Anticoagulant and Antiplatelet Therapy in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention

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Funding:
This study was supported by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan.

Disclosures: None of the authors have potential conflicts of interest.

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Abstract

The prevalence, intensity, safety, and efficacy of oral anticoagulation (OAC) in addition to dual antiplatelet therapy (DAPT) in "real world" atrial fibrillation (AF) patients undergoing percutaneous coronary intervention (PCI) have not yet been fully evaluated. In the CREDO-Kyoto registry cohort-2, 1057 AF patients (8.3%) were identified among 12716 patients undergoing first PCI. Cumulative 5-year incidence of stroke was higher in AF patients than in no-AF patients (12.8% versus 5.8%, P<0.0001). Although the majority of AF patients had $CHADS_2$ score ≥2 (75.2%), only 506 patients (47.9%) received OAC with warfarin at hospital discharge. Cumulative 5-year incidence of stroke in the OAC group was not different from that in the no-OAC group (13.8% versus 11.8%, P=0.49). Time in therapeutic range (TTR) was only 52.6% with an international normalized ratio (INR) of 1.6-2.6 and only 154 (37.7%) out of 409 patients with INR data had TTR ≥65%. Cumulative 5-year incidence of stroke in patients with TTR ≥65% was markedly lower than that in patients with TTR <65% (6.9% versus 15.1%, P=0.01). In a 4-month landmark analysis in the OAC group, there was a trend for higher cumulative incidences of stroke and major bleeding in the on-DAPT (N=286) than in the off-DAPT (N=173) groups (15.1% versus 6.7%, P=0.052 and 14.7% versus 8.7%, P=0.10, respectively). In conclusion, OAC was underused and its intensity was mostly suboptimal in "real world" AF patients undergoing PCI, which lead to inadequate stroke prevention. Long-term DAPT in patients receiving OAC did not reduce stroke incidence.

Key words: anticoagulation; atrial fibrillation; dual antiplatelet therapy; percutaneous coronary intervention

Introduction

It has been reported that 5-10% of patients undergoing percutaneous coronary intervention (PCI) have concomitant atrial fibrillation (AF).[1] Most of those patients have an indication for oral anticoagulation (OAC) to prevent stroke or systemic thromboembolism, and also for antiplatelet therapy (APT) to prevent ischemic cardiac events, particularly stent thrombosis (ST). Drug-eluting stents (DES) has become widely used, and dual APT (DAPT) with aspirin plus thienopyridine for 12 months or more is recommended after DES implantation.[1] Thus, AF patients undergoing PCI often have an indication for long-term use of OAC plus DAPT, though a great concern of bleeding complications has been raised for such a "triple" antithrombotic therapy.[2-7] However, the prevalence and intensity as well as the safety and efficacy of OAC in combination with DAPT in "real world" AF patients undergoing PCI have not yet been fully evaluated. For patients receiving triple therapy in the real world clinical practice, OAC could be less intensive due to a concern on bleeding complications. It is unknown, however, whether the less intensive OAC in patients receiving concomitant DAPT is effective in preventing stroke. Also unknown is the effect of DAPT on long-term cardiovascular outcomes in patients receiving concomitant OAC. Consequently, we investigated the practice pattern and outcome regarding OAC- and DAPT-use among AF patients in a large observational PCI database in Japan with 4-7 years of follow-up.

Methods

The CREDO-Kyoto (Coronary REvascularization Demonstrating Outcome Study in Kyoto) Registry Cohort-2 is a physician-initiated, non-company-sponsored, multicenter registry enrolling consecutive patients undergoing first coronary revascularization among 26 centers in Japan between January 2005 and December 2007. The relevant review boards or ethics committees in all 26 participating centers (Supplementary Appendix A) approved the research protocol.

A total of 15939 patients undergoing first coronary revascularization were enrolled in the registry. We excluded 99 patients who refused study participation, 2782 who underwent coronary artery bypass grafting, and 342 who died during the index hospitalization. Thus, the current study population consisted of 12716 patients undergoing first PCI who were alive at hospital discharge. (Figure 1).

Recommended antiplatelet regimen for PCI-stenting was aspirin (≥81mg daily) indefinitely and thienopyridine (200 mg

ticlopidine or 75 mg clopidogrel daily) for at least 3 months. Choices regarding duration of DAPT and administration of warfarin in AF patients were left to the discretion of each attending physician. Persistent discontinuation of the antithrombotic drugs was defined as withdrawal lasting for at least 2 months. Withdrawal of DAPT was defined as persistent discontinuation of either aspirin or thienopyridine.

We defined AF patients as those with a preexisting diagnosis of AF and those who developed new onset AF during their index hospitalization. The primary outcome measure was stroke including both ischemic and hemorrhagic strokes. Stroke was defined as an acute onset of a focal neurologic deficit of presumed vascular origin requiring hospitalization with symptoms lasting >24 hours or resulting in death. The types of strokes were distinguished by imaging studies to be either hemorrhagic or ischemic. Cerebral bleeding that occurred secondary to ischemic stroke was not regarded as hemorrhagic stroke.

The secondary outcome measures were all-cause death, myocardial infarction (MI), ST, and major bleeding. ST was defined as Academic Research Consortium (ARC) definite ST.[8] Major bleeding was defined as moderate or severe bleeding by Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) classification.[9]

Demographic, angiographic, and procedural data were collected from hospital charts or hospital databases according to prespecified definitions by experienced clinical research coordinators from the study management center (Research Institute for Production Development, Kyoto, Japan) (Supplementary Appendix B). Follow-up data were obtained from hospital charts or by contacting patients or physicians in charge. All the primary and secondary endpoints were adjudicated by the independent clinical event committee (Supplementary Appendix C).

Data for international normalized ratio (INR) during follow-up in AF patients receiving OAC were collected from the hospital charts of the centers where the index PCI was performed. Time in therapeutic range (TTR) in the OAC group was calculated by the Rosendaal method,[10] according to a therapeutic INR range of 1.6 to 2.6, which is recommended for elderly (≥70 years) patients in the Japanese guidelines.[11] Since the stroke event may affect the intensity of subsequent OAC, TTR in patients with such event during follow-up was calculated only using INR data before or at the time of the stroke.

