Bleeding Risk of Add-On Anti-Platelet Agents to Direct Oral Anticoagulants in Patients With Nonvalvular Atrial Fibrillation (From 2216 Patients in the DIRECT Registry)

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Clinical outcomes of the real-world Asian nonvalvular atrial fibrillation (NVAF) patients treated with DOAC and the incremental bleeding risk of add-on antiplatelet therapy to direct oral anticoagulants (DOACs) are still to be investigated. We conducted a single-center prospective observational registry of NVAF patients treated with DOACs: the DIRECT registry (UMIN000033283). All patients with NVAF (N = 2216) who were users of dabigatran (N = 648), rivaroxaban (N = 538), apixaban (N = 599), or edoxaban (N = 431) from June 2011 to November 2017 were enrolled (71.6 ± 10.8 years, 36.4% female, follow-up duration: 407.2 ± 388.3 days). No add-on antiplatelet agent was prescribed to 1,739 patients, while single and dual antiplatelet therapy (SAPT and DAPT) in combination with DOAC were prescribed to 411 and 66 patients, respectively. The primary safety endpoint was any bleeding which was defined as a composite of major bleeding according to the International Society on Thrombosis and Hemostasis criteria and clinically relevant non-major bleeding. Patients treated with add-on antiplatelet agents irrespective of SAPT or DAPT had a higher any-bleeding risk than those without (hazard ratio: 1.42; 95% confidence interval 1.16−1.74, p = 0.001). Multivariate adjusted hazard of add-on antiplatelet therapy was not statistically significant (hazard ratio: 1.20; 95% confidence interval 0.94−1.53, p = 0.147). In conclusion, NVAF patients treated with antiplatelet agents and DOAC had a significantly higher bleeding risk than those using DOAC only. However, after adjustment of patients' background, add-on antiplatelet therapy to DOAC itself did not influence to a bleeding risk. **(Am J Cardiol 2019;123:1293−1300)**

Long-term treatment with oral anticoagulants is required for patients with atrial fibrillation (AF) to prevent ischemic stroke. Direct oral anticoagulant (DOAC) rather than vitamin K antagonist (warfarin) is becoming widespread because of its better safety and comparable efficacy.[1−3] AF patients undergoing percutaneous coronary intervention (PCI) with metallic stent implantation are increasing all over the world because of the overlapped risk factors of coronary artery disease and AF. For these patients, $P2Y_{12}$ inhibitor (clopidogrel) in addition to the DOAC is recommended to prevent stent thrombosis immediately after the index procedure to 1 year.[4−7] While combination of vitamin K antagonist and antiplatelet therapy is associated with a high annual risk of fatal and non-fatal bleeding episodes (4%−16%),[8,9] incremental bleeding risk of add-on antiplatelet agents to DOAC is still to be investigated. In the present study, we investigated the clinical outcomes of the real-world Asian NVAF patients treated with DOAC and antiplatelet agents, and evaluated the incremental bleeding risk of additional antiplatelet therapy to DOAC in a large pooled population.

Methods

We conducted a single-center prospective observational registry of NVAF patients with DOACs: the DIRECT registry (UMIN000033283). All serial adult patients (aged ≥18 years) in our institution with NVAF who were users of dabigatran, rivaroxaban, apixaban, or edoxaban from June 2011 to November 2017 were enrolled. If a patient ever used DOACs during the study period, the first fill of DOACs was defined as the index medication. The treatment period was defined as the time from the first administration of a drug to last follow-up or 2 days after the trial drugs were discontinued if the patient quitted the medication. In the present study, we divided all patients into 3 groups: DOAC only, DOAC + single antiplatelet therapy (SAPT), and DOAC + dual antiplatelet therapy (DAPT). For an exploratory purpose only, patients with DOAC plus antiplatelet therapy (either SAPT or DAPT) were further divided into 4 groups according to the DOAC types (dabigatran, rivaroxaban, apixaban, and edoxaban) to evaluate impacts of the DOAC type on clinical endpoints.

The primary safety endpoint was any bleeding which was defined as a composite of major bleeding according to the International Society on Thrombosis and Haemostasis

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(ISTH) criteria and clinically relevant non-major bleeding. The co-primary safety endpoint was the major bleeding, which was defined, according to the ISTH criteria, as clinically overt bleeding accompanied by a decrease in the hemoglobin level of at least 2 g per deciliter or transfusion of at least 2 units of packed red cells, occurring at a critical site, or resulting in death.[10] The secondary endpoints were all-cause death, all myocardial infarction, and stroke.[11] Clinical events were monitored by questioning, physical examination, laboratory test, and electrocardiogram at each outpatient visits every 2 to 4 months. The primary analysis was performed under the intention-to-treat framework on the full analysis set of patients. Regimen of antiplatelet agents at the time of the DOAC initiation was used for the categorization of the group. The independent clinical event committee whose members were unaware of the treatment group adjudicated all clinical events. Written informed consent was obtained from all enrolled patients. This study was approved by the Osaka Police Hospital Ethical Committee.

