Impact of Direct Oral Anticoagulant Off-Label Reduced Dose in Combination With Antiplatelet Agents on Clinical Outcome — Propensity Score-Matching Analysis From the DIRECT Real-World Non-Valvular Atrial Fibrillation Registry —

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Background: The association between direct oral anticoagulant (DOAC) dose and clinical outcomes when used with antiplatelets still remains to be investigated.

Methods and Results: We conducted a prospective registry of non-valvular atrial fibrillation (AF) patients with DOAC: the DIRECT registry (n=2,216; follow-up, 407±388 days). We analyzed patients taking standard dose (n=907) and off-label reduced dose (n=338) DOAC in this sub-analysis. These patients were further stratified by add-on antiplatelets. Because DOAC dose was not randomly selected, potential confounding factors were eliminated through a propensity score-matching technique. The primary endpoint was clinically significant bleeding. The secondary endpoint was major adverse cardiovascular events (MACE; composite of all-cause death, all myocardial infarction, and stroke/systemic embolism). In patients with DOAC only/DOAC+antiplatelets, we successfully matched 212/62 patients who received off-label reduced dose DOAC with 212/62 standard dose patients. Off-label DOAC dose reduction did not have a significant impact on bleeding (HR, 1.123; 95% CI: 0.730–1.728, P=0.596) or MACE (HR, 1.107; 95% CI: 0.463–2.648, P=0.819) in patients with DOAC only, whereas in patients with add-on antiplatelets, off-label dose reduction significantly reduced bleeding (HR, 0.429; 95% CI: 0.212–0.868, P=0.019) without increasing MACE (HR, 2.205; 95% CI: 0.424–11.477, P=0.348).

Conclusions: Reduced DOAC dose in combination with antiplatelet agents was associated with fewer bleeding complications than standard-dose therapy with no reduction in efficacy.

Key Words: Antiplatelet; Atrial fibrillation; Direct oral anticoagulant; Off-label dose reduction

Atrial fibrillation (AF) patients with atherosclerotic cardiovascular disease need both anticoagulants and antiplatelets. Direct oral anticoagulants (DOAC) are currently used as the first-line drug for AF, while warfarin is used for non-valvular AF (NVAF).1–4 The standard criteria for DOAC dose selection may be used for stroke prevention, but it is not clear whether the standard criteria for DOAC dose reduction still apply when DOAC are used with antiplatelet agents, and no randomized trials have been conducted so far to compare standard dose and reduced dose DOAC when used with antiplatelets.

Subgroup analysis from the DIRECT registry provided a hypothesis-generating result.5 Our group evaluated the impact of add-on antiplatelets to DOAC on clinical outcomes. The subgroup with reduced DOAC dose did not have an increased bleeding risk with add-on antiplatelet therapy. However, patients with regular DOAC dose had significantly increased bleeding risk. The incidence of thromboembolic events did not significantly differ between the regular and reduced dose groups. This suggests that the appropriate dose of DOAC in the case of add-on antiplatelet therapy could be less than the standard dose. The aim of the present study was therefore to assess the hypothesis that the appropriate DOAC dose for use with antiplatelets can be less than the standard dose.
Methods

Subjects
We conducted a single-center prospective observational registry of NVAF patients with DOAC: Safety and effectiveness of 4 Different Direct Oral anticoagulants, dabigatran, rivaroxaban, apixaban and edoxaban in the real-world Clinical practice: DIRECT registry (UMIN000033283). All serial adult patients (aged ≥18 years) at Osaka Police Hospital with NVAF who were users of dabigatran, rivaroxaban, apixaban, or edoxaban from June 2011 to November 2017 were enrolled. If a patient ever used DOAC during the study period, the first fill of DOAC was defined as the index medication. The treatment period was defined as the
In the present sub-analysis of the DIRECT registry, we analyzed patients taking standard dose and off-label reduced dose DOAC. Off-label reduced dose DOAC is defined as a prescribed DOAC standard dose that has been reduced for some reason. Patients with appropriately reduced dose, overdose, or DOAC contraindication were excluded. The patients were further stratified into those with and without antiplatelet therapy.

