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Real-world comparison of in-hospital complications after catheter ablation for atrial fibrillation between non-antivitamin K anticoagulants and warfarin: A propensity-matched analysis using nation-wide database

Koji Miyamoto [a], Shunsuke Murata [b], Misa Takegami [b], Kenzaburo Nakajima [a], Tsukasa Kamakura [a], Mitsuru Wada [a], Kohei Ishibashi [a], Yuko Inoue [a], Satoshi Nagase [a], Takeshi Aiba [a], Kunihiro Nishimura [b], Kengo Kusano [a,*]

[a] Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan
[b] Department of Preventive Medicine and Epidemiology, National Cerebral and Cardiovascular Center, Suita, Japan

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ABSTRACT

Background: Few large-scale, real-world studies have compared the efficacy and safety of non-antivitamin K anticoagulants (NOACs) with that of warfarin in catheter ablation (CA) for atrial fibrillation (AF).
Methods: This retrospective, cross-sectional study used a nationwide administrative claims database, to compare complication-incidence rates following CA for AF between NOAC-treated patients and warfarin-treated matched cohorts in the real-world. Among the 32,797,540 records between June 2011 and August 2020 from 426 hospitals, 41,347 patients (38,065 on NOACs and 3,282 on Warfarin) were considered eligible. After performing propensity matching, 6,564 patients (3,282 per group) were analyzed.
Results: The overall complication incidence was significantly lower in the NOACs group than in the warfarin group (2.3 % vs. 4.0 %; $P < 0.001$, odds ratio [OR]: 0.55, 95 % confidence interval [CI]: 0.41–0.74). Although no significant differences in the incidence of cardiac tamponade (1.0 % vs. 1.1 %; $P = 0.90$, OR: 0.97, 95 % CI: 0.60–1.56) and major bleeding (0.6 % vs. 0.7 %; $P = 0.54$, OR: 0.83, 95 % CI: 0.44–1.52) were noted, blood transfusion requirements (0.6 % vs. 1.2 %; $P = 0.02$, OR: 0.52, 95 % CI: 0.30–0.88) and vascular complications (0.2 % vs. 0.5 %; $P = 0.02$, OR: 0.33, 95 % CI: 0.12–0.79) were significantly lower in the NOACs group than in the warfarin group. Furthermore, the thromboembolic event incidence was significantly lower in the NOACs group than in the warfarin group (0.5 % vs. 1.2 %; $P < 0.001$, OR: 0.36, 95 % CI: 0.19–0.64).
Conclusions: NOACs should be considered as a first-line therapy for periprocedural anticoagulation in patients undergoing CA for AF.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia and an independent risk factor for thromboembolisms [1–3]. Oral anticoagulation (OAC) is the most important medication for the clinical management of AF [4]. Multiple randomized controlled trials (RCTs) have shown that non-antivitamin K anticoagulants (NOACs) are superior or non-inferior to warfarin in the prevention of thromboembolisms and are associated with a lower or similar rate of bleeding events in patients with non-valvular AF and have replaced warfarin as the first-line OAC for non-valvular AF [5–8].

Catheter ablation (CA) has emerged as a common AF treatment for the improvement of the quality of life (QOL) and reduction of the risk of thromboembolisms, cardiovascular events, and mortality [9,10]. However, patients undergoing CA for AF encounter procedure-related risks of major bleeding and thromboembolism, and *peri*-procedural

Abbreviations: AF, atrial fibrillation; QOL, quality of life; CA, catheter ablation; CI, confidence interval; DPC, Diagnosis Procedure Combination; ICD-10, International Classification of Diseases, 10th revision; AFL, atrial flutter; AT, atrial tachycardia; TIA, transient ischemic attack; MDV, Medical Data Vision; OAC, oral anticoagulation; OR, odds ratio; PSM, propensity-score matching; RCT, randomized controlled trial.

