Chapter 2
Recurrence of Stroke in Patients with AF Using NOACs

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Abstract *Objective*: To evaluate the risk factors of recurrent thromboembolic cerebral infarction in patients with non-valvular atrial fibrillation (NVAF), who were treated with non-vitamin K antagonist oral anticoagulants (NOACs).

Methods: The data of patients is collected from the database of our institute for about 3 years (between 2013 April and 2015 December).

Results: We analyzed 16 patient's data (14 male, 2 female, median age 67.0 years) in whom recurrent thromboembolic cerebral infarction occurred despite receiving NOACs. 14 of 16 patients with recurrent ischemic stroke received reduced dose drug, and in 10 of 14 patient with reduced dose drug, inappropriate dose setting (i.e., out of drug dose criteria of NOACs) has been selected by the physicians or practitioner concerning about the risk for intracranial hemorrhage and patient's age. After we have changed to the appropriate dose, recurrence of thromboembolic cerebral infarction was not observed.

More than 70 % of recurrent cerebral infarction occurred in patients with inappropriate underdose use of NOACs.

Conclusions: This paper demonstrates that patients with inappropriate reduced dose selection of NOACs carry a significant risk of recurrent thromboembolic cerebral infarction despite treated with NOACs anticoagulation, highlighting the need for appropriate drug dose selection for stroke prevention in real-world NVAF patients.

Keywords Recurrent stroke • NOAC • Inappropriate dose setting

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2.1 Introduction

AF (atrial fibrillation) is a great potential risk factor for cerebral stroke, and AF-associated strokes often lead to severe resulting in disability or death [1–4]. Incidence of AF in the general population ranges from 0.85 to 4.1 per 1000 person-years [5, 6] and increases substantially with age.

Oral anticoagulation with the vitamin K antagonist (VKA) warfarin reduces risk of AF-related thromboembolism and is recommended for a wide number [7] of indications, but how to use this drug is limited by a narrow therapeutic window, drug and food interactions, the need for coagulation monitoring, and the risk of bleeding. According to real-world data, warfarin has been under-used for patients with AF because of high risk of bleeding and intracranial hemorrhage, which lead to the recurrence of any stroke and cerebral infarction [8, 9].

Recently, several non-vitamin K antagonist oral anticoagulants (NOACs) have been developed. Randomized clinical trials (RCTs) comparing NOACs with warfarin demonstrated that NOACs are as safe and effective as warfarin to prevent thromboembolic strokes and systemic embolisms in patients with non-valvular AF (NVAF) [10–14]. Current AF guidelines recommended to use NOACs as first choice [15–17], based on these evidences. Subgroup analysis of the trials indicated that patients with previous stroke or TIA are at high risk of recurrent stroke [1] and of cerebral hemorrhage from anticoagulation therapy [18, 19].

Each NOACs have two types of drug dose, normal dose and reduced dose, and we must select the drug dose based on the patient's age, body weight, and renal function (creatinine clearance: CCr).

Selection criteria for drug dose are different for each NOAC.

The dose of apixaban is 5 mg twice daily or 2.5 mg twice daily for patients with two or more of the following factors: age 80 years or older, body weight 60 kg or less, and serum creatinine 133 μmol/L or greater. ARISTOTLE trial [12] demonstrated that of patients with previous stroke or TIA randomly assigned apixaban, 7 % received the reduced dose (2.5 mg twice daily) and 93 % received the normal dose (5 mg twice daily).

Rivaroxaban is 15 mg daily or 10 mg daily in patients with CCr 30–49 mL/min.

Dabigatran is an oral reversible direct thrombin inhibitor that can be given in fixed daily doses (110 mg or 150 mg twice daily) independent of age or body weight.

However, the analysis reports of real-world thromboembolic stroke recurrence in patients with NVAF using NOACs are rare.

The available RCT shows that in patients on NOACs, the rate of thromboembolic stroke or systemic embolism was 2.07–2.79 per 100 patient-years of follow-up in the NOACs group [10–14, 20].

Analysis of data about stroke recurrence in patients with NOACs can be adequately helpful in the management of stroke survivors who carry high recurrent thromboembolic risk.

