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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Comparison of Long-Term Outcomes Between Combination Antiplatelet and Anticoagulant Therapy and Anticoagulant Monotherapy in Patients With Atrial Fibrillation and Left Atrial Thrombi

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Background: Anticoagulation for patients with atrial fibrillation (AF) complicated by left atrial thrombi (LAT) is a frequent cause of bleeding complications, but risk factors remain unknown.

Methods and Results: Of 3,139 AF patients who underwent transesophageal echocardiography, 82 with LAT under anticoagulation were included in this study. Patients treated with combination antiplatelet and anticoagulant therapy (n=31) were compared with those receiving anticoagulant monotherapy (n=51) to investigate the effects of antiplatelet agents during anticoagulation on bleeding complications. Over a mean (±SD) follow-up of 878±486 days, bleeding events occurred more frequently in the combination therapy than monotherapy group (58% vs. 20%; P<0.001), but there was no significant difference in embolic events (6.5% vs. 3.9%; P=0.606). Kaplan-Meier analysis also showed a significantly higher rate of bleeding events in the combination therapy group, but no significant difference in the rate of embolic events. Inverse probability of treatment weighting revealed that combination therapy was independently associated with an increased risk of bleeding (hazard ratio [HR] 2.98, 95% confidence interval [CI] 1.14–7.89, P=0.026), but not with the risk of embolic events (HR 0.30, 95% CI 0.04–2.59, P=0.275). Net clinical benefit analysis was almost negative for combination therapy vs. monotherapy.

Conclusions: In patients with AF and LAT, combination therapy was significantly associated with an increased risk of bleeding events, but not with a reduced risk of embolic events.

Key Words: Atrial fibrillation; Bleeding; Inverse probability of treatment weighting; Left atrial thrombi; Net clinical benefit

The development of left atrial thrombi (LAT) remains a significant problem in patients with atrial fibrillation (AF) because LAT cause stroke and systemic embolism.[1] Although current AF guidelines recommend 3–4 weeks of anticoagulation for LAT on transesophageal echocardiography (TEE),[2] clinical evidence supporting the efficacy and safety of anticoagulation for LAT are both limited and outdated.[3] Recently, we reported on the clinical consequences in patients with AF and LAT detected by TEE who received standard anticoagulation; we found

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that the event rate of ischemic stroke and systemic embolism was relatively low in these patients, whereas the rate of bleeding was relatively high.[4] These findings are consistent with earlier studies,[5–7] and suggest that anticoagulation for the resolution of LAT requires particular attention to bleeding. However, risk factors for bleeding during anticoagulation in patients with AF and LAT remain unknown. Patients with AF complicated by coronary artery disease or atherosclerotic stroke require the simultaneous use of antiplatelets and an anticoagulant, but this has been associated with a high bleeding risk and no additional preventive benefit against thrombotic events compared with anticoagulation alone.[8] However, to date no study has examined the effects and risk of the simultaneous use of antiplatelets and anticoagulants in the setting of AF with LAT, in which the reinforcement of therapeutics to resolve thrombi should be considered.

In this study we evaluated the effects and risk of the simultaneous use of antiplatelets and anticoagulants in the treatment of LAT using a database of AF patients with LAT we reported previously.[4]

Methods

Study Patients

This study was conducted by the Osaka Cardiovascular Conference (OCVC; a list of investigators is given in the **Appendix**) with the participation of members of 6 high-volume hospitals that make up the OCVC arrhythmia team. The organization of the OCVC and the data collection methods of the registry of AF patients with TEE-detected LAT have been reported elsewhere.[4] The protocol of the present study was approved by the institutional review board of each participating hospital.

Patients with AF who underwent TEE between January 2010 and December 2012 were eligible for inclusion in this study. TEE was indicated primarily by the need to check for thrombi before catheter ablation or cardioversion. Patients without LAT, as well as those who did not receive continuous anticoagulation or whose anticoagulation and antiplatelet data were not available, were excluded from the study. The remaining patients (AF patients with LAT identified by TEE and receiving anticoagulation) were enrolled in the study and their data analyzed.

All data were collected retrospectively from patient medical records. Because of the retrospective design of the study, we did not obtain written informed consent, but rather used the opt-out method of informed consent based on a statement displayed on the institutional website in accordance with Japanese clinical research guidelines. This study followed the ethical guidelines outlined in the Declaration of Helsinki.

