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Clinical benefits and risks of antithrombotic therapy in patients with atrial fibrillation with comorbidities – A report from the CHART-2 Study

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ABSTRACT

Background: The benefits of antithrombotic therapy (ATT) for atrial fibrillation (AF) are occasionally offset by major bleeding complications. However, the clinical benefits and risks of ATT in AF patients, with special references to comorbidities, such as heart failure (HF), coronary artery disease (CAD), and the patterns of AF, remain to be fully elucidated.

Methods: A total of 3221 consecutive AF patients from our Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study (N = 10,219) were divided into 4 groups based on ATT at enrollment; no-ATT, anticoagulant alone, antiplatelet alone, and both of them (AC&AP). Then, efficacy and safety outcomes including thromboembolic events, major bleeding, and mortality were evaluated among the 4 groups.

Results: Anticoagulant monotherapy was associated with reduced risk of ischemic stroke in patients with but not in those without HF, CAD, or non-paroxysmal AF. Although there was no significant difference in major bleeding among the 4 groups, a composite of thromboembolism and major bleeding occurred more frequently in the AC&AP group, even in combination with anticoagulants and single antiplatelet therapy, indicating that the combination therapy is more harmful than anticoagulant monotherapy for AF patients, especially for those with HF or CAD. Lastly, no-ATT group was associated with worse prognosis compared with other 3 groups.

Conclusions: These results indicate that ATT is beneficial for AF patients particularly for those with HF, CAD, or non-paroxysmal AF and that among ATT, anticoagulant monotherapy may be most profitable for both clinical benefits and risks for AF patients.

1. Introduction

Atrial fibrillation (AF) is a common arrhythmia and remains one of the major causes of stroke and heart failure (HF) in the world [1]. AF is associated with increased risk of stroke by 5-fold, HF by 3-fold, and mortality by 2-fold [2]. Regarding the management of AF, anticoagulant use is recommended to reduce the risk of stroke and mortality [3]. However, the benefits of antithrombotic therapy (ATT) are occasionally offset by bleeding complications, especially when anticoagulants are concomitantly prescribed with antiplatelets due to atherothrombotic comorbidities such as coronary artery disease (CAD) [4,5]. Although 10–20% of AF patients have CAD [6,7], it remains to be elucidated whether antiplatelets should be discontinued in CAD patients requiring prolonged use of anticoagulants [8]. Thus, evidence to guide optimal ATT is still needed in clinical practice, particularly after the launch of direct oral anticoagulants (DOACs) [9].

On the other hand, AF and HF often coexist due to common risk factors, and AF patients with HF have a higher risk of thromboembolism and mortality compared with those without HF [10]. However, the

Abbreviations: AF, atrial fibrillation; ATT, antithrombotic therapy; CHART-2, Chronic Heart Failure Analysis and Registry in the Tohoku District-2; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; GI, gastrointestinal; HF, heart failure; ICH, intracranial hemorrhage; SAPT, single antiplatelet therapy.

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impacts of ATT on prognosis in AF patients with HF still remain unclear. Furthermore, current guidelines recommend that selection of ATT should be based on the risk of thromboembolism irrespective of whether AF pattern is paroxysmal, persistent, or permanent [1,2,11]. However, it remains controversial whether the effect of ATT is consistent through all the types of AF.

In this study, we explored the clinical benefits and risks of ATT and the relationship between ATT and prognosis in AF patients in our Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2) Study [12,13]. We specially focused on how comorbid HF, CAD, and the patterns of AF influence the prognostic impacts of ATT in AF patients.

2. Methods

Details of the methods are provided in the Supplementary file.

3. Results

3.1. Patient characteristics

Table 1 shows the baseline clinical characteristics among the 4 groups. Among them, only 10.4% had reduced left ventricular ejection fraction (LVEF) lower than or equal to 40%, while 61.6% had current or past history of HF. Of note, 37.1% of patients did not use warfarin at baseline. Among those who received warfarin therapy at baseline, <50% of them were treated within the therapeutic range of prothrombin time-international normalized ratio (PT-INR). Regarding comorbidities and medical treatments, patients treated with warfarin had less frequencies of paroxysmal AF and history of HF; more common uses of β-blockers, diuretics, and digitalis; higher levels of b-type natriuretic peptide (BNP) and larger left atrial diameter. In contrast, male sex, CAD, diabetes mellitus, dyslipidemia, and statin use were more common in patients treated with antiplatelets. These results indicate that selection of ATT by attending cardiologists may depend on concomitant comorbidities and patterns of AF.

3.2. Efficacy of antithrombotic therapies in AF patients

During the median 6.2-year follow-up, the AC group had the lowest incidence of both ischemic stroke and stroke death among the 4 groups (Fig. 1A and Table S1). In multiple Cox proportional hazards models, the no-ATT and the AC&AP groups were associated with significantly higher risk of ischemic stroke than the AC group (Fig. 1B). Regarding stroke death, only the no-ATT group had significantly higher risk as compared with the AC group (Fig. 1B). In subgroup analysis regarding HF, the AC group had the lowest incidence of ischemic stroke in AF patients with HF (Fig. S2A and Table S1). Interestingly, multiple Cox proportional hazards models showed that, as compared with the AC group, other 3 groups in AF patients with HF had significantly higher risk of ischemic stroke (Fig. 1C), indicating the superiority of anticoagulant monotherapy in AF patients with HF, but not in those without HF. Furthermore, the AC group had the lowest incidence of ischemic stroke in AF patients with CAD (Fig. S2B and Table S1). In multiple Cox proportional hazards models, as compared with the AC group, the no-ATT group had significantly higher risk of ischemic stroke in AF patients with CAD, but not in those without CAD (Fig. 1C). In addition, among AF patients with CAD, both the AP and the AC&AP groups had significantly higher risk of ischemic stroke compared with the AC group, while it was not the case among those without CAD (Fig. 1C). In subgroup analysis for AF patterns, non-paroxysmal AF patients had 2-fold higher incidence of ischemic stroke compared with paroxysmal AF patients in the no-ATT group (Table S1), and the Kaplan-Meier estimates showed that all ATT groups had lower incidence of ischemic stroke compared with the no-ATT group in non-PAF patients (Fig. S2C). In multiple Cox proportional hazards models, the no-ATT group had significantly higher risk of ischemic stroke in non-paroxysmal AF patients, but not in paroxysmal AF patients (Fig. 1C). Taken together, these results indicate that anticoagulant monotherapy was associated with reduced risk of ischemic stroke especially in those with HF, CAD, or non-paroxysmal AF.