The aim of our study is to analyze the real-world data of patients with NVAF who survived a recurrent thromboembolic stroke and in whom anticoagulation therapy

with NOACs is treated and to evaluate the mechanisms of recurrence of stroke in NVAF patients using NOACs.

2.2 Materials and Methods

We retrospectively conducted study of patients with NVAF who are treated with anticoagulation therapy with NOACs during 3 years (between 2013 April to 2015 December) after the adoption of NOACs in our hospital.

All patients were treated in the Departments of Neurosurgery and Stroke Center at Shinko Memorial Hospital, Kobe Japan. This study included 16 consecutive patients with NVAF who was afflicted with recurrent thromboembolic cerebral infarction despite using NOACs.

The number of recurrent stroke patients with each NOAC is 2 patients with dabigatran, 10 patients with rivaroxaban, 6 patients with apixaban, and as reference 20 consecutive patients of recurrent cerebral infarction who are treated with warfarin.

To identify patients who were prescribed with NOACs and warfarin, we confirmed each patient's prescription data. We confirmed the diagnosis of NVAF by checking medical records and adherence of drugs by checking the remaining amount of the drugs or interview with patient's family members. Patients with valvular heart disease and thromboembolic infarction of undetermined source were excluded.

The institutional review board of Shinko Memorial Hospital approved this study.

Data on patient age, gender, underlying disease, risk factors, and accompanying medications were obtained from medical records and laboratory data. Creatinine clearance (CCr) was calculated using the Cockcroft–Gault formula [21]. Hypertension was defined as a systolic blood pressure more than 140 mmHg and a diastolic blood pressure more than 90 mmHg. Diabetes mellitus was defined by treatment with hypoglycemic medications or poor glycemic control (defined as a glycohemoglobin A1c more than 6.5 %). Coronary artery disease was defined based on positive stress test results, coronary angiography demonstrating at least 75 % of stenosis, coronary spastic angina documented by an acetylcholine provocation test, a history of prior myocardial infarction, or a history of revascularization procedures. Heart failure was defined according to the American College of Cardiology/American Heart Association criteria [22].

The CHADS2 score (congestive heart failure, hypertension, age more than 75, diabetes, stroke [doubled])and the CHA2DS2-VASc score (congestive heart failure/left ventricular dysfunction, hypertension, age more than 75 [doubled], diabetes, stroke[doubled] – vascular disease – age 65–74, and sex category [female]) were used to measure stroke risk.

HAS-BLED score (hypertension, abnormal renal/liver function [one or two points], stroke, bleeding history or predisposition, labile international normalized ratio, and elderly (>65 years) drugs/alcohol concomitantly [one or two points]) were used to measure hemorrhage risk.

In patients treated with warfarin, we collected prothrombin time-international normalized ratio (PT-INR) data.

Information of patients was obtained from medical records, interview with patient's family members, and the patients' practitioners.

Thromboembolic events included cerebral infarction and transient ischemic attack (TIA). Ischemic cerebral infarction was defined as the sudden onset of a new focal neurological deficit lasting more than 24 h that could not be explained by other causes. TIA was diagnosed when the neurological deficit lasted less than 24 h. Computed tomography or magnetic resonance imaging was performed in all patients.

Statistical analysis summary data were presented either as the mean and standard deviation (SD) and were compared between groups using the Student's t-test and the Mann–Whitney U-test. The cumulative rates of persistence for the prescribed drugs were calculated using the Kaplan–Meier method. Differences in persistence rates were compared using the long rank test. P values less than 0.05 were considered significant.

Data analyses were performed using SPSS statistical software (version11.01, SPSSInc., Chicago, Illinois).

2.3 Results

The clinical database of the usage of each NOACs in our hospital for the 406 patients with NVAF is summarized in Fig. 2.1. Of the 406 patients, 100 (24.7 %) received dabigatran (normal dose 25(25 %); reduced dose 75(75 %)), 130 (32.0 %) received rivaroxaban (normal dose (44.7 %); reduced dose (55.3 %)), and 176 (43.3 %) received apixaban (normal dose (57.4 %); reduced dose (42.6 %)). Of note, in all cases of each NOACs, rates of reduced dose patients were greatly higher compared with that of patients on published RCT data [10–14].