LAT was defined as discrete echo-dense masses in the left atrium or left atrial appendage with different echo densities from the adjacent endocardium and independent motion relative to the chamber wall.[9] Major bleeding was defined as intracranial hemorrhage, bleeding requiring surgery or transfusion, or a ≥4 g/dL decrease in hemoglobin level, with reference to the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial.[10] Minor bleeding was defined as clinically documented bleeding not meeting the criteria for major bleeding. Patients who were administered one or more antiplatelet agents in addition to anticoagulant after thrombus detection were defined as patients receiving combination therapy, whereas patients receiving anticoagulant alone after thrombus detection were defined as those undergoing monotherapy. Treatment was selected at the discretion of the attending physician in accordance with the practical guidelines. "Medication" was defined as the treatment used for long-term treatment for LAT resolution, rather than that used in the acute phase when LAT was first identified. In patients treated with warfarin, the time in therapeutic range (TTR) was calculated, which is a standard measure of warfarin treatment that incorporates both the frequency of international normalized ratio (INR) measurements and their actual values to assume daily INR values and defines the percentage of time in range for each patient.[11] The therapeutic range of INR was set as 2.0–3.0 for patients <70 years of age and 1.6–2.6 for those ≥70 years of age in accordance with clinical guidelines.[12] The effects of antiplatelet therapy during anticoagulation on long-term outcomes were determined comparing outcomes between patients receiving combination therapy and those receiving monotherapy.

Statistical Analysis

Continuous variables are expressed as the mean±SD, whereas categorical data are presented as absolute values and percentages. Tests for significance were conducted using the unpaired t-test or non-parametric test (Mann-Whiney U-test) for continuous variables, and the Chi-squared test or Fisher's exact test for categorical variables. Long-term outcomes were estimated using Kaplan-Meier curves and statistical significance was determined using the log-rank test. For missing values in the dataset, the multiple imputation by chained equations (MICE) method was used, an established imputation method creating multiple complete data sets in which the missing values are replaced by estimates from a specified regression model using the observed data. Fifty datasets were created using the MICE package in R (R Foundation for Statistical Computing, Vienna, Austria) and these results pooled.

Furthermore, to adjust for potential confounding in direct comparisons between patients receiving combination therapy and monotherapy, weighted Cox regression models were established with inverse probability of treatment weighting (IPTW) because of the observational nature of the study.[13] In IPTW, the weights for patients receiving combination therapy were the inverse of the propensity score, whereas the weights for patients receiving monotherapy were the inverse of 1−propensity score. The probability of receiving combination therapy, which was the propensity score, for each patient was calculated using multivariate logistic regression analysis based on clinically relevant covariates (age, sex, congestive heart failure, hypertension, diabetes, stroke, persistent AF, ischemic heart

The Osaka CardioVascular Conference (OCVC) Investigators are listed in the **Appendix**.
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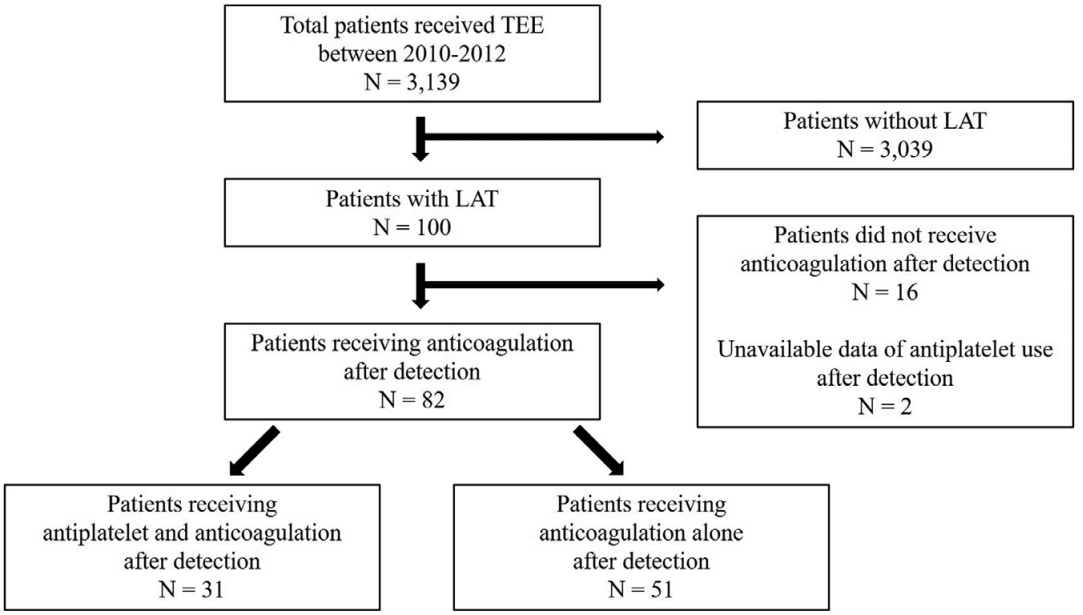