Data are presented as values and percentages, mean value ± SD or median with first quartile to third quartile [Q1-Q3]. Categorical variables were compared with the χ^2 test or the Fisher exact test. Continuous variables were compared using the

Student *t* test or Wilcoxon rank sum test based on their distributions. Cumulative incidence was estimated by the Kaplan-Meier method and differences were assessed with the log-rank test.

We used the Cox proportional hazard model to adjust for the differences in baseline patient characteristics, procedural factors, medications, and center. The unadjusted and adjusted risk for clinical event was expressed as a hazard ratio (HR) with its 95% confidence interval (CI). The detailed methods of the multivariable analyses are described in Supplementary Methods.

The landmark analysis based on DAPT-use at 4-month after the index PCI was conducted as described previously.[12] Eligible patients for the landmark analysis were those who were alive and free from stroke, MI, ST and major bleeding at the 4-month landmark point. Taking a 1-month window period, the 4-month landmark point was selected because DAPT for at least 3-month had been recommended after implantation of sirolimus-eluting stent, which was the most commonly used DES in this study population.

All analyses were conducted by two physicians (Goto K and Nakai K) and a statistician (Morimoto T) with the use of SAS 9.2 and JMP 7.0 (SAS Institute Inc, Cary, NC). All the statistical analyses were 2-tailed, and probability values <0.05 were considered statistically significant.

Results

Among the entire 12716 study patients, 1057 patients (8.3%) had AF. Baseline characteristics of the entire study population comparing AF and no-AF patients are shown in Supplementary Table 1. During the median follow up of 5.1 (Q1-Q3: 4.3–5.9) years, a total of 2065 patients died and 800 patients had strokes. Cumulative 5-year incidence of stroke was significantly higher in AF patients than in no-AF patients (12.8% and 5.8%, $P<0.0001$) (Figure 2A). After adjusting confounders, the excess risk of AF patients relative to no-AF patients for stroke remained significant (Table 2).

Among 1057 AF patients, although a large number of patients had a $CHADS_2$ score ≥ 2, only 506 patients (47.9%) received OAC with warfarin (Table 1).

Patients receiving OAC at hospital discharge as compared with no-OAC patients had higher prevalence of persistent or permanent AF, although the distributions of the $CHADS_2$ score were similar between the 2 groups (Table 1 and Supplementary Figure 1). The vast majority of OAC patients received concomitant DAPT, even though DAPT was less prevalent in OAC

patients than in no-OAC patients.

After 5 years, OAC was discontinued in 22.7% of patients in the OAC group, while OAC was started in 31.6% of patients in the no-OAC group (Supplementary Figure 2). Cumulative 5-year incidence of stroke was high and not significantly different between the OAC and no-OAC groups (13.8% and 11.8%, P = 0.49) (Figure 2B). Even after adjustment of baseline differences, the effect of OAC for stroke remained insignificant. Cumulative incidence of major bleeding also showed no difference between the OAC and no-OAC groups. Cumulative incidence of MI as well as ST was significantly lower in the OAC group than in the no-OAC group (Table 2).

TTR during follow-up was available in 409 patients (80.8%) in the OAC group, excluding 66 patients with no INR data and 31 patients with only one INR data (Figure 1). The median of available INR data per patient was 17 (Q1-Q3; 6-35), and median interval of INR measurements was 49 (Q1-Q3; 30-90) days.

With a therapeutic INR range of 2.0 to 3.0, the average TTR was only 24.2%, and most of the time (72.4%) was spent below the therapeutic INR range. Only 22 patients (5.4%) had TTR ≥65%. Even with a therapeutic INR range of 1.6 to 2.6, the average TTR was 52.6%, and only 154 patients (37.7%) had TTR ≥65% (Figure 3A, 3B).

Baseline characteristics including the $CHADS_2$ score were similar between the 2 groups of patients with TTR ≥65% (N=154) and TTR <65% (N=255) with the INR range of 1.6 to 2.6 (Supplementary Table 2). Cumulative 5-year incidence of stroke was significantly lower in patients with TTR ≥65% than in those with TTR <65% (6.9% and 15.1%, P=0.01) (Figure 2C). After adjusting confounders, TTR ≥65% remained to be significantly associated with lower risk of stroke (Table 2). Among 68 patients in the OAC group who had stroke during follow up, INR data within 30 days before or at the time of the stroke were available in 27 patients. Ischemic stroke occurred mostly in patients with latest INR values of <1.6 (Figure 3C).

During follow-up, DAPT was maintained more frequently in the OAC group than in the no-OAC group (Supplementary Figure 3). At 4-month, DAPT was maintained in 286 (62.3%) out of 459 OAC patients eligible for the landmark analysis. The on-DAPT patients at 4-month more often had multivessel coronary artery disease and DES-use as compared with the off-DAPT patients (Supplementary Table 3). The average TTR was significantly lower in on-DAPT than in off-DAPT patients (49.2% versus 59.1%, P=0.002). Cumulative incidences of stroke and major bleeding including hemorrhagic stroke tended to be higher in

on-DAPT than in off-DAPT patients (Figure 4). There were no differences in the cumulative incidences of MI and ST regardless of DAPT use at 4-month (Supplementary Table 4).

Discussion

The main findings of the present study were as follows: (1) In "real world" AF patients undergoing PCI, OAC was underused, and its intensity was mostly suboptimal; (2) OAC at hospital discharge was not associated with lower stroke incidence presumably due to its low intensity overall; (3) Optimal as compared to suboptimal OAC was associated with markedly lower stroke incidence; (4) Prolonged DAPT in addition to OAC did not reduce stroke risk.

To date, there have been no randomized controlled trials assessing the efficacy and safety of OAC in AF patients receiving DAPT. The present study evaluated the "real world" practice pattern and long-term outcomes of anticoagulant and antiplatelet therapy in over 1000 AF patients undergoing PCI from a large observational database. The median follow-up duration of 5.1-year was the longest among the studies and detailed APT and OAC data during follow up were available including INR values. Although Lamberts et al. recently reported results of a nationwide cohort study in Denmark including approximately twelve thousands AF patients hospitalized with MI or for PCI,[5,6] the duration of follow-up was short (mean; 288 days) and detailed data regarding APT and OAC during follow up were not available. The present study showed that optimization of OAC is crucial for stroke prevention in AF patients even in the setting of post-PCI with mandatory DAPT. On the other hand, no clinical benefit but possible harm of prolonged DAPT beyond 4-month after PCI was suggested.

