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Antiplatelets for Cardiovascular Disease in Non-valvular AF with Rivaroxaban: A Subanalysis of the EXPAND Study

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Aim: In this subanalysis of the EXPAND study, we evaluated the risks and benefits of rivaroxaban plus antiplatelet therapy (APT) for patients with non-valvular atrial fibrillation (NVAF) complicated by stable coronary artery disease (CAD), ischemic stroke, or peripheral artery disease (PAD).

Methods: From the EXPAND study population (n=7,141), patients with NVAF complicated by stable CAD (n=886), ischemic stroke (n=1,231), or PAD (n=160) were included. Patients complicated by any of them were set as ALL (n=2,030). Patients were all treated with rivaroxaban (10 or 15 mg/day) with (+) or without (–) APT. Efficacy outcomes were symptomatic stroke + systemic embolism (SE), symptomatic stroke + SE + myocardial infarction + cardiovascular death, and all-cause death. Safety outcomes included major and any bleeding. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for differences between the APT(+) and APT(–) groups.

Results: There were no significant differences in the efficacy outcomes between the APT(+) and APT(–) groups in the ALL cohort or in the CAD and STROKE sub-cohorts. In the PAD subcohort, the HR [95% CI] for all-cause death in the APT(+) group increased (4.43 [1.05–18.71]; p=0.043). In the APT(+) group, the HR [95% CI] for any bleeding increased in the ALL cohort (1.28 [1.01–1.62]; p=0.044) and STROKE subcohort (1.42 [1.01–2.01]; p=0.047), and for major bleeding in the CAD subcohort (2.00 [1.01–3.93]; p=0.046).

Conclusions: Rivaroxaban with APT did not reduce ischemic outcomes in patients with stable CAD or ischemic stroke; however, it did increase the risk of bleeding in patients with stable CAD or ischemic stroke.

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Key words: **Rivaroxaban, Antiplatelet therapy, Non-valvular atrial fibrillation, Stroke, Bleeding**

Abbreviations: **ACT: Anticoagulant therapy, AF: Atrial fibrillation, AFIRE: AF and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease, aHR: Adjusted hazard ratio, APT: Antiplatelet therapy, CAD: Coronary artery disease, CI: Confidence interval, CV: Cardiovascular, DOAC: Direct oral anticoagulant, EXPAND: Evaluation of the effectiveness and safety of Xa inhibitors for the prevention of stroke and systemic embolism in a nationwide cohort of Japanese patients Diagnosed as NVAF, MI: Myocardial infarction, NVAF: Non-valvular atrial fibrillation, PAD: Peripheral artery disease, SE: Systemic embolism, TIA: Transient ischemic attack**

Introduction

Avoiding stroke is of the highest importance in the management of patients with non-valvular atrial fibrillation (NVAF), and the use of direct oral anticoagulants (DOACs) based on risk stratification has been established as a guideline-based treatment approach for NVAF[1-3]. The significant risk factors that are often present in patients with NVAF have been integrated into the $CHADS_2$ and CHA_2DS_2-VASc scores for stroke risk assessment and HAS-BLED score for bleeding risk assessment. Atherosclerotic diseases, such as coronary artery disease (CAD)[4], ischemic stroke[5, 6], and peripheral artery disease (PAD)[7], are included as risk factors for anticoagulant use, as they are frequently observed as comorbidities in patients with atrial fibrillation (AF)[4].

Over the decades, evidence has shown that antiplatelet therapy (APT) is beneficial for improving the prognosis of patients with atherosclerotic diseases[8-10]. However, the combined use of DOACs and APT in patients with NVAF complicated by atherosclerotic diseases has been reported to increase the risk[11-12]. For example, in patients with stable CAD with NVAF, the AF and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease (AFIRE) trial[12] examined the benefit of anticoagulant therapy alone versus anticoagulant therapy combined with APT. The trial showed that rivaroxaban (DOAC) monotherapy was not inferior to combination therapy (rivaroxaban with a single APT) in terms of efficacy, with comparable event rates for the composite endpoint of stroke, systemic embolism (SE), myocardial infarction (MI), unstable angina requiring revascularization, and death from any cause[12]. However, rivaroxaban monotherapy is superior to combination therapy in terms of safety, with a lower event rate for major bleeding[12]. Although the risk–benefit weighting of combined antithrombotic therapy (APT plus DOAC therapy) has been examined in patients with NVAF and stable CAD, it has not yet been explored in patients with NVAF and ischemic stroke or PAD.

Aim

This study is a subanalysis of the EXPAND study (Evaluation of effectiveness and safety of Xa inhibitor for the prevention of stroke and systemic embolism in a nationwide cohort of Japanese patients diagnosed as NVAF)[13, 14]. It was conducted to evaluate the risks and benefits of rivaroxaban alone versus rivaroxaban plus single APT in patients with stable cardiovascular (CV) disease (CAD, ischemic stroke, or PAD).