* Corresponding author at: Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, 6-1, Kishibe shinmachi, Suita, Osaka 564-8565, Japan.
E-mail address: kusanokengo@ncvc.go.jp (K. Kusano).

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complications are reportedly in the range of 1.0–4.5 % [11–13].

Hence, periprocedural anticoagulation should minimize the risk of bleeding and thromboembolisms, and optimal periprocedural management with OACs is required in patients undergoing CA for AF. RCTs of various NOACs (VENTURE AF, RE-CIRCUIT, AXAFA-AFNET, and ELIMINATE-AF) have already compared the safety and efficacy of NOACs with that of warfarin in patients undergoing CA for AF and reported the periprocedural use of NOACs to be associated with lower or similar rates of bleeding and thromboembolic events as compared with warfarin use [14–17].

Although these RCTs revealed the safety and efficacy of NOACs as periprocedural anticoagulants in CA for AF, those studies applied strict patient eligibility criteria that excluded some patients who had been treated in clinical practice; therefore, they were not fully representative of an unselected, real-world population. Furthermore, the results of these studies might have been biased and underpowered owing to the relatively small sample sizes. Accordingly, whether the study results from these RCTs can be generalized to a wider patient population in the real-world remains unknown; moreover, few large-scale, real-world studies have compared the efficacy and safety of NOACs with that of warfarin in CA for AF.

The hypothesis of the current study was that bleeding complications after CA for AF occur less frequently in patients treated with NOACs (NOACs group) than in those treated with warfarin (warfarin group). To test this hypothesis, the current study applied a retrospective, cross-sectional design based on a nationwide administrative claims database and compared the incidence of complications following CA for AF between NOAC-treated patients and warfarin-treated patients using matched cohorts in the real-world.

2. Methods

2.1. Data source

We used data from Medical Data Vision Co., Ltd. (MDV; Tokyo, Japan). The MDV database is derived from the health claims, Diagnosis Procedure Combination (DPC) system, and flat-fee payment system in Japan. The MDV database includes the following information on each patient: age, sex, height, weight, body mass index, main diagnoses and comorbidities, drugs and devices, diagnostic and therapeutic procedures, length of hospital stay, and discharge status. The details of the DPC system and database have been described elsewhere [18,19].

2.2. Study population

The MDV database, which represents the Japanese population, contained 32,797,540 health records from 426 acute-care hospitals that were collected between June 2011 and August 2020. Patients registered in the MDV database were selected using the following steps (Fig. 1):

Step 1: We extracted data on patients diagnosed with any arrhythmia.
Step 2: We extracted data on patients who were hospitalized for AF as the "main diagnosis", "admission-precipitating diagnosis", "most resource-consuming diagnosis", and/or "second most resource-consuming diagnosis".
Step 3: We excluded patients with (1) atrial flutter (AFL) or atrial tachycardia (AT) identified with a "main diagnosis", "admission-precipitating diagnosis", "most resource-consuming diagnosis", and/or "second most resource-consuming diagnosis"; (2) patients who did not undergo CA of AF; (3) age < 20 years; (4) CA for AF other than radiofrequency CA or Cryoballoon; (5) absent clinical data; and (6) prescription for both NOACs and warfarin. We determined that cases without a transseptal puncture (code of K5951) did not undergo CA of AF.
Step 4: We performed propensity-score matching (PSM) with the following variables: age, sex, body mass index, congestive heart failure, hypertension, diabetes mellitus, stroke/transient ischemic attack (TIA), vascular disease, dyslipidemia, radiofrequency ablation, and concomitant use of antiplatelet drugs.