Categorical variables are expressed as counts (percentages) and compared with $\chi 2$ or Fisher exact test. Continuous variables are expressed as mean ± SD or median (interquartile range) and compared using Student *t* test, Mann−Whitney *U* test, ANOVA, or Kruskal-Wallis test as appropriate. Normality of distribution was tested by the Kolmogorov-Smirnov test. Outcomes were assessed according to the 3 groups, DOAC only, DOAC + SAPT, and DOAC + DAPT, in a time-to-first-event fashion with the Kaplan−Meier method and compared with the log-rank test. The impact of add-on antiplatelet agents on primary and secondary endpoints was assessed with Cox proportional hazards model without and with multivariate adjustment including following factors: age, female gender, creatinine clearance, hypertension, diabetes mellitus, history of PCI or CABG, and history of bleeding. The consistency of the effect of add-on antiplatelet therapy (either SAPT or DAPT) in subgroups was assessed with formal interaction testing for the primary endpoints of any bleeding and major bleeding and secondary endpoints.

For an exploratory purpose only, in patients with antiplatelet therapy irrespective of SAPT or DAPT, impact of DOAC type on bleeding risk with reference to the dabigatran, which was commercially available earlier than the others, was assessed using a multivariate Cox proportional hazards model with or without adjustment with following factors: age, gender, body weight, hypertension, creatinine clearance, history of stroke, and history of bleeding.[12] These factors were determined by reference to the components of the HAS-BLED score.[12] A probability value of less than 0.05 was considered statistically significant. All analyses were undertaken using SPSS 24.0 (IBM Corporation, Armonk, NY).

Results

A total of 2216 patients [dabigatran (N = 648), rivaroxaban (N = 538), apixaban (N = 599), and edoxaban (N = 431)] were enrolled in the present registry. DOAC only, DOAC + SAPT, and DOAC + DAPT groups consist of 1739, 411, and 66 patients, respectively. Baseline characteristics of each group are presented in Table 1. Patients in DOAC + SAPT and DOAC + DAPT groups were older and had more comorbidities such as hypertension, diabetes mellitus, and chronic heart failure as compared to those in DOAC only group (p <0.001), resulting in higher $CHADS_2$ score, CHA_2DS_2-VASc score, HAS-BLED score, and ORBIT score. Follow-up duration in whole population was 407 ± 388, 312 [interquartile range 70,618] days.

Figure 1 and 2 depict Kaplan-Meier curves for the primary and secondary endpoints stratified according to the use of antiplatelet therapy (SAPT or DAPT). The primary safety endpoint of any bleeding more frequently occurred in patients with DOAC plus antiplatelet therapy irrespective of SAPT or DAPT than in patients with DOAC only (hazard ratio [HR]: 1.42; 95% confidence interval [CI] 1.16 −1.74, p = 0.001) (Figure 1). No significant difference was found between SAPT and DAPT patients (p = 0.861). Major bleeding did not differ between those with and without antiplatelet therapy (HR: 1.33; 95% CI 0.84−2.11, p = 0.218) (Figure 1). However, the incidence of major bleeding was numerically higher in patients with DOAC plus DAPT than the others (DOAC only 3.9% vs DOAC + SAPT 4.6% vs DOAC + DAPT 9.1%, p = 0.107). The incidences of all cause death, all myocardial infarction and stroke were not significantly different between those with and without antiplatelet therapy (Figure 2). Impacts of add-on antiplatelet agents assessed by Cox regression model were tabulated in Table 2. Nonadjusted hazard of any bleeding was significantly high, whereas adjusted hazards were nonsignificant for all endpoints.

The results regarding the primary endpoints of any bleeding and major bleeding were consistent among most subgroups (Figure 3). Impact of add-on antiplatelet therapy to DOACs on bleeding risk was consistent across 4 different DOAC types (p for interaction = 0.253). Add-on antiplatelet therapy had significantly higher any-bleeding risks in patients with regular dose of DOACs (HR: 1.77; 95% CI 1.31−2.39, p <0.001), whereas it did not in those with reduced dose of DOACs (HR: 1.18; 95% CI 0.91−1.55, p = 0.219) (p for interaction = 0.048). Influence of add-on antiplatelet therapy to secondary outcomes including all cause death, all myocardial infarction, and stroke was also consistent among most subgroups (Figure 4). Dose of DOACs did not have a significant interaction with the impact of add-on antiplatelet therapy on all secondary endpoints (p >0.05).