Methods

The EXPAND Study

The EXPAND study was a multicenter, prospective, observational cohort study conducted to evaluate the efficacy and safety of rivaroxaban in Japanese patients with NVAF in real-world clinical practice (ClinicalTrials.gov NCT02147444). The detailed study design and results have been previously described[13, 14]. Briefly, patients with NVAF, who were ≥ 20 years of age, and who started rivaroxaban at a dose of 10 mg/day or 15 mg/day, which is the approved dose in Japan based on the J-ROCKET AF trial[15], were eligible for inclusion. Patients with or without concomitant APT [APT(+) or APT(–)] at the initiation of rivaroxaban were included. The continuation, modification, or discontinuation of APT at the initiation of rivaroxaban was performed at the discretion of the investigator. Follow-up was

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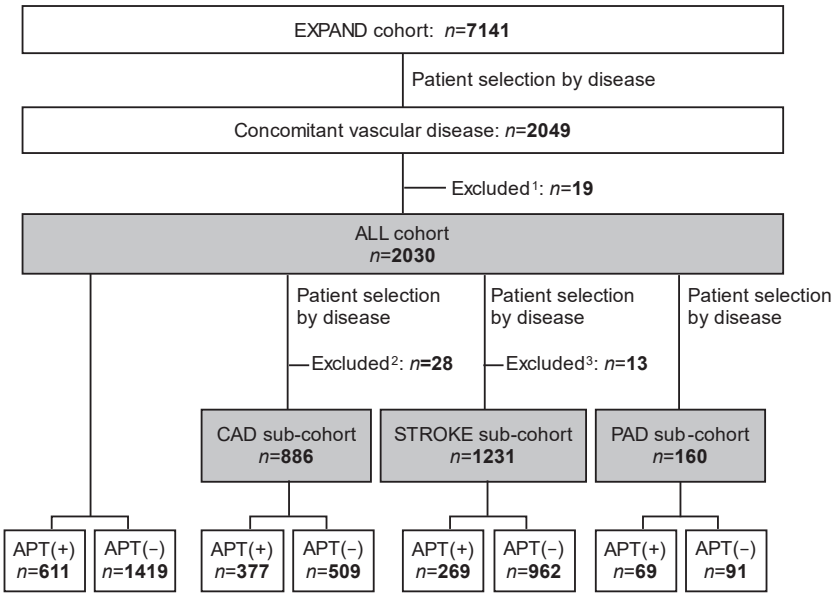

Fig. 1. Patient disposition

The excluded APT regimens: 1) antiplatelet monotherapy with no information on drug name; 2) eicosapentaenoic acid monotherapy or cilostazol monotherapy (no indication of CAD); and 3) eicosapentaenoic monotherapy (no indication of stroke). APT, antiplatelet therapy; CAD, coronary artery disease; PAD, peripheral artery disease.

started at the initiation of rivaroxaban and continued even when rivaroxaban was discontinued. Patients were also followed-up for continuation of anticoagulant therapy and APT. The final analysis population consisted of 7,141 patients, and the mean follow-up period was 897 ± 207 days. The outcomes identified in clinical practice were reported, including all-cause mortality (1.6% per year), combined stroke and SE (1.2% per year), and major bleeding (1.0% per year)[13].

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The study was conducted in accordance with the Ethical Guidelines for Clinical Studies from the Japanese Ministry of Health, Labour, and Welfare, and all applicable laws and regulations in Japan. The protocol was reviewed and approved by the institutional review boards and/or ethics committees of all the participating study sites. All patients provided their written informed consent prior to enrollment.

Subanalysis Cohort

Among the entire cohort of patients included in the EXPAND study, those with CAD (MI or angina pectoris), ischemic stroke (including transient ischemic attack [TIA]), or PAD were selected for inclusion in the present subanalysis. The patient disposition is shown in **Fig. 1.**

Patients who underwent APT with a single agent that was not indicated for their respective diseases (e.g., patients with CAD on cilostazol monotherapy or eicosapentaenoic acid monotherapy) were excluded. Patients with ischemic cerebral infarction within 2 weeks prior to the start of rivaroxaban therapy or patients undergoing dual APT (aspirin + thienopyridine) were excluded because these patients were considered to be in an acute state of vascular disease. By applying the inclusion and exclusion criteria, patients with stable CV disease were identified and defined as the ALL cohort.

Patients in the ALL cohort were included in the CAD, STROKE (including TIA), and/or PAD subcohorts. Patients with more than one of these conditions were duplicated in the corresponding subcohort. For the ALL cohort and each of the 3 subcohorts, comparisons were made for each of the safety and efficacy outcomes between the APT(–) group (rivaroxaban alone) and the APT(+) group (rivaroxaban plus APT).

Continuation of Anticoagulant Therapy and APT (Exposure)

To assess the continuation of anticoagulant therapy (rivaroxaban) and APT (exposure to treatment), the number and proportion of on-treatment patients among those who continued to receive anticoagulant therapy during follow-up were calculated at 180, 360, 720, and 900 days after

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starting rivaroxaban. After starting anticoagulant therapy, it is possible that the initial dose of rivaroxaban would be changed, rivaroxaban would be changed to another anticoagulant (DOAC or warfarin), or rivaroxaban would be temporarily suspended. To ensure consistency in the research question of this subanalysis, anticoagulant therapy was continued until the last dose of any anticoagulant was administered. Similarly, APT for patients in the APT(+) group was continued until the last dose of any antiplatelet was administered. Any temporary interruption to APT during the study or a change to another APT was considered a continuation of APT.

Efficacy and Safety Outcomes

Five of the predefined primary or secondary outcomes from the EXPAND study[13, 14] were set as the outcomes of this subanalysis. Specifically, the efficacy outcomes were a composite of symptomatic stroke and SE, which was the primary efficacy outcome of the EXPAND study: a composite of symptomatic stroke, SE, MI, and cardiovascular (CV) death, and all-cause death. The safety outcomes were major bleeding events (according to the International Society on Thrombosis and Hemostasis major bleeding criteria[16]) and all bleeding events (any bleeding).