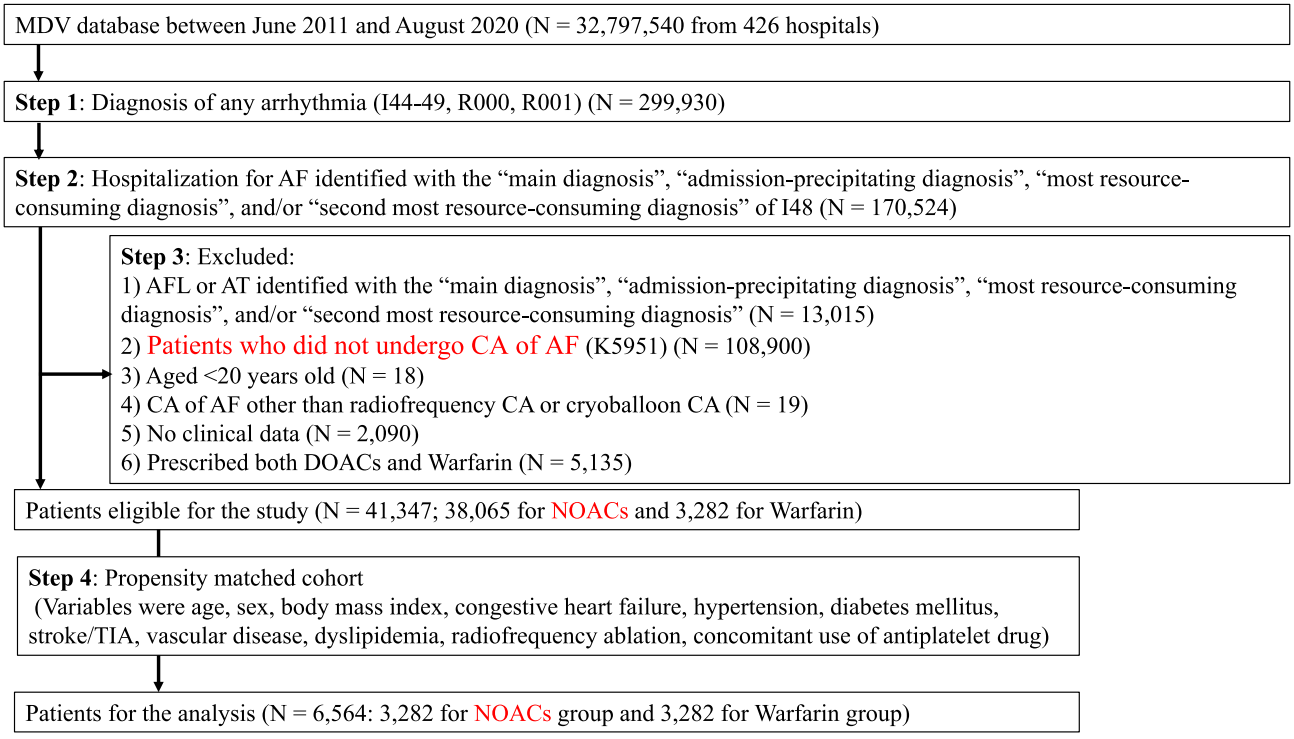

Fig. 1. Study flowchart MDV = Medical Data Vision, AF = atrial fibrillation, AFL = atrial flutter, AT = atrial tachycardia, CA = catheter ablation, NOACs = non-antivitamin K anticoagulants, TIA = transient ischemic attack.

2.3. Definition of complications

We used the International Classification of Diseases, 10th revision (ICD-10) diagnosis and DPC procedure codes to identify the common in-hospital complications due to CA for AF [18,19]. In-hospital complications were extracted from a maximum of four to 10 diagnoses coded under "conditions arising after admission" [19]. Complications were defined under the following ICD-10 diagnosis and DPC procedure codes (**Supplemental Table**): cardiac complications (cardiac tamponade: I31.9, I97.1, or J98.5, and/or pericardial drainage as J048 or J0021; myocardial infarctions: I21–23; vasospastic angina: I20.1; complete atrioventricular block: I44.2; and sick sinus syndrome: I45.5 or I49.5), pulmonary complications (pneumothoraxes: J930, J931, J938, or J939; hemothorax: J942; and pneumonia: J15.9J18.9, or J69.0), neurological complications (phrenic nerve palsy: G58.8; stroke and TIA: G45, or I63), vascular access complications (hematoma: S701, S801, T140 or T810; and/or pseudoaneurysms: I72.4), major bleeding (I31.9, I97.1, J98.5, J048, J0021, or other fatal bleedings), thromboembolism (H342, I24, I269, I740, I741, I744, I748, I749, K550, K868, N280, or T790), blood transfusion (K920), cardiothoracic surgery (K539), and in-hospital death. The complications were collected only during the current hospitalization.

