68.8)	189 (66.6)	0.61
Body weight, kg	61.4 ± 12.7	60.9 ± 12.9	62.0 ± 12.5	0.26
Sustained* AF, *n* (%)	230 (37.3)	153 (45.9)	77 (27.1)	< 0.0001
Congestive heart failure, *n* (%)	194 (31.4)	129 (38.7)	65 (22.9)	< 0.0001
Hypertension, *n* (%)	370 (59.9)	192 (57.7)	178 (62.7)	0.22
Diabetes mellitus, *n* (%)	201 (32.6)	124 (37.2)	77 (27.1)	0.008
Prior stroke or TIA, *n* (%)	117 (18.9)	88 (26.4)	29 (10.2)	<0.0001
Vascular disease, *n* (%)	158 (25.6)	104 (31.2)	54 (19.0)	0.0006
Creatinine clearance, ml/min	73.1 ± 43.3	64.2 ± 28.8	83.6 ± 53.9	<0.0001
TTR (warfarin users), %	71.8 ± 18.4	71.8 ± 18.4		
BNP, pg/mL	147 ± 164	181 ± 191	108 ± 114	<0.0001
$CHADS_2$ score	1.95 ± 1.38	2.22 ± 1.43	1.63 ± 1.24	<0.0001
CHA_2DS_2-VASc score	3.22 ± 1.82	3.57 ± 1.82	2.81 ± 1.73	<0.0001
HAS-BLED score	1.56 ± 1.19	1.87 ± 1.26	1.19 ± 0.99	<0.0001
LA diameter, mm	43.9 ± 7.8	45.7 ± 7.8	41.7 ± 7.3	<0.0001
Anti-platelet drugs, *n* (%)	122 (19.8)	66 (19.8)	56 (19.7)	1.00
Under-dosing of DOAC, *n* (%)			23 (8.1)	
Over dosing of DOAC, *n* (%)			19 (6.7)	
Follow-up duration, years	3.1 ± 2.0	4.1 ± 2.1	2.0 ± 1.4	<0.0001

Data are presented as n (%) or mean ± standard deviation

AF atrial fibrillation, *BNP* brain natriuretic peptide, *LA* left atrial, *TIA* transient ischemic attack, *TTR* time in therapeutic range

*Sustained AF refers to persistent or permanent AF

†*p* value was derived from comparison analysis between Warfarin and DOAC groups

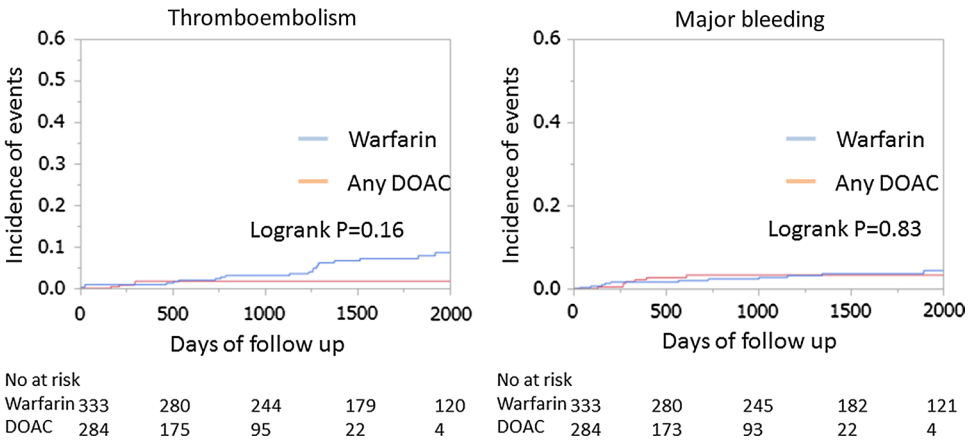

Fig. 1 Incidence of thromboembolism and hemorrhagic events during follow-up period (warfarin vs. DOAC group)

to thromboembolic events was 395,629 ± 487,822 yen/person-year. The mean costs of hospitalization for thromboembolism in the warfarin group and DOAC group were 254,991 ± 76,881 yen/person-year and 1,169,146 ± 180,361 yen/person-year, respectively ($P<0.0001$). In contrast, the mean cost of hospitalization due to bleeding events was 2,249,304 ± 4,522,950 yen/person-year. The mean costs of hospitalization for bleeding in the warfarin group and DOAC group were 1,449,128 ± 1,248,764 yen/person-year and 3,735,346 ± 1,701,779 yen/person-year, respectively ($P=0.29$).