Statistical Analysis

Kaplan–Meier survival curves were drawn to show the efficacy and safety outcome events in the APT(+) and APT(–) groups in the ALL cohort and in the CAD, STROKE, and PAD subcohorts. Adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) were calculated for each outcome. *P*-values for comparisons between the APT(+) and APT(–) groups were calculated using univariate and multivariate Cox proportional hazards regression analyses.

The covariates included in the multivariate analysis of the efficacy outcome assessment were CHA_2DS_2-VASc score components of age, sex, heart failure, hypertension, diabetes mellitus, stroke, and vascular disease. In the multivariate analysis of the safety outcome assessment, the following covariates were set with reference to the HAS-BLED score: age, systolic blood pressure, abnormal liver function, abnormal renal function, history of bleeding or tendency to bleed, stroke, and heavy alcohol consumption. The labile international normalized ratio was not included as a covariate, because warfarin was not used in the EXPAND cohort. All covariates were entered into the model and no statistical variable selection was performed.

A subgroup analysis was also conducted to investigate whether the effects of APT on outcomes were consistent across the three CV diseases (CAD, ischemic stroke, and PAD). As the 3 subcohorts involved duplication of some patients, they were re-stratified from the ALL cohort into 3 subcohorts without duplication (patients with CAD only, patients with stroke only, and patients with PAD only/patients with multiple CV diseases). *P*-values for interactions were calculated. *P* values of <0.05 were considered to indicate statistical significance.

Results

Analysis Population

In the present subanalysis, the ALL cohort (n=2,030) and 3 subcohorts (CAD, n=886; STROKE, n=1,231; PAD, n=160) were delineated **(Fig. 1)**. Patients in the ALL cohort and each subcohort were further classified into the APT(–) and APT(+) groups. Patients with 2 or more of CAD, stroke, TIA, or PAD were duplicated in each corresponding subcohort if not excluded by non-indicated APT use. The background characteristics of patients in the ALL cohort and each subcohort are shown in **Table 1**.

Demographic and Baseline Characteristics

Age was generally similar between the APT(+) and APT(–) groups in each subcohort, although there was a significant difference between the APT(+) and APT(–) groups in the CAD subcohort [73.4±7.9 years in APT(+) vs. 74.7±8.0 years in APT(–), p=0.013].

The proportion of patients with comorbidities of CV diseases and their risk factors tended to be higher in the APT(+) group. The proportion of patients with hypertension was 7–10% higher in the APT(+) group than in the APT(–) group in the CAD (84.4% vs. 74.7%, $p<0.001$) and STROKE (81.4% vs. 70.0%, $p<0.001$) subcohorts. Similarly, the proportion of patients with diabetes mellitus was largely higher in the APT(+) group than that in the APT(–) group in the CAD (44.8% vs. 28.9%, $p<0.001$) and STROKE (44.6% vs. 22.2%, $p<0.001$) subcohorts. Finally, a larger proportion of patients in the CAD (377 of 886 [42.6%]) and PAD (69 of 160 [43.1%]) subcohorts were treated with concomitant APT in comparison to the STROKE subcohort (269 of 1,231 [21.9%]) **(Fig. 1)**.

Continuation of Anticoagulant Therapy and APT During the Follow-up Period

The breakdown of APT agents in the APT(+) group at the start of rivaroxaban treatment (beginning

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Table 1. Background characteristics of patients in the ALL cohort and in the CAD, STROKE, and PAD subcohorts