The selection of drug dose was determined by physicians or cardiologist that belongs to our hospital or by practitioner around our hospital, based on the conviction of them.

The reason for the selection of reduced dose NOACs was to avoid drug-induced catastrophic intracranial hemorrhage, especially with elderly patients.

Figure 2.2 demonstrates real-world proportion to select whether normal or reduced dose of rivaroxaban. Fifty-six of 60 (93 %) of patients with CCr ≧50 mL/min and 4 (7 %) with CCr < 50 mL/min received normal dose (15 mg) of rivaroxaban. On the other hand, of note, 39 of 68 (57 %) of patients with CCr ≧50 mL/min and 29 (43 %) with CCr < 50 mL/min received reduced dose (10 mg). These 57 % of patients with CCr ≧50 mL/min, receiving reduced dose of rivaroxaban, should receive normal dose (15 mg). This data demonstrated that inappropriate reduced dose selection of rivaroxaban was 57 % with real-world NVAF patients.

Case: An 87-year-old man was admitted to the emergency room for confused mental status and left-side weakness. He had been treated with reduced dose of

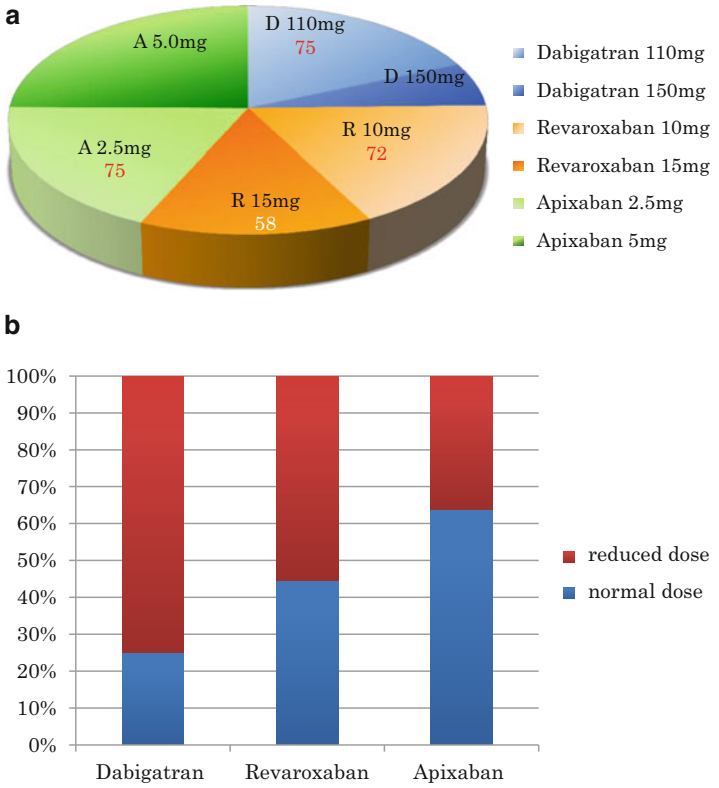

Fig. 2.1 (**a**) The clinical database of the use of each NOAC in our hospital for antithrombotic therapy for the 406 patients with NVAF is summarized in Fig. 2.1. (**b**) Dose selection of 406 patients, dabigatran (normal dose 25(25 %); reduced dose 75(75 %)), rivaroxaban (normal dose (44.7 %); reduced dose (55.3 %)), and apixaban (normal dose (57.4 %); reduced dose (42.6 %)). In all cases of each NOACs, the rate of reduced dose patients was greatly higher compared with that of patients on published RCT data

