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An Open-Label Randomized Trial Comparing Oral Anticoagulation with and without Single Antiplatelet Therapy in Patients with Atrial Fibrillation and Stable Coronary Artery Disease Beyond One Year after Coronary Stent Implantation: The OAC-ALONE Study

Running Title: *Matsumura-Nakano et al.; Oral Anticoagulation Alone for AF and Stable CAD*

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Abstract

Background: Despite recommendations in the guidelines and consensus documents, there has been no randomized controlled trial evaluating oral anticoagulation (OAC) alone without antiplatelet therapy (APT) in patients with atrial fibrillation (AF) and stable coronary artery disease (CAD) beyond 1 year after coronary stenting.

Methods: This study was a prospective, multicenter, open-label, non-inferiority trial, comparing OAC alone to combined OAC and single APT among AF patients beyond 1 year after stenting in a 1:1 randomization fashion. The primary endpoint was a composite of all-cause death, myocardial infarction (MI), stroke, or systemic embolism. The major secondary endpoint was a composite of primary endpoint or major bleeding according to the International Society on Thrombosis and Haemostasis (ISTH) classification. Although the trial was designed to enroll 2,000 patients during 12 months, enrollment was prematurely terminated after enrolling 696 patients in 38 months.

Results: Mean age was 75.0±7.6 years, and 85.2% of patients were men. OAC was warfarin in 75.2% and direct oral anticoagulants in 24.8% of patients. The mean $CHADS_2$ score was 2.5±1.2. During a median follow-up interval of 2.5 years, the primary endpoint occurred in 54 patients (15.7%) in the OAC alone group and in 47 patients (13.6%) in the combined OAC and APT group (HR, 1.16; 95% confidence interval [CI], 0.79-1.72; P=0.20 for non-inferiority; P=0.45 for superiority). The major secondary endpoint occurred in 67 patients (19.5%) in the OAC alone group and in 67 patients (19.4%) in the combined OAC and APT group (HR, 0.99; 95% CI, 0.71-1.39; P=0.016 for non-inferiority; P=0.96 for superiority). MI occurred in 8 (2.3%) and 4 (1.2%) patients, while stroke or systemic embolism occurred in 13 (3.8%) and 19 (5.5%) patients, respectively. Major bleeding occurred in 27 (7.8%) and 36 (10.4%) patients, respectively.

Conclusions: This randomized trial did not establish non-inferiority of OAC alone to combined OAC and APT in patients with AF and stable CAD beyond 1 year after stenting. Because patient enrollment was prematurely terminated, the study was underpowered and inconclusive. Future larger studies are required to establish the optimal antithrombotic regimen in this population.

Clinical Trial Registration: URL: http://www.clinicaltrials.gov. Unique identifier: NCT01962545.

Key Words: atrial fibrillation; coronary artery disease; oral anticoagulation; percutaneous coronary intervention

Clinical Perspective

What is new?

- In patients with atrial fibrillation (AF) and stable coronary artery disease (CAD) beyond 1 year after coronary stenting, the optimal antithrombotic regimen remains uncertain although some guidelines recommend oral anticoagulation (OAC) alone.
- The present study is the first randomized trial comparing OAC alone and combination of OAC and single antiplatelet therapy (APT).
- The trial failed to establish non-inferiority of OAC alone compared to a regimen of OAC and single APT, because patient enrollment was prematurely terminated, leading to an underpowered sample size.

What are the clinical implications?

- Large, adequately powered, randomized trials are needed to determine the optimal antithrombotic regimen in this population.

Introduction

There remain unsettled issues on the antithrombotic therapy in patients with concomitant atrial fibrillation (AF) and stable coronary artery disease (CAD), who underwent percutaneous coronary intervention (PCI) with stents. Antiplatelet therapy (APT) is regarded as an essential treatment in preventing thrombotic events including stent thrombosis in patients with CAD,[1-3] while oral anticoagulation (OAC) is superior to APT in preventing thromboembolic events, ischemic stroke in particular, in patients with AF.[4,5] Several recent clinical trials in AF patients undergoing PCI-stenting have demonstrated that dual therapy with OAC and platelet $P2Y_{12}$ receptor inhibitor was associated with lower risk for bleeding without increasing thrombotic events compared to triple therapy with OAC and dual APT (DAPT) up to 1 year after coronary stenting.[6-8] Beyond 1 year after coronary stenting, the European Society of Cardiology (ESC) guidelines have consistently recommended lifelong OAC without APT in patients with AF.[9-12] The North American expert consensus documents also recommend OAC alone for patients with low thrombotic and high bleeding risk.[13,14] However, despite the guidelines' recommendation and several supportive observational studies,[15-17] there has been no randomized controlled trial evaluating the efficacy and safety of OAC monotherapy in patients with AF and stable CAD. In routine clinical practice, antiplatelet agents are often used in combination with OAC in this setting,[18,19] although the combination is associated with higher bleeding risk.[20-22] Accordingly, we conducted a randomized trial comparing OAC alone to a combination of OAC and APT in patients with concomitant AF and stable CAD beyond 1 year after coronary stenting.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design

The OAC-ALONE (Optimizing Antithrombotic Care in patients with AtriaL fibrillatiON and coronary stEnt) study was a prospective, multicenter, randomized, open-label, non-inferiority trial, comparing OAC alone with combined OAC and single APT in patients with concomitant AF and stable CAD, who had received coronary stents more than 1 year ago. We enrolled patients who were treated with a combination of an oral anticoagulant, and a single antiplatelet agent. Detailed inclusion and exclusion criteria are described in the online-only Data Supplement Appendix A.

Patients were randomly assigned in a 1:1 ratio to the OAC alone group or to the combined OAC and APT group, stratified by center. Randomization was performed centrally through an electronic data capture (EDC) system with a stochastic minimization algorithm to balance treatment assignments. Study-group assignments were blinded to the statistician, members of the independent clinical event committee, steering committee, and the sponsor (Daiichi Sankyo). The sponsor was involved in study protocol design, but not in the study conduct, data collection, statistical analysis, and writing of the manuscript. Complete lists of the study organization, participating centers and investigators are available in the online-only Data Supplement Appendix B and C. The study protocol was approved by the institutional review board at each participating center. Written informed consent was obtained from all patients.

Antithrombotic Therapy

OAC could be either warfarin or direct oral anticoagulants (DOACs). The recommended target international normalized ratio (INR) range for dose adjustment of warfarin was 2.0-3.0 in patients <70 years of age, and 1.6-2.6 in patients ≥70 years of age based on Japanese guidelines.[23] INR measurements were recommended at least every 3 months. Patients receiving warfarin were eligible for the trial, only if INR at the time of enrollment was ≥1.6. The approved

standard or reduced doses of DOACs for AF were dabigatran 150 or 110 mg twice daily, rivaroxaban 15 or 10 mg once daily, apixaban 5 or 2.5 mg twice daily, and edoxaban 60 or 30 mg once daily. We recommended dose reduction of DOACs based on the formal criteria for each DOAC, although we allowed dose reduction of DOACs at the discretion of patient or physician. Only aspirin (81-324 mg/day) or clopidogrel (75 mg/day) was allowed as an antiplatelet agent at the time of enrollment.

Follow-up and Endpoints

All study patients were followed until 1 year after the last patient enrollment. Follow-up was obtained from hospital charts, or by contacting patients or referring physicians. The study secretariat conducted monitoring through the electronic database, and inconsistencies were resolved by queries to the site investigators.

The primary endpoint was a composite of all-cause death, myocardial infarction (MI), stroke, or systemic embolism. The major secondary endpoint was a composite of primary endpoint or major bleeding according to the International Society on Thrombosis and Haemostasis (ISTH) classification.[24] Other secondary endpoints included the individual components of primary endpoint, cardiovascular death, stent thrombosis, major bleeding, and hospitalization for heart failure. Major bleeding was defined according to ISTH criteria, but bleeding events according to the Thrombolysis in Myocardial Infarction (TIMI) classification were also assessed.[25] In a post hoc analysis, we assessed ischemic endpoint defined as a composite of cardiovascular death, MI, ischemic stroke, or systemic embolism, and also assessed ischemic or bleeding endpoint defined as a composite of ischemic endpoint or major bleeding. Cardiovascular death, MI, and stent thrombosis were defined according to the Academic Research Consortium (ARC) definitions.[26] Only ARC definite stent thrombosis was adjudicated as stent thrombosis. Stroke was defined as the acute onset of a focal neurologic deficit of

presumed vascular origin lasting ≥24 hours. Strokes were categorized as either hemorrhagic or ischemic on the basis of brain imaging studies. Cerebral bleeding that occurred secondary to ischemic stroke was not regarded as hemorrhagic stroke. All clinical events comprising the primary and secondary endpoints were blindly adjudicated by an independent clinical event committee. Detailed definitions of the endpoints are described in the online-only Data Supplement Appendix D.