Patients with DOAC plus antiplatelet therapy (N = 477) were further divided into 4 groups according to the DOAC types (Online Table 1). SAPT and DAPT use were balanced amongst 4 different DOACs. Edoxaban and apixaban were more frequently prescribed for patients with higher age, female gender, lower body weight, lower hemoglobin, and lower creatinine clearance than dabigatran and rivaroxaban. Online Table 2 summarizes impacts of 4 different DOACs on bleeding risks in patients with antiplatelet therapy (N = 477). Crude analysis presented that patients with rivaroxaban, apixaban, and edoxaban with reference to those with dabigtran had additional risk for any bleeding, whereas adjusted analysis demonstrated that only patients with apixaban and edoxaban were associated with higher any bleeding risks as compared to those with the dabigatran. As to major bleeding, crude analysis presented that patients with

Table 1
Baseline characteristics: Patients with DOAC only versus DOAC + SAPT versus DOAC + DAPT

	DOAC	DOAC + SAPT	DOAC + DAPT	Total	p value
Number	1739	411	66	2216	-
Type of DOAC					0.005
Dabigatran	527/1739 (30.3%)	100/411 (24.3%)	21/66 (31.8%)	648/2216 (29.2%)	
Rivaroxaban	429/1739 (24.7%)	94/411 (22.9%)	15/66 (22.7%)	538/2216 (24.3%)	
Apixaban	438/1739 (25.2%)	145/411 (35.3%)	16/66 (24.2%)	599/2216 (27.0%)	
Edoxaban	345/1739 (19.8%)	72/411 (17.5%)	14/66 (21.2%)	431/2216 (19.4%)	
Dose of DOAC					
Dabigatran					0.089
110 mg once daily	0/527 (0.0%)	1/100 (1.0%)	0/21 (0.0%)	1/648 (0.2%)	
75 mg twice daily	5/527 (0.9%)	3/100 (3.0%)	0/21 (0.0%)	8/648 (1.2%)	
110 mg twice daily	362/527 (68.7%)	74/100 (74.0%)	15/21 (71.4%)	451/648 (69.6%)	
150 mg twice daily	160/527 (30.4%)	22/100 (22.0%)	6/21 (28.6%)	188/648 (29.0%)	
Rivaroxaban					0.001
10 mg once daily	141/429 (32.9%)	41/94 (43.6%)	11/15 (73.3%)	193/538 (35.9%)	
15 mg once daily	288/429 (67.1%)	53/94 (56.4%)	4/15 (26.7%)	345/538 (64.1%)	
Apixaban					0.001
2.5 mg twice daily	155/438 (35.4%)	76/145 (52.4%)	9/16 (56.3%)	240/599 (40.1%)	
5 mg twice daily	283/438 (64.6%)	69/145 (47.6%)	7/16 (43.8%)	359/599 (59.9%)	
Edoxaban					0.799
15 mg once daily	1/345 (0.3%)	0/72 (0.0%)	0/14 (0.0%)	1/431 (0.2%)	
30 mg once daily	231/345 (67.0%)	52/72 (72.2%)	11/14 (78.6%)	294/431 (68.2%)	
60 mg once daily	113/345 (32.8%)	20/72 (27.8%)	3/14 (21.4%)	136/431 (31.6%)	
Regular dose	844/1739 (48.5%)	164/411 (39.9%)	20/66 (30.3%)	1028/2216 (46.4%)	<0.001
Type of antiplatelet					
Aspirin	-	296/411 (72.0%)	63/66 (95.5%)	359/2216 (16.2%)	-
Clopidogrel	-	83/411 (20.2%)	45/66 (68.2%)	128/2216 (5.8%)	-
Prasugrel	-	0/411 (0.0%)	6/66 (9.1%)	6/2216 (0.3%)	-
Ticlopidine	-	5/411 (1.2%)	2/66 (3.0%)	7/2216 (0.3%)	-
Cilostazol	-	27/411 (6.6%)	16/66 (24.2%)	43/2216 (1.9%)	-
Age (years)	70.7 ± 11.2, 72.0 [65, 79]	74.7 ± 8.9, 76.0 [69, 81]	74.6 ± 7.7, 73.0 [68.75, 82]	71.6 ± 10.8, 73.0 [65, 79]	<0.001
Women	656/1739 (37.7%)	132/411 (32.1%)	18/66 (27.3%)	806/2216 (36.4%)	0.031
Body weight (kg)	60.9 ± 14.6, 60.0 [50.2, 70]	60.3 ± 12.4, 60.1 [51.2, 69.5]	61.2 ± 12.3, 60.4 [54.375, 68.6]	60.8 ± 14.2, 60.0 [50.7, 69.9]	0.960
Body mass index (kg/m^2)	23.3 ± 4.0, 23.1 [20.7, 25.5]	23.5 ± 4.1, 23.3 [21.0, 26.1]	22.9 ± 3.9, 23.0 [20.1, 25.2]	23.4 ± 4.1, 23.1 [20.8, 25.6]	0.466
Persistent or longstanding persistent atrial fibrillation	706/1733 (40.7%)	152/409 (37.2%)	23/66 (34.8%)	881/2208 (39.9%)	0.288
Hypertension	1199/1739 (68.9%)	374/411 (91.0%)	55/66 (83.3%)	1628/2216 (73.5%)	<0.001
Diabetes mellitus	426/1739 (24.5%)	161/411 (39.2%)	32/66 (48.5%)	619/2216 (27.9%)	<0.001
Dyslipidemia	1066/1738 (61.3%)	320/411 (77.9%)	58/66 (87.9%)	1444/2215 (65.2%)	<0.001
Coronary artery disease (History of percutaneous coronary intervention or coronary artery bypass graft)	39/1735 (2.2%)	154/411 (37.5%)	46/65 (70.8%)	239/2211 (10.8%)	<0.001
Peripheral vascular disease	74/1458 (5.1%)	68/365 (18.6%)	16/56 (28.6%)	158/1879 (8.4%)	<0.001
Chronic heart failure	393/1739 (22.6%)	119/411 (29.0%)	13/66 (19.7%)	525/2216 (23.7%)	0.018
Radiofrequency catheter ablation	273/1739 (15.7%)	31/411 (7.5%)	4/66 (6.1%)	308/2216 (13.9%)	<0.001
History of bleeding	426/1735 (24.6%)	149/409 (36.4%)	24/66 (36.4%)	599/2210 (27.1%)	<0.001
History of stroke	283/1739 (16.3%)	144/411 (35.0%)	20/66 (30.3%)	447/2216 (20.2%)	<0.001