Discussion

The present study demonstrates that thromboembolic and hemorrhagic events during follow-up of non-valvular AF were not statistically different between treatment with

Table 2 Multivariate Cox-proportional hazard regression models in NVAF patients

Variables	Thromboembolic events		Hemorrhagic events	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Warfarin use	1.35 (0.47–4.88)	0.60	0.35 (0.12–1.06)	0.06
CHA_2DS_2-VASc score	1.62 (1.31–2.01)	< 0.0001		
Sustained* AF	1.04 (0.46–2.33)	0.93		
Ccr** < 50 ml/min	1.97 (0.85–4.60)	0.11		
HAS-BLED score			2.38 (1.81–3.13)	< 0.0001

CI confidence interval; other abbreviations as in Table 1

*Sustained AF refers to persistent or permanent AF

**Ccr refers to creatinine clearance

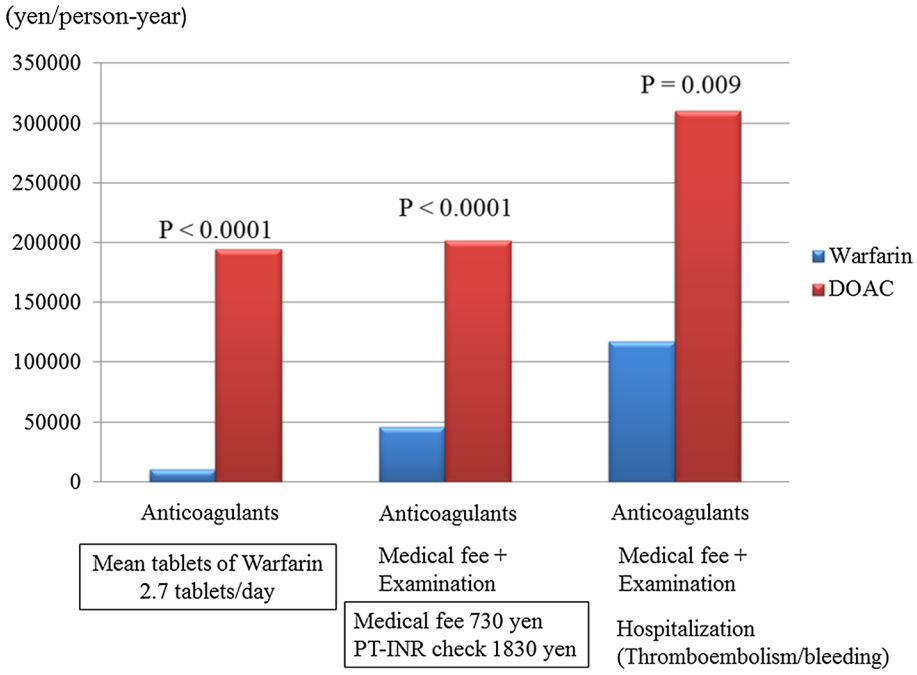

Fig. 2 Comparison of the costs between warfarin and DOAC group. During follow-up, a mean number of warfarin tablets were 2.7 tablets/day. The medical fee in outpatient clinic was 730 yen/time in warfarin and DOAC group. The cost for measurement of prothrombin–international normalized ratio (PT–INR) was 1830 yen/time in warfarin group

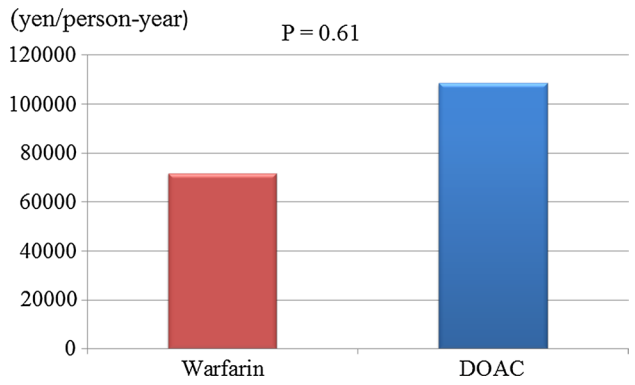

Fig. 3 Total cost during hospitalization between warfarin and DOAC group

warfarin and that with DOACs when authorized cardiologists carefully examine these patients. Under these conditions, estimated total medical fee can be lower in treatment with warfarin than that with DOACs. These results suggest that under carful patients' care by authorized cardiologists use of warfarin can be economically advantageous for non-valvular AF in comparison with that of DOACs. In contrast, the majority of warfarin patients in Japan are managed by general physicians. We expect that good warfarin control by general physicians in addition to cardiologists would to lead to lower medical costs.