Standard dose-reduction criteria for DOAC are summarized in Table 1. There are a few differences between the US and Japanese criteria. The present study used the Japanese criteria. With regard to dabigatran, the criteria are only a recommendation, but we applied these criteria in the present study to consistently classify the patients into standard and reduced dose DOAC. With regard to dabigatran, the criteria are only a recommendation, but we applied these criteria in the present study to consistently classify the patients into standard and reduced dose DOAC. Off-label reduced dose DOAC is defined as a prescribed DOAC standard dose that has been reduced for some reason. Patients with appropriately reduced dose, overdose, or DOAC contraindication were excluded. The patients were further stratified into those with and without antiplatelet therapy.

**Table 2. Overall Cohort: Patient Background**

| Variable                        | Standard dose (n=753) | Off-label reduced dose (n=248) | P-value | Standard dose (n=154) | Off-label reduced dose (n=90) | P-value |
|---------------------------------|----------------------|-------------------------------|---------|-----------------------|-------------------------------|---------|
| Age (years)                     | 65.48±10.14, 66.00   | 68.56±10.79, 69.00            | <0.001  | 70.12±7.25, 71.00     | 72.39±8.88, 72.00             | 0.031   |
| Body weight (kg)                | 67.04±14.10, 67.00   | 63.30±12.81, 63.70            | <0.001  | 65.72±11.18, 66.45    | 63.03±11.99, 63.60            | 0.078   |
| Female                          | 178 (23.6)           | 95 (38.3)                     | <0.001  | 33 (21.4)             | 23 (25.6)                     | 0.528   |
| Hypertension                    | 505 (67.1)           | 161 (64.9)                    | 0.536   | 139 (90.3)            | 81 (90.0)                     | >0.999  |
| Diabetes mellitus               | 186 (24.7)           | 58 (23.4)                     | 0.733   | 75 (48.7)             | 34 (37.8)                     | 0.110   |
| Dyslipidemia                    | 488 (64.8)           | 150 (60.5)                    | 0.224   | 130 (84.4)            | 72 (80.0)                     | 0.385   |
| Statin use                      | 207 (27.5)           | 64 (25.8)                     | 0.622   | 103 (66.9)            | 49 (54.4)                     | 0.057   |
| No. antiplatelets               |                      |                               |         |                       |                               |         |
| None                            | 753 (100.0)          | 248 (100.0)                   | >0.999  | 140 (90.9)            | 75 (83.3)                     | 0.100   |
| Single                          | 14 (9.1)             |                               |         | 15 (16.7)             |                               | 0.100   |
| Dual                            |                      |                               |         |                       |                               |         |
| Type of antiplatelets           |                      |                               |         |                       |                               |         |
| Aspirin                         |                      |                               |         |                       |                               |         |
| Cilostazol                      |                      |                               |         |                       |                               |         |
| Clopidogrel                     |                      |                               |         |                       |                               |         |
| Ticlopidine                     |                      |                               |         |                       |                               |         |
| Persistent or longstanding AF   | 301 (40.1)           | 99 (40.2)                     | >0.999  | 65 (42.5)             | 25 (27.8)                     | 0.028   |
| History of HF                   | 131 (17.4)           | 41 (16.5)                     | 0.846   | 35 (22.7)             | 19 (21.1)                     | 0.873   |
| History of bleeding             | 154 (20.5)           | 49 (19.8)                     | 0.856   | 48 (31.2)             | 28 (31.1)                     | >0.999  |
| CAD                             | 60 (8.0)             | 16 (6.5)                      | 0.491   | 95 (61.7)             | 59 (65.6)                     | 0.584   |
| History of PCI or CABG          | 11 (1.5)             | 4 (1.6)                       | 0.772   | 60 (39.0)             | 39 (43.8)                     | 0.499   |
| History of stroke               | 94 (12.5)            | 39 (15.7)                     | 0.197   | 41 (26.6)             | 37 (41.1)                     | 0.023   |
| Liver dysfunction               | 279 (37.1)           | 87 (35.1)                     | 0.595   | 63 (40.9)             | 33 (36.7)                     | 0.587   |
| Creatinine (mg/dL)              | 0.83±0.22, 0.81      | 0.83±0.24, 0.80               | 0.930   | 0.91±0.29, 0.88       | 0.93±0.30, 0.93               | 0.759   |
| CrCl (mL/min)                   | 85.23±30.51, 78.49   | 75.76±26.44, 71.57            | <0.001  | 71.12±18.75, 69.72    | 67.28±26.03, 63.13            | 0.183   |
| Hemoglobin (g/dL)               | 13.99±1.90, 14.10    | 13.46±1.87, 13.50             | <0.001  | 13.56±1.76, 13.50     | 13.24±1.68, 13.15             | 0.170   |
| Modified HAS-BLED score1,2      | 1.97±1.13, 2.00      | 2.08±1.22, 2.00               | 0.203   | 3.73±0.94, 4.00       | 3.82±1.09, 4.00               | 0.473   |
| ORBIT score1                    | 1.35±1.48, 1.00      | 1.62±1.71, 1.00               | 0.015   | 2.96±1.57, 3.00       | 3.33±2.02, 3.00               | 0.110   |
| CHADS2 score                    | 1.52±1.20, 1.00      | 1.67±1.30, 1.00               | 0.086   | 2.45±1.19, 2.00       | 2.73±1.29, 2.50               | 0.082   |