Despite three-forth of AF patients having a $CHADS_2$ score ≥2, OAC was used only in 47.9% of patients in this study, which is consistent with previous reports. Among previous observational studies that included patients undergoing PCI with an indication for OAC, the prevalence of OAC ranged from 9-85% with an average of 51%.[2, 4-7, 13] Thus, in "real world" AF patients undergoing PCI, OAC is underused presumably due to physicians' concern for bleeding complications. Most previous studies, indeed, showed high hemorrhagic risk for triple therapy,[2-7] up to 6 times higher than no-triple therapy.[2]

OAC with dose-adjusted warfarin as compared to either placebo, aspirin, or DAPT was associated with marked risk reduction for stroke in randomized controlled trials.[14,15] Furthermore, several previous observational studies in the PCI setting also showed better cardiovascular outcomes, despite excess in bleeding events, in patients receiving OAC than in patients not receiving

OAC.[4-7,16] In the present study, however, OAC at hospital discharge was not associated with lower risk for stroke. The main reason for the lack of efficacy for OAC in preventing stroke could be the low intensity of OAC observed in the present study. Only 37.7% of patients had TTR ≥65% even when the therapeutic INR range was set at lower range of 1.6 to 2.6. Patients with TTR ≥65% actually had a markedly lower risk for stroke than patients with TTR <65%.

There is insufficient data regarding the intensity of OAC in AF patients undergoing PCI. Only two observational studies have addressed this issue to date, although TTR data were not available. Rossini et al. prospectively evaluated 102 patients targeting INR in the range of 2.0-2.5, and INR at 30-day post PCI was within the target range in 81 patients (79.4%). Patients with an INR above the target range was associated with extremely high bleeding events as compared to those with an INR within the target range (33% versus 4.9%, P<0.0001).[3] Also, Gao et al. prospectively evaluated 267 AF patients receiving OAC, and 1457 (72%) out of 2023 measured INR values were within the target range of 1.8-2.5. INR values at the time of major bleeding were above the target range in all cases.[4] Presumably due to the prospective design, the INR control in these two studies was excellent. However, in "real world" AF patients undergoing PCI, OAC may be less intensive than that observed in prospective studies or randomized controlled trials. In the non-PCI AF population, TTR in the retrospective studies range from 29-75% with an average of 53% in contrast to that in the randomized controlled trials, ranging from 44-73% with an average of 67%.[17] In the real world PCI population with mandatory DAPT at hospital discharge, the intensity of OAC could be further shifting to lower INR control due to physicians' concern for bleeding complications, as shown in our study. Conversely, however, the current study strongly suggests that the optimization of OAC would be crucial for stroke prevention in AF patients undergoing PCI.

In the present study, DAPT was maintained beyond 4-month in a significant proportion of AF patients with OAC. In the 4-month landmark analysis, OAC was less intensive in on-DAPT than in off-DAPT patients, leading to a trend toward higher incidence of stroke in on-DAPT patients. Also, on-DAPT patients tended to have higher risk of major bleeding compared with off-DAPT patients. Furthermore, there was no difference in the risk of MI or ST between the two groups. Recent several randomized controlled trials and observational studies enrolling patients mostly without AF suggested that prolonged DAPT after PCI, compared to short-term, did not demonstrate better cardiovascular outcomes including ST, but was associated with excess bleeding events.[18-20] Considering the increased risk of major bleeding in the setting of triple therapy, duration of DAPT should be

as short as possible. To reduce stroke risk, we should focus more on optimizing OAC rather than prolonging DAPT. The What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing (WOEST) study demonstrated that triple therapy (OAC plus DAPT) as compared with double therapy (OAC plus clopidogrel) was associated with significantly higher rates of bleeding events without any improvement of cardiovascular outcomes.[21] Double therapy with OAC plus a thienopyridine may be an attractive alternative to triple therapy. The recent report by Lamberts et al. also supports this therapeutic concept.[6]

There are several important limitations in this study. First, due to the observational study design, we could not deny the influence of selection bias and unmeasured confounders regarding the effect of OAC on stroke reduction. Second, stroke was not adjudicated by neurologists in routine. Third, we did not have INR data for all patients with OAC, and the number and interval of INR measurements varied widely among patients. Forth, there was substantial cross-over between the OAC and no-OAC groups during follow-up, although the degree of cross-over was relatively low as compared to recent OAC studies.[15,22] Fifth, there may be some difference in the intensity of OAC for AF patients in a real clinical practice between Asian and Western countries. Asians have been reported to be associated with 4 times higher risk of intracranial hemorrhage than Caucasians under OAC with warfarin.[23] Also, Japanese elderly patients are known to have high risk of major bleeding at the INR level of >2.6,[24,25] which lead to the recommendation of low intensity INR control (1.6-2.6) for elderly patients in the Japanese guidelines.[11] Indeed, Asian physicians prefer low intensity INR control regardless of patient's age even in the setting of randomized controlled trials.[26,27] Finally, TTR cut-off level of 65% according to the INR range of 1.6-2.6 was not pre-specified. However, the results were consistent even when the TTR cut-off level was set at either 60% or 70% (Supplementary Figure 4).

Disclosures

None of the authors have potential conflicts of interest.

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Figure legends

Figure 1

Study flow chart.

CABG=coronary artery bypass grafting, M=months.

Figure 2

Cumulative incidence of stroke comparing (A) AF versus no-AF patients, (B) OAC versus no-OAC at hospital discharge in AF patients, and (C) TTR≥65% versus TTR<65% in the OAC patients.

Figure 3

(A) Percentages of time spent below, within, and above the therapeutic INR range in the OAC group.

(B) Distributions of TTR in the OAC group.

(C) Latest INR value within 30 days before or at the time of stroke in the OAC group.

Figure 4

Cumulative incidence of (A) stroke and (B) major bleeding in the OAC patients based on DAPT use at the 4-month landmark point.