2.4. Sample size and power

Sample-size calculation was based on the primary hypothesis. The incidence rates of major bleeding after CA for AF have been reported to be 0–3 % and 1–4 % in the NOAC and warfarin groups, respectively [14–17]. Based on these data, the major bleeding rates after CA were assumed to be 1 % and 2 % in the NOAC and warfarin groups, respectively. After a calculation, the sample size was set at 2,316 patients per group, with a power of 80 %, based on a significance level of 0.05.

2.5. Statistical analysis

We used PSM to balance the patient characteristics between the NOACs and warfarin groups. The PSM was conducted based on the following covariates: age, sex, body mass index, congestive heart failure, hypertension, diabetes mellitus, stroke/TIA, vascular disease, dyslipidemia, radiofrequency ablation, and concomitant use of antiplatelets. Each NOAC-treated patient was matched to a warfarin-treated patient in a 1:1 ratio. We compared the complication rates between the NOACs and warfarin groups using matched cohorts.

Regarding the patient characteristics, the categorical variables are presented as absolute and relative frequencies, and continuous variables are presented as the mean ± standard deviation for normally distributed data or median with the interquartile range (25th–75th percentiles) for skewed data, as appropriate. A multivariable Cox regression analysis was performed to compare the incidence of complications between the NOAC and warfarin groups. Odds ratios (ORs) with 95 % confidence intervals (95 % CIs) were calculated. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using R software (version 4.0.3).

3. Results

3.1. Study population

First, we identified 299,930 patients diagnosed with arrhythmias based on ICD-10 codes between June 2011 and August 2020 (Fig. 1, Step 1). Among them, we extracted 170,524 patients who were hospitalized for AF and identified with ICD-10 codes I48 (Fig. 1, Step 2). Thereafter, we excluded patients with (1) AFL or AT as the "main diagnosis", "admission-precipitating diagnosis", "most resource-consuming diagnosis", and/or "second most resource-consuming diagnosis" (N = 13,015); (2) patients who did not undergo CA of AF (N = 108,900); (3) aged < 20 years (N = 18); (4) a CA procedure other than radiofrequency CA or cryoballoon CA (N = 19); (5) absent clinical data (N = 2,090); and (6) prescriptions for both NOACs and warfarin (N = 5,135). (Fig. 1, Step 3). A total of 41,347 patients (38,065 on NOACs and 3,282 on warfarin) were considered eligible for the study. Finally, we performed PSM, and 6,564 patients (3,282 patients in each group) were included in the analysis (Fig. 1, Step 4).

The patient characteristics and covariate balance of both groups are shown in Table 1 and Fig. 2. The mean age was 67.4 ± 9.2 years and 67.3 ± 9.2 years in the NOACs and warfarin groups, respectively, and 27.7 % of the patients were female. Among the patients, 45.1 % had heart failure, 53.6 % hypertension, 20.4 % diabetes mellitus, 28.1 % hyperlipidemia, 1.8 % stroke or TIA, 20.6 % ischemic heart disease, and 20.8 % concomitant antiplatelet drug use. The patients in the NOACs group were prescribed dabigatran (N = 581), rivaroxaban (N = 923), apixaban (N = 784), or edoxaban (N = 994).