Data given as mean±SD, n (%), or median (IQR). †To calculate the ORBIT bleeding and HAS-BLED scores, multiple imputation of missing values was performed taking into account the correlation between all potential predictors.‡ Modified HAS-BLED score: in the DIRECT registry, we did not evaluate prothrombin time-international normalized ratio (PT-INR) in daily clinical practice due to the use of DOAC. The criterion “labile INR” in the HAS-BLED score was therefore set to zero in all patients. AF, atrial fibrillation; CABG, coronary artery bypass graft; CAD, coronary artery disease; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; HF, heart failure; PCI, percutaneous coronary intervention.

Circulation Reports Vol.2, June 2020
Table 3. Patient Background After Propensity Score Matching

| Variable                        | Standard dose (n=212) | Off-label reduced dose (n=212) | P-value | Standard dose (n=62) | Off-label reduced dose (n=62) | P-value |
|---------------------------------|-----------------------|---------------------------------|---------|----------------------|-------------------------------|---------|
| Age (years)                     | 69.9±8.32, 70.00      | 68.5±11.25, 70.00               | 0.138   | 72.4±7.04, 74.00     | 72.2±9.19, 73.00              | 0.887   |
| Body weight (kg)                | 64.3±10.90, 65.00     | 64.1±12.41, 64.15               | 0.864   | 63.9±10.76, 63.85    | 64.9±12.22, 65.00             | 0.649   |
| Female                          | 50 (23.6)             | 72 (34.0)                       | 0.024   | 12 (19.4)            | 12 (19.4)                     | >0.999  |
| Hypertension                    | 143 (67.5)            | 140 (66.0)                      | 0.837   | 54 (87.1)            | 56 (90.3)                     | 0.778   |
| Diabetes mellitus               | 51 (24.1)             | 54 (25.5)                       | 0.822   | 25 (40.3)            | 26 (41.9)                     | >0.999  |
| Dyslipidemia                    | 137 (64.6)            | 128 (60.4)                      | 0.422   | 50 (80.6)            | 51 (82.3)                     | >0.999  |
| Statin use                      | 69 (32.5)             | 53 (25.0)                       | 0.107   | 37 (59.7)            | 37 (59.7)                     | >0.999  |
| No. antiplatelets               |                       |                                 |         |                      |                               |         |
| None                            | 212 (100.0)           | 212 (100.0)                     | >0.999  | 51 (82.3)            | 51 (82.3)                     | >0.999  |
| Single                          | 11 (17.7)             | 11 (17.7)                       | >0.999  |                      |                               |         |
| Dual                            |                       |                                 |         |                      |                               |         |
| Type of antiplatelets           |                       |                                 |         |                      |                               |         |
| Aspirin                         |                       |                                 |         |                      |                               |         |
| Cilostazol                      | 46 (74.2)             | 44 (71.0)                       | 0.841   | 6 (9.7)              | 7 (9.7)                       | >0.999  |
| Clopidogrel                     | 4 (6.5)               | 6 (9.7)                         | 0.743   | 22 (35.5)            | 23 (35.5)                     | >0.999  |
| Ticlopidine                     | 1 (1.6)               | 1 (1.6)                         | >0.999  | 1 (1.6)              | 1 (1.6)                       | >0.999  |