Table 1. Baseline characteristics of AF patients comparing those with and without OAC at hospital discharge

	AF patients (N=1057)	OAC group (N=506)	No-OAC group (N=551)	P value
Age (years)	72.5±9.3	72.0±8.8	73.0±9.7	0.04
Age ≥75 years	477 (45.1%)	212 (41.9%)	265 (48.1%)	0.04
Male	752 (71.1%)	383 (75.7%)	369 (67.0%)	0.002
AF type				
Paroxysmal	652 (61.7%)	247 (48.8%)	405 (73.5%)	<0.0001
Persistent / Permanent	302 (28.6%)	207 (40.9%)	95 (17.2%)	
Unknown	103 (9.7%)	52 (10.3%)	51 (9.3%)	
Body mass index < 25.0 kg/m^2	766 (72.5%)	356 (70.4%)	410 (74.4%)	0.14
Acute myocardial infarction	392 (37.1%)	168 (33.2%)	224 (40.7%)	0.01
Hypertension	902 (85.3%)	435 (86.0%)	467 (84.8%)	0.58
Diabetes mellitus	362 (34.2%)	177 (35.0%)	185 (33.6%)	0.63
On insulin therapy	60 (5.7%)	25 (4.9%)	35 (6.4%)	0.32
Current smoker	237 (22.4%)	118 (23.3%)	119 (21.6%)	0.50
Heart failure	417 (39.5%)	201 (39.7%)	216 (39.2%)	0.86
Shock at presentation	98 (9.3%)	39 (7.7%)	59 (10.7%)	0.09
Multivessel coronary artery disease	529 (50.0%)	238 (47.0%)	291 (52.8%)	0.06
Ejection fraction	55.4±14.1	54.4±14.4	56.4±13.8	0.04
Mitral regurgitation grade 3/4	109 (10.3%)	53 (13.8%)	56 (15.2%)	0.59
Prior myocardial infarction	128 (12.1%)	62 (12.3%)	66 (12.0%)	0.89
Prior stroke	196 (18.5%)	96 (19.0%)	100 (18.2%)	0.73
Prior intracranial bleeding	27 (2.6%)	7 (1.4%)	20 (3.6%)	0.02
Peripheral vascular disease	87 (8.2%)	53 (10.5%)	34 (6.2%)	0.01

eGFR<30, not on dialysis	59 (5.6%)	28 (5.5%)	31 (5.6%)	0.95
Dialysis	48 (4.5%)	19 (3.8%)	29 (5.3%)	0.24
Anemia (Hb <11.0 g/dl)	153 (14.5%)	56 (11.1%)	97 (17.6%)	0.002
Platelet $<100\times10^9/L^3$	30 (2.8%)	13 (2.6%)	17 (3.1%)	0.61
Chronic obstructive pulmonary disease	43 (4.1%)	20 (4.0%)	23 (4.2%)	0.86
Liver cirrhosis	30 (2.8%)	17 (3.4%)	13 (2.4%)	0.33
Malignancy	108 (10.2%)	47 (9.3%)	61 (11.1%)	0.34
$CHADS_2$ score	2.4±1.3	2.4±1.2	2.4±1.3	0.85
$CHADS_2$ score ≥2	795 (75.2%)	389 (76.9%)	406 (73.7%)	0.23
CHA_2DS_2-VASc score	4.5±1.5	4.5±1.5	4.6±1.6	0.29
Stent use	959 (90.7%)	447 (88.3%)	512 (92.9%)	0.01
DES use	506 (47.9%)	264 (52.2%)	242 (43.9%)	0.007
Aspirin	1037 (98.1%)	495 (97.8%)	542 (98.4%)	0.52
Thienopyridine	1005 (95.1%)	473 (93.5%)	532 (96.6%)	0.02
DAPT	989 (93.6%)	465 (91.9%)	524 (95.1%)	0.03
Warfarin	506 (47.9%)	506 (100%)	0 (0%)	—
Statins	430 (40.7%)	210 (41.5%)	220 (39.9%)	0.60
Beta-blockers	403 (38.1%)	221 (43.7%)	182 (33.0%)	0.0004
ACE-I/ARB	646 (61.1%)	328 (64.8%)	318 (57.7%)	0.02
Proton pump inhibitors	310 (29.3%)	132 (26.1%)	178 (32.3%)	0.03

ACE-I=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, DES=drug-eluting stent, DAPT=dual antiplatelet therapy, and eGFR=estimated glomerular filtration rate.