3.2. Complications and in-hospital death

The major complications and in-hospital deaths in each group are shown in Figs. 3 and 4. The incidence of overall complications was significantly lower in the NOAC group than in the warfarin group (2.3 % vs. 4.0 %; P < 0.001, OR: 0.55, 95 % CI: 0.41–0.74). Although no

Table 1
Patient Characteristics.

Variables	NOACs N = 3,282	Warfarin N = 3,282
Mean age, years	67.4 ± 9.2	67.3 ± 9.2
Age, n (%)		
25–29	1 (0.0)	1 (0.0)
30–34	7 (0.2)	7 (0.2)
35–39	27 (0.8)	26 (0.8)
40–44	49 (1.5)	45 (1.4)
45–49	76 (2.3)	75 (2.3)
50–54	117 (3.6)	127 (3.9)
55–59	281 (8.6)	297 (9.0)
60–64	507 (15.4)	484 (14.7)
65–69	760 (23.2)	772 (23.5)
70–74	720 (21.9)	723 (22.0)
75–79	530 (16.1)	513 (15.6)
80–84	190 (5.8)	187 (5.7)
85–	17 (0.5)	25 (0.8)
Sex, female, n (%)	909 (27.7)	906 (27.6)
Mean BMI, kg/m^2	24.1 ± 3.5	24.1 ± 3.9
Heart failure, n (%)	1,492 (45.5)	1,466 (44.7)
Hypertension, n (%)	1,795 (54.7)	1,723 (52.5)
Diabetes mellitus, n (%)	682 (20.8)	659 (20.1)
Hyperlipidemia, n (%)	935 (28.5)	911 (27.8)
Stroke or TIA, n (%)	69 (2.1)	50 (1.5)
Ischemic heart disease, n (%)	700 (21.3)	652 (19.9)
Mean $CHADS_2$ score	1.48 ± 0.96	1.42 ± 0.95
0, n (%)	522 (15.9)	557 (17.0)
1	1,190 (36.3)	1,231 (37.5)
2	1,128 (34.4)	1,092 (33.3)
3	376 (11.5)	350 (10.7)
4	61 (1.9)	52 (1.6)
5	4 (0.1)	0 (0)
6	1 (0.0)	0 (0)
Mean CHA_2DS_2-VASc score	2.79 ± 1.45	2.77 ± 1.41
0, n (%)	164 (5.0)	154 (4.7)
1	472 (14.4)	454 (13.8)
2	776 (23.6)	828 (25.2)
3	872 (26.6)	901 (27.5)
4	602 (18.3)	560 (17.1)
5	291 (8.9)	294 (9.0)
6	85 (2.6)	77 (2.3)
7	19 (0.6)	12 (0.4)
8	1 (0.0)	2 (0.1)
Concomitant use of an antiplatelet agent, n (%)	693 (21.1)	672 (20.5)

NOACs = non-antivitamin K anticoagulants, BMI = body mass index, TIA = transient ischemic attack.