(*continued on next page*)

Table 1 (*Continued*)

	DOAC	DOAC + SAPT	DOAC + DAPT	Total	p value
Hemoglobin (g/dl)	13.5 ± 2.0, 13.5 [12.3, 14.9]	13.0 ± 2.0, 13.1 [11.5, 14.4]	12.9 ± 1.7, 12.7 [11.475, 14.225]	13.4 ± 2.0, 13.4 [12.1, 14.8]	<0.001
Creatinine (mg/dl)	0.9 ± 0.3, 0.8 [0.68, 0.98]	0.9 ± 0.3, 0.9 [0.74, 1.08]	1.0 ± 0.4, 0.9 [0.765, 1.0575]	0.9 ± 0.3, 0.8 [0.69, 1]	<0.001
Creatinine clearance (ml/min)	70.7 ± 31.4, 66.2 [49.3, 86.3]	60.1 ± 23.0, 58.8 [43.3, 74.2]	58.9 ± 19.2, 59.6 [49.2, 70.5]	68.4 ± 30.0, 64.1 [48.0, 82.9]	<0.001
$CHADS_2$ score	1.9 ± 1.4, 2.0 [1, 3]	2.8 ± 1.3, 3.0 [2, 4]	2.6 ± 1.4, 2.0 [2, 4]	2.1 ± 1.4, 2.0 [1, 3]	<0.001
CHA_2DS_2-VASc score	3.0 ± 1.8, 3.0 [2, 4]	4.6 ± 1.6, 5.0 [3, 6]	4.6 ± 1.6, 4.0 [4, 6]	3.4 ± 1.9, 3.0 [2, 5]	<0.001
Modified HAS-BLED score*	2.2 ± 1.1, 2.0 [1, 3]	3.9 ± 1.0, 4.0 [3, 4]	3.8 ± 1.0, 4.0 [3, 5]	2.5 ± 1.3, 2.0 [2, 3]	<0.001
ORBIT score	1.8 ± 1.7, 2.0 [0, 3]	3.6 ± 1.8, 3.0 [2, 5]	3.6 ± 2.0, 3.0 [2, 5]	2.2 ± 1.9, 2.0 [0, 4]	<0.001
Follow-up duration (day)	406.2 ± 392.1, 303.0 [63, 617]	399.1 ± 362.1, 329.0 [86, 615]	486.2 ± 439.2, 382.3 [116.5, 731.75]	407.2 ± 388.3, 311.8 [70, 617.75]	0.269

Data are expressed as mean ± standard deviation, median [interquartile], or number (percentage).

* Modified HAS-BLED score:[12] In the DIRECT registry, we did not evaluate PT-INR in our daily clinical practice due to the use of DOAC. The criterion "labile INR" in the HAS-BLED score was therefore set to zero point in all patients.

apixaban and edoxaban had higher risk than those with dabigatran, while adjusted analysis demonstrated that only patients with edoxaban had significantly higher risk than those with dabigatran.

Discussion

Main findings of the present study can be summarized as follows: (1) In the Asian real-world clinical practice, NVAF patients treated with antiplatelet agents and DOAC had a significantly higher bleeding risk than those using DOAC only; (2) The incidences of all cause death, all myocardial infarction and stroke were not significantly different between those with and without antiplatelet therapy; (3) Impact of add-on antiplatelet therapy to DOACs on bleeding risk was consistent across most subgroups including 4 different DOAC types; (4) Multivariate adjusted model presented that add-on antiplatelet therapy to DOAC itself did not influence to bleeding and thromboembolic event risks.