Figure 1. Flow chart of patient selection. TEE, transesophageal echocardiography; LAT, left atrial thrombi.

disease, malignant disease, thrombus mobility). Univariate Cox regression analysis was used to examine the association between TTR and outcomes. Subgroup analysis and interaction analysis were performed by Cox regression analysis.

Net clinical benefit (NCB) analysis was performed using the weight reported by Singer et al.[14] The NCB for receiving combination therapy compared with monotherapy was calculated using the following formula:

$$NCB = (IS_{Mono} - IS_{Combo}) + 1.5 \times (ICH_{Mono} - ICH_{Combo})$$

where IS_{Mono} is the rate of ischemic stroke on monotherapy, IS_{Combo} is the rate of ischemic stroke on combination therapy, and ICH_{Mono} and ICH_{Combo} are the rates of intracranial hemorrhage on monotherapy and combination therapy, respectively. A positive NCB means that receiving combination therapy is more beneficial than receiving monotherapy, whereas a negative NCB means that receiving combination therapy is more harmful. The 95% confidence intervals (CIs) of the NCB were obtained by bootstrapping.

Statistical significance was defined as 2-tailed $P<0.05$. For subgroup analyses, $P<0.05$ and $P_{Interaction}<0.10$ were considered statistically significant. Analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA) or R version 3.5.1 (R Foundation for Statistical Computing).

Results

Study Population

LAT was detected in 100 of the 3,139 AF patients who underwent TEE at 6 hospitals. After excluding 16 patients who did not use anticoagulants and 2 with no data regarding antiplatelet use, 82 patients (2.6% of the study population) with LAT under anticoagulation were included in this study. Antiplatelets were administered to 31 patients (38%; combination therapy) after thrombus detection, whereas 51 patients (62%; monotherapy) did not receive antiplatelets after thrombus detection (**Figure 1**).

Baseline Characteristics

Baseline characteristics are given in **Table 1**, including the number of patients for whom specific data were available. There was no significant difference between patients receiving combination therapy and monotherapy with regard to age, sex, or persistent AF. Moreover, a past history of hypertension, diabetes, stroke, and ischemic heart disease was more frequently observed in patients receiving combination therapy. There was no significant difference in thrombus mobility between patients receiving combination therapy and those receiving monotherapy.

Treatment for LAT

There was no significant difference in the type of anticoagulant used between the 2 groups. Thirty patients receiving combination therapy and 45 patients receiving monotherapy used warfarin (97% vs. 88%; P=0.180). One patient receiving combination therapy and no patients receiving monotherapy used rivaroxaban (3.2% vs. 0%; P=0.378), and no patients receiving combination therapy and 6 receiving monotherapy used dabigatran (0% vs. 12%; P=0.078). Most patients (91%) used warfarin because most patients were enrolled before the use of direct oral anticoagulants (DOAC) became widespread. There was no significant difference in TTR for LAT between the combination therapy and monotherapy groups (50±27% vs. 46±30%, respectively; P=0.486). Of the patients receiving combination therapy, 27 took aspirin (87%), 5 took clopidogrel (16%), and 2 took other antiplatelet agents (6.5%). Three patients receiving combination therapy took 2 antiplatelet drugs (9.7%).