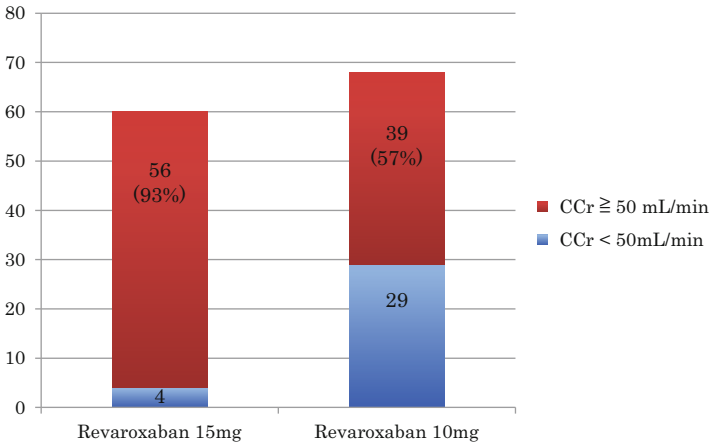

Fig. 2.2 Real-world proportion to select whether normal or reduced dose of rivaroxaban. Thirty-nine of 68 (57 %) of patients with CCr ≧50 mL/min received reduced dose (10 mg). These 57 % of patients with CCr ≧50 mL/min should receive normal dose (15 mg)

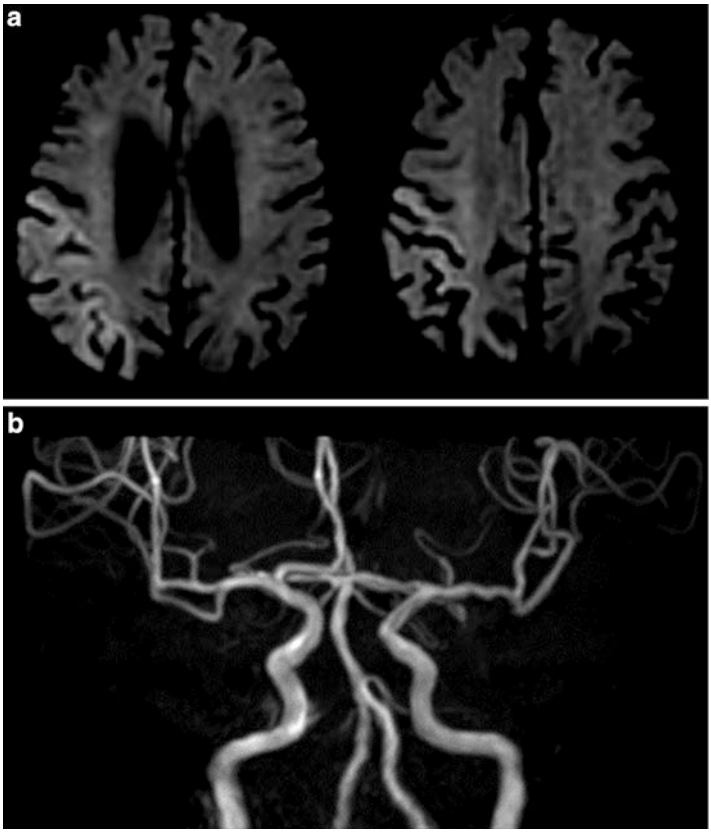

Fig. 2.3 (**a**) Magnetic resonance diffusion weighted imaging revealed acute ischemic infarction in the right middle cerebral artery (MCA) territory. (**b**) Magnetic resonance angiogram imaging revealed no stenosis or occlusion of the right MCA. The patient was diagnosed with TIA due to cardiogenic embolism and recanalization of the occluded MCA in natural course

rivaroxaban (10 mg) for 2 years due to AF and cardiogenic thromboembolic cerebral infarction. He had also been diagnosed and managed for diabetes mellitus. A neurologic examination revealed confused mental status, unresponsiveness to visual threatening, gaze preponderance to the right side, and left-sided hemiparesis. Neurological deficits except slight left motor weakness recovered within several minutes after admission. Magnetic resonance diffusion weighted imaging revealed acute ischemic infarction in the right middle cerebral artery (MCA) territory (Fig. 2.3). The transthoracic echocardiogram findings were consistent with ischemic heart disease with moderate left ventricular systolic dysfunction (left ventricular ejection fraction, 25–30 %), AF with enlargement of both atria, and moderate tricuspid regurgitation. According to coagulation assays on admission, the activated partial thromboplastin time (aPTT) was 38 s (reference, 29.1–41.9 s), and the international normalized ratio (INR) was 1.09 (reference, 0.90–1.10). Magnetic

resonance angiogram imaging revealed no stenosis or occlusion of right MCA. He was diagnosed with TIA due to cardiogenic embolism and recanalization of the occluded MCA in natural course.