Sample Size Calculation

The study was a non-inferiority trial powered for non-inferiority of OAC alone to combined OAC and APT in terms of the primary endpoint. We expected patient enrollment to last 1 year, with an anticipated average follow-up period of 1.5-year. In the CREDO-Kyoto PCI/CABG registry cohort-2,[27] the cumulative incidence of death, MI, or stroke between 1- and 2.5-year (during 1.5-year period) after PCI-stenting was 12.1% in AF patients with <75 years of age and receiving warfarin. Considering the possibility of lower-risk patients being enrolled in the study, we assumed an event rate of 8.0% (2/3 of 12.1%) during an average follow-up of 1.5-year. Non-inferiority margin was set as 4.0%, half of the assumed true event rate. Thus, a total of 1,934 patients were expected to yield 90% power to detect non-inferiority at a level of 1-sided type 1 error of 0.025. Given potential drop outs during follow-up, a total of 2,000 patients were planned to be enrolled. However, due to slow patient enrollment, the trial was extended, and finally, following the approval of the data and safety monitoring board, the steering committee prematurely terminated patient enrollment on December 31, 2016, after enrolling 696 patients in 38 months. Final follow-up was collected between October 1, 2017 and May 18, 2018. Because the extended trial duration resulted in longer follow-up interval, the anticipated event rate was assumed to be higher than originally planned. Therefore, the protocol and the trial registration were amended to set a non-inferiority margin as 1.5 on the hazard ratio (HR) scale for the

primary and major secondary endpoints on September 4, 2017, which corresponded to the original non-inferiority margin of 4.0% for 8.0% (50% of the expected event rate).

Statistical Analysis

Categorical variables are expressed as number and percentage, and compared using the chi-square test or Fisher exact test as appropriate. Continuous variables are expressed as mean ± standard deviation or median with interquartile range (IQR), and compared using the Student t-test or Wilcoxon rank sum test based on their distributions. Time in therapeutic range (TTR) during follow-up was calculated by the Rosendaal method.[28]

Clinical outcomes were analyzed according to the intention-to-treat principle. Each endpoint as well as crossover and changes of antithrombotic regimen was assessed by the Kaplan-Meier method and compared by a log-rank test. Effect of treatment was compared by the Cox proportional hazard model and expressed as a HR with a 95% confidence interval (CI). Proportional hazard assumptions were assessed on the plots of log(time) vs. log [−log(survival)], and were verified as acceptable. The statistical significance of possible heterogeneity in the treatment effect across several prespecified subgroups was assessed with interaction terms in the Cox proportional hazard models.

All statistical analyses were performed by a physician (Y. Matsumura-Nakano) and a statistician (T. Morimoto) with the use of JMP version 12.0 and SAS version 9.4 (SAS Institute, Cary, North Carolina). All reported P values were 2-sided, and P values of <0.05 were regarded as statistically significant except for non-inferiority testing in which one-sided P values of <0.025 were considered statistically significant.

Results

Study Population

From November 5, 2013 to December 28, 2016, a total of 696 patients from 111 centers were enrolled. Excluding 6 patients who withdrew consent, 690 patients were included in the current analysis; 344 patients in the OAC alone group, and 346 patients in the combined OAC and APT group (Figure 1). After randomization, we identified, but did not exclude 14 patients who did not meet the inclusion criteria (protocol violation); 6 patients who had a history of balloon angioplasty only without stenting, 2 patients who received PCI within 12 months, 4 patients treated with OAC and DAPT, 1 patient treated with OAC alone, and 1 patient receiving warfarin with INR of <1.6.

The study population included large proportions of patients with advanced age (mean age of 75.0 years), diabetes mellitus, heart failure, and prior MI. Types of AF were paroxysmal in 43.6%, persistent in 7.2%, and permanent in 49.1% of patients. The mean $CHADS_2$ and CHA_2DS_2-VASc scores were 2.5±1.2 and 4.6±1.4, respectively. The proportion of patients with HAS-BLED score ≥3 was 44.2%. Median interval from the last PCI to study enrollment was 4.5 (IQR: 2.1-7.6) years, and drug-eluting stent (DES) was used in 71.2% of patients. OAC was warfarin in 75.2% and DOACs in 24.8% of patients. APT was aspirin in 85.9% and clopidogrel in 14.5% of patients. The baseline characteristics and medications were well balanced between the 2 groups except for the higher prevalence of renal insufficiency without hemodialysis (P=0.01) and lower prescription rate of proton pump inhibitors (P=0.02) in the OAC alone group (Table 1).

Antithrombotic Therapy During Follow-up

Complete clinical follow-up was achieved in 680 patients (98.6%) with a median follow-up interval of 2.5 (IQR: 1.8-3.4) years (Figure 1). The final follow-up data were obtained from hospital charts in 597 patients (87.8%), from referring physicians in 63 patients (9.3%), and by contacting patients in 20 patients (2.9%). During follow-up, changes in antithrombotic regimen

except for the types and doses of OAC occurred in 63 patients (18.3%) in the OAC alone group and in 67 patients (19.4%) in the combined OAC and APT group (Figure I in the online-only Data Supplement). Crossover to the alternative regimen occurred in 42 patients (12.2%) in the OAC alone group mainly due to progression of CAD (PCI procedures in the majority) during follow-up (N=30, 71.4%), and in 31 patients (9.0%) in the combined OAC and APT group mainly due to bleeding events (N=15, 48.4%) and physicians' discretion or patients' request concerning bleeding (N=11, 35.5%) (Figure 2 and Table I in the online-only Data Supplement). Warfarin was changed to DOACs in 44 patients (17.3%) in the OAC alone group, and in 43 patients (16.3%) in the combined OAC and APT group. DOACs were changed to warfarin in 2 patients (2.2%) in the OAC alone group, and in 2 patients (2.4%) in the combined OAC and APT group.

TTR was available in 486 (93.6%) out of 519 patients who were initially treated with warfarin. The median of available INR data per patients was 14 (IQR: 8-21). With the predefined therapeutic INR range according to the Japanese guidelines (2.0-3.0 for those <70 years and 1.6-2.6 for those ≥70 years), mean TTR was 75.6% in the OAC alone group and 73.1% in the combined OAC and APT group (P=0.38) (Figure 3A). Using a post hoc therapeutic INR range of 2.0-3.0 regardless of age, mean TTR was 54.9% in the OAC alone group and 47.9% in the combined OAC and APT group (P=0.004). (Figure 3B). Most of the time out of the therapeutic INR range was spent below the INR range.

Clinical Outcomes

The primary endpoint occurred in 54 patients (15.7%) in the OAC alone group, and in 47 patients (13.6%) in the combined OAC and APT group. Non-inferiority of OAC alone to combined OAC and APT was not met for the primary endpoint (HR, 1.16; 95% CI, 0.79-1.72; P=0.20 for non-inferiority; P=0.45 for superiority) (Figure 4A, and Table 2). The major

secondary endpoint occurred in 67 patients (19.5%) in the OAC alone group, and in 67 patients (19.4%) in the combined OAC and APT group. Non-inferiority of OAC alone to combined OAC and APT was met for the major secondary endpoint (HR, 0.99; 95% CI, 0.71-1.39; P=0.016 for non-inferiority; P=0.96 for superiority) (Figure 4B, and Table 2).

Among the individual secondary endpoints, dominant types of events included hospitalization for heart failure, all-cause death, major bleeding, cardiovascular death, stroke or systemic embolism, and MI with decreasing frequency in order (Table 2). MI occurred in 8 patients (2.3%) in the OAC alone group, and in 4 patients (1.2%) in the combined OAC and APT group, while stroke or systemic embolism occurred in 13 (3.8%) and 19 patients (5.5%), respectively. Stent thrombosis occurred only in 2 patients (0.58%) in the OAC alone group, and MI was a rare cause of death (Table II in the online-only Data Supplement). All MIs occurred in patients treated with warfarin (Table 3). ISTH major bleeding occurred in 27 patients (7.8%) in the OAC alone group, and in 36 patients (10.4%) in the combined OAC and APT group (HR, 0.73; 95% CI, 0.44-1.20; P=0.22) (Table 2 and Table III in the online-only Data Supplement). TIMI major bleeding occurred in 17 (4.9%) and 29 patients (8.4%), respectively (HR, 0.57; 95% CI, 0.31-1.03; P=0.07) (Table 2). In the post hoc analysis, the ischemic endpoint, defined as a composite of cardiovascular death, MI, ischemic stroke, or systemic embolism, occurred in 36 patients (10.5%) in the OAC alone group, and 31 patients (9.0%) in the combined OAC and APT group (HR, 1.17; 95% CI, 0.73-1.91; P=0.32 for non-inferiority; P=0.51 for superiority). The ischemic or bleeding endpoint, defined as a composite of ischemic endpoint or ISTH major bleeding, occurred in 55 patients (16.0%) in the OAC alone group, and in 59 patients (17.1%) in the combined OAC and APT group (HR, 0.92; 95% CI 0.64-1.33; P=0.009 for non-inferiority; P=0.66 for superiority) (Table 2).