3.3. Benefits and risks of antithrombotic therapies in AF patients

The AC group had significantly lower incidence of thromboembolism compared with other 3 groups (Fig. 2A and Table S2). Similarly, the no-ATT group was associated with significantly higher risk of thromboembolism than the AC group in the multiple Cox proportional hazards model (Fig. 2B). In contrast, the AC&AP group had higher incidence of major bleeding and net clinical outcome compared with other 3 groups (Fig. 2A and Table S2). Multiple Cox proportional hazards models showed that the risk of net clinical outcome was significantly higher in the no-ATT and the AC&AP groups compared with the AC group (Fig. 2B), whereas the AC&AP group tended to have higher risk of thromboembolism and major bleeding. Importantly, as compared with the AC group, the AC&AP group had significantly greater risk of net clinical outcome in AF patients with HF or CAD (Fig. 2C). Furthermore, the AC&AP group had a significant increase in the risk of major bleeding in AF patients with HF (Fig. S3). Taken together, anticoagulant monotherapy could be more profitable than the combination of anticoagulants and antiplatelets in AF patients, particularly for those with HF, or CAD. Additionally, the no-ATT group was associated with a significant increase in the risk of net clinical outcome compared with the AC group in AF patients with HF, CAD, or non-paroxysmal AF (Fig. 2C). Among the major bleeding, the incidence of major bleeding other than ICH, particularly major GI bleeding, was higher in the AC&AP group, while that of ICH was comparable among the 4 groups (Fig. S4A, Table S3). Similar results were found in multiple Cox proportional hazards models that showed a significantly higher risk of major bleeding other than ICH and that of major GI bleeding in the AC&AP group as compared with the AC group (Fig. S4B).

To further explore whether a content of antiplatelets affects the benefit-risk balance of ATT, we divided the AC&AP group into AC + SAPT and AC + DAPT groups and then compared these groups with the AC group (Fig. S1). Kaplan-Meier estimates showed that both the AC + SAPT and the AC + DAPT groups had increased event rates of thromboembolism and major bleeding than the AC group (Fig. 3A). Importantly, the incidence rate of net clinical outcome was progressively increased in order of the AC, the AC + SAPT and the AC + DAPT groups (Fig. 3A, $P < .05$ for trend test adjusted by prespecified covariates). As shown in Fig. 3B, the AC + SAPT group had significantly greater risk of net clinical outcome compared with the AC group. Similarly, the AC + SAPT group had significantly greater risk of net clinical outcome in AF patients with HF and in those with CAD compared with the AC group (Fig. 3C), indicating that even the combination of anticoagulant with SAPT could be more harmful than anticoagulant monotherapy in AF patients with HF and in those with CAD. Of note, although the risk of ICH was comparable between the AC and AC + SAPT group, that of major bleeding other than ICH and that of major GI bleeding were significantly higher in the AC + SAPT group as compared with the AC group (Fig. S5).

3.4. Long-term prognosis of AF patients and antithrombotic therapies

The incidence of all-cause mortality was higher in the no-ATT group, whereas there was no difference in cardiovascular or non-cardiovascular mortality among the 4 groups (Fig. S6 and Table S4). Multiple Cox proportional hazards models showed that only the no-ATT group, but not the AP or the AC&AP groups, was significantly associated with worse prognosis compared with the AC group (Fig. S6B). Interestingly, when compared with the no-ATT group, other 3 ATT groups had significantly improved all-cause mortality (aHR 0.62, 0.66 and 0.69 for the AC, the AP and the AC&AP groups, respectively, all P

Table 1
Baseline patient characteristics.