Table 2. Unadjusted and adjusted clinical outcomes during follow-up

	No. of Events (5-year cumulative incidence)		*P Value*	Unadjusted HR (95%CI)	Adjusted HR (95%CI)	*P Value*
(A) AF versus No-AF	***AF (N=1057)***	***No-AF (N=11659)***				
Stroke*	134 (12.8%)	666 (5.8%)	<0.0001	2.47 (2.05-2.97)	2.00 (1.65-2.43)	<0.0001
Ischemic or unspecified†	113 (10.9%)	515 (4.4%)	<0.0001	2.68 (2.19-3.29)	2.16 (1.74-2.67)	<0.0001
Hemorrhagic	23 (2.4%)	164 (1.5%)	0.02	1.69 (1.09-2.61)	1.40 (0.89-2.21)	0.15
All-caused death	312 (27.6%)	1753 (13.9%)	<0.0001	2.18 (1.93-2.46)	1.43 (1.26-1.62)	<0.0001
Major bleeding	166 (16.7%)	1200 (10.2%)	<0.0001	1.66 (1.41-1.95)	1.22 (1.03-1.44)	0.02
Myocardial infarction	61 (6.5%)	559 (4.7%)	0.0497	1.30 (1.00-1.70)	1.22 (0.93-1.61)	0.15
Stent thrombosis‡	18 (1.7%)	185 (1.6%)	0.62	1.13(0.70-1.83)	1.17 (0.71-1.93)	0.53
(B) OAC versus No-OAC	***OAC (N=506)***	***No-OAC (N=551)***				
Stroke*	68 (13.8%)	66 (11.8%)	0.49	1.13 (0.80-1.58)	1.20 (0.83-1.73)	0.34
Ischemic	57 (11.5%)	56 (10.3%)	0.59	1.11 (0.77-1.60)	1.22 (0.82-1.83)	0.33
Hemorrhagic	13 (3.2%)	10(1.6%)	0.42	1.41 (0.62-3.21)	2.68 (0.78-9.24)	0.12
All-caused death	142 (25.5%)	170 (29.4%)	0.35	0.90 (0.72-1.12)	0.93 (0.72-1.19)	0.56
Major bleeding	74 (16.2%)	92 (17.1%)	0.29	0.85 (0.63-1.15)	0.81 (0.58-1.13)	0.21
Myocardial infarction	17 (4.5%)	44 (8.5%)	0.001	0.40 (0.23-0.71)	0.39 (0.21-0.74)	0.004
Stent thrombosis‡	4 (1.0%)	14 (2.5%)	0.03	0.31 (0.10-0.93)	0.14 (0.03-0.82)	0.03
(C) TTR ≥65% versus <65%	***TTR ≥65% (N=154)***	***TTR <65% (N=255)***				
Stroke*	11 (6.9%)	36 (15.1%)	0.01	0.44 (0.22-0.87)	0.37 (0.16-0.86)	0.02
Ischemic	8 (4.9%)	30 (12.6%)	0.01	0.38 (0.18-0.84)	0.30 (0.11-0.81)	0.02
Hemorrhagic	4 (3.1%)	7 (3.4%)	0.85	0.89 (0.26-3.02)	—**	—
All-caused death	31 (17.8%)	74 (25.9%)	0.02	0.62 (0.41-0.94)	0.86 (0.51-1.43)	0.56
Major bleeding	17(10.4%)	44(19.6%)	0.06	0.59(0.34-1.04)	0.50 (0.25-1.01)	0.053
Myocardial infarction	4 (3.1%)	10 (5.0%)	0.41	0.62 (0.19-1.97)	—**	—
Stent thrombosis‡	1 (0.9%)	3 (1.3%)	0.57	0.53 (0.06-5.09)	—**	—

AF=atrial fibrillation, CI=confidence interval, HR=hazard ratio, OAC=oral anticoagulation, and TTR=time in therapeutic range.

* The sum of the numbers of ischemic (or unspecified) and hemorrhagic stroke events is not necessarily equal to the number of overall stroke events because of patients with multiple events.

† Only 8 out of 800 strokes (1.0%) were unspecified because of lack of imaging information, all of which were in no-AF patients.

‡Academic Research Consortium definite. ** Not available because of small number of events.

Figure 1

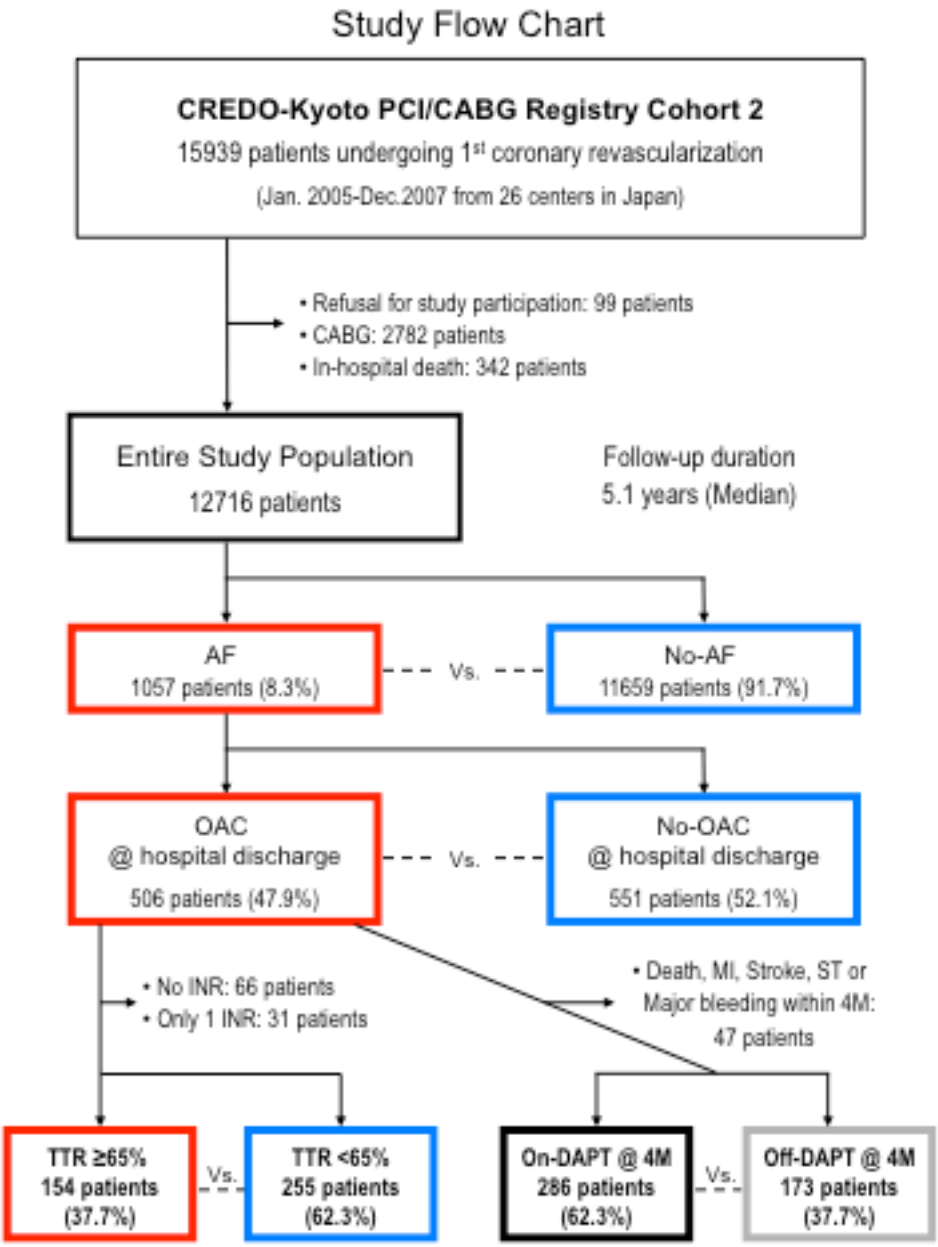
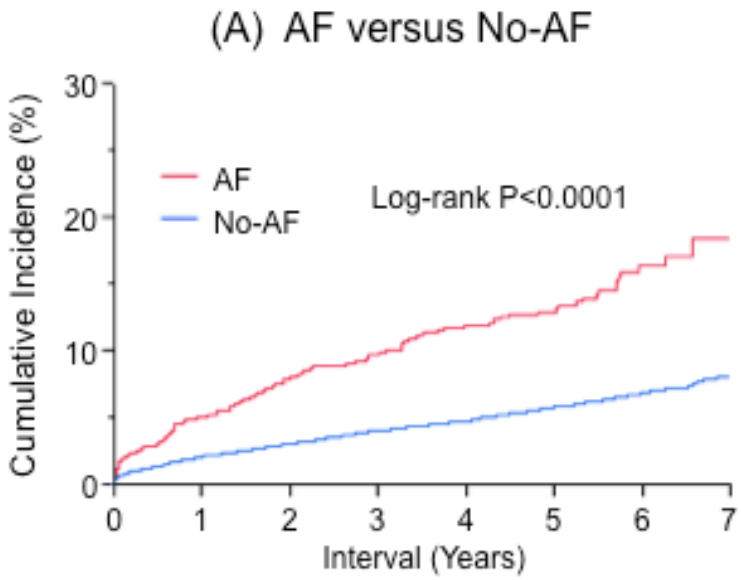
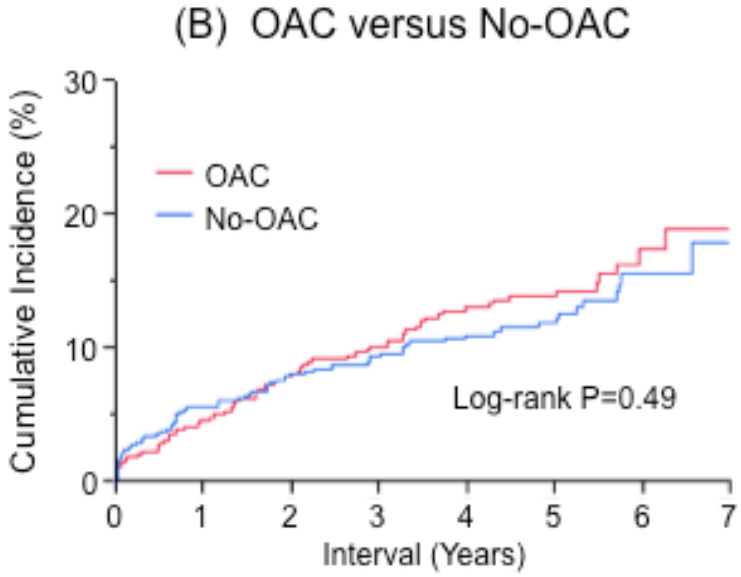