A baseline assessment revealed that he had a serum creatinine concentration of 0.79 mg/dL and a CCr of 60 mL/min and HAS-BLED score of 2, so he should receive normal dose of rivaroxaban after the onset of previous cerebral infarction.

The decision was made to change from reduced dose of rivaroxaban to normal dose of apixaban because the patient suffered a recurrent ischemic stroke despite receiving rivaroxaban treatment. Apixaban was started at a dosage of 5 mg twice daily, 2 days after the cessation of rivaroxaban. The patient improved and completely recovered without any neurological deficit, and no recurrent of ischemic stroke was observed after 6 months of apixaban usage.

Figure 2.4 demonstrated real-world proportion to select whether normal or reduced dose of each NOAC for the NVAF patients with recurrent cerebral infarction despite receiving NOACs.

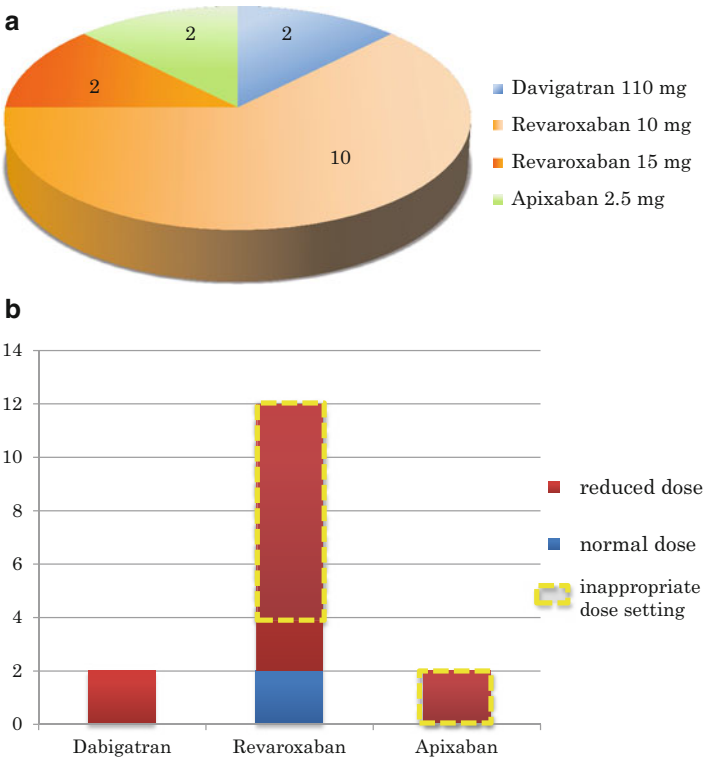

Fig. 2.4 (**a**) Real-world proportion to select whether normal or reduced dose of each NOACs for the NVAF patients with recurrent cerebral infarctions. (**b**) Eight of ten patients with reduced dose should receive normal dose (15 mg daily) based on the drug dose criteria of rivaroxaban. Similarly, all of two patients with recurrent stroke despite using apixaban received reduced dose (2.5 mg twice daily) drug and should receive normal dose (5 mg twice daily) based on the drug dose criteria of apixaban

Ten of 12 NVAF patients with recurrent stroke despite using rivaroxaban received reduced dose (10 mg daily) drug, and 8 of 10 patients with reduced dose should receive normal dose (15 mg daily) based on the drug dose criteria of rivaroxaban.

Similarly, all of two patients with recurrent stroke despite using apixaban received reduced dose (2.5 mg twice daily) drug and should receive normal dose (5 mg twice daily) based on the drug dose criteria of apixaban.

Two patients with recurrent stroke despite using dabigatran received reduced dose (110 mg) drug, but dabigatran can be given in fixed daily doses (110 mg or 150 mg twice daily) independent of age or body weight.