	no-ATT (N = 382)	AC (N = 1101)	AP (N = 824)	AC&AP (N = 914)	P value
Age (years)	71.4 ± 12.5	69.7 ± 10.6	73.0 ± 10.1	70.1 ± 9.3	<0.001
Female sex (N, %)	152 (39.8)	386 (35.1)	224 (27.2)	247 (27.0)	<0.001
BMI (kg/m^2)	23.5 ± 3.8	23.5 ± 3.7	23.8 ± 3.8	23.7 ± 3.4	0.247
Paroxysmal AF	230 (60.2)	288 (26.2)	396 (48.1)	274 (30.0)	<0.001
Smoking (N, %)	132 (36.1)	442 (43.0)	345 (44.6)	395 (45.2)	0.021
Etiology of HF (N, %)					
Coronary artery disease	83 (21.7)	159 (14.4)	405 (49.2)	432 (47.3)	<0.001
Dilated cardiomyopathy	30 (7.9)	161 (14.6)	70 (8.5)	95 (10.4)	<0.001
Hypertrophic cardiomyopathy	32 (8.4)	49 (4.5)	22 (2.7)	30 (3.3)	<0.001
Hypertensive heart disease	152 (39.8)	209 (25.4)	453 (41.1)	208 (22.8)	<0.001
Valvular heart disease	49 (12.8)	183 (16.6)	86 (10.4)	111 (12.1)	<0.001
Previous history (N, %)					
Heart failure	199 (52.1)	726 (65.9)	456 (55.3)	602 (65.9)	<0.001
Hypertension	336 (88.0)	953 (86.6)	766 (93.0)	828 (90.6)	<0.001
Diabetes mellitus	113 (29.6)	329 (29.9)	296 (35.9)	367 (40.2)	<0.001
Dyslipidemia	272 (71.2)	784 (71.2)	629 (76.3)	732 (80.1)	<0.001
Hyperuricemia	176 (46.1)	626 (56.9)	448 (54.4)	554 (60.6)	<0.001
Stroke	75 (19.6)	272 (24.7)	183 (22.2)	284 (31.1)	<0.001
Cancer	64 (16.8)	168 (15.3)	129 (15.7)	132 (14.4)	0.747
Myocardial infarction	25 (6.5)	56 (5.1)	209 (25.4)	232 (25.4)	<0.001
$CHADS_2$ score	2.4 (1.3)	2.6 (1.3)	2.7 (1.3)	2.9 (1.3)	<0.001
CHA_2DS_2-VASc score	3.7 (1.7)	3.8 (1.6)	4.1 (1.6)	4.2 (1.7)	<0.001
Hemodynamic and LV function					
Systolic BP (mmHg)	126.4 ± 19.1	124.2 ± 18.4	129.7 ± 18.3	124.5 ± 17.9	<0.001
Diastolic BP (mmHg)	72.3 ± 11.6	72.8 ± 12.1	74.3 ± 12.5	72.4 ± 11.9	0.005
Heart rate (bpm)	72.1 ± 16.2	74.2 ± 16.2	73.1 ± 15.6	73.6 ± 16.2	0.146
LVEF (%)	63.0 ± 13.9	58.8 ± 13.9	60.6 ± 13.3	58.1 ± 13.9	<0.001
≤40% (N, %)	30 (7.9)	124 (11.3)	76 (9.2)	106 (11.6)	0.105
40–50% (N, %)	33 (8.6)	126 (11.4)	80 (9.7)	121 (13.2)	0.041
≥50% (N, %)	308 (80.6)	828 (75.2)	634 (76.9)	667 (73.0)	0.023
LAD (mm)	43.3 ± 8.6	47.9 ± 9.7	44.0 ± 9.0	47.9 ± 9.3	<0.001
LVDd (mm)	49.0 ± 8.3	51.2 ± 8.9	50.0 ± 7.5	51.6 ± 8.1	<0.001
Laboratory findings					
Hemoglobin (g/dl)	13.0 ± 2.1	13.5 ± 2.0	13.3 ± 1.9	13.4 ± 2.1	<0.001
Albumin (g/dl)	4.0 ± 0.5	4.1 ± 0.5	4.1 ± 0.5	4.0 ± 0.5	0.081
Triglyceride (mg/dl)	118.2 ± 67.2	125.4 ± 95.1	121.5 ± 82.6	126.2 ± 80.0	0.254
HDL-C (mg/dl)	53.2 ± 15.8	53.5 ± 15.4	53.6 ± 16.5	52.3 ± 15.8	0.333
LDL-C (mg/dl)	109.1 ± 31.4	107.0 ± 31.3	104.4 ± 30.2	104.2 ± 29.7	0.076
HbA1C (%)	6.1 ± 0.9	6.1 ± 0.9	6.2 ± 0.9	6.3 ± 1.0	0.003
eGFR (ml/min/1.73m^2)	61.1 ± 21.2	62.9 ± 19.5	59.8 ± 20.0	59.6 ± 18.5	<0.001
BNP (median, IQR, pg/ml)	101 (50, 222)	143 (75, 255)	118 (55, 227)	138 (72, 266)	<0.001
PT-INR (median, IQR)	1.54 (1.09, 1.75)	1.76 (1.50, 2.10)	1.09 (1.01, 1.34)	1.77 (1.50, 2.14)	<0.001
Within therapeutic range (%)[c]	NA	49.4	NA	49.2	0.995[a]
Medications (N, %)					
Antiplatelets					
Aspirin	NA	NA	762 (92.5)	815 (89.5)	0.038[b]
P2Y12 inhibitors	NA	NA	203 (24.6)	177 (9.4)	0.009[b]
PDE inhibitors	NA	NA	75 (9.1)	75 (8.2)	0.563[b]
β-blockers	137 (35.9)	531 (48.2)	323 (39.2)	472 (51.6)	<0.001
CCBs	158 (41.4)	379 (34.4)	398 (48.3)	376 (41.1)	<0.001
Diuretics	155 (40.6)	637 (57.9)	374 (45.4)	529 (57.9)	<0.001
Digitalis	101 (26.4)	506 (46.0)	273 (33.1)	393 (43.0)	<0.001
RAS inhibitors	199 (52.1)	731 (66.4)	559 (67.8)	625 (68.4)	<0.001
Statins	62 (16.2)	227 (20.6)	235 (28.5)	316 (34.6)	<0.001

Results are expressed as mean ± SD or frequency (%).
AC, anticoagulant; AF, atrial fibrillation; AP, antiplatelet; ATT, antithrombotic therapy; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CCB, calcium channel blockers; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LAD, left atrial dimension; LDL-C, low-density lipoprotein cholesterol; LV, left ventricle; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NA, not applicable; PT-INR, prothrombin time-international normalized ratio; PDE, phosphodiesterase; RAS, renin-angiotensin system.
[a] Comparison between the AC and the AC&AP groups.
[b] Comparison between the AP and the AC&AP groups.
[c] PT-INR 2.0–3.0 for patients aged < 70 and 1.6–2.6 for those aged ≥ 70 according to the Japanese Circulation Society guidelines.