Study Flow Chart
CREDO-Kyoto PCI/CABG Registry Cohort 2
15939 patients undergoing 1st coronary revascularization
(Jan. 2005-Dec.2007 from 26 centers in Japan)
• Refusal for study participation: 99 patients
• CABG: 2782 patients
• In-hospital death: 342 patients
Entire Study Population
12716 patients
Follow-up duration
5.1 years (Median)
AF
1057 patients (8.3%)
Vs.
No-AF
11659 patients (91.7%)
OAC
@ hospital discharge
506 patients (47.9%)
Vs.
No-OAC
@ hospital discharge
551 patients (52.1%)
• No INR: 66 patients
• Only 1 INR: 31 patients
• Death, MI, Stroke, ST or
Major bleeding within 4M:
47 patients
TTR ≥65%
154 patients
(37.7%)
Vs.
TTR <65%
255 patients
(62.3%)
On-DAPT @ 4M
286 patients
(62.3%)
Vs.
Off-DAPT @ 4M
173 patients
(37.7%)

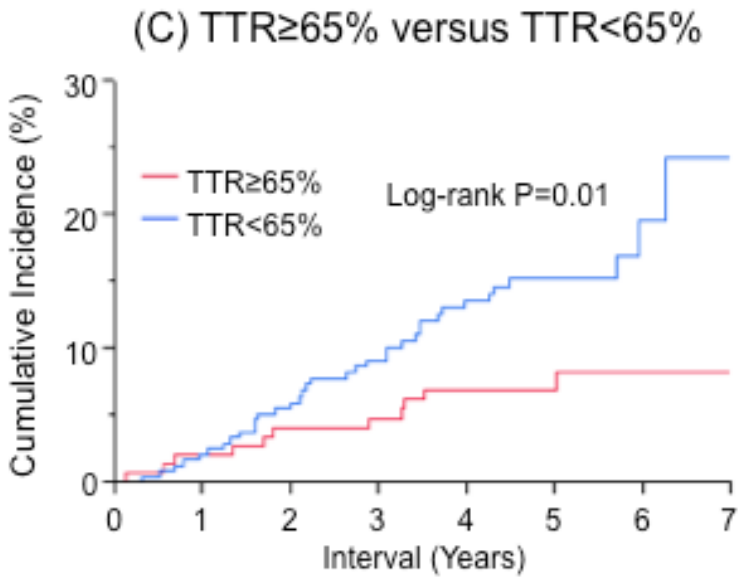
Figure 2



Interval	0 day	1 year	2 years	3 years	4 years	5 years	6 years	7 years
AF group								
N of patients with events		52	79	95	114	120	132	134
N of patients at risk	1057	935	855	784	717	454	171	18
Cumulative incidence		5.0%	7.9%	9.7%	11.9%	12.8%	16.3%	18.3%
No-AF group								
N of patients with events		237	342	445	518	603	651	666
N of patients at risk	11659	10929	10469	9976	9421	6127	2625	244
Cumulative incidence		2.1%	3.0%	4.0%	4.7%	5.8%	6.9%	8.0%