To summarize the above data, 14 of 16 patients with recurrent ischemic stroke, despite of using NOACs, received reduced dose drug, and in 10 of 14 patient with reduced dose drug, inappropriate dose setting (i.e., out of drug dose criterion of NOACs) has been selected by the physicians or practitioner.

After we have changed to the appropriate dose, the recurrence of thromboembolic cerebral infarction was not observed.

More than 70 % of recurrent cerebral infarction occurred in patients with inappropriate underdose use of NOACs.

2.4 Discussion

2.4.1 Warfarin Versus NOACs

The main aim of anticoagulant therapy in a patient of AF is to avoid consequences of arterial thrombus formation, including peripheral embolism, especially cerebral infarction.

Considering the growing number of AF patients and the fact that AF occurs in 15 % of the whole stroke population, the importance of both effective and safe antithrombotic treatment should be emphasized [23–25]. According to previously performed RCTs and guidelines, the application of oral anticoagulants is recommended for stroke prevention in AF patients [8–14].

For many years, VKA was used in that patient group, resulting in a significant stroke rate reduction exceeding the efficacy of antiplatelet treatment [8, 9].

Significant problems related to anticoagulant therapy with VKA are high rate of intracranial hemorrhage, relatively narrow therapeutic window and poor adherence, drug and food interactions, and the need for coagulation monitoring [26].

So, despite the high rate of stroke in patients with AF, an even smaller proportion of patients are properly treated with anticoagulants, which lead to the recurrence of any stroke and cerebral infarction [8, 9].

The introduction of NOACs creates a potential opportunity to bridge the gap between the need of anticoagulant treatment and practice application of this kind of therapy.

That could result not only in high-treatment efficacy but also in obtaining higher rates of successful anticoagulant treatment in AF patients with proper anticoagulant protection.

According to the RCTs inducted, high efficacy and safety of NOACs was documented in patients with NVAF [10–14]. At least the non-inferiority efficacy and safety of NOACs in the prevention of stroke and systemic embolism was documented in studies, as compared with VKA studies [10–14].

An encouraging safety profile, especially in the aspect of intracranial hemorrhage, was simultaneously confirmed. The promising results of randomized trials were also confirmed in meta-analyses [10–14]. Recently published meta-analyses related to NOACs in NVAF demonstrated that the benefit of NOAC use was greater than that of warfarin in terms of stroke reduction and systemic embolism.

According to the results from the Danish Registry [27], the mortality among patients using NOACs was lower than among those treated with VKA.

2.4.2 Frequency of Anticoagulants Use

According to the randomized clinical trials of effects of antithrombotic therapy in patients with NVAF [5], warfarin use has increased gradually. Previously warfarin was used for 8–17 % of patients with AF [28] but had increased to 51.7 % of NVAF patients in the present study. Approximately 50 % of NVAF patients with high risk of embolism received anticoagulation with warfarin; that is, anticoagulant use is still insufficient among patients with NVAF treated by cardiologists and practitioners. The intensities of warfarin therapy in the previous reviews were slightly lower than those recommended by the guideline [29]. The under-use of anticoagulant warfarin might be based on data from prospective, secondary prevention trials [30].

In many NVAF patients, the antithrombotic therapy did not follow the guideline [29]. Warfarin, rather than other antiplatelet drugs like aspirin, was used more frequently to patients aged 75 years old or younger. Only one fifth of patients aged over 75 years were given warfarin. In previous studies, warfarin use was less frequent for older patients [31]; that was because of high risk of major bleeding and other complications in the elderly patients; however, warfarin can be used safely and efficiently among older patients (over 90 years old) without any risk factors for intracranial bleeding.

2.4.3 Under-Use of Warfarin and NOACs

First, based on clinical trials, an INR of 2–3 is recommended to prevent thromboembolic events in patients with NVAF [29], but for Japanese patients, an INR of 1.6–2.6 is considered appropriate, based on prospective, secondary prevention trials [30]. This narrow therapeutic window might lead to the inconvenience of INR monitoring and poor patient adherence. However, several studies about the relationship between INR score and stroke or bleeding risk have shown that an INR of below 2.0 is associated with a greater increase in the risk of stroke than the increase in the risk of bleeding associated with an INR of more than 3.0 [32, 33].