< .05) and cardiovascular mortality (aHR 0.66, 0.61 and 0.64, all P < .05) in multiple Cox proportional hazards models.

4. Discussion

The major findings of the present study are as follows; (1) anticoagulant monotherapy was associated with reduced risk of ischemic stroke in AF patients especially in those with HF, CAD, or non-paroxysmal AF, (2) the combination therapy with anticoagulants and antiplatelets had significantly greater risk of a composite of thromboembolism and major bleeding than anticoagulant monotherapy in AF patients especially when complicated with HF or CAD, (3) even the combination of anticoagulants and SAPT had significantly greater risk of the composite endpoint than anticoagulant monotherapy in AF patients, especially when complicated with HF or CAD, (4) the combination therapy had significantly greater risk of major bleeding other than ICH or major GI bleeding, and (5) AF patients without ATT were associated with worse prognosis. The present study provides the intriguing evidence on ATT

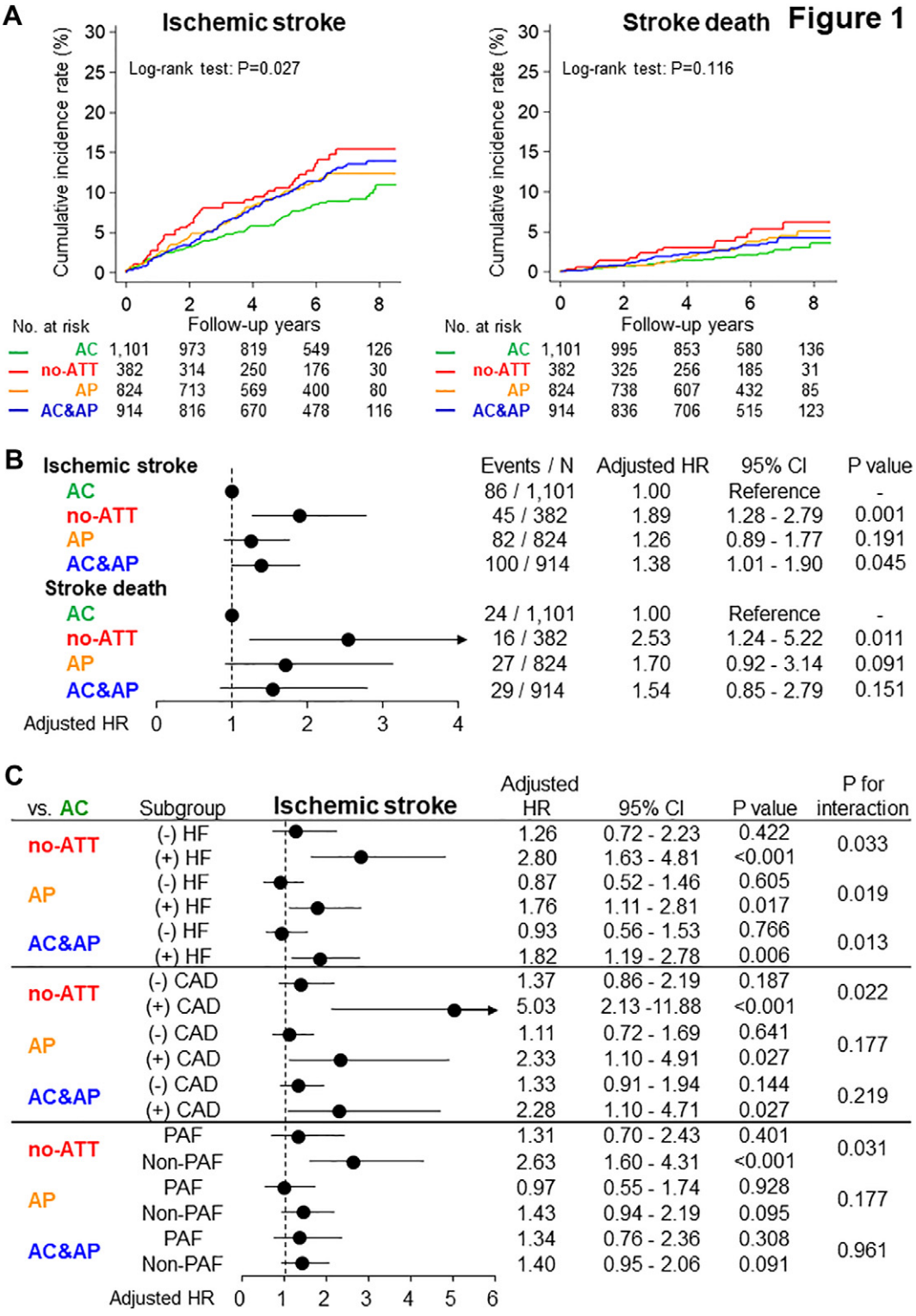


Fig. 1. Benefits of antithrombotic therapy in AF patients. A: Cumulative incidence of ischemic stroke (left panel) and stroke death (right panel) in AF patients by ATT. B: Results of multiple Cox proportional hazards models regarding ischemic stroke and stroke death. C: Results of multiple Cox proportional hazards models regarding ischemic stroke in AF patients with following comorbidities: HF, CAD and paroxysmal AF. The AC group was used as a reference. Variables adjusted in multiple Cox proportional hazards models were age, sex, BMI, eGFR, paroxysmal AF, smoking, following medications: β-blocker, CCB, diuretic, digitalis, RAS inhibitor and statin, and following history: CAD, diabetes mellitus, dyslipidemia, HF, hypertension and stroke. AC, anticoagulant; AF, atrial fibrillation; AP, antiplatelet; ATT, antithrombotic therapy; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; PAF, paroxysmal atrial fibrillation; RAS, renin-angiotensin system.