Table 1. Baseline Characteristics

	All (n=82)	Combination therapy (n=31)	Monotherapy (n=51)	P-value
Age (years)	67±10	69±9	66±11	0.156
Male sex	62/82 (76)	24/31 (77)	38/51 (75)	0.766
Height (cm; n=79)	163±10	163±10	162±10	0.572
Body weight (kg; n=69)	62±13	63±12	61±13	0.406
Congestive heart failure	58/82 (71)	25/31 (81)	33/51 (65)	0.124
Hypertension	51/82 (62)	24/31 (77)	27/51 (53)	0.027
Diabetes	28/81 (35)	16/30 (53)	12/51 (24)	0.006
Stroke	34/82 (41)	18/31 (58)	16/51 (31)	0.017
Persistent atrial fibrillation	54/72 (75)	19/26 (73)	35/46 (76)	0.777
Ischemic heart disease	21/81 (26)	15/30 (50)	6/51 (12)	<0.001
Malignant disease	10/80 (13)	3/29 (10)	7/51 (14)	0.740
CHA_2DS_2-VASc score (n=80)				
0–2	26/80 (33)	6/29 (21)	20/51 (39)	0.089
3–5	32/80 (40)	11/29 (38)	21/51 (41)	0.776
≥6	22/80 (28)	12/29 (41)	10/51 (20)	0.036
Thrombus mobility	18/72 (25)	7/29 (24)	11/43 (26)	0.890
Prior time in therapeutic range (%; n=62)	30±28	30±26	30±29	0.995
Prior use of antithrombotic drug				
Warfarin	68/82 (83)	26/31 (84)	42/51 (82)	0.859
Dabigatran	4/82 (4.9)	1/31 (3.2)	3/51 (5.9)	1.000
Aspirin	28/82 (34)	25/31 (81)	3/51 (5.9)	<0.001
Clopidogrel	6/82 (7.3)	4/31 (13)	2/51 (3.9)	0.193
Other antiplatelet drug	3/82 (3.7)	1/31 (3.2)	2/51 (3.9)	1.000

Unless indicated otherwise, data are given as the mean±SD or as n (%), with the number of patients with data available given as the denominator.

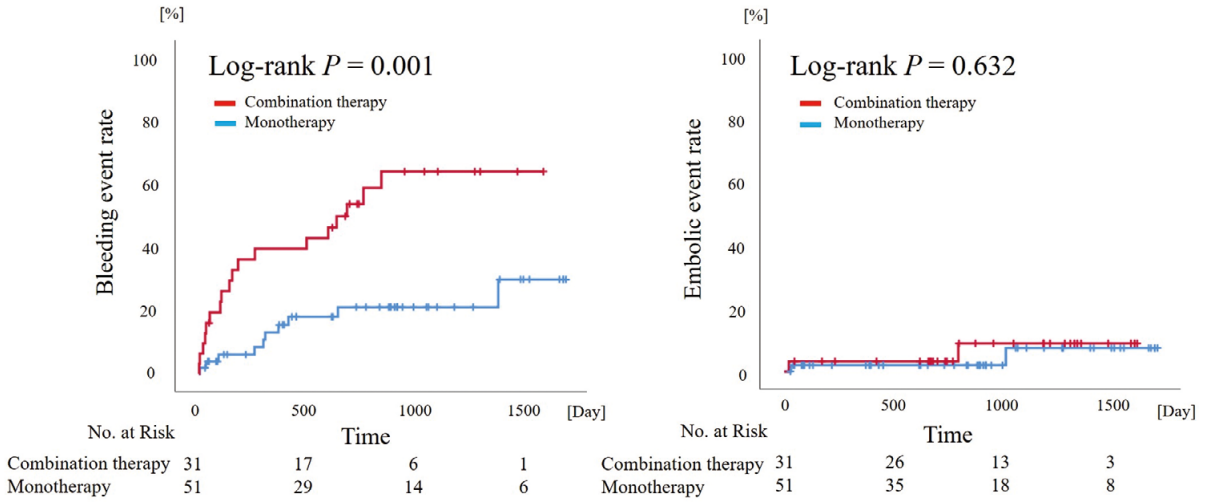

Figure 2. Bleeding event rate and embolic event rate. (**Left**) Bleeding events and (**Right**) embolic events evaluated by Kaplan-Meier analysis. Results of log-rank tests are shown in each panel.