In the PIONEER AF-PCI trial and RE-DUAL PCI trial, bleeding rate according to the ISTH criteria at 12 months ranged from 15.4 to 16.8%.[5,6] In the present study, the Kaplan Meier estimated incidence of any bleeding at 12 months was 29.6% and 26.2% in DOAC + SAPT and DAOC + DAPT groups, respectively. Possible reasons of the higher incidence of the bleeding in the present study as compared to the previous trials are as follows: (1) Our registry included only Asian population who are at higher bleeding risk than Western population.[13] Asian in the previous trials was quite few (3.5%−4.7%) and majority was Western[5]; (2) More elderly patients were enrolled in the present study (approximately 75 years) than previous trial (approximately 70 years); (3) Randomized controlled trials basically enroll highly selected patient population whereas our registry included miscellaneous patients, which would provide real-world clinical perspective.

In the nationwide Danish registry of AF all-comers with myocardial infarction, the 360-day bleeding risk was increased on triple therapy compared with vitamin K antagonist (warfarin) plus a single antiplatelet agent (HR 1.36, 95% CI 0.95−1.95) without differences in ischemic events (HR 1.15, 95% CI 0.95−1.40).[14,15] The results of the recent PCI trials also demonstrated triple therapy (DAPT + warfarin) had a higher bleeding risk than dual therapy (DOAC + P2Y12 inhibitor) in patients undergoing PCI.[5−7] However, bleeding data of the triple therapy including DOAC was not available so far. The present study showed that the real-world Asian NVAF population treated with DOAC and add-on antiplatelet therapy had a significantly increased bleeding risk; and its incremental risk was similar in those with SAPT and DAPT. The incremental bleeding risks in patients treated with add-on antiplatelet therapy on DOAC were consistent across most subgroups including gender, age, renal function, etc. (Figure 3 and Figure 4). However, the bleeding risk of add-on antiplatelet agents was cancelled by multivariate adjustment including ORBIT- and HAS-BLED-composing factors,[12,16] suggesting that the incremental bleeding risk of add-on antiplatelet agents might be negligible when compared with the effect of DOAC.