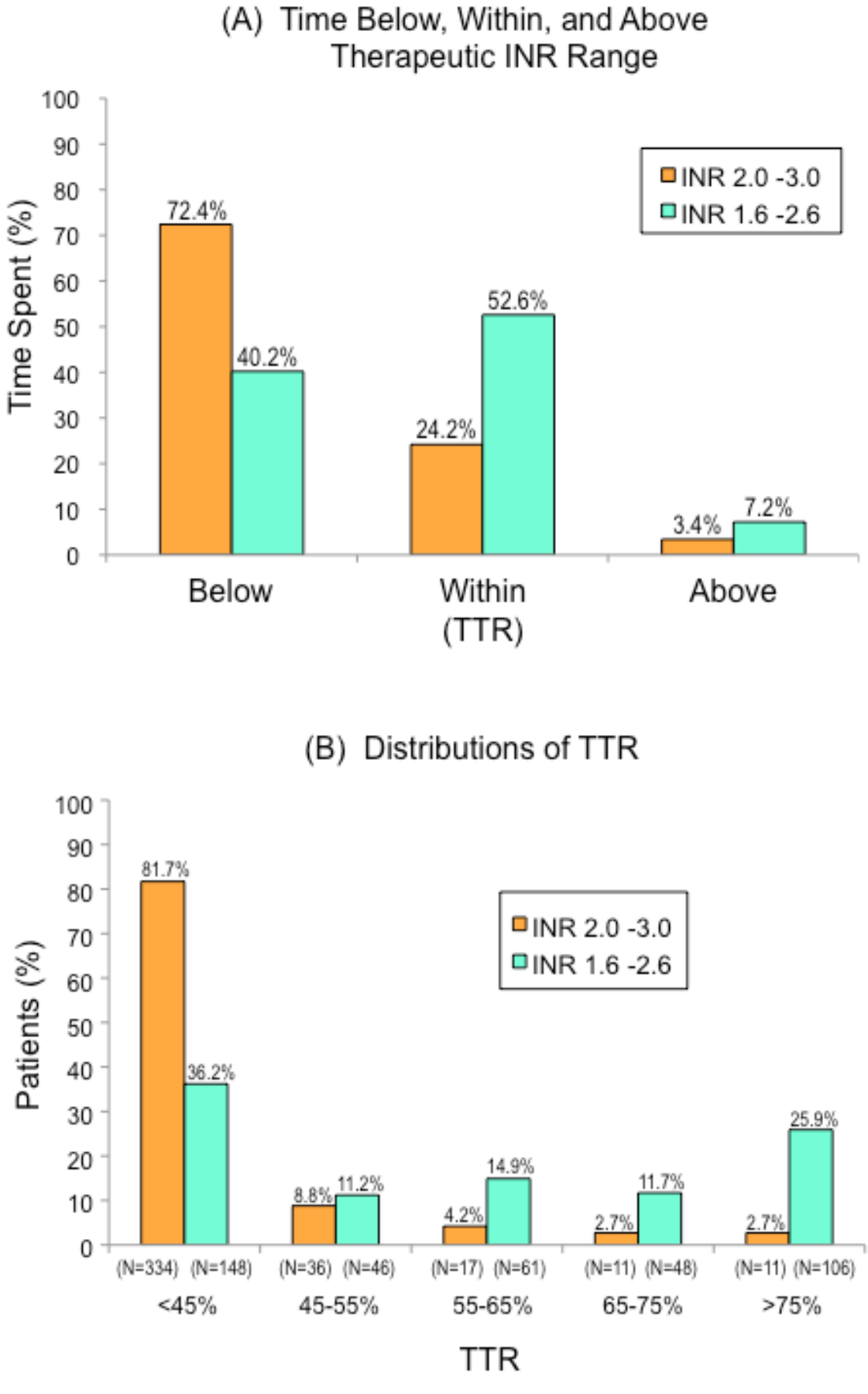


Interval	0 day	1 year	2 years	3 years	4 years	5 years	6 years	7 years
OAC group								
N of patients with events		22	37	47	59	62	67	68
N of patients at risk	506	449	412	379	346	217	78	9
Cumulative incidence		4.5%	7.8%	10.1%	13.0%	13.8%	17.3%	18.8%
No-OAC group								
N of patients with events		30	42	48	55	58	65	66
N of patients at risk	551	487	444	406	374	239	94	10
Cumulative incidence		5.5%	8.0%	9.3%	10.9%	11.8%	15.4%	17.8%



Interval	0 day	1 year	2 years	3 years	4 years	5 years	6 years	7 years
TTR≥65% group								
N of patients with events		3	6	7	10	10	11	11
N of patients at risk	154	149	140	134	125	81	38	3
Cumulative incidence		2.0%	4.0%	4.7%	6.9%	6.9%	8.1%	8.1%
TTR<65% group								
N of patients with events		5	13	21	30	33	35	36
N of patients at risk	255	236	214	194	173	104	30	3
Cumulative incidence		2.0%	5.5%	9.1%	13.4%	15.1%	19.5%	24.2%

Figure 3


(A) Time Below, Within, and Above Therapeutic INR Range
Time Spent (%)
100
90
80
70
60
50
40
30
20
10
0
INR 2.0 -3.0
INR 1.6 -2.6
72.4%
40.2%
24.2%
52.6%
3.4%
7.2%
Below
Within (TTR)
Above
(B) Distributions of TTR
Patients (%)
81.7%
36.2%
8.8%
11.2%
4.2%
14.9%
2.7%
11.7%
2.7%
25.9%
(N=334) (N=148)
(N=36) (N=46)
(N=17) (N=61)
(N=11) (N=48)
(N=11) (N=106)
<45%
45-55%
55-65%
65-75%
>75%
TTR