Category	ALL			CAD			STROKE			PAD		
	APT(+)	APT(−)	*p*-value	APT(+)	APT(−)	*p*-value	APT(+)	APT(−)	*p*-value	APT(+)	APT(−)	*p*-value
n	611	1419		377	509		269	962		69	91	
Male	473 (77.4)	999 (70.4)	0.001	298 (79.0)	344 (67.6)	<0.001	204 (75.8)	697 (72.5)	0.277	58 (84.1)	64 (70.3)	0.06
Age, years												
<64	67 (11.0)	192 (13.5)	0.142	40 (10.6)	56 (11.0)	0.185	27 (10.0)	135 (14.0)	0.218	5 (7.2)	15 (16.5)	0.246
65–74	244 (39.9)	512 (36.1)		162 (43.0)	184 (36.1)		96 (35.7)	335 (34.8)		24 (34.8)	35 (38.5)	
75–84	258 (42.2)	593 (41.8)		147 (39.0)	219 (43.0)		128 (47.6)	411 (42.7)		30 (43.5)	30 (33.0)	
85–94	42 (6.9)	122 (8.6)		28 (7.4)	50 (9.8)		18 (6.7)	81 (8.4)		10 (14.5)	11 (12.1)	
Mean (SD)	73.6 (7.0)	73.8 (8.4)	0.582	73.4 (7.9)	74.7 (8.0)	0.013	74.3 (7.4)	73.7 (8.5)	0.306	75.5 (7.6)	73.2 (9.2)	0.091
Comorbidities												
Hypertension	511 (83.6)	1014 (71.5)	<0.001	318 (84.4)	380 (74.7)	<0.001	219 (81.4)	673 (70.0)	<0.001	60 (87.0)	73 (80.2)	0.293
Hyperlipidemia	410 (67.1)	623 (43.9)	<0.001	282 (74.8)	268 (52.7)	<0.001	167 (62.1)	394 (41.0)	<0.001	42 (60.9)	34 (37.4)	0.004
Diabetes mellitus	257 (42.1)	354 (24.9)	<0.001	169 (44.8)	147 (28.9)	<0.001	120 (44.6)	214 (22.2)	<0.001	23 (33.3)	38 (41.8)	0.325
Any stroke	285 (46.6)	975 (68.7)	<0.001	87 (23.1)	120 (23.6)	0.873	269 (100.0)	962 (100.0)	NA	28 (40.6)	18 (19.8)	0.005
Ischemic stroke	253 (41.4)	840 (59.2)	<0.001	72 (19.1)	95 (18.7)	0.931	242 (90.0)	840 (87.3)	0.290	27 (39.1)	13 (14.3)	<0.001
Cerebral hemorrhage	7 (1.1)	49 (3.5)	0.003	4 (1.1)	17 (3.3)	0.042	4 (1.5)	36 (3.7)	0.079	2 (2.9)	3 (3.3)	1.000
TIA	44 (7.2)	157 (11.1)	0.007	14 (3.7)	21 (4.1)	0.862	41 (15.2)	157 (16.3)	0.708	4 (5.8)	5 (5.5)	1.000
CHF	200 (32.7)	360 (25.4)	0.001	136 (36.1)	175 (34.4)	0.619	76 (28.3)	215 (22.3)	0.051	37 (53.6)	26 (28.6)	0.002
Myocardial infarction	162 (26.5)	92 (6.5)	<0.001	149 (39.5)	92 (18.1)	<0.001	35 (13.0)	21 (2.2)	<0.001	12 (17.4)	7 (7.7)	0.083
Angina	310 (50.7)	441 (31.1)	<0.001	287 (76.1)	441 (86.6)	<0.001	77 (28.6)	92 (9.6)	<0.001	31 (44.9)	19 (20.9)	0.002
PAD	69 (11.3)	91 (6.4)	<0.001	32 (8.5)	24 (4.7)	0.025	28 (10.4)	16 (1.7)	<0.001	69 (100.0)	91 (100.0)	NA
CHA_2DS_2-VASc												
1	0 (0.0)	2 (0.1)	0.151	0 (0.0)	2 (0.4)	0.429	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
2	21 (3.4)	65 (4.6)		17 (4.5)	33 (6.5)		1 (0.4)	26 (2.7)	<0.001	3 (4.3)	8 (8.8)	0.001
3–5	399 (65.3)	969 (68.3)		257 (68.2)	334 (65.6)		123 (45.7)	616 (64.0)		33 (47.8)	65 (71.4)	
6–9	191 (31.3)	383 (27.0)		103 (27.3)	140 (27.5)		145 (53.9)	320 (33.3)		33 (47.8)	18 (19.8)	
HAS-BLED												
0	0 (0.0)	59 (4.5)	<0.001	0 (0.0)	42 (8.7)	<0.001	0 (0.0)	11 (1.2)	<0.001	0 (0.0)	8 (9.3)	<0.001
1	43 (7.5)	455 (34.5)		34 (9.6)	262 (54.4)		4 (1.6)	171 (19.3)		3 (4.5)	47 (54.7)	
2	254 (44.2)	619 (47.0)		208 (58.6)	139 (28.8)		40 (15.8)	536 (19.3)		29 (43.9)	22 (25.6)	
3	223 (38.8)	164 (12.4)		87 (24.5)	36 (7.5)		162 (64.0)	147 (16.6)		27 (40.9)	9 (10.5)	
4	49 (8.5)	20 (1.5)		25 (7.0)	3 (0.6)		42 (16.6)	18 (2.0)		6 (9.1)	0 (0.0)	
5	6 (1.0)	1 (0.1)		1 (0.3)	0 (0.0)		5 (2.0)	1 (0.1)		1 (1.5)	0 (0.0)	
Smoking												
Never	306 (50.1)	836 (58.9)	<0.001	191 (50.7)	302 (59.3)	0.004	145 (53.9)	577 (60.0)	0.034	24 (34.8)	42 (46.2)	0.356
Past smoker	257 (42.1)	461 (32.5)		163 (43.2)	165 (32.4)		107 (39.8)	303 (31.5)		34 (49.3)	38 (41.8)	
Current smoker	48 (7.9)	122 (8.6)		23 (6.1)	42 (8.3)		17 (6.3)	82 (8.5)		11 (15.9)	11 (12.1)	

Data are *n* (%) unless specified otherwise.
APT, antiplatelet therapy; CAD, coronary artery disease; CHF, congestive heart failure; PAD, peripheral artery disease; SD, standard deviation; TIA, transient ischemic attack.

of follow-up) was as follows: aspirin, *n*=309 (82%); clopidogrel, *n*=62 (16%); ticlopidine, *n*=6 (2%) in the CAD subcohort (*n*=377 patients); aspirin *n*=139 (52%), clopidogrel *n*=78 (29%), cilostazol *n*=39 (14%), and ticlopidine *n*=13 (5%) in the STROKE subcohort (*n*=269 patients); and aspirin *n*=44 (64%), clopidogrel *n*=13 (19%), and cilostazol *n*=12 (17%) in the PAD subcohort (*n*=69 patients). Among the patients treated with APT prior to starting rivaroxaban, the proportion of patients who discontinued APT at the initiation of rivaroxaban was 18% (80/457) in the CAD subcohort, 30% (130/399) in the STROKE subcohort, and 17% (14/83) in the PAD subcohort. Among the patients who continued follow-up, a high proportion remained on antithrombotic therapy throughout the follow-up period, with ≥ 97% on anticoagulant therapy and ≥ 90% on APT (Table 2).