| Persistent or longstanding AF   | 99 (46.7)             | 89 (42.2)                       | 0.379   | 26 (42.6)            | 19 (30.6)                     | 0.193   |
| History of HF                   | 48 (22.6)             | 38 (17.9)                       | 0.277   | 19 (30.6)            | 12 (19.4)                     | 0.213   |
| History of bleeding             | 47 (22.2)             | 45 (21.2)                       | 0.906   | 18 (28.0)            | 20 (32.3)                     | 0.846   |
| CAD                             | 20 (9.4)              | 11 (5.2)                        | 0.134   | 38 (61.3)            | 39 (62.9)                     | >0.999  |
| History of PCI or CABG          | 3 (1.4)               | 3 (1.4)                         | >0.999  | 28 (45.2)            | 27 (43.5)                     | >0.999  |
| History of stroke               | 32 (15.1)             | 31 (14.6)                       | >0.999  | 25 (40.3)            | 22 (35.5)                     | 0.711   |
| Liver dysfunction               | 90 (42.5)             | 77 (36.3)                       | 0.233   | 20 (32.3)            | 23 (37.1)                     | 0.706   |
| Creatinine (mg/dL)              | 0.98±0.28, 0.97       | 0.85±0.25, 0.82                 | <0.001  | 1.04±0.37, 0.96      | 0.95±0.29, 0.94               | 0.120   |
| CrCl (mL/min)                   | 65.28±20.53, 59.98    | 76.46±27.53, 72.05              | <0.001  | 59.24±15.81, 58.32   | 68.33±26.96, 63.13            | 0.024   |
| Hemoglobin (g/dL)               | 32.20±10.15, 13.65    | 13.55±1.85, 13.60               | 0.990   | 13.21±1.90, 13.20    | 13.28±1.68, 13.15             | 0.829   |
| Modified HAS-BLED score†‡       | 2.20±1.14, 2.00       | 2.08±1.23, 2.00                 | 0.307   | 3.81±1.04, 4.00      | 3.77±1.05, 4.00               | 0.863   |
| ORBIT score                     | 2.02±1.0, 2.00        | 1.65±1.31, 1.00                 | 0.026   | 3.39±1.79, 3.00      | 3.47±2.04, 3.00               | 0.815   |
| CHADS2 score                    | 1.77±1.29, 1.00       | 1.72±1.33, 1.00                 | 0.683   | 2.82±1.40, 2.00      | 2.68±1.25, 2.00               | 0.543   |

Data given as mean±SD, n (%), or median (IQR). †To calculate the ORBIT bleeding and HAS-BLED score, multiple imputation of missing values was performed taking into account the correlation between all potential predictors. A regression model was used for the imputation using the following variables as predictors: age, gender, body weight, diabetes mellitus, dyslipidemia, CAD, peripheral artery disease, creatinine, CrCl, and estimated glomerular filtration rate. Modified HAS-BLED score: in the DIRECT registry, we did not evaluate PT-INR in daily clinical practice due to the use of DOAC. The criterion “labile INR” in HAS-BLED score was therefore set to zero in all patients. Abbreviations as in Table 2.

off-label dose reduction groups.

Endpoints

The primary endpoint was clinically significant bleeding, which was defined as a composite of major bleeding according to the International Society on Thrombosis and Haemostasis (ISTH) criteria and clinically relevant non-major bleeding. The major bleeding according to the ISTH criteria was defined as clinically overt bleeding accompanied by a decrease in hemoglobin ≥2 g/dL or transfusion ≥2 units packed red cells, occurring at a critical site, or resulting in death. The secondary endpoint was major adverse cardiovascular event (MACE: a composite of all-cause death, all myocardial infarction, and stroke/systemic embolism). Clinical events were monitored by questioning, physical examination, laboratory test, and electrocardiogram at each outpatient visit every 2-4 months. An independent clinical event committee whose members were unaware of the treatment group adjudicated all clinical events.