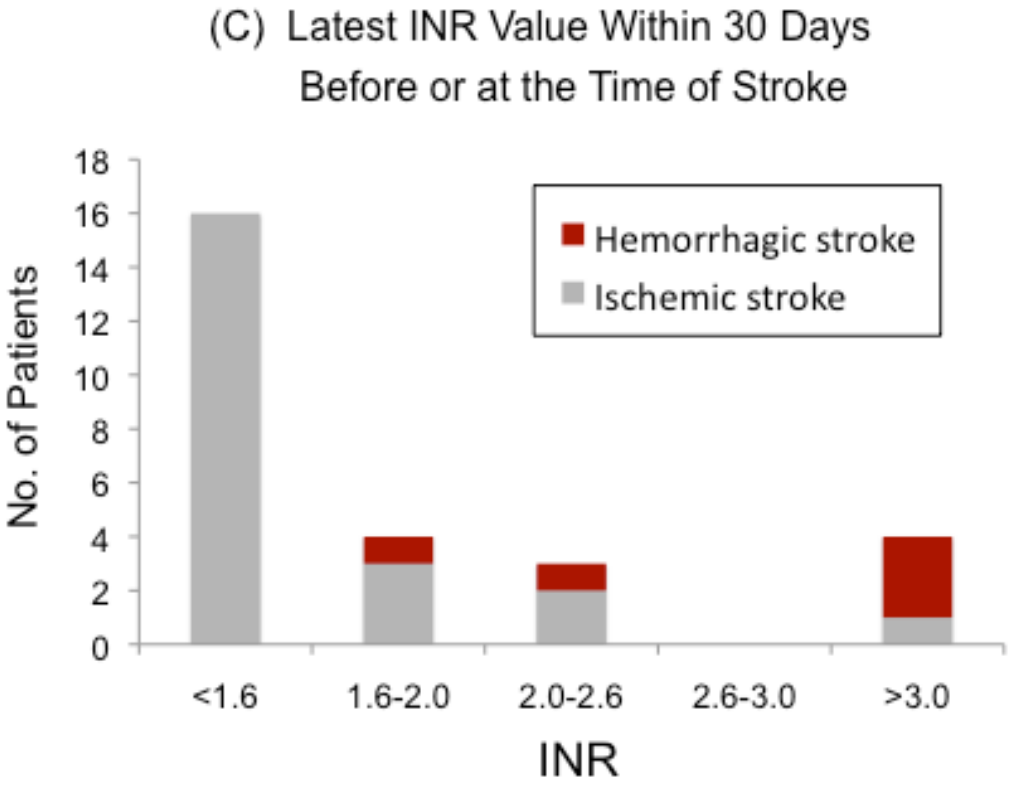
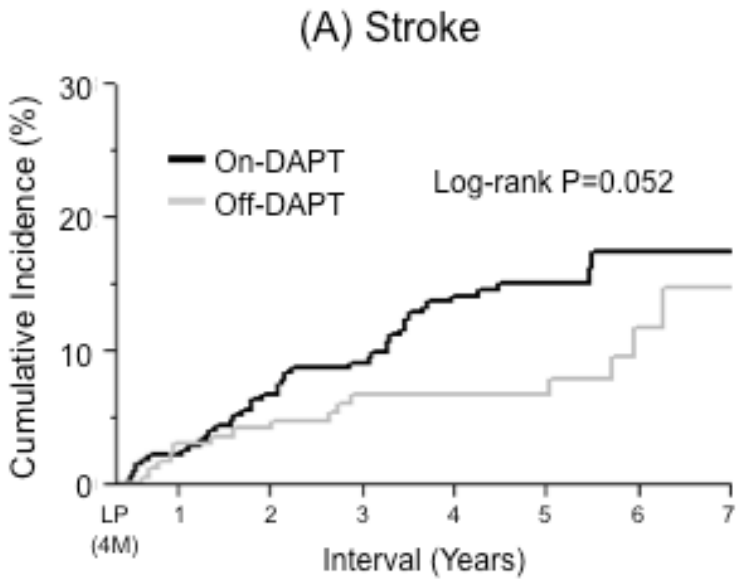
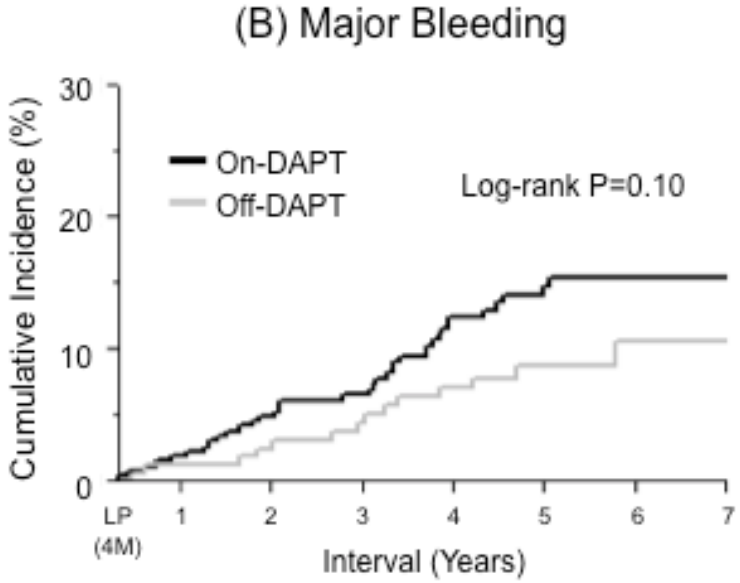

(C) Latest INR Value Within 30 Days
Before or at the Time of Stroke
No. of Patients
18
16
14
12
10
8
6
4
2
0
Hemorrhagic stroke
Ischemic stroke
<1.6
1.6-2.0
2.0-2.6
2.6-3.0
>3.0
INR

Figure 4



Interval	4 months	1 year	2 years	3 years	4 years	5 years	6 years	7 years
On-DAPT group								
N of patients with events		6	18	24	36	38	40	40
N of patients at risk	286	265	243	223	202	126	36	4
Cumulative incidence		2.2%	6.7%	9.1%	14.1%	15.1%	17.4%	17.4%
Off-DAPT group								
N of patients with events		5	7	11	11	11	14	15
N of patients at risk	173	166	155	143	131	85	41	6
Cumulative incidence		2.9%	4.1%	6.7%	6.7%	6.7%	11.7%	14.7%



Interval	4 months	1 year	2 years	3 years	4 years	5 years	6 years	7 years
On-DAPT group								
N of patients with events		5	13	17	31	35	36	36
N of patients at risk	286	264	247	227	201	123	38	4
Cumulative incidence		1.8%	4.9%	6.4%	12.4%	14.7%	15.4%	15.4%
Off-DAPT group								
N of patients with events		2	4	7	11	13	14	14
N of patients at risk	173	169	159	148	134	84	40	6
Cumulative incidence		1.2%	2.4%	4.3%	7.0%	8.7%	10.6%	10.6%