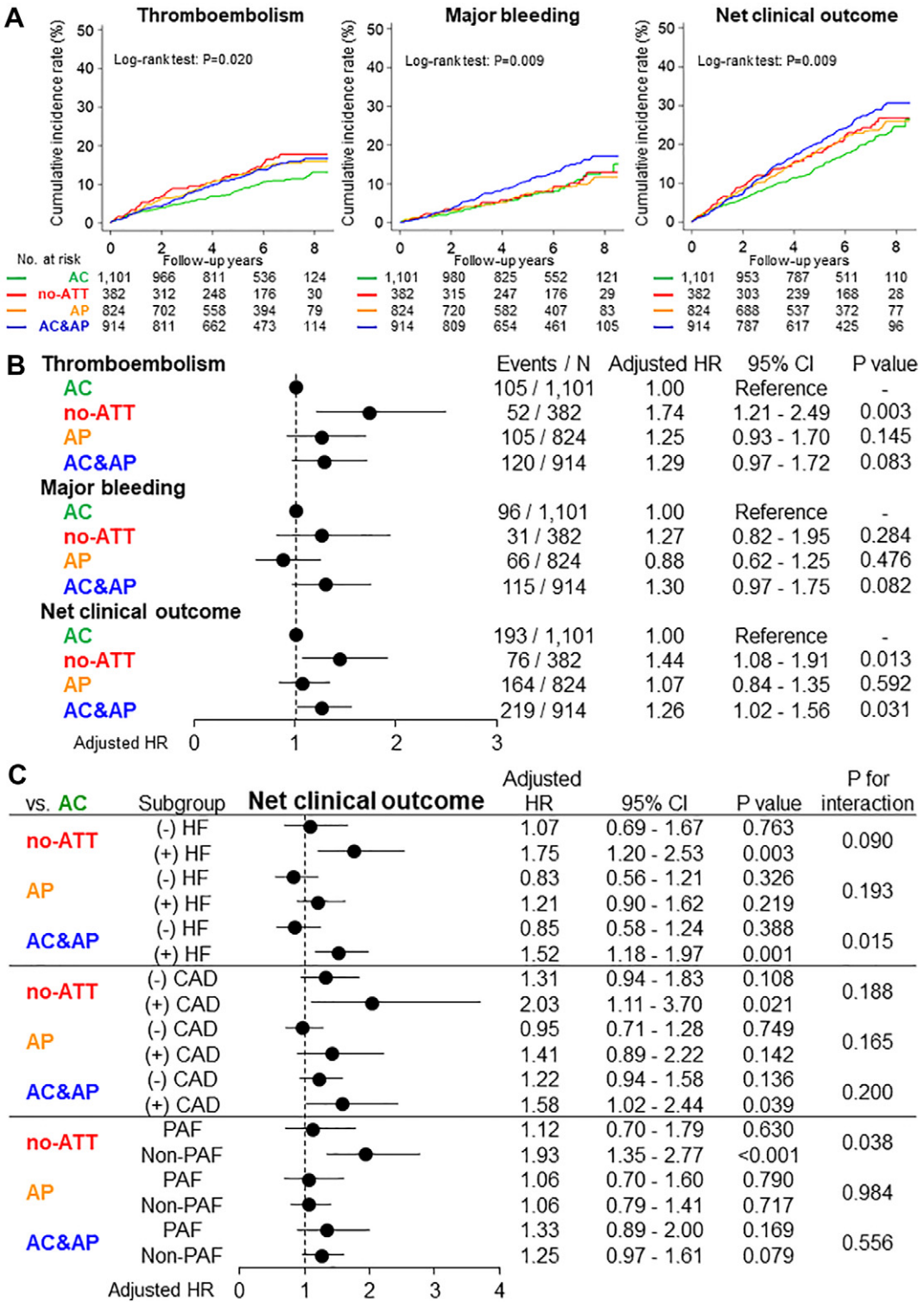
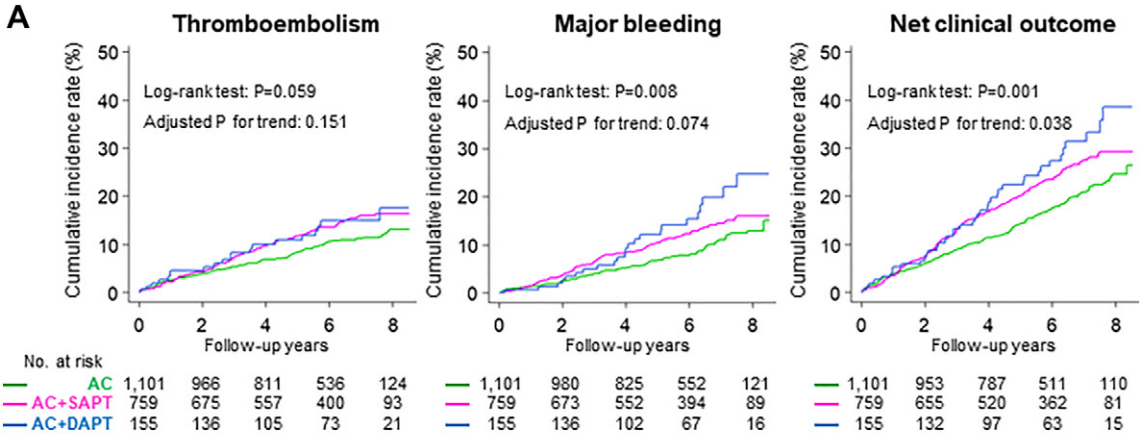
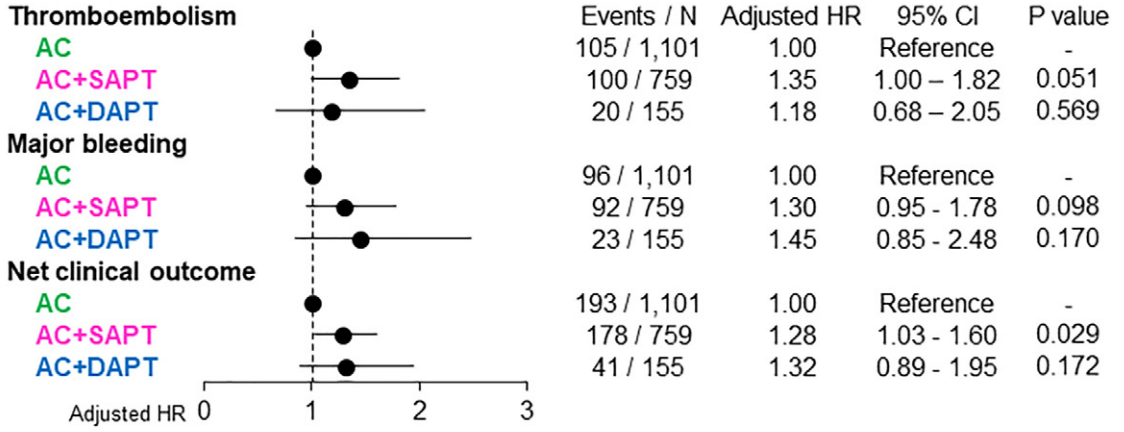