Outcomes

Over a follow-up period of 878±486 days, bleeding events occurred more frequently in the combination therapy than monotherapy group (n=18 [58%] vs. n=10 [20%]; P<0.001). Intracranial hemorrhage occurred in 3 patients receiving combination therapy, but in no patient receiving monotherapy (9.7% vs. 0%, respectively; P=0.051). There was no significant difference in the frequency of ischemic stroke or systemic embolism between the combination therapy and monotherapy groups (n=2 [6.5%] vs. n=2 [3.9%], respectively; P=0.606). Ischemic stroke occurred in 1 patient each in the combination therapy and monotherapy groups (3.2% vs. 2.0%, respectively; P=1.000). Kaplan-Meier analysis also revealed a significantly higher rate of bleeding

Table 2. Long-Term Outcomes

	All (n=82)	Combination therapy (n=31)	Monotherapy (n=51)	P-value
Ischemic stroke and systemic embolism	4 (4.9)	2 (6.5)	2 (3.9)	0.606
Ischemic stroke	2 (2.4)	1 (3.2)	1 (2.0)	1.000
Transient ischemic attack	1 (1.2)	1 (3.2)	0 (0)	0.378
Coronary artery thromboembolism	1 (1.2)	0 (0)	1 (2.0)	1.000
All bleeding	28 (34)	18 (58)	10 (20)	<0.001
Major bleeding	11 (13)	6 (19)	5 (10)	0.218
Intracranial hemorrhage	3 (3.7)	3 (9.7)	0 (0)	0.051
Gastrointestinal bleeding	2 (2.4)	1 (3.2)	1 (2.0)	1.000
Blood transfusion	4 (4.9)	3 (9.7)	1 (2.0)	0.149
Hemoglobin decrease ≥4 g/dL	3 (3.7)	2 (6.5)	1 (2.0)	0.554
Requiring surgery	2 (2.4)	0 (0)	2 (3.9)	0.524
Minor bleeding	19 (23)	13 (42)	6 (12)	0.002
Spontaneous bleeding	15 (18)	11 (36)	4 (7.8)	0.003
Urinary tract bleeding	4 (4.9)	3 (9.7)	1 (2.0)	0.149
Alveolar hemorrhage	4 (4.9)	3 (9.7)	1 (2.0)	0.149
Gastrointestinal bleeding	3 (3.7)	2 (6.5)	1 (2.0)	0.554
Subcutaneous bleeding	2 (2.4)	2 (6.5)	0 (0)	0.140
Subconjunctival bleeding	1 (1.2)	1 (3.2)	0 (0)	0.378
Epistaxis	1 (1.2)	0 (0)	1 (2.0)	1.000
Traumatic bleeding	6 (7.3)	4 (13)	2 (3.9)	0.193
Confirmed left atrial thrombi resolution	41 (50)	17 (55)	24 (47)	0.494

Unless indicated otherwise, data show n (%).

Table 3. HRs for Combination Therapy vs. Monotherapy as a Reference for Outcome by Cox Regression Models With MICE and IPTW

Dependent variable	Independent variable	Statistical method	HR (95% CI)	P-value
Bleeding	Combination therapy	Crude	3.58 (1.65~7.78)	0.001
		MICE and IPTW	2.98 (1.14~7.89)	0.026
Embolic event	Combination therapy	Crude	1.61 (0.23~11.4)	0.635
		MICE and IPTW	0.30 (0.04~2.59)	0.275

CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; MICE, multiple imputation by chained equations.

Table 4. Net Clinical Benefit Analysis to Prevent Stroke

Treatment	Combination therapy	Monotherapy (reference)
No. events (per 100 person-years)		
Ischemic stroke	1 (1.26)	1 (0.84)
Intracranial hemorrhage	3 (3.93)	0 (0)
Net clinical benefit (95% CI)	−6.32 (−14.83~0.00)	–

CI, confidence interval.

events in the combination therapy group, but no significant difference in the rate of embolism events between the 2 groups (**Figure 2**). Repeat TEE at follow-up was performed in 41 patients (50%). Resolution of LAT was confirmed in 40 of the 41 patients, whereas in the remaining patient it was confirmed by a modality other than TEE. The frequency of confirmed LAT resolution did not differ significantly between the combination therapy and monotherapy groups (n=17 [55%] vs. monotherapy n=24 [47%], respectively; P=0.494). Details of outcomes of embolic and bleeding events are given in **Table 2**.