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Table 2. Continuation of ACT and APT

	Group	APT(+) group					APT(–) group				
	Days from initial RIV administration	0	180	360	720	900	0	180	360	720	900
ALL	Ongoing follow-up, *n*	611	607	592	530	326	1419	1398	1369	1246	797
	Continuing ACT	611 (100)	600 (99)	582 (98)	518 (98)	319 (98)	1419 (100)	1381 (99)	1346 (98)	1205 (97)	772 (97)
	Continuing APT	611 (100)	595 (98)	571 (96)	492 (93)	294 (90)					
CAD	Ongoing follow-up, *n*	377	375	368	329	204	509	502	493	443	273
	Continuing ACT	377 (100)	372 (99)	363 (99)	322 (98)	197 (97)	509 (100)	496 (99)	487 (99)	429 (97)	265 (97)
	Continuing APT	377 (100)	370 (99)	356 (97)	306 (93)	185 (91)					
STROKE	Ongoing follow-up, *n*	269	267	257	227	144	962	947	926	843	551
	Continuing ACT	269 (100)	264 (99)	253 (98)	223 (98)	143 (99)	962 (100)	935 (99)	908 (98)	816 (97)	535 (97)
	Continuing APT	269 (100)	259 (97)	250 (97)	211 (93)	129 (90)					
PAD	Ongoing follow-up, *n*	69	69	67	58	31	91	90	88	80	55
	Continuing ACT	69 (100)	67 (97)	66 (99)	56 (97)	30 (97)	91 (100)	89 (99)	87 (99)	78 (98)	54 (98)
	Continuing APT	69 (100)	66 (96)	65 (97)	57 (98)	30 (97)					

Data are *n* (%) unless specified otherwise.
ACT, anticoagulant therapy; APT, antiplatelet therapy; CAD, coronary artery disease; PAD, peripheral artery disease; RIV, rivaroxaban.

Efficacy Outcomes

The Kaplan–Meier curves and HRs for the efficacy outcomes obtained from the Cox proportional-hazards logistic regression analysis for the ALL cohort are shown in **Fig. 2a–c**. The number of events, rates, adjusted HRs, and 95% CIs for the ALL cohort and 3 subcohorts are shown in **Fig. 3**.

In the ALL cohort and the CAD and STROKE subcohorts, there were no significant differences in any of the three efficacy outcomes (stroke + SE, stroke + SE + MI + CV death, and all-cause death) between the APT(+) and APT(–) groups **(Figs. 2 and 3)**. In the PAD subcohort, there was no significant difference in the occurrence of stroke + SE or stroke + SE + MI + CV death between the APT(+) and APT(–) groups. However, the rate of all-cause death was significantly higher in the APT(+) group (5.59 events/100 person-years) than in the APT(–) group (1.33 events/100 person-years) (aHR 4.43 [95% CI 1.05–18.71]; p=0.043) in the PAD subcohort **(Fig. 3)**.

Safety Outcomes

The Kaplan–Meier curves and aHRs for the safety outcomes obtained from the Cox proportional hazards logistic regression analysis for the ALL cohort are shown in **Fig. 2d–e**. The number of events, rates, aHRs, and 95% CIs for the ALL cohort and three subcohorts are shown in **Fig. 3**.

The point estimate of the HR for major bleeding in the APT(+) to APT(–) group exceeded 1 in all subcohorts (ALL, 1.51; CAD, 2.00; STROKE, 1.42; PAD, 2.06), but only the CAD subcohort reached statistical significance **(Fig. 3)**. In the CAD subcohort, the rate of major bleeding in the APT(+) group (2.27 events/100 person-years) was significantly higher than that in the APT(–) group (1.29 events/100 person-years) (aHR 2.00 [95% CI 1.01–3.93]; p=0.046) **(Fig. 3)**. The number (proportion) of patients with major bleeding in the ALL cohort was as follows: In the APT(+) group (n=611), 27 patients (4.4%) experienced major bleeding, including 8 (1.3%) with intracranial bleeding, 12 (2.0%) with gastrointestinal bleeding, and 7 (1.1%) with other major bleeding events. In the APT(–) group (n=1419), 40 patients (2.8%) experienced major bleeding, including 21 (1.5%) with intracranial bleeding, 11 (0.8%) with gastrointestinal bleeding, and 8 (0.6%) with other major bleeding events.

The rate of any bleeding in the APT(+) group was significantly higher than that in the APT(–) group in the ALL cohort (8.75 vs. 6.75 events/100 person-years) (aHR 1.28 [95% CI 1.01–1.62]; p=0.044) and the STROKE subcohort (7.84 vs. 6.04 events/100 person-years) (aHR 1.42 [95% CI 1.01– 2.01]; p=0.047) **(Figs. 2 and 3)**. In the PAD subcohort, there were no significant differences in the rates of major bleeding or any bleeding between the APT(+) and APT(–) groups **(Fig. 3)**.

Differences Across CV Diseases

A subgroup analysis to analyze the differences in the effects of APT on each efficacy and safety outcome was performed after patients were re-stratified into the CAD only (n=656), stroke only (n=1,013), and PAD/multiple CV disease (n=334) subgroups. The p-value for the interaction between the 3 subgroups for each of the 3 efficacy and 2 safety outcomes did not demonstrate any significant interaction (p for