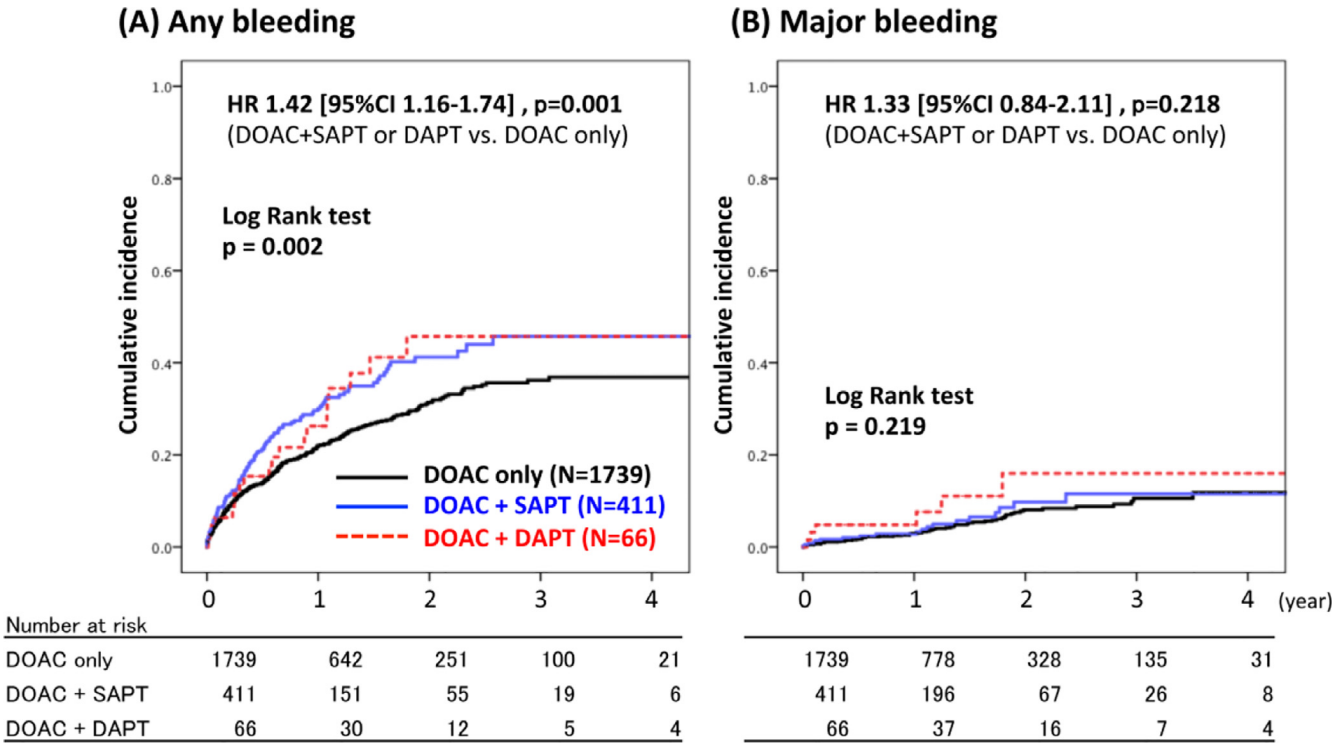

Figure 1. Kaplan Meier analysis for primary safety endpoints. Kaplan Meier curves for any bleeding (A) and major bleeding (B) according to the ISTH criteria. Abbreviations: CI, confidence interval; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; HR, hazard ratio; SAPT, single antiplatelet therapy.

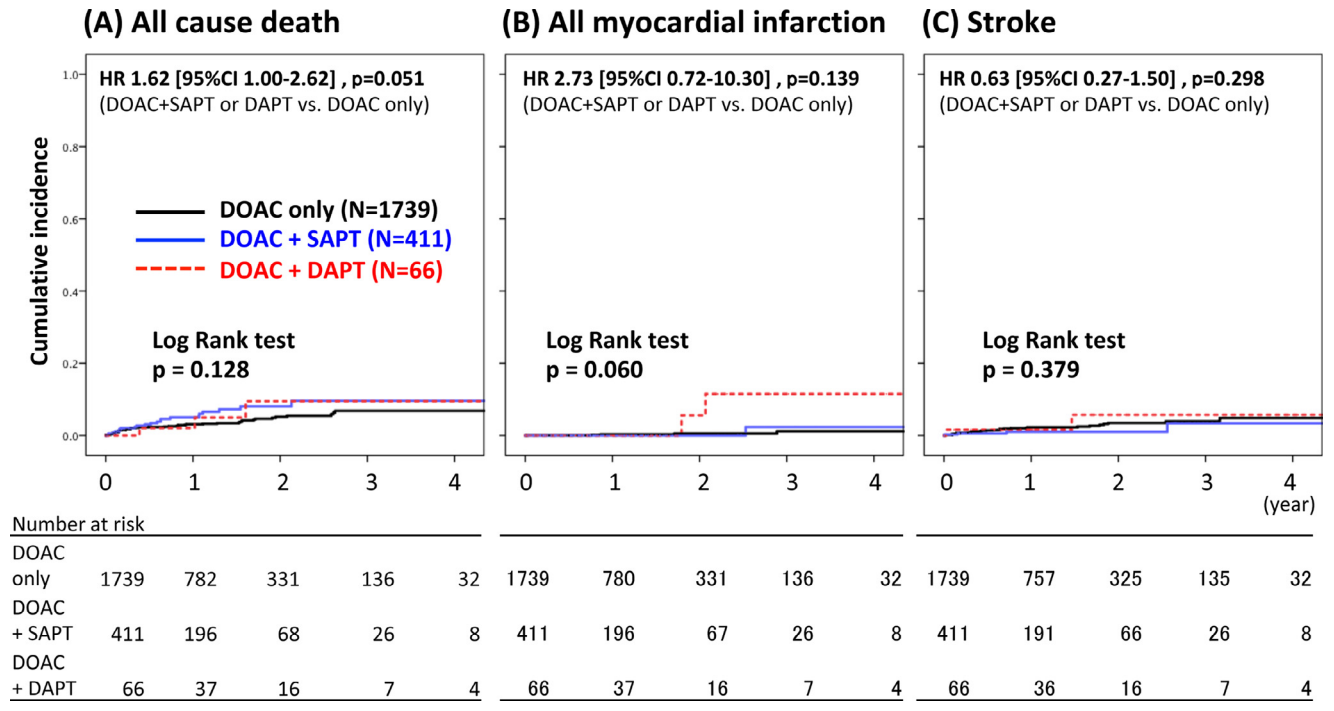

Figure 2. . Kaplan Meier analysis for secondary endpoints. Kaplan Meier curves for all cause death (A), all myocardial infarction (B), and stroke (C). Abbreviations are as in Figure 1.

Table 2
Impact of add-on antiplatelet agents on clinical outcomes

	Nonadjusted		Adjusted*	
	Hazard ratio [95% confidence interval]	p value	Hazard ratio [95% confidence interval]	p value
Any bleeding	1.418 [1.162−1.732]	0.001	1.198 [0.938−1.530]	0.147
Major bleeding	1.279 [0.803−2.037]	0.300	0.854 [0.474−1.536]	0.598
All-cause death	1.618 [0.999−2.620]	0.051	1.430 [0.815−2.508]	0.212
All myocardial infarction	2.726 [0.721−10.301]	0.139	0.737 [0.093−5.842]	0.773
Stroke	0.612 [0.258−1.456]	0.267	0.456 [0.160−1.300]	0.142

* The impact of add-on antiplatelet agents on primary and secondary endpoints was assessed with Cox proportional hazards model without and with multivariate adjustment including following factors: age, female gender, creatinine clearance, hypertension, diabetes mellitus, history of percutaneous coronary intervention or coronary artery bypass graft, and history of bleeding.