After adjusting for the clinically relevant baseline using IPTW after MICE, patients with combination therapy had an increased risk of bleeding and no significant difference in the risk of embolic events compared with patients receiving monotherapy (**Table 3**). NCB analysis suggested that receiving combination therapy was more harmful than receiving monotherapy in patients with AF and LAT

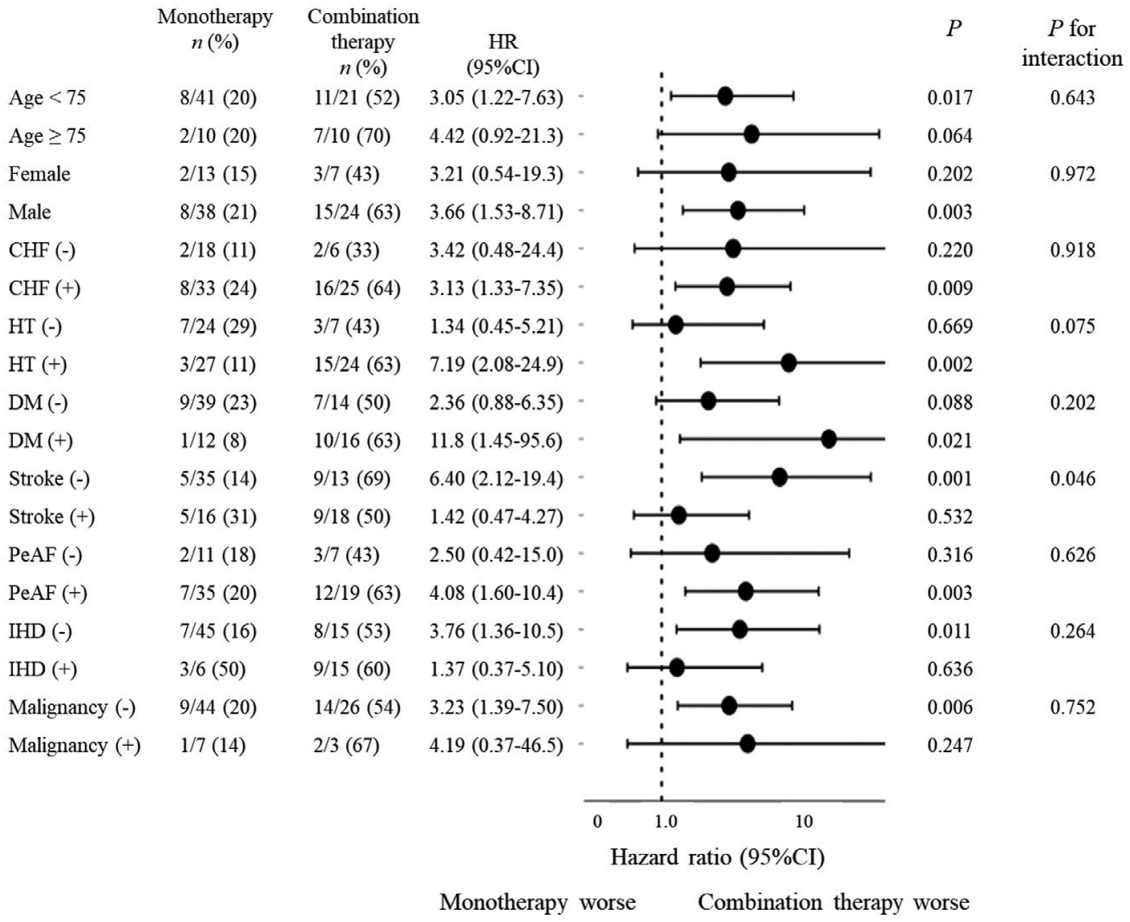

Figure 3. Subgroup analyses of bleeding events stratified according to the receipt of antiplatelets during anticoagulation. CHF, congestive heart failure; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; HT, hypertension; IHD, ischemic heart disease; PeAF, persistent atrial fibrillation.

(**Table 4**). TTR was not associated with either embolic events (hazard ratio [HR] 1.03, 95% CI 0.99–1.07, P=0.152) or bleeding events (HR 1.01, 95% CI 0.99–1.02, P=0.272).

Subgroup analyses regarding bleeding events showed that there was no subgroup in which combination therapy exhibited lower bleeding risk than monotherapy. In patients aged <75 years, male patients, those with congestive heart failure, hypertension, diabetes, or persistent AF, and those without stroke, ischemic heart disease, and malignancy, combination therapy was associated with a significantly higher risk of bleeding. Significant interactions for risk of bleeding were observed between combination therapy and stroke, as well as between combination therapy and hypertension (**Figure 3**).