For the prespecified subgroups, there was no significant interaction between the various

subgroups for the primary and major secondary endpoints except for prior MI which was driven by the difference in the rate of non-cardiovascular death (Figure 5 and Table IV in the online-only Data Supplement).

Discussion

The present study is the first randomized trial comparing OAC alone to combined OAC and APT in patients with concomitant AF and stable CAD beyond 1 year after coronary stenting. However, patient enrollment was prematurely terminated because of its extremely slow pace, leading to a severely underpowered sample size. As a result, the non-inferiority of OAC alone to combined OAC and APT was not met for the primary composite endpoint of all-cause death, MI, stroke, or systemic embolism, although it was met for the major secondary endpoint (a composite of primary endpoint or major bleeding).

The ESC practice guidelines' recommendation of lifelong OAC without APT in patients with concomitant AF and stable CAD was based on studies from the pre-stent era, demonstrating that warfarin alone was at least as effective as aspirin in reducing cardiovascular events in post MI patients.[9,29,30] Subsequently, a large nationwide Danish registry also supported the guidelines' recommendation, demonstrating that warfarin monotherapy was superior to aspirin in the prevention of coronary events, and warfarin plus APT may not be more protective, but associated with excess bleeding risk, although only 156 out of 950 patients (16.4%) in the warfarin alone group had received coronary stenting.[16] After the introduction of DOACs, the subsequent ESC consensus document and guidelines have recommended lifelong OAC alone with either warfarin or DOACs in AF patients with stable CAD,[10,11] based on the results of the phase III randomized trials comparing warfarin and DOACs in the stroke prevention for non-valvular AF, which showed comparable protective effect for MI between warfarin and DOACs.[31-35] However, in

routine clinical practice, antiplatelet agents are still commonly used in combination with OAC beyond 1 year after coronary stenting,[18,19] mainly due to concern related to risk of stent thrombosis after cessation of APT.[3,36,37] Actually, in the present study, difficulty in patient enrolment mainly stemmed from substantial reluctance of cardiologists to withdraw APT in stented patients due to these concerns. Indeed, as far as we know, there is no ongoing randomized trial focusing on the efficacy and safety of OAC alone in AF patients with coronary stents, despite the recommendations in the guidelines and consensus documents.[9-14]

In the present study, non-inferiority of OAC alone to combined OAC and APT was not established for the primary endpoint because of inadequate statistical power. There was a slight numerical excess of the primary endpoint in the OAC alone group as compared with the combined OAC and APT group (54 versus 47). However, it appeared largely driven by non-cardiovascular death (20 versus 14), which seems unlikely to be causally related to the difference in the antithrombotic regimen (Table IV in the online-only Data Supplement). The incidence of stent thrombosis, the most dreaded stent-related adverse event, was acceptably low in the OAC alone group (0.23%/year),[38-40] and the incidence of MI was also acceptable (0.93%/year).[40,41] Nevertheless, there were numerically fewer MI and stent thromboses in the combined OAC and APT group. Therefore, continuation of single APT on top of OAC beyond 1 year after stenting might be preferable for AF patients with high thrombotic and low bleeding risk. Importantly, however, AF patients post stenting are often elderly and thus, are at high risk of bleeding. The average age of the patient population was 75.0 years in the present study, and 74.2 years in the Danish registry.[16] Indeed, in the present study, the incidence of ISTH major bleeding was more than 5 times higher than that of MI. Even by the more stringent criteria of TIMI classification, the incidence of major bleeding was approximately 4 times higher than that of MI, and MI was fatal in only 1 patient, while the bleeding was fatal in 11 patients. This begs the question of

whether more intensive antithrombotic therapy adding APT on top of OAC could have benefits in preventing thrombotic events surpassing the associated risk of increased bleeding events. In addition, the present study showed the non-inferiority of OAC alone to combined OAC and APT in terms of the major secondary endpoint (primary endpoint or major bleeding) and the post hoc ischemic or bleeding endpoint, suggesting that a combination of OAC and APT did not provide net clinical benefit over OAC alone.

Another important issue on the antithrombotic therapy in patients with concomitant AF and stable CAD after PCI-stenting is the underuse of OAC due to concern on bleeding, because APT is considered mandatory in these patients.[19,27] Indeed, in the Danish registry, 59.3% of patients were treated with APT only without OAC.[16] We should promote the use of anticoagulation in patients with concomitant AF and CAD, because OAC is superior to APT in preventing thromboembolic events in patients with AF.[4,5] Furthermore, intensity of anticoagulation tends to be less stringent in patients receiving both OAC and APT,[27] which was also observed in the present study. Therefore, implementation of OAC monotherapy might lead to better control of anticoagulation, which was reported to be associated with lower risk for thromboembolic events.[42,43]

This trial has several important limitations. First and foremost, the number of enrolled patients was much smaller than originally designed because patient enrollment was prematurely terminated due to slow enrollment. In addition, the non-inferiority margin was redefined during the course of the study to adjust for the extended follow-up period. As a result, the non-inferiority of OAC alone was not met for the primary endpoint due to the inadequate statistical power of the study, and the trial must be considered inconclusive. Second, the non-inferiority margin of 1.5 on the HR scale was very large. Third, there was substantial crossover to the alternative antithrombotic regimen, 12.2% in the OAC alone group and 9.0% in the combined

OAC and APT group, although most of the reasons for the crossover were considered clinically appropriate (Table I in the online-only Data Supplement). Fourth, required follow-up information was partly not prospectively collected in a standardized manner. The final follow-up data were obtained from referring physicians in 63 patients (9.3%) and by contacting patients in 20 patients (2.9%), which might have led to some inaccuracy of those data. Fifth, the open-label trial design presumably affected the intensity of OAC toward more intensive INR control in the OAC alone group as compared with the combined OAC and APT group. Sixth, in the present study, the predefined therapeutic INR range for elderly (≥70 years) patients receiving warfarin was 1.6-2.6 according to the Japanese guidelines, while the global standard INR range is 2.0-3.0 regardless of age. The recommendation of the lower INR control for the elderly patients in the Japanese guidelines is based on the previous reports showing high risk for bleeding, particularly intracranial hemorrhage, in Asian elderly patients.[44,45] Actually, Asian physicians prefer low intensity INR control even in the setting of randomized controlled trials.[46,47] Seventh, the approved standard dose of rivaroxaban in Japan is 15mg daily, while the global approved standard dose is 20mg daily. However, the average body weight of Asian AF patients is approximately 3/4 of that of Caucasian patients,[31,47] leading to comparable blood concentration between Japanese patients taking 15mg of rivaroxaban and Caucasian patients taking 20mg of rivaroxaban.[46] Despite the above differences in the OAC regimen in Japan, the incidence of stroke or systemic embolism as well as the incidence of MI observed in the present study was acceptably low, 1.8%/year and 0.69%/year, respectively. Eighth, only a quarter of patients received DOACs, which have become more frequently used than warfarin.[31-35] Finally, the type of single antiplatelet agent was either aspirin or clopidogrel in the present study, leading to further heterogeneity in the antithrombotic regimen. However, in a previous large-scale randomized trial, aspirin and clopidogrel provided comparable long-term cardiovascular

outcomes in post MI patients.[48]

Conclusions

The present study is the first randomized trial comparing OAC alone versus combined OAC and single APT in patients with AF and stable CAD beyond 1 year after coronary stenting. However, non-inferiority of OAC alone to combined OAC and APT for the composite primary endpoint of all-cause death, MI, stroke, or systemic embolism was not established due to inadequate statistical power. Therefore, the present trial is inconclusive, and warrants future larger studies.

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Table 1. Baseline Characteristics.