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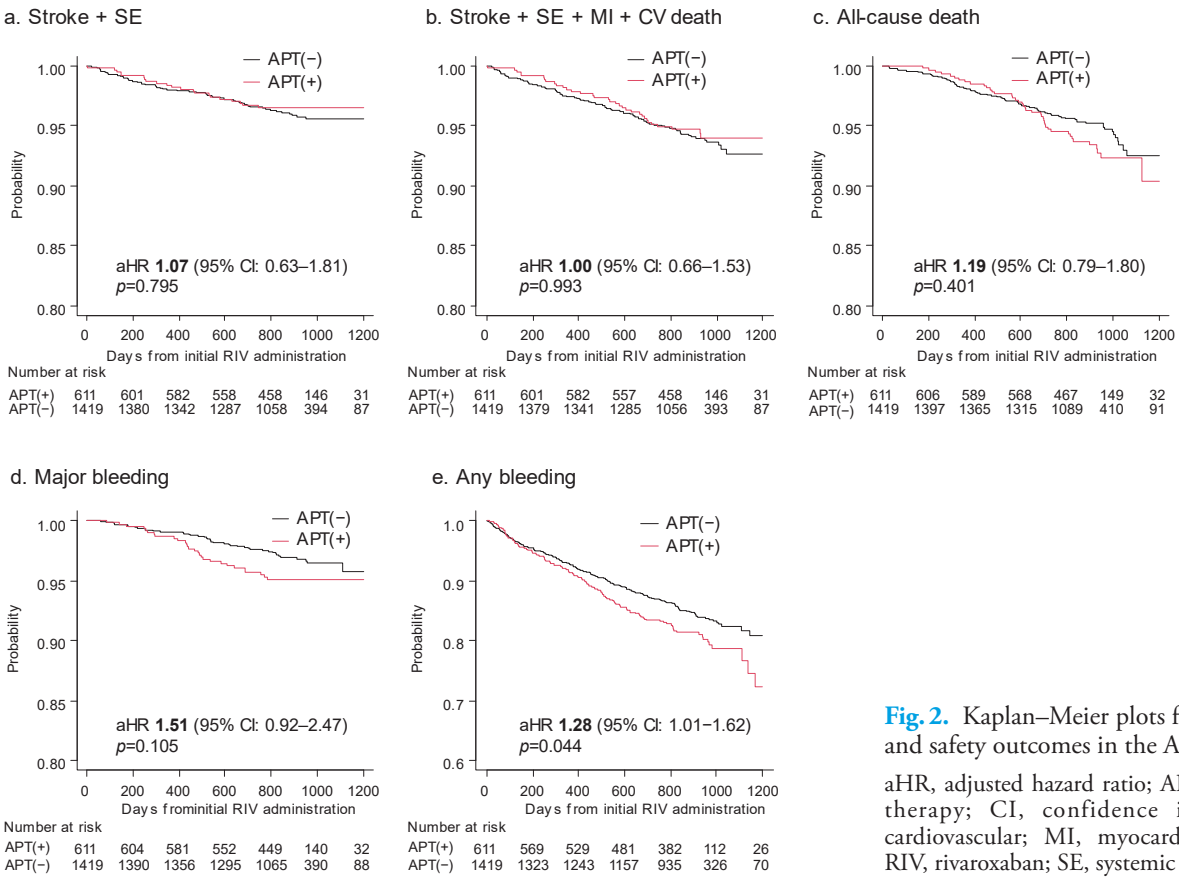

Fig. 2. Kaplan–Meier plots for the efficacy and safety outcomes in the ALL cohort

aHR, adjusted hazard ratio; APT, antiplatelet therapy; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; RIV, rivaroxaban; SE, systemic embolism.

Endpoint	Group	No. of events/total (events/100 py) APT(+)		APT(−)		Adjusted HR HR (95% CI)	P-value
Stroke + SE	ALL	22/611	(1.50)	56/1419	(1.63)	1.07 (0.63–1.81)	0.795
	CAD	11/377	(1.12)	11/509	(0.89)	1.26 (0.51–3.09)	0.621
	STROKE	15/269	(2.26)	47/962	(2.03)	1.03 (0.54–1.94)	0.933
	PAD	4/69	(2.52)	4/91	(1.80)	1.40 (0.30–6.61)	0.671
Stroke + SE + MI + CV death	ALL	35/611	(2.39)	84/1419	(2.45)	1.00 (0.66–1.53)	0.993
	CAD	18/377	(1.83)	20/509	(1.61)	1.03 (0.51–2.08)	0.939
	STROKE	21/269	(3.16)	66/962	(2.85)	1.06 (0.62–1.80)	0.840
	PAD	7/69	(4.40)	7/91	(3.16)	1.34 (0.42–4.29)	0.619
All-cause death	ALL	42/611	(2.83)	74/1419	(2.12)	1.19 (0.79–1.80)	0.401
	CAD	27/377	(2.73)	32/509	(2.55)	0.85 (0.48–1.51)	0.580
	STROKE	20/269	(2.94)	52/962	(2.20)	1.24 (0.70–2.18)	0.457
	PAD	9/69	(5.59)	3/91	(1.33)	4.43 (1.05–18.71)	0.043
Major bleeding	ALL	28/611	(1.92)	44/1419	(1.28)	1.51 (0.92–2.47)	0.105
	CAD	22/377	(2.27)	16/509	(1.29)	2.00 (1.01–3.93)	0.046
	STROKE	11/269	(1.65)	30/962	(1.28)	1.42 (0.70–2.85)	0.330
	PAD	3/69	(1.92)	3/91	(1.36)	2.06 (0.36–11.92)	0.420
Any bleeding	ALL	115/611	(8.75)	213/1419	(6.75)	1.28 (1.01–1.62)	0.044
	CAD	88/377	(10.21)	88/509	(7.84)	1.35 (0.99–1.84)	0.057
	STROKE	47/269	(7.84)	130/962	(6.04)	1.42 (1.01–2.01)	0.047
	PAD	13/69	(9.11)	24/91	(12.57)	0.69 (0.33–1.44)	0.320

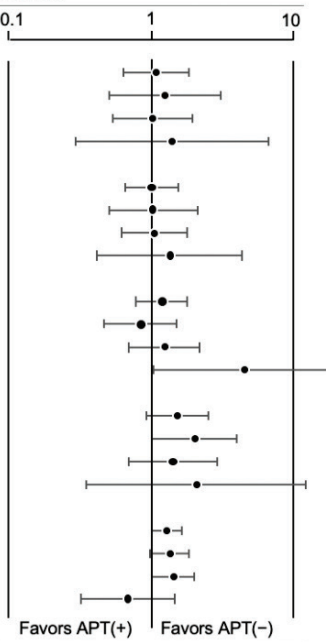

Fig. 3. Events, rates, aHRs, and 95% CIs for the efficacy and safety outcomes with concomitant use of APT

aHR, hazard ratio; APT, antiplatelet therapy; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; PAD, peripheral artery disease; py, person-years; SE, systemic embolism.