In the present study, we assessed influence of DOAC types as an exploratory analysis. Bleeding risks of apixaban and edoxaban assessed with Cox proportional hazards model were numerically higher than dabigatran and rivaroxaban (Online Table 2). Baseline characteristics stratified by DOAC types (Online Table 1) clearly showed that apixaban and edoxaban were prescribed for patients with higher bleeding risk than dabigatran and rivaroxaban, reflecting our real-world clinical prescription manner. Hazards of bleeding events in patients with 4 different DOACs were adjusted with multiple factors. Nevertheless, there should be several unknown factors strongly influencing the results of the current analysis. The current results just descriptively provided the real-world data and needs to be interpreted with caution.

The present prospective observational registry would have, to date, relatively large Asian cohort and long follow-up period. Data of the fourth DOAC, edoxaban was uniquely available due to the geographical reason. A few limitations, however, need to be acknowledged. First, the present study is a single center prospective registry. A part of our analysis, especially the analysis stratified by different 4 DOACs, would not have enough statistical power. Second, there should be unknown relevant factors which were not integrated into the adjustment of multivariate Cox hazard model. Readers should keep in their mind that the

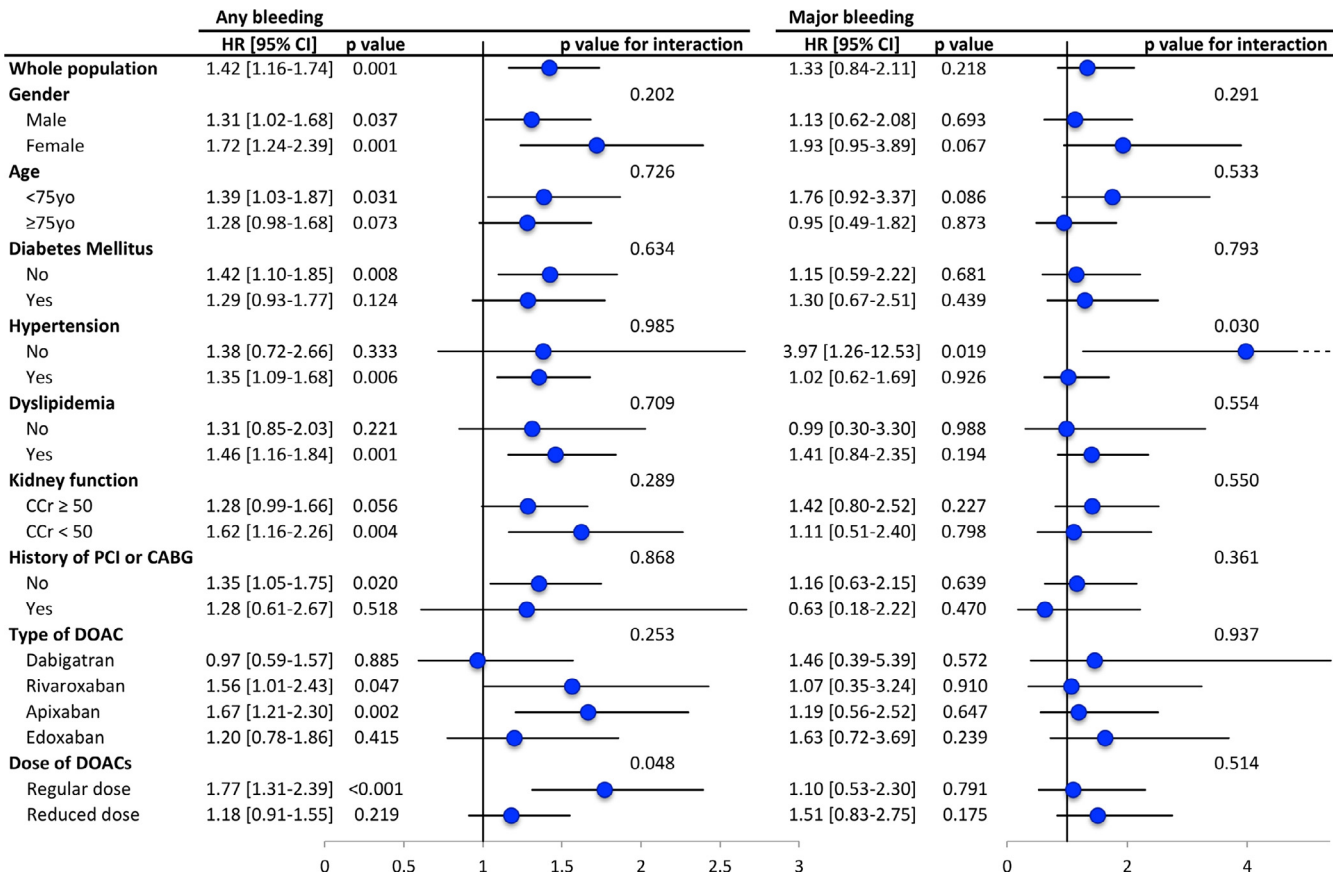