Characteristics	OAC alone		Combined OAC and APT	
	(N=344)		(N=346)	
Age, y	74.9±0.4		75.2±0.4	
Age ≥75 y	190	(55.2)	185	(53.5)
Male sex	294	(85.5)	294	(85.0)
Body mass index	24.3±3.4		24.4±3.4	
Hypertension	292	(84.9)	301	(87.0)
Diabetes mellitus	152	(44.2)	138	(39.9)
On insulin therapy	30	(8.7)	26	(7.5)
Dyslipidemia	294	(85.5)	298	(86.1)
Current smoker	27	(7.9)	23	(6.7)
Heart failure	140	(40.7)	151	(43.6)
Ejection fraction ≤40 %	49	(15.2)	60	(18.6)
Prior myocardial infarction	129	(37.5)	137	(39.6)
Prior stroke	55	(16.0)	49	(14.2)
Aortic/Peripheral vascular disease	40	(11.6)	42	(12.1)
eGFR <30 ml/min/1.73m^2, not on hemodialysis	34	(10.0)	17	(4.9)
Hemodialysis	2	(0.6)	2	(0.6)
Anemia (Hemoglobin <11 g/dl)	44	(12.9)	34	(9.9)
Thrombocytopenia (Platelet <10×10^4 /μl)	12	(3.5)	18	(5.2)
Chronic obstructive pulmonary disease	12	(3.5)	14	(4.1)
Chronic liver disease	10	(2.9)	6	(1.7)
Malignancy	53	(15.4)	52	(15.0)
$CHADS_2$ score	2.6±1.2		2.5±1.2	
0	11	(3.2)	9	(2.6)
1	49	(14.2)	59	(17.1)
2	112	(32.6)	118	(34.1)
≥3	172	(50.0)	160	(46.2)
CHA_2DS_2-VASc score	4.6±1.4		4.6±1.4	
0	0	(0.0)	0	(0.0)
1	1	(0.3)	3	(0.9)
2	20	(5.8)	15	(4.3)
≥3	323	(93.9)	328	(94.8)
HAS-BLED score				
0	0	(0.0)	0	(0.0)
1	18	(5.2)	12	(3.5)
2	176	(51.2)	179	(51.7)
≥3	150	(43.6)	155	(44.8)
Type of atrial fibrillation				
Paroxysmal	158	(45.9)	143	(41.3)
Persistent	27	(7.9)	23	(6.7)
Permanent	159	(46.2)	180	(52.0)

Procedural characteristics				
Number of PCI procedures	1 (1-3)		1 (1-2)	
Number of stents	2 (1-3)		2 (1-3)	
Type of stent				
Drug-eluting	246	(71.7)	240	(70.6)
1st generation	80	(23.4)	74	(22.0)
2nd generation	165	(48.3)	163	(48.4)
Bare metal	97	(28.3)	100	(29.4)
Left main coronary stenting	23	(6.7)	22	(6.4)
Multivessel stenting	119	(34.6)	119	(35.0)
Years from the last PCI	4.4 (1.8-7.7)		4.6 (2.4-7.4)	
Medications				
Aspirin	294	(85.5)	299	(86.4)
Clopidogrel	52	(15.1)	48	(13.9)
Warfarin	255	(74.1)	264	(76.3)
INR at enrollment	2.05 (1.81-2.35)		2.02 (1.80-2.27)	
DOACs	89	(25.9)	82	(23.7)
Approved dose	72	(80.9)	68	(82.9)
Standard dose	35	(39.3)	40	(48.8)
Reduced dose	37	(41.6)	28	(34.1)
Non-approved dose	17	(19.1)	14	(17.1)
Over-dose	4	(4.5)	0	(0)
Under-dose	13	(14.6)	14	(17.1)
Dabigatran	21	(23.6)	20	(24.4)
Rivaroxaban	24	(27.0)	17	(20.7)
Apixaban	32	(36.0)	37	(45.1)
Edoxaban	12	(13.5)	8	(9.8)
Statins	268	(77.9)	277	(80.1)
Beta-blockers	219	(63.7)	234	(67.6)
ACE-I/ARB	227	(66.0)	235	(67.9)
NSAIDs	15	(4.4)	16	(4.6)
Proton pump inhibitors	183	(53.2)	216	(62.4)

Categorical variables were presented as number (percentage), and continuous variables were presented as mean ± standard deviation or median with interquartile range. Values were missing for body mass index in 14 patients, ejection fraction in 44 patients, eGFR in 5 patients, anemia in 3 patients, thrombocytopenia in 3 patients, number of PCI procedures in 3 patients, number of stents in 3 patients, type of stent in 1 patient, and type of drug-eluting stent in 5 patients. ACE-I=angiotensin-converting enzyme inhibitor; APT=antiplatelet therapy; ARB=angiotensin receptor blocker; DOACs=direct oral anticoagulants; eGFR=estimated glomerular filtration rate; INR=international normalized ratio; NSAIDs=non-steroidal anti-inflammatory drugs; OAC=oral anticoagulation; PCI=percutaneous coronary intervention.

Table 2. Clinical Outcomes.

Endpoints	OAC alone (N=344) N of patients with event (Crude incidence rate /Annualized event rate, %)		Combined OAC and APT (N=346)		Hazard Ratio (95% CI)	P value for non-inferiority	P value
Primary endpoint:							
A composite of all-cause death, myocardial infarction, stroke, or systemic embolism	54	(15.7/6.4)	47	(13.6/5.5)	1.16 (0.79-1.72)	0.20	0.45
Major secondary endpoint:							
A composite of all-cause death, myocardial infarction, stroke, systemic embolism, or ISTH major bleeding	67	(19.5/8.1)	67	(19.4/8.2)	0.99 (0.71-1.39)	0.016	0.96
Other secondary endpoints:							
All-cause death	40	(11.6/4.6)	31	(9.0/3.5)	1.30 (0.82-2.10)		0.27
Cardiovascular death	20	(5.8/2.3)	17	(4.9/1.9)	1.18 (0.62-2.28)		0.62
Myocardial infarction	8	(2.3/0.93)	4	(1.2/0.46)	2.03 (0.64-7.59)		0.23
Stent thrombosis	2	(0.58/0.23)	0	(0.0/0.0)	NA*		0.15†
Stroke or systemic embolism	13	(3.8/1.5)	19	(5.5/2.2)	0.69 (0.33-1.38)		0.29
Stroke‡	13	(3.8/1.5)	18	(5.2/2.1)	0.73 (0.35-1.47)		0.38
Ischemic stroke	12	(3.5/1.4)	12	(3.5/1.4)	1.01 (0.45-2.27)		0.99
Hemorrhagic stroke	4	(1.2/0.46)	6	(1.7/0.69)	0.66 (0.17-2.32)		0.52
Systemic embolism	1	(0.29/0.11)	2	(0.58/0.23)	0.94 (0.81-1.09)		0.42
ISTH major bleeding	27	(7.8/3.2)	36	(10.4/4.3)	0.73 (0.44-1.20)		0.22
Fatal bleeding	7	(2.0/0.80)	4	(1.2/0.45)	1.77 (0.54-6.77)		0.35
Intracranial bleeding	9	(2.6/1.0)	14	(4.0/1.6)	0.63 (0.26-1.43)		0.27
TIMI major bleeding	17	(4.9/1.9)	29	(8.4/3.4)	0.57 (0.31-1.03)		0.07
minor bleeding	5	(1.5/0.58)	6	(1.7/0.69)	0.84 (0.24-2.78)		0.77
Hospitalization for heart failure	39	(11.3/4.7)	41	(11.8/4.9)	0.96 (0.62-1.49)		0.85
Post hoc endpoints:							

Ischemic endpoint							
A composite of cardiovascular death, myocardial infarction, ischemic stroke, or systemic embolism	36	(10.5/4.2)	31	(9.0/3.6)	1.17 (0.73-1.91)	0.32	0.51
Ischemic or bleeding endpoint							
A composite of cardiovascular death, myocardial infarction, ischemic stroke, systemic embolism, or ISTH major bleeding	55	(16.0/6.7)	59	(17.1/7.2)	0.92 (0.64-1.33)	0.009	0.66

Data were presented as number of patients with event, crude and annualized incidence rates, and hazard ratios with 95% CIs of OAC alone relative to combined OAC and APT for each endpoint by the Cox proportional hazard model. The annualized event rate represented the average number of events per patient during a 1-year period.

* Not available because of no event in the combined OAC and APT group.

† Assessed by the log-rank test. All other P values were assessed by the Cox proportional hazard models.

‡ The sum of the numbers of ischemic and hemorrhagic stroke events was not necessarily equal to the number of overall stroke events because of 3 patients with both ischemic and hemorrhagic stroke in the OAC alone group.

APT=antiplatelet therapy; CI=confidence interval; ISTH=International Society on Thrombosis and Haemostasis; NA=not available; OAC=oral anticoagulation; TIMI= Thrombolysis in Myocardial Infarction.

Table 3. Details of Patients with Myocardial Infarction.