Fig. 2. Clinical benefits and risks of antithrombotic therapy in AF patients. A: Cumulative incidence of thromboembolism (left panel), major bleeding (center panel) and net clinical outcome (right panel) in AF patients by ATT. B: Results of multiple Cox analyses regarding thromboembolism, major bleeding and net clinical outcome by ATT. C: Results of multiple Cox proportional hazards models regarding net clinical outcome in AF patients with following comorbidities: HF, CAD and paroxysmal AF. The AC group was used as a reference. Thromboembolism consists of a composite of ischemic stroke, myocardial infarction and systemic embolism. Net clinical outcome consists of a composite of thromboembolism and major bleeding. Variables adjusted in multiple Cox proportional hazards models were age, sex, BMI, eGFR, paroxysmal AF, smoking, following medications: β-blocker, CCB, diuretic, digitalis, RAS inhibitor and statin, and following history: CAD, diabetes mellitus, dyslipidemia, HF, hypertension and stroke. AC, anticoagulant; AF, atrial fibrillation; AP, antiplatelet; ATT, antithrombotic therapy; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; PAF, paroxysmal atrial fibrillation; RAS, renin-angiotensin system.





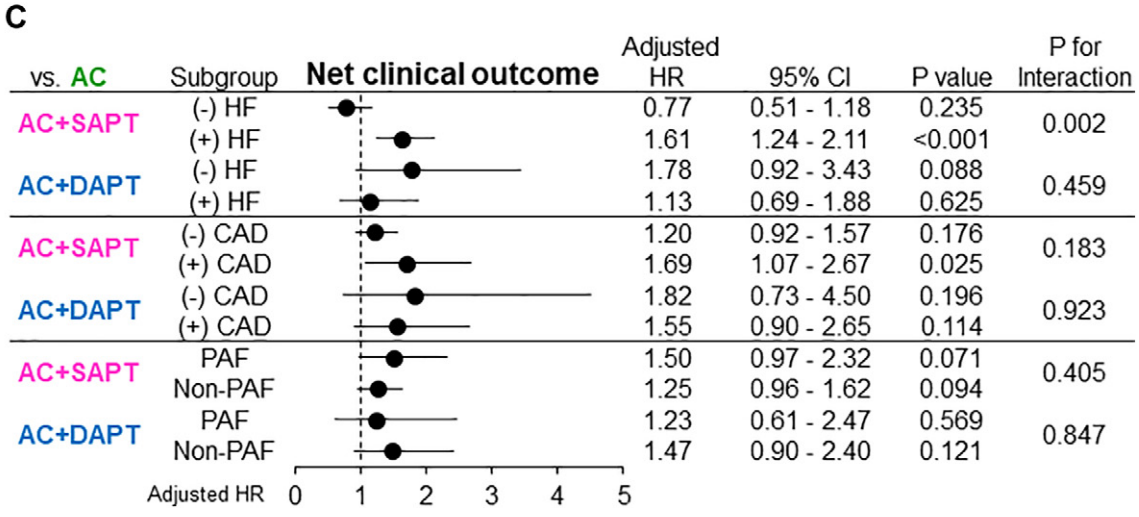


Fig. 3. Clinical benefits and risks of the combination therapy with anticoagulants and antiplatelets in AF patients. A: Cumulative incidence of thromboembolism (left panel), major bleeding (center panel) and net clinical outcome (right panel) in AF patients using anticoagulant monotherapy, the combination of anticoagulants plus SAPT, and that with those plus DAPT. B: Results of multiple Cox analyses regarding thromboembolism, major bleeding and net clinical outcome in AF patients using anticoagulant monotherapy, the combination of anticoagulants plus SAPT, and that with those plus DAPT. C: Results of multiple Cox proportional hazards models regarding net clinical outcome in AF patients with following comorbidities: HF, CAD, and paroxysmal AF. The AC group was used as a reference. Thromboembolism consists of a composite of ischemic stroke, myocardial infarction and systemic embolism. Net clinical outcome consists of a composite of thromboembolism and major bleeding. Variables adjusted in multiple Cox proportional hazards models were age, sex, BMI, eGFR, paroxysmal AF, smoking, following medications: β-blocker, CCB, diuretic, digitalis, RAS inhibitor and statin, and following history: CAD, diabetes mellitus, dyslipidemia, HF, hypertension and stroke. AC, anticoagulant; AF, atrial fibrillation; AP, antiplatelet; ATT, antithrombotic therapy; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; CI, confidence interval; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; PAF, paroxysmal atrial fibrillation; RAS, renin-angiotensin system; SAPT, single antiplatelet therapy.

in the management of AF patients, particularly with special references to HF, CAD, and the patterns of AF.

4.1. Relationship between efficacy of antithrombotic therapy and comorbidities in AF patients

Accumulated evidence supports the benefit of oral anticoagulants for stroke prevention in AF patients [3]. Consistently, the present study showed that anticoagulant monotherapy was significantly associated with reduced risk of ischemic stroke in AF patients, especially comorbid with HF, CAD, or non-paroxysmal AF.

HF is an important component of the currently available risk scores [14–16]. However, recent studies did not support this notion, as HF was not an independent risk factor for stroke in AF patients [17,18]. In the present study, anticoagulant monotherapy showed the superiority in reducing ischemic stroke over the no-ATT, the AP, or the AC&AP groups in AF patients with but not in those without HF. This finding can be supported by the fact that >80% of stroke in AF patients with HF are due to cardiogenic embolism that can be prevented by oral anticoagulants [19]. On the other hand, it has been reported that averaged time in therapeutic range (TTR) was lower in AF patients with HF [20], with resultant increased risk of thromboembolism. However, this may not be the case in the present study, since the value of PT-INR was comparable between the AC and the AC&AP groups, even in AF patients with HF (1.79 and 1.79 for the AC and the AC&AP groups, respectively).