Statistical Analysis

Categorical variables are expressed as n (%) and were compared using the chi-squared test or Fisher exact test. Continuous variables are expressed as mean±SD or median (IQR) and were compared using the Student t-test, Mann-Whitney U-test, ANOVA, or Kruskal-Wallis test as appropriate. Normality of distribution was tested using the
DOAC Dose in Combination With Antiplatelets

Results

Subjects
A total of 2,216 patients ( dabigatran, n=648; rivaroxaban, n=538; apixaban, n=599; and edoxaban, n=431) were enrolled in the present registry. Mean follow-up duration in the whole population was 407±388 days (median, 312 days; IQR, 70–618 days). Patient selection is shown in Figure 1. Appropriate standard dose DOAC was prescribed in 907 patients, whereas off-label reduced dose DOAC was used in 338 patients. The other patients (appropriate

Kolmogorov-Smirnov test.
As noted here in the present study, we analyzed patients taking standard dose and off-label reduced dose DOAC. These patients were further stratified into those with and without antiplatelet therapy. Because DOAC dose was not randomly selected, potential confounding factors were eliminated through a propensity score-matching technique. Propensity scores for the estimated probability of off-label reduced dose in each patient were generated using a multiple logistic regression model. The final model consisted of 18 variables (type of DOAC, age, sex, body weight, hemoglobin, creatinine clearance, diabetes mellitus, hypertension, dyslipidemia, statin use, liver dysfunction, histories of stroke, coronary artery disease [CAD], heart failure, percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG], radiofrequency catheter ablation, bleeding, and liver dysfunction). In patients with DOAC only, we successfully matched 212 patients who received off-label reduced dose DOAC with 212 standard dose patients through 2-digit score-matching. The AUC was 0.781 (95% CI: 0.720–0.842) for this model. As a sensitivity analysis, we also conducted multivariate Cox regression analysis. The impact of off-label reduced dose DOAC as compared with the standard dose was assessed with/without adjustment for age, female sex, body weight, creatinine clearance, diabetes mellitus, and hypertension. Outcomes were assessed according to the 2 groups (i.e., standard dose group and off-label dose-reduction group) in a time-to-first-event fashion with the Kaplan-Meier method and compared using the log-rank test. P<0.05 was considered statistically significant. All analyses were undertaken using SPSS 24.0 (IBM Corporation, Armonk, NY, USA).

Figure 2. Kaplan-Meier analysis for primary and secondary endpoints. Kaplan-Meier curves for (A,C) clinically significant bleeding and (B,D) major adverse cardiovascular events (MACE; composite of all-cause death, all myocardial infarction, and stroke/systemic embolism) in patients with direct oral anticoagulants (DOAC) only and DOAC plus antiplatelet therapy.
Table 2. Baseline characteristics of the overall population

| Category                        | Standard dose group | Off-label reduced dose group | HR (95% CI) | P-value |
|---------------------------------|---------------------|-----------------------------|-------------|---------|
| N                               | 753 n=248           | n=212                       | 0.630       |         |
| Clinically significant bleeding | 29.0 (2.5)          | 28.7 (3.8)                  | 1.082       |         |
| Major bleeding                  | 9.1 (2.0)           | 6.7 (2.2)                   | 0.925       |         |
| MACE                            | 6.2 (1.5)           | 7.7 (2.2)                   | 1.609       |         |
| All-cause death                 | 2.6 (1.1)           | 5.0 (1.8)                   | 3.100       |         |
| MI                              | 0.9 (0.7)           | NE                          | 0.027       |         |
| Stroke                          | 3.5 (1.1)           | 2.4 (1.4)                   | 0.711       |         |