Patient	Age	Gender	Assigned	Years from	At enrollment			Days from	ARC	STEMI	Stent	Fatal	At the time of event		
Number			therapy	the last PCI	OAC	APT	INR	enrollment	Classification		thrombosis		OAC	APT	INR
2	78	Female	OAC alone	13.9	Warfarin		2.40	833	Spontaneous	No	No	No	Warfarin		2.41
50	80	Female	OAC alone	5.9	Warfarin		2.44	35	Spontaneous	NA	No	Yes	Warfarin		3.22
83	74	Male	OAC alone	4.8	Warfarin		1.76	447	Spontaneous	Yes	Yes	No	Warfarin		1.66
163	81	Male	OAC plus APT	6.2	Warfarin	Aspirin	2.17	288	Spontaneous	No	No	No	Warfarin	Aspirin	NA
175	73	Male	OAC plus APT	1.5	Warfarin	Aspirin	2.26	131	Spontaneous	Yes	No	No	Warfarin	Aspirin	1.58
286	77	Male	OAC plus APT	4.5	Warfarin	Aspirin	1.62	403	Spontaneous	No	No	No	Warfarin	Aspirin	2.15
289	85	Male	OAC plus APT	2.9	Warfarin	Aspirin	2.76	389	Spontaneous	No	No	No	Warfarin	Aspirin	2.01
329	80	Male	OAC alone	7.0	Warfarin		1.70	537	Spontaneous	No	No	No	Warfarin		2.87
337	82	Male	OAC alone	2.7	Warfarin		1.67	42	Spontaneous	No	No	No	Warfarin		1.31
349	77	Male	OAC alone	4.5	Warfarin		3.18	372	Spontaneous	No	No	No	Warfarin		2.07
416	81	Male	OAC alone	3.3	Warfarin		1.83	252	Spontaneous	Yes	Yes	No	Warfarin		1.62
547	74	Male	OAC alone	2.3	Warfarin		2.26	679	Spontaneous	No	No	No	Warfarin		2.03

APT=antiplatelet therapy; ARC=Academic Research Consortium; INR=international normalized ratio; NA=not available; OAC=oral anticoagulation; PCI=percutaneous coronary intervention; STEMI=ST-segment elevation myocardial infarction.

Stent thrombosis in the patient No. 83 occurred 6.0 years after implantation of a sirolimus-eluting stent, and stent thrombosis in the patient No. 416 occurred 12.7 years after implantation of a bare-metal stent.

Figure Legends

Figure 1. Study Flow Chart.

Follow-up interval was presented as median with interquartile range.

* Final follow-up data were collected between October 1, 2017 and May 18, 2018.

AF=atrial fibrillation; APT=antiplatelet therapy; OAC=oral anticoagulation.

Figure 2. Cumulative Incidence of Crossover from the Original Regimen.

Crossover indicated changes in antithrombotic regimen from OAC alone to OAC plus APT (single or dual APT), or from OAC plus single APT to OAC alone.

APT=antiplatelet therapy; OAC=oral anticoagulation.

Figure 3. Time in Therapeutic Range in Patients Receiving Warfarin.

(A) Time spent below, within, and above the predefined therapeutic INR range based on the Japanese guidelines, (B) Time spent below, within, and above the post hoc therapeutic INR range of 2.0-3.0, and (C) Time spent in the INR ranges of <1.6, 1.6-2.0, 2.0-2.6, 2.6-3.0, and >3.0.

APT=antiplatelet therapy; INR=international normalized ratio; OAC=oral anticoagulation; TTR=time in therapeutic range.

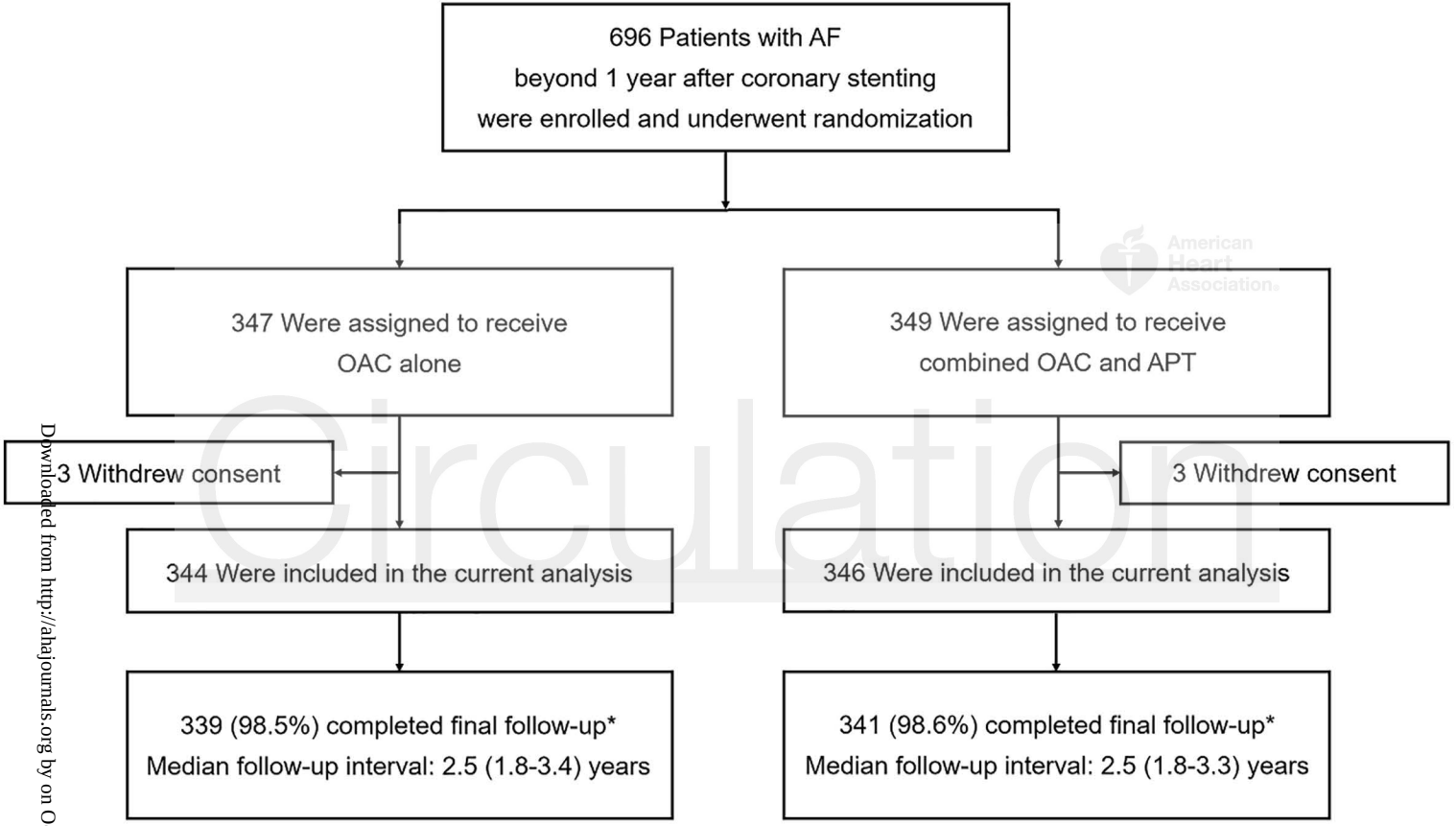
Figure 4. Cumulative Incidence of the Primary and Major Secondary Endpoints. Kaplan-Meier curves showing the cumulative incidence of the (A) Primary endpoint (a composite of all-cause death, myocardial infarction, stroke, or systemic embolism), and (B) Major secondary endpoint (a composite of primary endpoint or major bleeding).

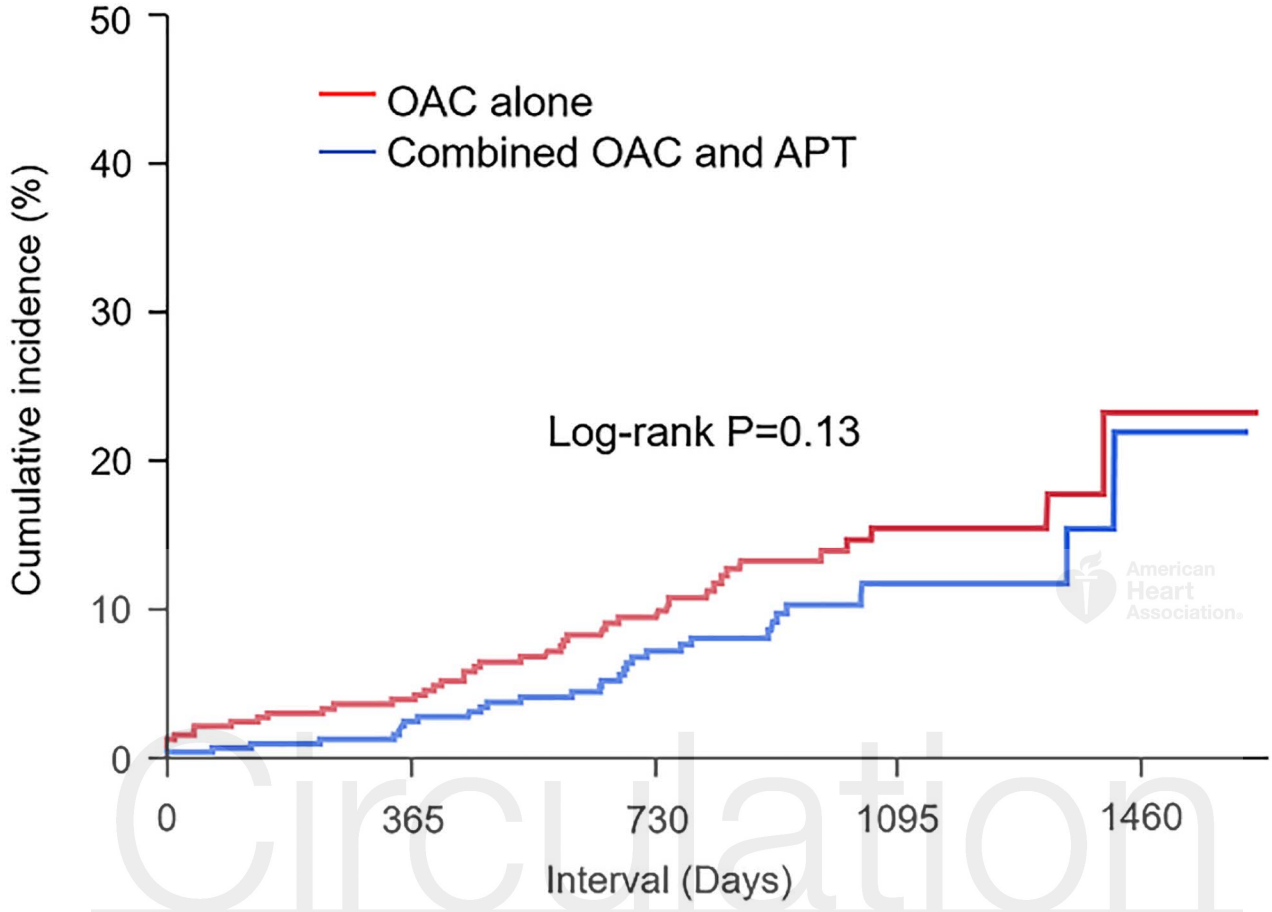
APT=antiplatelet therapy; OAC=oral anticoagulation.