Since the use of DOACs for treatment of non-valvular AF started, a number of evidence demonstrated the advantageous aspects of DOACs in terms of the occurrence of thromboembolic and hemorrhagic complication [17]. As for cost–benefit balance of the use of DOACs instead of warfarin, however, a few data exist regarding the economical analysis of use of DOACs. Hori et al. [18] reported the theoretical advantage of use of dabigatran based on its randomized control trials. According to their analysis, use

of increased medical fee by dabigatran has been cancelled by the reduction of the occurrence of stroke. This result was based on the analysis estimating the occurrence of stroke from the result not from real-world medicine but from well control trials. In the present study, the occurrence of thromboembolic and hemorrhagic events was not different between two groups. This may probably due to extremely careful treatment of patients by monitoring INR at least every two months during follow-up period.

Recently, Yamashita et al. [9] reported that the occurrence of thromboembolic and hemorrhagic events was not different between patients treated with DOACs and warfarin. In their cohort, the rate of warfarin users who suffered optimal time in therapeutic range shown by the JCS guideline [1] was 50–60% [19]. Even under these conditions, there was no evidence of the superiority of DOACs to warfarin in their study. One might speculate that there could be under dose of DOACs in terms of avoiding the possible occurrence of hemorrhagic complications. However, these results including our study indicate that in real world, it is still controversial to conclude the superiority or inferiority of both drugs for treatment of non-valvular AF. As observed in the present study, the total medical cost of AF patients can be reduced in warfarin use than that of DOACs without differences of the occurrence rates of thromboembolic or hemorrhagic events.

Clinical implications

The present study provides some important clinical implications. Total medical cost in Japan was 42 trillion yen in 2015 [8], contributing to compression of the national budgets. Particularly, new technology including catheter-based treatment of cardiovascular disease can increase the cost for treatment. Therefore, re-evaluation of the cost-effectiveness regarding anticoagulation therapy may partially contribute to reducing medical budget of Japan.

It is somewhat interesting to consider the effect of post-discharge fee such as social care on total cost using warfarin or DOAC. In the present study, we did not include the post-discharge fee, because the occurrence of thromboembolic and hemorrhagic events was not different between two groups. When the fee for these post-discharge patient cares is theoretically estimated by the methods of Hori et al. [18], this will cost 217,405 ± 62,245 yen in warfarin and 355,191 ± 67,401 yen/person in DOAC groups, yielding statistical insignificance between two groups probably due to large variation of each cost. In addition, these costs are quite flexible in accordance with the level of patient care and are difficult to exactly calculate in real-world setting. We should be careful to consider about actual fee for post-discharge patient care in the future.

Limitation

There remain several limitations. First, this is retrospective single-center evaluation. In addition, all enrolled patients were treated at a university hospital, whose patients may differ from those treated in a peripheral hospital, and consulting doctors consisted of only authorized cardiologists. Therefore, this was quite special observational study in terms of real-world clinics. However, as shown by Yamashita et al. [9], the obtained results regarding the occurrence of thromboembolic and hemorrhagic events were similar in both studies. This suggests that the occurrence of these events may be similar in cases consulted by general physicians and authorized cardiologists in real-world setting. Second, there were differences in thromboembolic risk (CHADS2 or CHA2DS2-VASc score, type of AF, renal function) at baseline between warfarin and DOACs group. Warfarin group had higher risk for thromboembolic events. However, even in this condition, warfarin group showed lower costs in clinical course. Third, cost of each drug changes year to year. For example, in 2018, the price of rivaroxaban of 15 mg declined from 545.60 to 534.30, or by −2.1% yen/tablet. Therefore, calculation of total cost should be carefully done when these fees change, although difference in price between warfarin and DOACs is large enough to be caught up. Fourth, we had no data about the costs of outpatient treatment for minor bleeding. Fifth, the absence of a need for coagulation monitoring with DOAC treatment may lead to a reduction of laboratory staff and this would affect the cost-effectiveness. We should consider these effects in the future.

Finally, we could not evaluate the quality adjusted life years or the incremental cost-effectiveness ratio, because our analysis was the retrospective design.

Conclusions

These results demonstrate that total cost with warfarin can be lower than DOAC in treatment for AF by authorized cardiologists in Japan. Further prospective randomized trials to evaluate cost-effectiveness of both drugs will confirm the present results.

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Compliance with ethical standards

Conflict of interest The authors received honoraria for lectures from Daiichi-Sankyo Co. Ltd., Boehringer Ingelheim Japan Co. Ltd., and received scholarship fund from Boehringer Ingelheim Japan Co. Ltd., Bayer Co. Ltd.

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