Table 3. Kaplan-Meier Estimated 2-Year Event Rate

| Category                        | Standard dose group | Off-label reduced dose group | HR (95% CI) | P-value |
|---------------------------------|---------------------|-----------------------------|-------------|---------|
| N                               | 753 n=248           | n=212                       | 0.630       |         |
| Clinically significant bleeding | 29.0 (2.5)          | 28.7 (3.8)                  | 1.082       |         |
| Major bleeding                  | 9.1 (2.0)           | 6.7 (2.2)                   | 0.925       |         |
| MACE                            | 6.2 (1.5)           | 7.7 (2.2)                   | 1.609       |         |
| All-cause death                 | 2.6 (1.1)           | 5.0 (1.8)                   | 3.100       |         |
| MI                              | 0.9 (0.7)           | NE                          | 0.027       |         |
| Stroke                          | 3.5 (1.1)           | 2.4 (1.4)                   | 0.711       |         |

Clinical Endpoints

Kaplan-Meier curves for the primary and secondary endpoints stratified according to DOAC dose in the propensity score-matched population are given in Figure 2. Event rates of clinically significant bleeding (log-rank P=0.596) and MACE (log-rank P=0.819) did not differ between standard dose and off-label reduced dose groups in patients with DOAC only. In patients with DOAC+add-on antiplatelets, the rate of clinically significant bleeding was significantly lower in patients with off-label reduced dose than in those with standard dose (log-rank P=0.015), while no significant difference was found in MACE rate (log-rank P=0.335). Off-label DOAC dose reduction did not have a significant impact on clinically significant bleeding (HR, 1.123; 95% CI: 0.730–1.728, P=0.596) or MACE (HR, 1.107; 95% CI: 0.463–2.648, P=0.819) in patients with DOAC only, whereas in patients with add-on antiplatelets, off-label dose reduction was associated with a lower rate of clinically significant bleeding (HR, 0.429; 95% CI: 0.212–0.868, P=0.019) without increasing the major cardiovascular risk (HR, 2.205; 95% CI: 0.424–11.477, P=0.348). Results of the Cox regression analysis in the overall cohort as a sensitivity analysis are presented in Supplementary Figure. Both propensity score matching and Cox regression modeling produced the same findings. Kaplan-Meier estimated 2-year event rates for the individual clinical endpoints before and after propensity score matching are summarized in Table 4.

Discussion

Main findings of the present study are as follows: (1) in patients treated with DOAC+add-on antiplatelets, off-label DOAC dose reduction was significantly associated with lower bleeding events without increasing the rate of MACE; and (2) in patients treated with DOAC only, off-label dose reduction did not have a significant impact on clinically significant bleeding or MACE.

In the present cohort, nearly half of the patients had a history of PCI or CAGB. The number of NVAF patients undergoing PCI with metallic stent implantation is increasing all over the world. In these patients, P2Y12 inhibitor in combination with DOAC is recommended by several guidelines and the consensus document. In contrast, one-third of the present cohort had a history of stroke. Optimal medical therapy including antiplatelet therapy is recommended for all patients with carotid artery stenosis and transient ischemic attack or stroke. However, the specific dose of DOAC to be used with antiplatelets is, in
both situations, yet to be clearly defined in any documents.

**Dose Selection in Previous Studies**

Recent trials (RE-DUAL PCI, PIONEER AF PCI, AUGUSTUS, ENTRUST AF PCI) evaluating the clinical outcomes of AF patients undergoing PCI demonstrated the feasibility of dual therapy DOAC plus P2Y12 inhibitor immediately after PCI.1–4 All trials demonstrated the superiority of DOAC over warfarin. Nonetheless, the DOAC dose varied between trials. In the RE-DUAL PCI trial, dabigatran 110 mg twice daily was mainly evaluated.1 In the PIONEER AF PCI trial, rivaroxaban 15 mg once daily and 2.5 mg twice daily were evaluated.2 Both trials assessed the reduced dose of DOAC in combination with antiplatelets. These trials implied the feasibility of reduced dose DOAC when used with add-on antiplatelets. In contrast, AUGUSTUS and ENTRUST AF PCI evaluated the standard dose of apixaban (5 mg twice daily) and edoxaban (60 mg one daily), respectively.3,4 The standard DOAC dose for stroke prevention was also proved to be safe when used with antiplatelets in comparison with warfarin. However, no head-to-head randomized trials comparing standard dose vs. reduced dose DOAC in combination with antiplatelets have been conducted to date.