With respect to AF patterns, current guidelines recommend that selection of ATT should be based on the risk of thromboembolism irrespective of AF patterns [2]. However, it remains controversial whether the type and duration of AF affect the risk of ischemic stroke. Rizos et al. reported that paroxysmal AF was more frequent than persistent AF in patients with acute stroke and those with transient ischemic attack patients [21]. In contrast, the sub-study of the ACTIVE-W trial showed that paroxysmal AF had a similar risk for thromboembolism compared with sustained AF [22]. However, the sub-studies of the DOAC trials showed that persistent AF was associated with higher risk of stroke as compared with paroxysmal AF [23,24]. In the present study, non-paroxysmal AF patients had 2-fold higher incidence of ischemic stroke compared with paroxysmal AF patients in the no-ATT group. Also, we found that the no-ATT group was associated with higher risk of ischemic stroke than the AC group especially in non-paroxysmal AF patients, indicating the beneficial effect of anticoagulants in those patients.

Interestingly, we found that AF patients treated with both anticoagulants and antiplatelets had higher risk of ischemic stroke compared with those with anticoagulant alone. With regard to baseline characteristics, the AC&AP group, as compared with the AC group, had higher prevalence of male sex, hypertension, dyslipidemia, diabetes mellitus, CAD, previous stroke, and lower renal function. All these factors are precipitating factors or consequences of atherosclerosis, one of the major causes of ischemic stroke [25]. Indeed, in the present study, this was the case for AF patients with CAD. Thus, it is possible that patients in the AC&AP group are likely to have atherosclerotic stroke more than those in the AC group, although it is also possible that other unadjusted precipitating factors, such as inflammation [25], could be involved in the difference in the risk of ischemic stroke.

4.2. Benefit-risk balance between anticoagulant monotherapy and the combination of anticoagulant and antiplatelet drugs

In the present study, we found that the combination therapy with anticoagulants and antiplatelets, even combination with SAPT, was associated with a significant increase in the risk of the composite outcome of thromboembolism and major bleeding, especially when complicated with HF or CAD. Increase in the incidence of major bleeding caused by the combination of anticoagulants and antiplatelets has already been reported in the studies from the Western countries [5,26,27]. With regard to CAD, a Danish nationwide cohort study showed that the combination of antiplatelets and warfarin was associated with increased bleeding risk without greater reduction in the risk of coronary events or thromboembolism [28]. Recently, a Japanese community-based registry showed that AF patients with the combination of anticoagulants and antiplatelets had higher incidences of major bleeding and thromboembolism compared with anticoagulant monotherapy [29]. Considering these reports and the present findings, anticoagulant monotherapy may be more profitable than the combination therapy in AF patients. However, the present results may not be applied to patients with acute coronary syndrome or venous thromboembolism, since our CHART-2 Study enrolled stable patients and nearly 80% of the patients were outpatients.