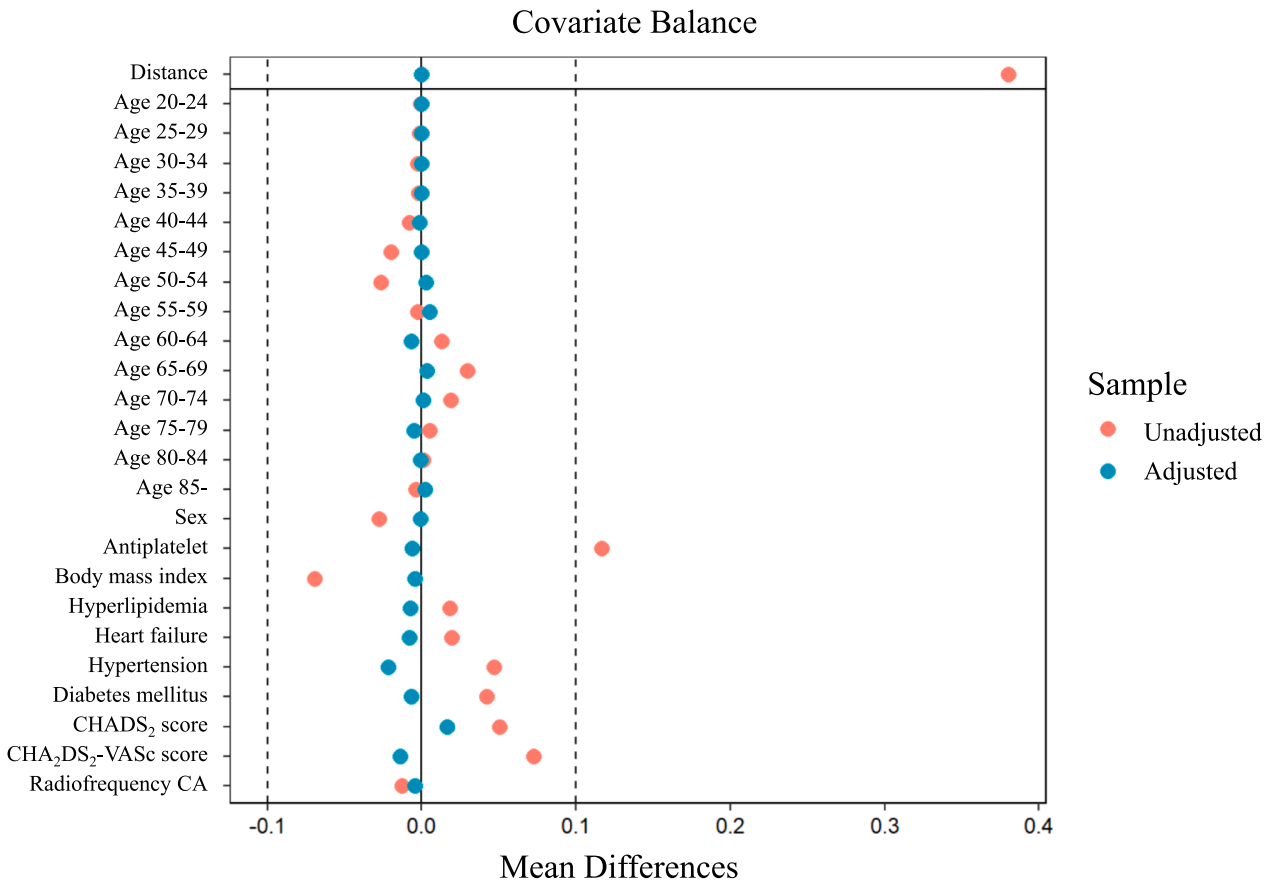

Fig. 2. Covariate balance of this study. CA = catheter ablation.