Second, previous studies indicate that approximately 50–60 % of NVAF patients do not have contraindications to anticoagulation with warfarin, and the risk of bleeding seems the most frequent cause of hesitation in using warfarin [34].

Surprisingly, there were approximately 30 % of NVAF patients with risk factors for embolism, who did not have any apparent reasons for the nonuse or under-use of warfarin including paroxysmal AF in the study by Bradley et al. [35].

Patients with atrial fibrillation and prior stroke or transient ischemic attack were found to be undertreated with NOAC anticoagulation therapy in this study, similar to the cases of VKA warfarin. All guidelines recommend that AF patients at high risk for stroke should receive anticoagulation therapy with warfarin; however, despite the effective prophylaxis of warfarin, patients with AF at high risk for stroke are often undertreated.

The Euro-Heart Survey, the study of stroke prevention in AF in 35 European countries, concluded that real-world antithromboembolic therapy in AF patients was not well tailored to the patient's stroke risk profile [26]; additionally, a US population-based study reported that 41 % of AF patients at high risk for stroke did not receive warfarin [36].

The under-use of oral anticoagulation therapy in the AF patients may have many reasons [37–39]. These include low levels of therapy initiation, the narrow therapeutic window (INR 2–3 in NVAF) leading to the inconvenience of INR monitoring, and patient adherence, and especially fear of drug-induced renal dysfunction and catastrophic intracranial hemorrhage might contribute to the NOAC underutilization for AF as well as warfarin.

In this respect, the results of postregistration observational studies related to real-world efficacy and safety are also important. We analyzed the results of 18 NVAF patients with recurrent cerebral infarction treated by the means of NOACs in a real-world clinical setting. Our study indicated that in 16 of 18 patients, the dose of drugs was reduced, and in 14 of 16 patients with reduced dose drugs, inappropriate dose setting has been selected by the physicians or practitioner concerning about the risk for bleeding or drug-induced renal dysfunction based on the conviction of them.

Actually we observed major bleeding in the patients with NOACs; however, the definition of major bleeding differed from each studies and the validity of the comparison is limited. Predictors for bleeding in patients with anticoagulants include many clinical factors, such as history of myocardial infarction, ischemic heart disease, uncontrolled hypertension, previous cerebrovascular disease, anemia or a history of systemic bleeding, and, what is most important, concomitant use of anticoagulant such as antiplatelet agents like aspirin [40].

Some studies show no increase in bleeding with increasing age [41]; the other analysis clearly demonstrated that increasing age raises the risk of intracranial bleeding [42]. In addition, the increased risk of bleeding with oral anticoagulants was far smaller than the beneficial reduction in risk of stroke [42].

Importantly, in AF patients, some risk factors like diabetes mellitus, controlled hypertension, and gender for anticoagulation-related bleeding are also indications for the use of anticoagulants.

Our study indicated that the inappropriate under-use of NOACs is greatly related to high risk of recurrent cerebral infarction in AF patients in real-world clinical practice and reflects the need for improvements in setting appropriate drug dose of NOACs for high-risk patients with AF.

2.4.4 Limitations

First, in these analyses, patient's economical context, patients' refusal, and their life expectancy were not included as reasons for nonuse or under-use of NOACs. Second, the incidence of intracranial hemorrhage is greatly higher in Japanese subjects than in Caucasian subject [43], which could lead, at least in part, to the under-use of NOACs. Third, the present data were collected from only our hospital and might not represent nationwide trends of NOAC use in Japan. Finally, patients being treated with non-anticoagulant therapies (antiplatelets, such as aspirin) might mitigate the strength of a general claim of "under-use treatment."

2.5 Conclusions

Real-world clinical benefit of NOACs resulted in the high efficacy and acceptable safety in the treatment of patient with NVAF, if we use NOACs with proper dosage, but under-use of NOACs leads to high rate of stroke recurrence. This paper demonstrates the under-use of NOACs for real-world NVAF patients with an elevated risk of recurrent stroke, highlighting the need for appropriate drug dose selection for stroke prevention in NVAF patients.

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