In the present study, the combination therapy showed no significant increase in the risk of thromboembolism or major bleeding as compared with anticoagulant monotherapy, whereas the previous reports from US and Europe showed a significant increase [5,26,27]. This discrepancy could be explained in part by ethnic/geographical differences. When compared with non-Asians, Asians have a higher risk for ICH, major bleeding, and stroke, as well as difficulties in maintaining a high TTR [30], all of which were confirmed by the sub-studies of the DOAC trials [31–33]. Also, differences in the frequencies of genetic polymorphisms regarding warfarin metabolic enzymes, such as VKORC1 and CYP2C9 [34], and/or drug-food interactions of warfarin, such as Chinese herbs [35], could result in the fluctuation of TTR and thus affect the risks and benefits of ATT in Asians. In addition, HF is independently associated with lower TTR [20]. Indeed, in the present study, <50% of patients taking warfarin were treated within the therapeutic range of PT-INR, a consistent finding with the Fushimi AF registry in Japan [36]. Thus, lower TTR could be associated not only with increased thromboembolism but also with reduced major bleeding in AF patients using warfarin in the present study, although TTR values were not available. On the other hand, the combination therapy was associated with a significant increase in the risk of major bleeding in AF patients with HF in the present study. This could be explained by the result of the AFFIRM trial that showed HF and use of warfarin or aspirin were associated with a significant increase in the risk of major bleeding [37]. Thus, both anticoagulants and antiplatelets could increase major bleeding additively or synergistically in AF patients with HF. Lip et al. reported that LV dysfunction was a significant predictor for major bleeding in AF patients [38]. However, this may not be the case in the present study, since the proportion of HF with reduced LV ejection fraction (HFrEF) was comparable between the AC and the AC&AP groups.

Of note, we found that the combination therapy, even combination of anticoagulant therapy and SAPT, had a significantly greater risk of major GI bleeding, but not ICH, as compared with anticoagulant monotherapy. Hansen et al. reported that the combination therapy with aspirin and warfarin had an increased risk of GI bleeding [5]. In the present study, nearly 90% of AF patients received aspirin as an antiplatelet in the combination therapy. It is well known that concomitant aspirin use is a significant predictor of major bleeding for AF patients with anticoagulants [38]. Even in the era of DOACs, GI bleeding remains a major concern in AF patients since a meta-analysis of randomized DOAC trials showed a significantly increased risk of GI bleeding [39]. Thus, routine use of proton pump inhibitors (PPIs) may be strongly recommended for AF patients treated with ATT [8], since the efficacy of PPIs in reducing the rate of recurrent GI bleeding has been well established [40]. On the other hand, Hansen et al. also reported in the same study that the combination therapy had a greater risk of ICH [5]. Although Asians have higher risk of ICH, crude incidence rates were comparable between the present and their studies (approximately 0.6–0.8%/year). It is possible that this relatively low incidence of ICH in the present study is attributed to the frequency of antihypertensive drugs, since hypertension is an established risk factor for ICH in the general populations and warfarin users [41].

Finally, we were unable to examine the effect of triple combination therapy with warfarin and DAPT in AF patients because of the small

number of such patients. However, recent studies demonstrated that the rate of major bleeding in the triple combination therapy was significantly greater than monotherapy, whereas the efficacy was comparable in AF patients undergoing percutaneous coronary intervention [42,43].

4.3. Antithrombotic therapy and long-term prognosis of AF patients

A previous meta-analysis showed that adjusted-dose warfarin substantially reduced all-cause death in AF patients compared with no ATT, whereas aspirin had no effect [3]. In addition, guideline-adherent approach reduced the events of all-cause and cardiovascular mortalities [44]. In the present study, only the no-ATT group, but not the AP or the AC&AP groups, was significantly associated with worse prognosis. Interestingly, even antiplatelets alone significantly reduced the risk of all-cause and cardiovascular mortality as compared with the no-ATT group. This result conflicts with the current guidelines [1,2,11] and a previous RCT that showed that antiplatelet monotherapy was not effective for prevention of stroke or cardiovascular death in AF patients [45,46]. This inconsistency could be explained by the characteristics of the CHART-2 Study as follows; 1) the study population was older and comorbidities, such as hypertension, diabetes mellitus, and especially HF, were more prevalent [12,13]. For example, the proportion of current or past history of HF in the present study (61.6%) was higher in the ACTIVE-W (~30%) [45] and the JAST (~10%) trials [46], 2) median follow-up period was longer compared with the ACTIVE-W (1.3 years) and the JAST (2.2 years) trials, and 3) the number of cardiovascular death was highest (497, 226, and 6 events, respectively). Thus, the present results indicate that ATT, even antiplatelet monotherapy, has beneficial prognostic effects on long-term survival in AF patients.

4.4. Study limitations

Several limitations should be mentioned for the present study. First, our CHART-2 Study is an observational study for HF in Japan. Thus, a caution is needed when generalizing the present findings to other populations in different countries. Second, we did not consider adherence, discontinuation, changes, or crossover of ATT thereafter in the present study. Third, only warfarin was used at baseline since DOACs were not available in Japan during the enrollment period (2006–2010) of the CHART-2 Study. It is noteworthy that recent studies showed that DOACs reduced all-cause mortality compared with warfarin, mainly driven by a reduction in fatal bleedings [47], although they rather increased GI bleeding [39]. Thus, the benefit-risk balance of DOACs should be further examined in future studies. Fourth, since time in therapeutic range (TTR) of PT-INR was not available in the present study, information of anticoagulation quality was limited. Fifth, we did not distinguish the cause of ischemic stroke (e.g. lacunar infarction, atherosclerosis, and cardiac embolism). Finally, as a nature of an observational study, we should be cautious for potential confounding factors associated with unknown biases.

4.5. Conclusions

In the present study, we were able to demonstrate that ATT is beneficial for AF patients, particularly for those with HF, CAD, or non-paroxysmal AF and that among ATT, anticoagulant monotherapy may be most profitable for both clinical benefits and risks for AF patients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.09.022.

Declaration of competing interest

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