Discussion

This study of 82 patients with AF and LAT in the OCVC Registry showed a higher rate of bleeding in patients receiving combination therapy than in those receiving monotherapy. Combination therapy was independently associated with a higher risk of bleeding. In contrast, there was no significant difference between the 2 groups in the frequency of LAT resolution, ischemic stroke, or systemic embolism. Evaluation of overall benefit with NCB analysis showed that combination therapy may be more harmful than monotherapy. The present study is the first to examine the effects and risk of the simultaneous use of antiplatelets and anticoagulants in the setting of AF with LAT, in which thrombus resolution is strongly needed. Considering the very low rate of accidental discovery of LAT with TEE, this study is potentially valuable and important because it includes a relatively large number of patients with accidentally found LAT.

It has been reported that LAT is detected in 1.6–4.4% of patients with AF[6,15,16] and is a risk factor for stroke and embolism.[17,18] Recently, however, the rate of embolic events in patients with AF and LAT has decreased considerably due to advances in stroke prevention.[5,6,17] In contrast, bleeding during anticoagulation is frequently observed in patients with AF and LAT, with reported rates ranging from 8.3% to 36.8%,[5,7] suggesting that the prevention or control of bleeding is essential. The findings of the present study also support the importance of the prevention of bleeding during anticoagulation and may imply that combination therapy with antiplatelets and anticoagulants

should not be recommended as a therapeutic option for LAT.

The resolution rate of LAT in the present study was 50%. This is among the lower rates reported in previous studies, which ranged from 41.5% to 90%.[3,5,19–21] This lower rate is likely due to lower TTR (48%) after the detection of LAT. It is well known that the risk of bleeding complications associated with warfarin administration is higher in Asian than non-Asian populations.[22,23] Therefore, concern about bleeding may have led the doctors in this study to maintain low levels of anticoagulation, which, in turn, may have resulted in the low TTR and consequently low resolution rate.

Patients daily receiving antiplatelets are likely to have a past history of ischemic heart disease and stroke, as well as risk factors for atherosclerosis. These conditions may affect the risk of embolic and bleeding events. The sample size of the present study was too small to adjust for these variables in multivariate analysis. Accordingly, we used the IPTW method to reduce the effect of potential confounding factors. The IPTW analysis clearly showed a significantly increased risk of bleeding in patients with combination therapy and no significant difference in the risk of embolic events between the 2 groups, even after adjusting for confounding factors. Moreover, in our subgroup analyses, atherosclerotic diseases, such as stroke and ischemic heart disease, did not increase bleeding risk in patients receiving combination therapy. These results suggest that the pathological changes accompanying these diseases are unlikely to affect the risk of bleeding and that the combination therapy may not reduce the risk of embolic events.

Cox regression models of the risk of embolism were conflicting between the crude and IPTW method, albeit differences did not reach statistical significance. One reason for this may be the lack of statistical power due to the small number of embolic events. Therefore, we also examined NCB, which is commonly used as an index for risk benefits of antithrombotic therapy. The results of NCB analysis strongly suggested that combination therapy was more harmful than monotherapy.

In AF patients with stable coronary artery disease, the addition of antiplatelet therapy to warfarin does not appear to reduce the risk of recurrent coronary events or thromboembolism, but does significantly increase the risk of bleeding.[8] In line with this finding, Yasuda et al. recently reported that monotherapy with DOAC was non-inferior for efficacy and superior for safety to combination therapy with DOAC plus a single antiplatelet agent in patients with AF and stable coronary artery disease, including those after coronary stenting.[24] In contrast, another group could not demonstrate the non-inferiority of oral anticoagulant monotherapy (warfarin in 75.2% and DOAC in 24.8%) to combination therapy with an oral anticoagulant and an antiplatelet agent.[25] The difference between these 2 trials may result from differences in type of oral anticoagulant, patient background, or sample size. Nonetheless, it is recommended that all patients with AF who are more than 1 year after percutaneous coronary intervention should be switched from combination therapy with an antiplatelet and anticoagulant to monotherapy with an anticoagulant alone.[26] Therefore, the need to take both anticoagulants and antiplatelets is decreasing. The findings of the present study suggest that an anticoagulant alone would be a better treatment for LAT than both an antiplatelet and an anticoagulant, even in patients with coronary artery disease, and maximum efforts should be made to shorten the duration of combination therapy with antiplatelets and anticoagulants in patients with AF and LAT.