Figure 5. Pre-Specified Subgroup Analyses for the Primary and Major Secondary Endpoints. (A) Primary endpoint (a composite of all-cause death, myocardial infarction, stroke, or systemic embolism), and (B) Major secondary endpoint (a composite of primary endpoint or major bleeding).

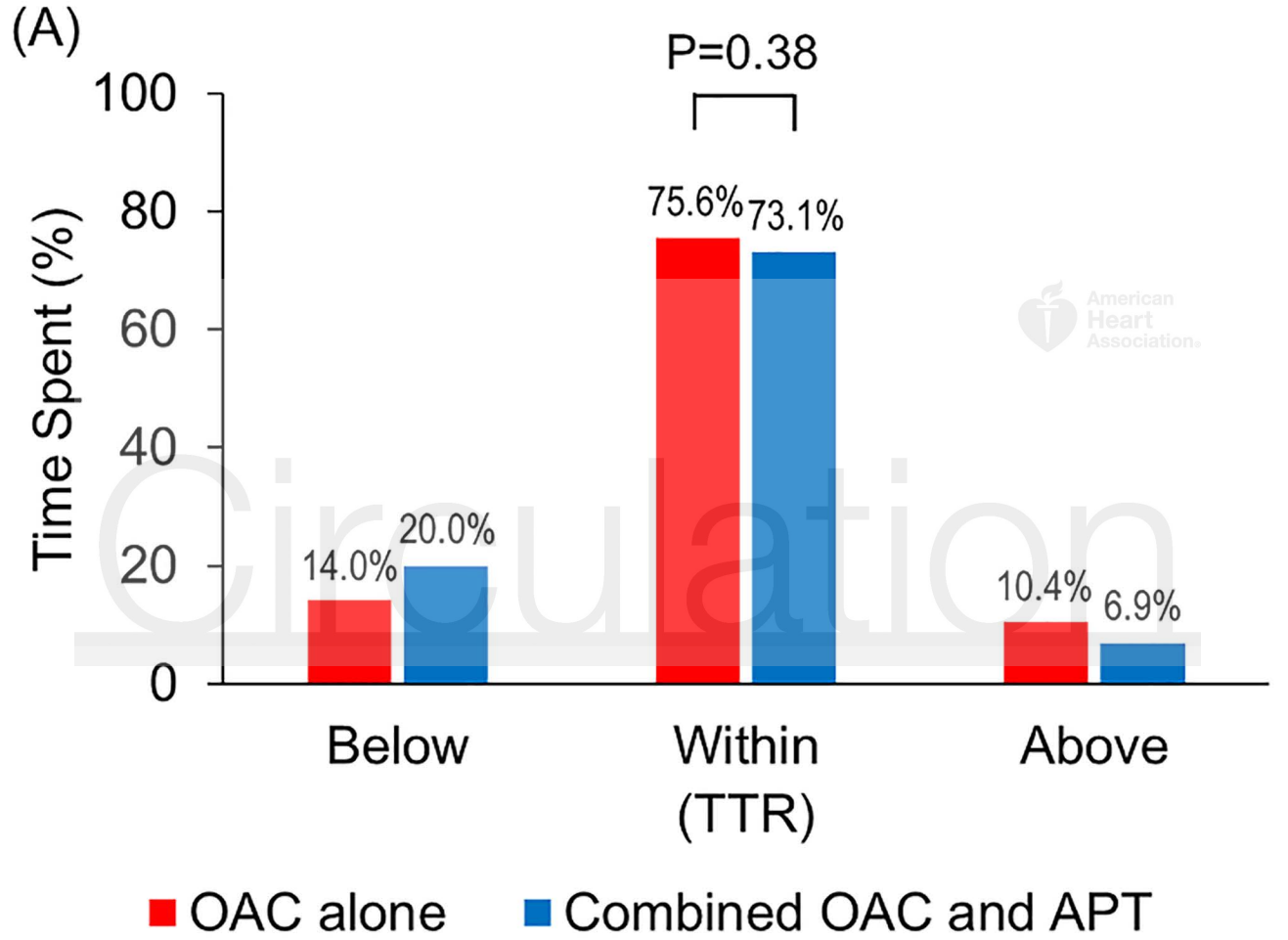
Data were presented as number of patients with event, crude incidence rates, and hazard ratios with 95% CIs of OAC alone relative to combined OAC and APT for the primary and major secondary endpoints.

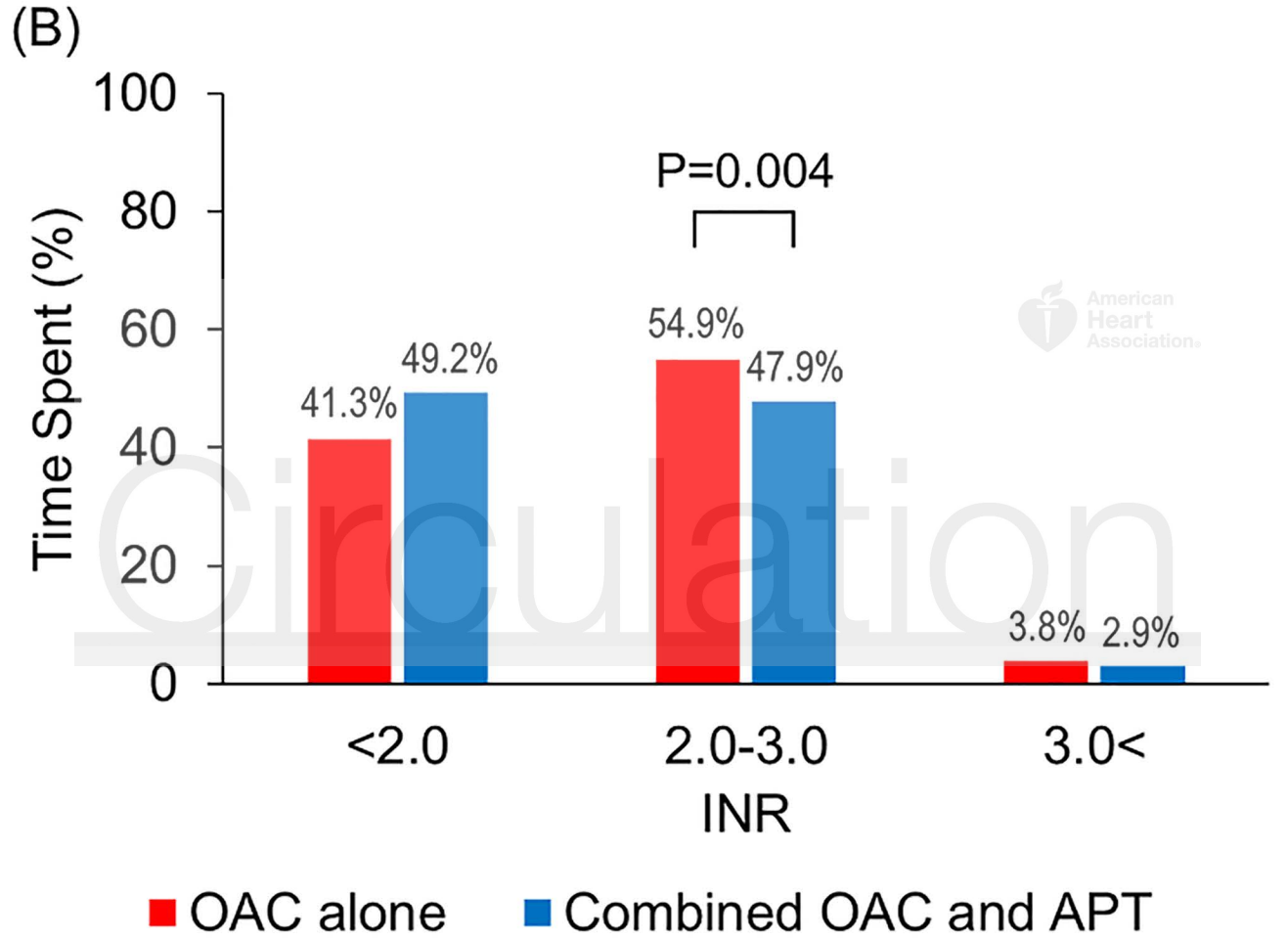
APT=antiplatelet therapy; CI=confidence interval; OAC=oral anticoagulation; PCI=percutaneous coronary intervention.