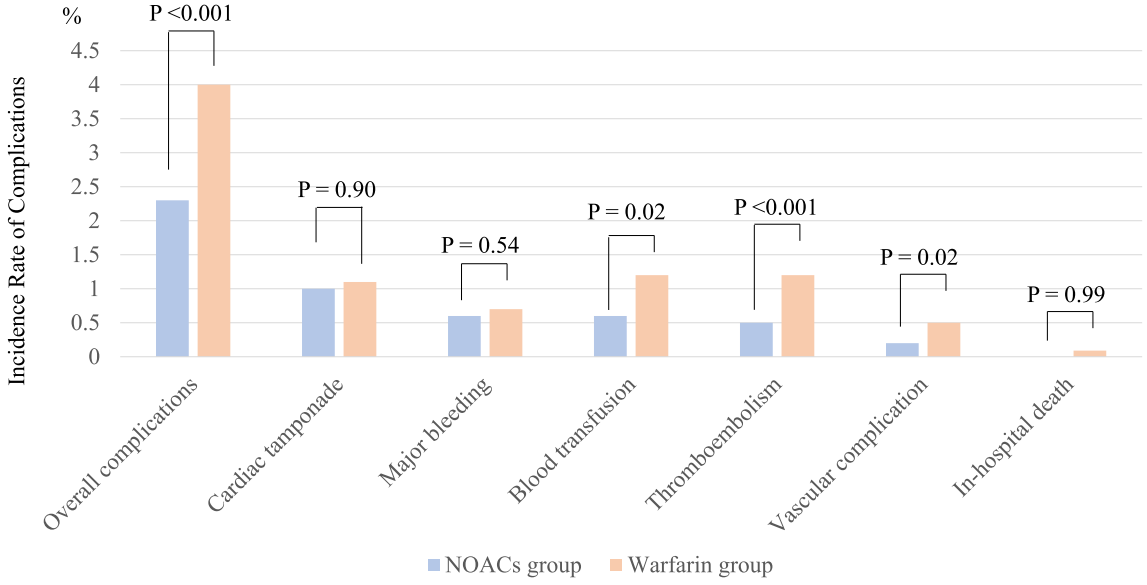

Fig. 3. Incidence rates of complications in each group.

significant differences in the incidence of cardiac tamponade (1.0 % vs. 1.1 %; P = 0.90, OR: 0.97, 95 % CI: 0.60–1.56) and major bleeding complications (0.6 % vs. 0.7 %; P = 0.54, OR: 0.83, 95 % CI: 0.44–1.52) were noted, the requirement for a blood transfusion (0.6 % vs. 1.2 %; P = 0.02, OR: 0.52, 95 % CI: 0.30–0.88) and vascular complications (0.2 % vs. 0.5 %; P = 0.02, OR: 0.33, 95 % CI: 0.12–0.79) were significantly lower in the NOAC group than in the warfarin group. Furthermore, the incidence of thromboembolic events was significantly lower in the NOAC group than in the warfarin group (0.5 % vs. 1.2 %; P < 0.001, OR: 0.36, 95 % CI: 0.19–0.64). No significant differences in the incidence of in-hospital death were observed (0 % vs. 0.09 %; P = 0.99). The median length of the hospital stay was 4.00 [2.00–254] for the NOAC group and

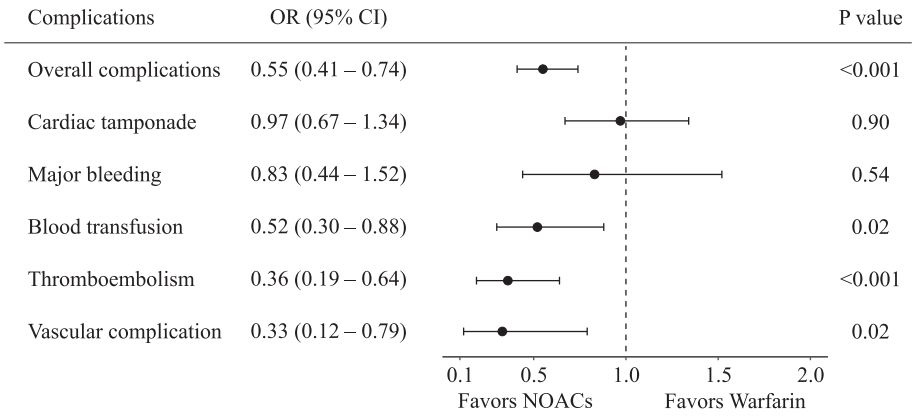

Fig. 4. ORs and 95 % CIs of Complications OR = odds ratio, CI = confidence interval.

5.00 [2.00–132] for the warfarin group (P < 0.001).

4. Discussion

The present study used a nationwide claims database containing data on more than 170,000 patients with AF from 426 hospitals between 2011 and 2020 to compare the safety and efficacy of NOAC with that of warfarin using PSM. The major findings of the current study are as follows: 1) the incidence of overall complications was significantly lower in the NOACs group than in the warfarin group; 2) although no significant differences in the incidence rates of cardiac tamponade and major bleeding complications were noted, the requirement for a blood transfusion and incidence of vascular complications were significantly lower in the NOAC group than in the warfarin group; and 3) the incidence of thromboembolic events was significantly lower in the NOAC group than in the warfarin group.