Figure 3. Subgroup analysis of the primary endpoints (safety endpoints) in patients with add-on antiplatelet therapy. Hazard ratio for any bleeding and major bleeding of add-on antiplatelet therapy was assessed in multiple subgroups. Abbreviations: CCr, creatinine clearance; CABG, coronary artery bypass graft; DOAC, direct oral anticoagulant; PCI, percutaneous coronary intervention.

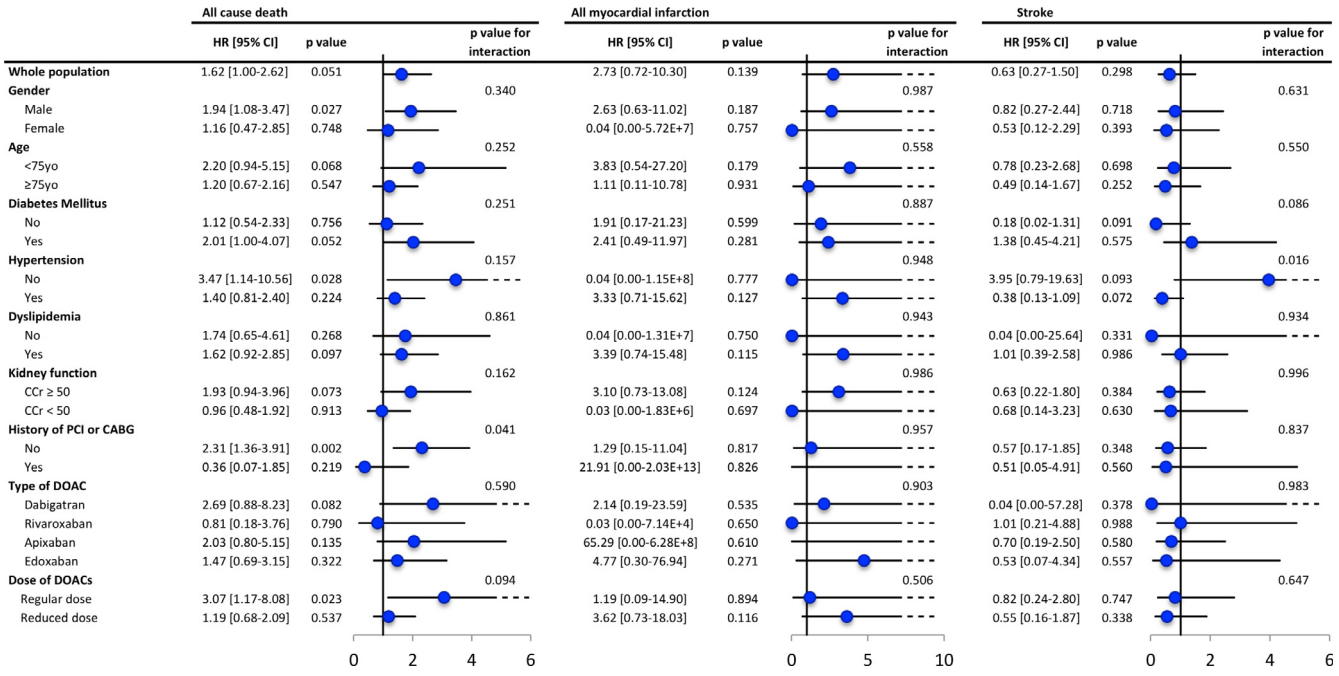

Figure 4. Subgroup analysis of the secondary endpoints (efficacy endpoints) in patients with add-on antiplatelet therapy. Hazard ratio for all cause death, all myocardial infarction, and stroke of add-on antiplatelet therapy was assessed in multiple subgroups. Abbreviations: CCr, creatinine clearance; CABG, coronary artery bypass graft; DOAC, direct oral anticoagulant; PCI, percutaneous coronary intervention.

current results reflect a "real-world" clinical data of Asian population and are just hypothesis-generating. Lastly, the follow-up duration was relatively short (approximately 1 year). The rate of bleeding events generally peaks within the first 30 days of initiation of drugs.[17] The current analysis, therefore, would provide us with results of the most critical phase. However, long-term follow-up data would be the next scientific interest. In conclusion, in the Asian real-world clinical practice, NVAF patients treated with antiplatelet agents and DOAC had a significantly higher bleeding risk than those using DOAC only. However, after adjustment of patient's background, add-on antiplatelet therapy to DOAC itself did not influence to a bleeding risk.

Disclosures

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Supplementary materials

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