Study Limitations

Several limitations of the present study warrant mention. First, the study used a retrospective observational design, and some data values were missing. We could not calculate bleeding risk scores, such as the HAS-BLED score,[27] because we did not have data regarding a history of bleeding and the use of non-steroidal anti-inflammatory drugs. Second, due to the low number of embolic events, analysis for the risk of embolism showed discrepant results between the crude analysis and weighted Cox regression model with IPTW. Third, we did not collect data of patients without LAT, and therefore could not compare outcomes between patients with or without LAT or investigate predictors of LAT. Fourth, the number of patients receiving DOAC was low (8.5%). DOAC is superior to warfarin in reducing cerebral hemorrhage.[28] Therefore, the incidence of bleeding could be lower in the current clinical setting. The application of these results to recent clinical settings requires additional data from DOAC patients. Conversely, the recent prevalence of warfarin use has been reported to range from 38% to 64% in the real-world AF population.[29–31] Therefore, the present study may provide useful information for a certain group of patients receiving anticoagulant therapy for LAT, especially those who use warfarin even in the DOAC era. Moreover, although TEE is the gold standard for identifying LAT, false-positive results are likely inevitable.[32] We did not routinely use other modalities to detect LAT, such as computed tomography or magnetic resonance imaging. Finally, although we showed that combination therapy conferred an independent risk of bleeding even after using MICE and IPTW, unmeasured bias could not be completely eliminated.

Conclusions

In patients with AF and LAT, combination therapy was not associated with a reduced risk of embolic events, but was associated with an increased risk of bleeding.

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Disclosures

S.H., K.I., A.H., M.M., Y.F., T.W., and H. Minamiguchi have received remuneration from Boehringer Ingelheim and Bayer. D.N. has received remuneration from Boehringer Ingelheim and Sanofi. Y.O. has received remuneration from Boehringer Ingelheim. K.K. has received remuneration from Boehringer Ingelheim, Bayer, and Sanofi. H. Mizuno has received remuneration from Boehringer-Ingelheim and Bayer, as well as research funding from Boehringer-Ingelheim. T. Kitamura has received remuneration from Bayer. Y.S. has received remuneration from Eizai, Boehringer-Ingelheim, Bayer, and Sanofi, served as a consultant to Boehringer-Ingelheim, Bayer, and Sanofi, holds patents with Eizai, Boehringer-Ingelheim, Bayer, and Sanofi,

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K.I. is a member of *Circulation Reports*' Editorial Team. The remaining authors have no conflicts of interest to report.

IRB Information

This study was approved by the Osaka University Clinical Research Review Committee (CRB5180007).

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Appendix

The Osaka CardioVascular Conference (OCVC) Arrhythmia Investigators are listed below.

Chair:
Yasushi Sakata (Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, Japan)

Secretariat:
Shungo Hikoso (Chief), Daisaku Nakatani, Hiroya Mizuno, Katsuki Okada, Tomoharu Dohi, Takayuki Kojima, Hirota Kida, Oeun Bolrathanak, Akihiro Sunaga, and Sugako Mitsuoka (Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, Japan)

Investigators (in alphabetical order of institution):
Toshiaki Mano and Masaharu Masuda (Kansai Rosai Hospital, Amagasaki, Japan); Masaaki Uematsu (National Hospital Organization Osaka National Hospital, Osaka, Japan); Takahisa Yamada, Yoshio Furukawa, and Masato Kawasaki (Osaka General Medical Center, Osaka, Japan); Yuji Okuyama and Kazunori Kashiwase (Osaka Minami Medical Center, Kawachinagano, Japan); Yoshiharu Higuchi, Akio Hirata, and Hitoshi Minamiguchi (Osaka Police Hospital, Osaka, Japan); Jun Tanouchi, Masami Nishino, and Yasuyuki Egami (Osaka Rosai Hospital, Sakai, Japan); Yasushi Matsumura, Toshihiro Takeda, Kentaro Ozu, and Takahumi Oka (Osaka University Graduate School of Medicine, Suita, Japan); Katsuomi Iwakura, Nobuaki Tanaka, and Koichi Inoue (Sakurabashi Watanabe Hospital, Osaka, Japan); Shiro Hoshida (Yao Municipal Hospital, Yao, Japan)