The impact of off-label DOAC dose on clinical outcomes was reported in the Japanese multicenter SAKURA AF registry.5–7 A total of 1,676 patients under any of the 4 DOAC regimens were followed up for a median of 39.3 months. Stroke/systemic embolism and death events were equivalent between the standard and under-dose groups, but major bleeding events tended to be lower in the under-dose group although the study did not focus on the impact of antiplatelet therapy.8 The results remind us of the importance of investigating the appropriate dose of DOAC in the cases of antiplatelet therapy, malignancy, high inflammatory status and so on.9,10

**Appropriate DOAC Dose With Antiplatelet Use**

Although a recent trial reported on the safety of mono-therapy rivaroxaban for patients with AF and CAD,11,12 a certain population such as those with first-generation drug-eluting stents, complex stenting and so on should have some benefits of add-on antiplatelets. We previously reported the increased bleeding risk in patients treated with add-on antiplatelet therapy on DOAC from the DIRECT registry.5 The subgroup of reduced dose DOAC did not have increased bleeding risk of add-on antiplatelet therapy or reduced efficacy endpoints (all-cause death, all myocardial infarction, and stroke). This hypothesis-generating result drove us to conduct the current study.

In the present study, off-label DOAC dose reduction according to the standard criteria significantly decreased the bleeding rates when used with antiplatelets, without worsening the rates of MACE. In order to investigate the reasons why physicians chose off-label reduced dose DOAC, we evaluated differences in the baseline characteristics of patients with standard dose vs. off-label reduced dose DOAC (Supplementary Table). The off-label dose reduction group was older and had lower body weight, lower creatinine clearance, lower hemoglobin, higher prescription rate of antiplatelets, higher rate of women and higher ORBIT, HASBLED and CHADS2 scores, which might have resulted in a higher all-cause mortality in the off-label reduced dose group than in the standard dose group. These factors were not included in the dose reduction criteria. However, in the real-world clinical settings, physicians consider these as an important factor for dose selection. We eliminated the possible confounders with the propensity score-matching method as much as possible, but the observational design would not allow the drawing of a robust conclusion. Further randomized clinical trials would be warranted to investigate the favorable DOAC dose in cases of dual anticoagulant and antiplatelet therapy. And, according to the present results, a large-scale non-inferiority randomized controlled trial is needed.

**Study Limitations**

First, given that the present study was a single-center prospective registry, patients included in the DIRECT registry represent a selected cohort of NVAF patients. Second, different dose and different standard criteria for dose reduction exist between Asia, Europe, and the USA. Finally, the observational design, small sample size and short follow-up period would not allow the drawing of robust conclusions. The current results are still limited to hypothesis generating, and the present study confirms that a further prospective large-scale non-inferiority randomized controlled trial is needed.

**Conclusions**

According to the present Asian real-world data, reduced dose DOAC in combination with antiplatelet agents was associated with fewer bleeding complications than standard dose therapy, with no reduction in efficacy. Further randomized clinical trials are warranted to investigate the favorable DOAC dose in cases of dual anticoagulant and antiplatelet therapy. The present study shows that a large-scale non-inferiority randomized controlled trial is needed.

**Acknowledgments**

We thank Ayaka Murakami, Yoko Inoue, Tomoe Yamamoto, Ayako Fukao, Naoki Mori, MD, Nanao Matsuaki, MD, Ryohei Mimiya, MD, Yuma Hamanaka, MD, Junichi Ohno, MD, Takashi Omatsu, MD, Nobuhiko Makino, MD, PhD, and Takaharu Hayashi, MD, PhD for their invaluable support in data collection and management.

**Data Availability**

The de-identified participant data will not be shared.

**Funding**

None.

**Conflict of Interest**

Y. Sotomi, A. Hirata, A. Hirayama, Y.H., and Y. Sakata received grants, travel expenses, and speaker honorarium from Daiichi-Sankyo, Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb.

**Disclosures**

A. Hirayama is a member of Circulation Reports’ Editorial Team. The other author declares no conflict of interest.

**IRB Information**

This study was approved by the Osaka Police Hospital Ethics Committee (reference no. 979).

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**Supplementary Files**

Please find supplementary file(s):

http://dx.doi.org/10.1253/circrep.CR-20-0026