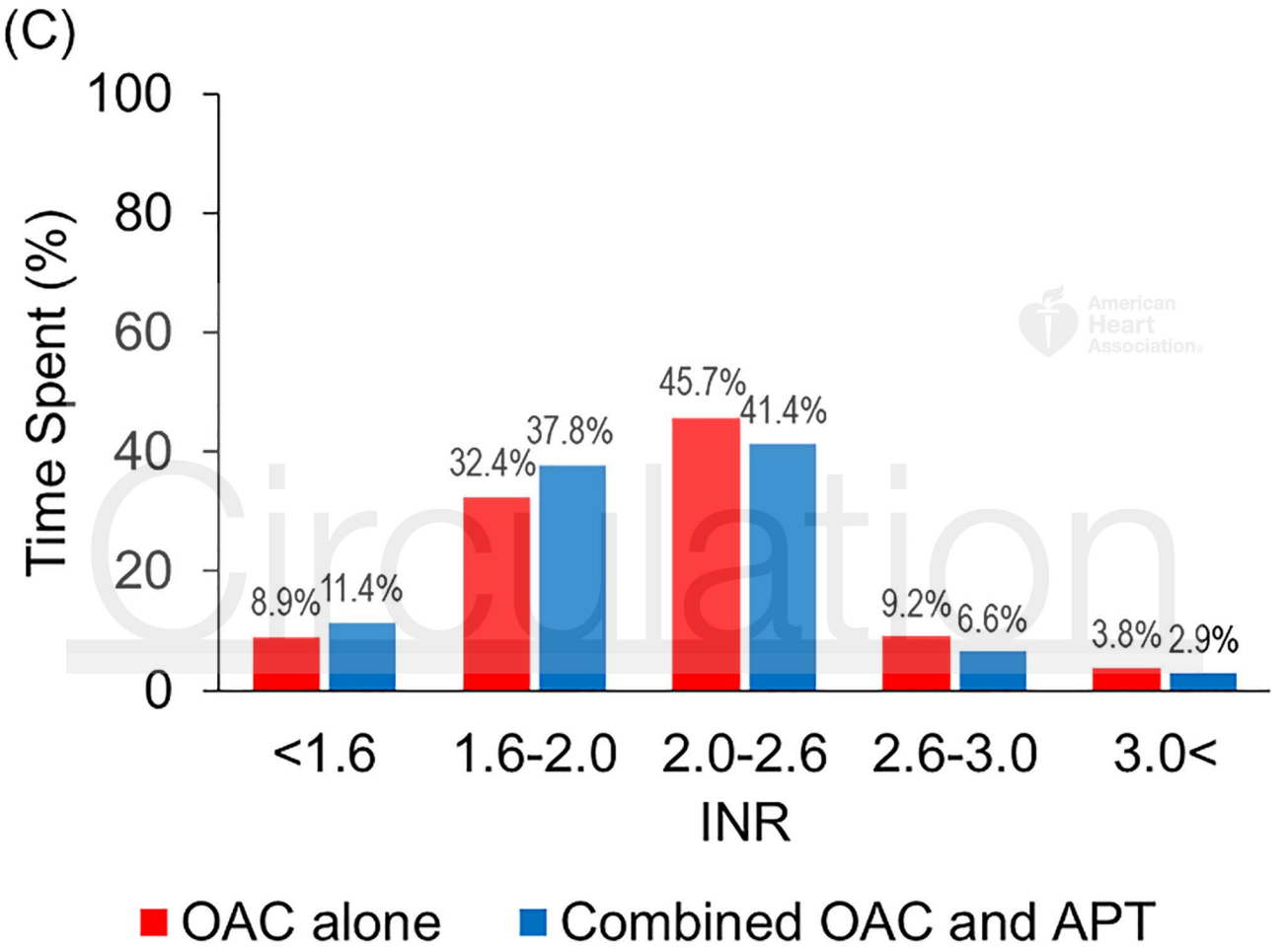


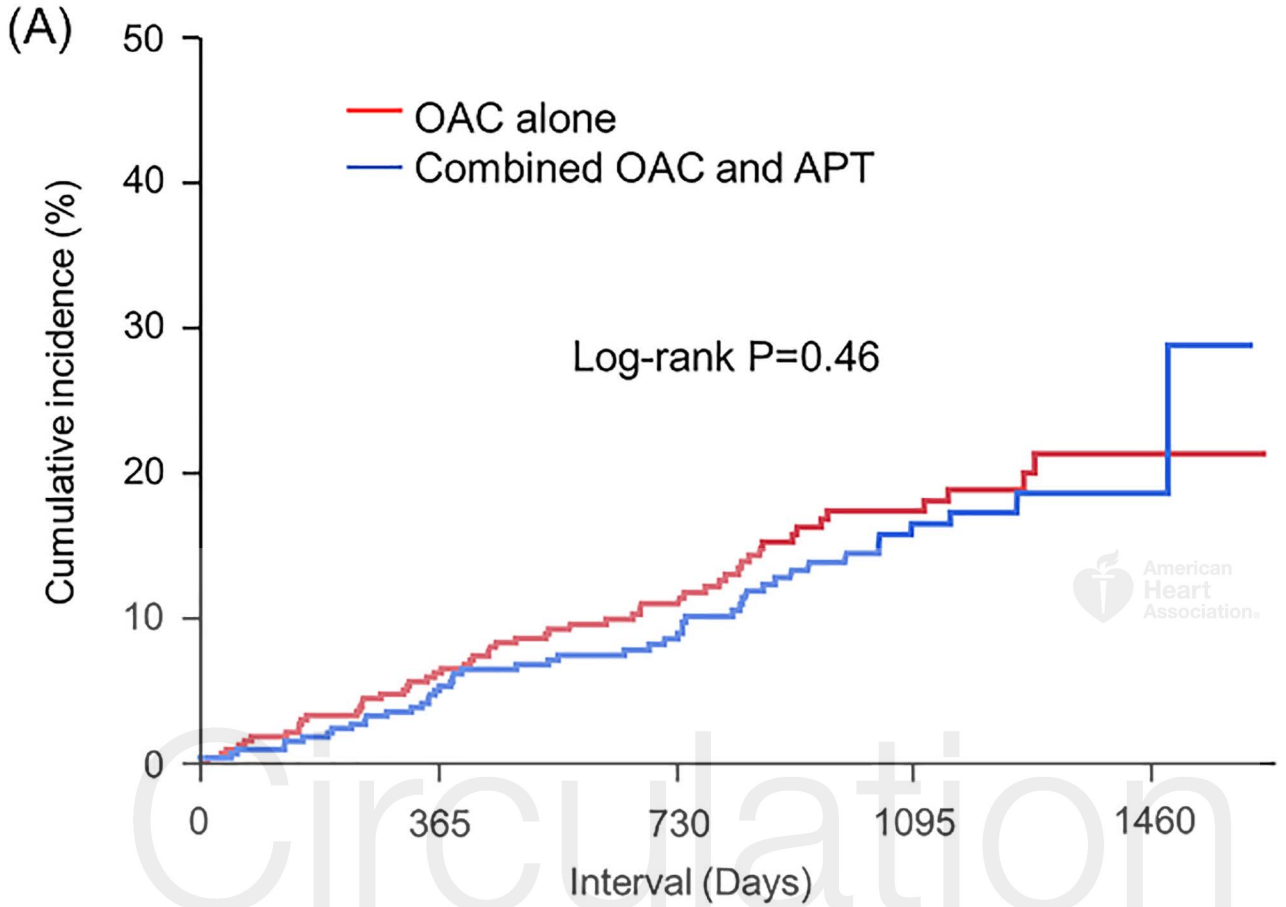


Interval (Days)	0	365	730	1095	1460
OAC alone					
N of patients at risk	344	311	214	105	10
N of patients with crossover		13	29	40	42
Cumulative Incidence		3.8%	9.4%	15.4%	23.1%
Combined OAC and APT					
N of patients at risk	346	323	227	109	10
N of patients with crossover		8	21	29	31
Cumulative Incidence		2.4%	7.1%	11.6%	21.8%