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interaction n=0.31–0.83), suggesting that the effects of concomitant APT on the efficacy and safety outcomes were similar between CAD, stroke, and PAD.

Discussion

Findings from the CAD and STROKE Sub-cohorts

In the CAD and STROKE subcohorts, there were no reductions in the occurrence of the 3 efficacy outcomes in the APT(+) group relative to the APT(–) group. However, there was a significant increase in the risk of major bleeding in the CAD subcohort in the APT(+) group relative to the APT(–) group (aHR, 2.00 [95% CI 1.01–3.93]; p=0.046). In the STROKE subcohort, there was a numerical increase in major bleeding in the APT(+) group relative to the APT(–) group, but the difference was not statistically significant. Regarding the occurrence of any bleeding, the results of the APT(+) and APT(–) groups were similar in the CAD (aHR 1.35 [95% CI 0.99–1.84]; p=0.057) and STROKE (aHR 1.42 [95% CI 1.01–2.01]; p=0.047) subcohorts, although the aHR in CAD subcohort did not reach a significant level. Therefore, we suggest that the concomitant use of APT with rivaroxaban may have a similar tendency to increase the risk of bleeding in these two CV diseases. It should be noted that the STROKE subcohort included patients with cerebral embolism (estimated to account for approximately 25%) who were not normally eligible for APT. These patients could not be excluded because of the absence of data to identify them among the patients with ischemic stroke. Although this subanalysis was originally designed to evaluate treatments for atherosclerotic disease, patients with cerebral embolism would have had a different risk profile for developing CV events from other patients in the STROKE subcohort. Therefore, interpretation of the STROKE subcohort results should consider this information.

Findings from the PAD Sub-cohort

In the PAD subcohort, the number of events for each outcome was small. Thus, the accuracy of HR estimations was insufficient (i.e., broad 95% CIs). However, the point estimates for the efficacy outcomes of stroke + SE (aHR 1.40) and stroke + SE + MI + CV death (aHR 1.34), as well as the safety outcome of major bleeding (aHR 2.06), in the PAD subcohort were comparable to those of the CAD and STROKE subcohorts. Thus, patients with PAD treated with rivaroxaban and concomitant APT may have a similar risk–benefit to those with stable CAD or stroke.

The increased risk of all-cause death in the PAD subcohort (aHR, 4.43 [95% CI 1.05–18.71]; p=0.043) in the present subanalysis may have been observed by chance because of the small sample size and small number of events in this subcohort. The aHR was disproportionally higher than the aHRs for the efficacy outcomes of stroke + SE (aHR 1.40) and stroke + SE + MI + CV death (aHR 1.34) as well as the safety outcomes of major bleeding (aHR 2.06) and any bleeding (aHR 0.69). This suggests that the increase in all-cause death in the APT(+) group could not be attributed to vascular causes and that it likely included patients with accidental death resulting from non-vascular causes.

Comparison with other Rivaroxaban Studies

In this subanalysis of the EXPAND study, rivaroxaban monotherapy at the approved dose of 10 or 15 mg/day in patients with NVAF and CV diseases, including CAD, stroke, or PAD, had comparable efficacy for event prevention and a lower risk of major or any bleeding in patients with CAD or stroke than rivaroxaban with concomitant APT. The benefit of rivaroxaban monotherapy was shown in the AFIRE trial for patients with stable CAD[12]; however, this has not been clearly demonstrated in patients with stable ischemic stroke or PAD. The most important finding in the present subanalysis is that common results were obtained for the STROKE and CAD subcohorts, which included a sufficient number of patients. Recently, a post-hoc analysis of the AFIRE trial showed that the benefits of rivaroxaban monotherapy were consistent in a subpopulation of patients with stable CAD who also had a history of MI, stroke, or PAD[17]. Although the STROKE subcohort in the present subanalysis comprised a population with and without CAD complications (although there were fewer patients with CAD complications) and had a different risk profile to the AFIRE post hoc population, we consider our findings to be supported by those reported in the AFIRE post hoc study[17].

Focusing on non-cardioembolic ischemic stroke or TIA as an example, guidelines recommend APT as the standard antithrombotic therapy for post-acute stroke patients. However, for patients with NVAF, the guidelines recommend the use of anticoagulants, especially DOACs, as standard therapy[18, 19]. Similarly, anticoagulants are recommended as antithrombotic therapy for patients with stable CAD or PAD complicated by NVAF[20-22]. However, there is no clear statement in these guidelines regarding the decision to continue or discontinue APT when anticoagulation therapy for NVAF is indicated in patients already receiving APT. This is considered to be one of the major reasons why combination treatment was often implemented in this study.