4.1. Comparison with previous studies

Regarding bleeding complications during CA for AF, several studies have reported that patients treated with NOACs experience fewer bleeding events than those treated with warfarin [14–17,20]. Brunetti et al. conducted a *meta*-analysis of four RCTs (VENTURE-AF, AXAFA, RE-CIRCUIT, and ELIMINATE-AF) that compared the safety and efficacy of NOACs with that of warfarin during CA for AF. The meta-analysis, which included 2,118 patients from the four RCTs, revealed a statistically significant reduction in major bleeding events in NOAC-treated patients compared with that in warfarin-treated patients (relative risk: 0.61, 95 % CI: 0.39–0.93, P = 0.02) and concluded that NOAC use during CA for AF is potentially superior to warfarin use during CA for AF in terms of bleeding complications. In the current study, although the frequencies of cardiac tamponade and major bleeding events were similar between the NOAC and warfarin groups, NOAC-treated patients had a significantly lower risk of a blood transfusion and vascular complications than those treated with warfarin. This was confirmed by Hagii et al. in which they showed that even when a patient treated with NOACs experiences major bleeding, the amount of bleeding is less than that in warfarin-treated patients, and fewer cases require blood transfusions than those on warfarin treatment [21].

Regarding thromboembolic complications during CA for AF, a meta-analysis of four RCTs revealed that NOAC-treated patients had a lower risk of thromboembolic events, however, this was not significant due to the small sample size (relative risk, 0.40; 95 % CI, 0.09–1.76; P = 0.23) [14–17,20]. Although the rate of thromboembolic events in the current study and the four RCTs was comparable in both the NOAC and warfarin groups, the difference between the two groups was statistically significant due to the adequate sample size. Other previous studies have reported the non-inferiority of NOACs in terms of thromboembolic complications [22]. It is speculated that the differences in thromboembolic complications among studies may be partially related to the differences in the sample size and patient characteristics (age, sex, comorbidities, and race). The lack of a difference in the incidence of in-hospital death was compatible with the previous studies, which may be related to the lower incidence of death in both groups.

4.2. NOACs as preprocedural anticoagulants

As demonstrated in the current and previous studies, periprocedural anticoagulation with NOACs is superior or non-inferior to that with warfarin in terms of bleeding and thromboembolic complications [14–17]. In addition, periprocedural anticoagulation with NOACs has certain advantages, such as the rapid onset of action, no requirement for frequent blood testing to monitor the international normalized ratio, no need for frequent dose adjustment, and fewer interactions with medications and food. Based on our findings, we believe that NOACs are suitable periprocedural anticoagulants as a first-line therapy in patients undergoing CA for AF.

4.3. Strengths and limitations of the study

We believe that the current study has several strengths: 1) the nationwide database, which represents the entire Japanese population; 2) no patient selection bias and a consecutive patient population; and 3) the inclusion of all four approved NOACs in the analyses. Notwithstanding, the present study also had certain limitations. First, because the database we used only included in-hospital CA-related complications, we could not analyze the post-discharge complications, such as atrioesophageal fistulae and pulmonary vein stenosis. Second, although the DPC data have been validated and are reliable, they may contain certain errors, and some data may be over- or underestimated [19]. Third, we could not specify how many patients underwent CA with or without an interruption of NOAC and warfarin.

5. Conclusions

Using a nationwide claims database, the present study revealed that the incidence rates of overall complications, bleeding complications requiring a blood transfusion, vascular complications, and thromboembolisms were significantly lower in NOAC-treated patients than in those treated with warfarin. On this premise, we believe that NOACs should be considered as a first-line therapy for periprocedural anticoagulation in patients undergoing CA for AF.

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Disclosure

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2023.101174.

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