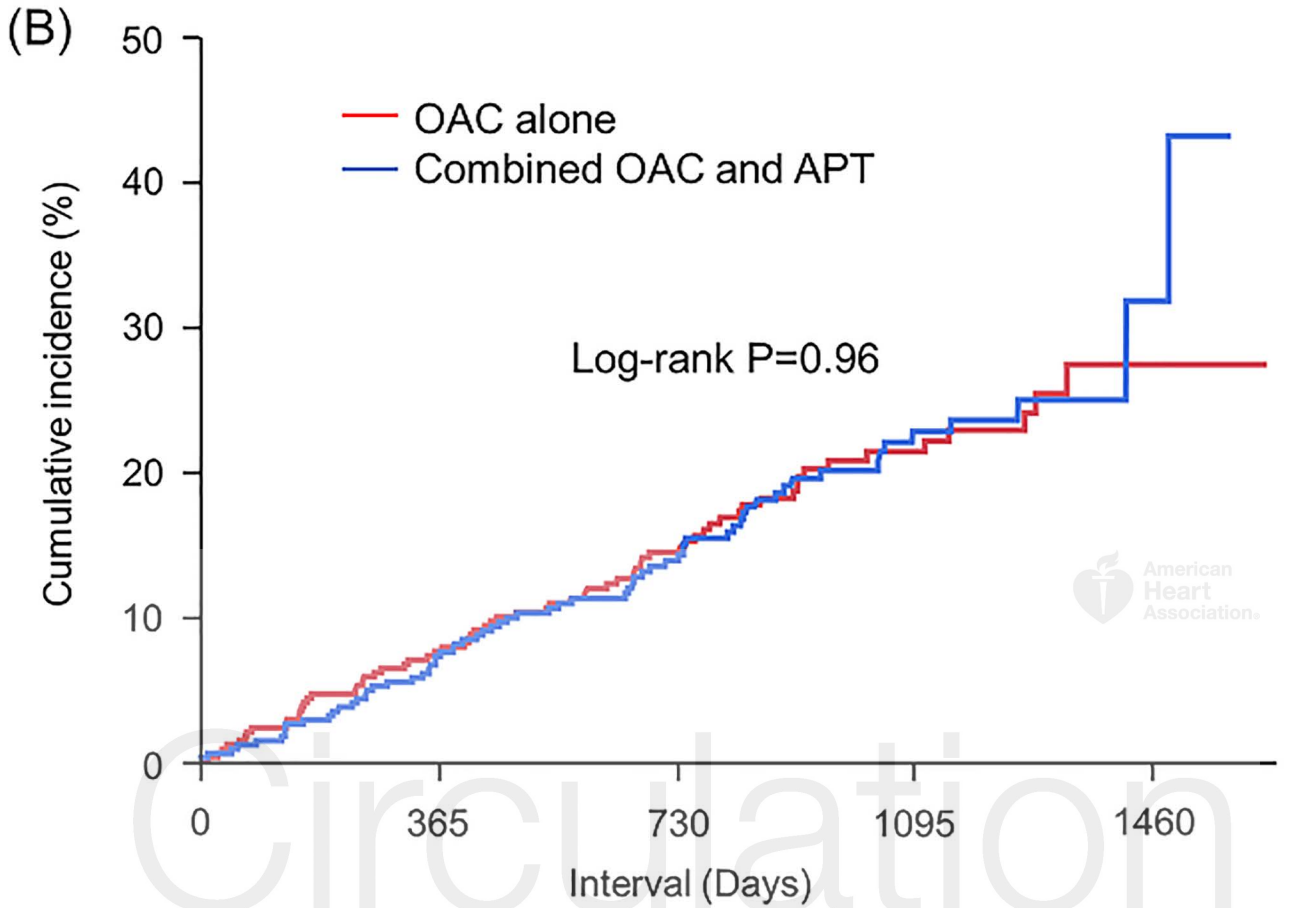






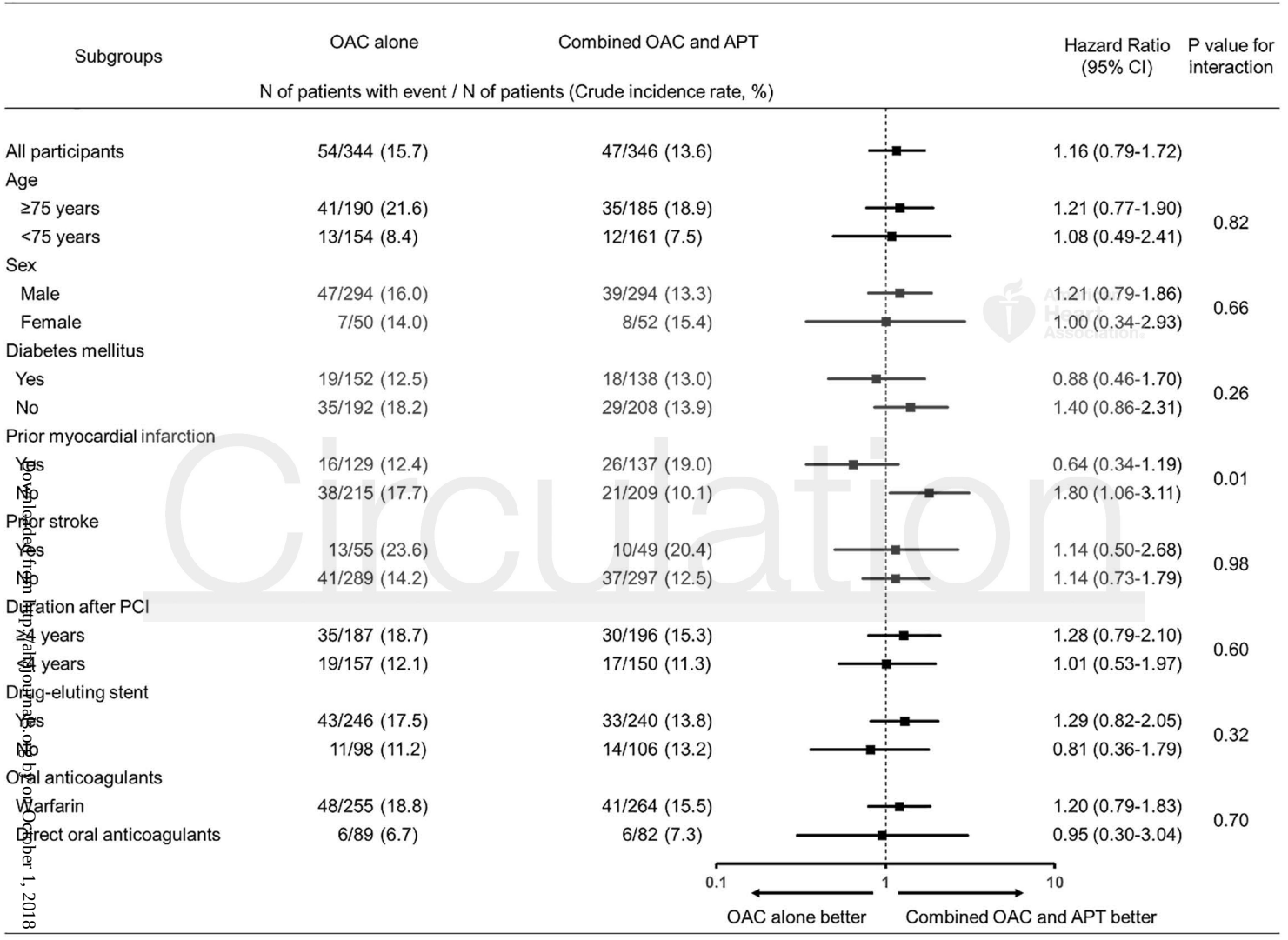


Interval (Days)	0	365	730	1095	1460
OAC alone					
N of patients at risk	344	319	236	122	12
N of patients with event		21	36	50	54
Cumulative Incidence		6.1%	10.9%	17.3%	21.2%
Combined OAC and APT					
N of patients at risk	346	325	238	113	10
N of patients with event		17	28	44	46
Cumulative Incidence		4.9%	8.5%	16.4%	18.5%



Interval (Days)	0	365	730	1095	1460
OAC alone					
N of patients at risk	344	314	227	115	12
N of patients with event		26	47	62	67
Cumulative Incidence		7.6%	14.4%	21.4%	27.3%
Combined OAC and APT					
N of patients at risk	346	317	223	105	8
N of patients with event		25	45	63	66
Cumulative Incidence		7.3%	13.9%	22.7%	31.8%

(A)



(B)