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The American College of Cardiology Expert Consensus Decision Pathway[23] is a report of optimal clinical practice and complements existing guidelines. It provides practical solutions for patients with stable CAD, ischemic stroke, or PAD who are undergoing APT and are newly diagnosed with AF. When oral anticoagulants are indicated as a result of risk assessment and after reassessing the original and current indication(s) for APT, the best management option is to discontinue APT and implement oral anticoagulant therapy alone (DOAC therapy is preferred) in most patients who have passed the stage at which APT is necessary[23]. The results of the present study support this statement. Of the patients in this EXPAND subanalysis who had already been treated with APT upon the initiation of rivaroxaban, most continued APT after starting rivaroxaban. In such situations, the decision of whether patients should continue APT should be based on current evidence and guidelines.

The results of this subanalysis of the EXPAND study may have been influenced by changes in platelet function associated with the administration of rivaroxaban. Alterations in platelet function via the inhibition of thrombin production are considered a common effect of DOACs, and the American College of Cardiology Expert Consensus Decision Pathway describes the use of DOACs in several clinical situations without distinguishing between DOAC drugs[23]. As rivaroxaban is known to directly inhibit factor Xa and thrombin via protease-activated receptor-1[24], it is unclear whether the results observed with rivaroxaban are common to other DOACs.

Limitations

The present subanalysis of the EXPAND study has some limitations that should be noted. First, the STROKE subcohort likely included patients with cerebral embolism, as no detailed information was available to identify and exclude cerebral embolism among patients with ischemic stroke. For this reason, the risk of the 2 efficacy outcomes that included stroke (stroke + SE and stroke + SE + MI + CV death) may have differed if patients with cerebral embolism, to whom APT was not normally administered, were excluded. The proportion of patients with cerebral embolism in the STROKE subcohort was estimated to be 25%. This inference was based on the EXPAND study data showing that 16% of the STROKE subcohort had TIA, whereas cerebral embolism accounted for 30% of cases of acute ischemic cerebral infarction, excluding TIA, according to a large Japanese stroke database[25]. Second, the sample size of this study was relatively small. A study with a sample size of approximately 10,000 patients would be needed to detect a group difference in the HR of 1.2 for an event with an incidence of 3%. Therefore, future large-sample studies are required to clarify our findings. Third, there were some differences in baseline clinical characteristics between the APT(+) and APT(–) groups. However, comparing populations with different background characteristics using statistical adjustments is common practice in observational studies. Therefore, in the future, double-blinded randomized controlled trials will be required to determine whether APT simply does not add any benefit to DOAC therapy or whether APT is actually harmful, as it could increase the risk of bleeding when used in combination with DOAC therapy. Fourth, information on the time elapsed since the onset of acute coronary disease or acute treatment (e.g., percutaneous coronary intervention) was not collected in the EXPAND dataset; thus, these factors were not considered when selecting patients with stable CAD. Fifth, exact details, such as the dosage of APT in the APT(+) group, could not be described because these data were not included in the EXPAND dataset. Finally, only Japanese patients were included in the EXPAND study, which may limit the generalizability of our findings to other populations.

Conclusion

The use of concomitant APT with rivaroxaban (10 or 15 mg/day) was not associated with a reduction in the occurrence of ischemic outcomes in patients with stable CAD, ischemic stroke, or PAD in this subanalysis of data obtained from the EXPAND study. However, the concomitant use of APT was associated with an increased occurrence of bleeding outcomes in patients with stable CAD and ischemic stroke.

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Conflict of Interest

All authors received funding support from Bayer Yakuhin Ltd. throughout the implementation of the EXPAND study, including reporting of this

subanalysis. Other disclosures are as follows: K.K. received honoraria from Bayer Yakuhin Ltd., Daiichi-Sankyo Co. Ltd., Novartis Pharma AG., Otsuka Pharmaceutical Co. Ltd., Bristol-Myers Squibb K.K., and Kowa Pharmaceutical Co. Ltd.; H.I. received honoraria from Daiichi-Sankyo Co. Ltd.; T.K. received honoraria from Daiichi-Sankyo Co. Ltd., and scholarship grants from Takeda Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., Nippon Boehringer Ingelheim Co. Ltd., Otsuka Pharmaceutical Co. Ltd., Daiichi-Sankyo Co. Ltd., Torii Pharmaceutical Co. Ltd., and AbbVie GK; T.Y. received honoraria from Daiichi-Sankyo Co. Ltd., Bayer Yakuhin Ltd., Bristol-Myers Squibb K.K., Novartis Pharma K.K., Otsuka Pharmaceutical Co. Ltd., and Nippon Boehringer Ingelheim Co. Ltd., fees for promotional materials from Daiichi-Sankyo Co. Ltd., and clinical research funding from Daiichi-Sankyo Co. Ltd.; W.S. received honoraria from Daiichi-Sankyo Co. Ltd., Nippon Boehringer Ingelheim Co. Ltd., Bayer Yakuhin Ltd., Pfizer Co. Ltd., Bristol-Myers Squibb K.K., Johnson & Johnson K.K., Boston Scientific Japan K.K., Medtronic Japan Co. Ltd., Janssen Pharmaceutical K.K., Japan Lifeline Co. Ltd., and Abbott Japan LLC; T.I. received honoraria from Bayer Yakuhin Ltd., and Daiichi-Sankyo Co. Ltd.

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Contributor Statements

All authors contributed substantially to the conceptualization, methodology, investigation, steering, and publication planning of the EXPAND study. K.K. devised the conceptualization and methodology and drafted the original manuscript. All authors critically reviewed and edited the manuscript and approved the final version.

Data Statement

The data from this EXPAND study subanalysis cannot be shared, as data from the original EXPAND study have not yet been shared.

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