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Effects of antiarrhythmic drug responsiveness and diagnosis-to-ablation time on outcomes after catheter ablation for persistent atrial fibrillation

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Abstract

Background: The impact of delaying atrial fibrillation catheter ablation (AFCA) for antiarrhythmic drug (AAD) management on the disease course remains unclear. This study investigated AFCA rhythm outcomes based on the diagnosis-to-ablation time (DAT) and AAD responsiveness in participants with persistent AF (PeAF).

Methods: We included data from 1038 AAD-resistant PeAF participants, all of whom had a clear time point for AF diagnosis, especially PeAF at diagnosis time, and had undergone an AFCA for the first time. Participants who experienced recurrences of paroxysmal type on AAD therapy were analyzed as a cohort of AAD-partial responders; those maintaining PeAF on AAD were AAD-non-responders. We determined the DAT cutoff for best discriminating long-term rhythm outcomes using a maximum log-likelihood estimation method based on the Cox proportional hazard regression model.

Results: Of the participants (79.8% male; median age 61), 806 (77.6%) were AAD-non-responders. AAD-non-responders had a higher body mass index and a larger left atrial diameter than AAD-partial-responders. They also had a higher incidence of AF recurrence after AFCA (adjusted hazard ratio 1.75, 95% confidence interval 1.33–2.30; log-rank $p < .001$) compared to AAD-partial-responders. The maximum log-likelihood estimation showed bimodal cutoffs at 22 and 40 months. The optimal DAT cutoff rhythm outcome was 22 months, which discriminated better in the AAD-partial-responders than in the AAD-non-responders.

Conclusions: Both DAT and AAD responsiveness influenced AFCA rhythm outcomes. Delaying AFCA to a DAT of longer than 22 months was inadvisable, particularly in the participants in whom PeAF was changed to paroxysmal AF during AAD therapy.

KEYWORDS
antiarrhythmic responsiveness, atrial fibrillation, atrial fibrillation catheter ablation, atrial fibrillation duration, clinical recurrence

1 | INTRODUCTION

Worldwide, atrial fibrillation (AF) is the most frequently encountered sustained cardiac arrhythmia, with a prevalence of 2%–4% in adults.[1–4] The aggressive rhythm control in patients with AF slows the progression of AF, especially paroxysmal AF,[5–8] and sinus restoration contributes to cardiac remodeling in these patients.[9] Recent studies have demonstrated that, when compared with medical therapy, atrial fibrillation catheter ablation (AFCA) reduces the mortality rate by approximately 40% in patients with heart failure.[10] Furthermore, AFCA was associated with a lower incidence of stroke and dementia.[11–13] As per the current 2020 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of AF, AFCA is a well-established standard procedure in cases of antiarrhythmic drugs (AADs)-resistant AF, as well as AF with combined left ventricular (LV) dysfunction.[14] However, pulmonary vein isolation (PVI), which has been a cornerstone of AFCA, is less effective in persistent AF (PeAF) than in paroxysmal AF (PAF).[15]

The duration between the time of the first AF diagnosis and the initiation of rhythm control therapy is known to be a prognostic factor for post-therapy outcomes.[16] Based on the findings of a randomized clinical trial (RCT) by Kirchhof et al., the need for aggressive rhythm management was emphasized, as early rhythm control in patients with AF has been shown to reduce adverse clinical outcomes.[17] Nevertheless, the evidence supporting the benefits of early AFCA and the optimal timing thereof is lacking. Moreover, limited literature exists regarding the correlation between the responsiveness of AF to AADs and rhythm outcomes subsequent to AFCA. Additionally, previous studies demonstrated inconsistent results regarding the correlation between AAD responsiveness and the success rate of AFCA.[18,19]

In this study, we aimed to evaluate and compare the rhythm outcomes subsequent to AFCA according to AAD responsiveness, as well as to investigate the impact of diagnosis-to-ablation time (DAT) on rhythm outcomes, particularly in participants with PeAF.

2 | METHODS

2.1 | Study population and definitions

From March 2009 to February 2023, 1038 participants with AAD-resistant PeAF from the Yonsei AF ablation registry, all of whom had a clear time point for the electrocardiographic (ECG) diagnosis of AF, especially PeAF at diagnosis time, had undergone a first-time AFCA. AFCA was performed in cases of AAD-refractory AF, as recommended in the current guidelines. Subsequently, regular follow-up consultations were conducted to analyze the cardiac rhythms in accordance with the ESC guidelines (Figure 1). PeAF was defined as an AF that lasted for more than 7 days.[14] The DAT time was defined as the period from the day AF was first confirmed by ECG to the day when the AFCA procedure was performed. Among the participants treated with AADs for AF, those who experienced a recurrence of a paroxysmal nature were classified as AAD-partial-responders, while those consistently presenting with PeAF were categorized as AAD-non-responders.

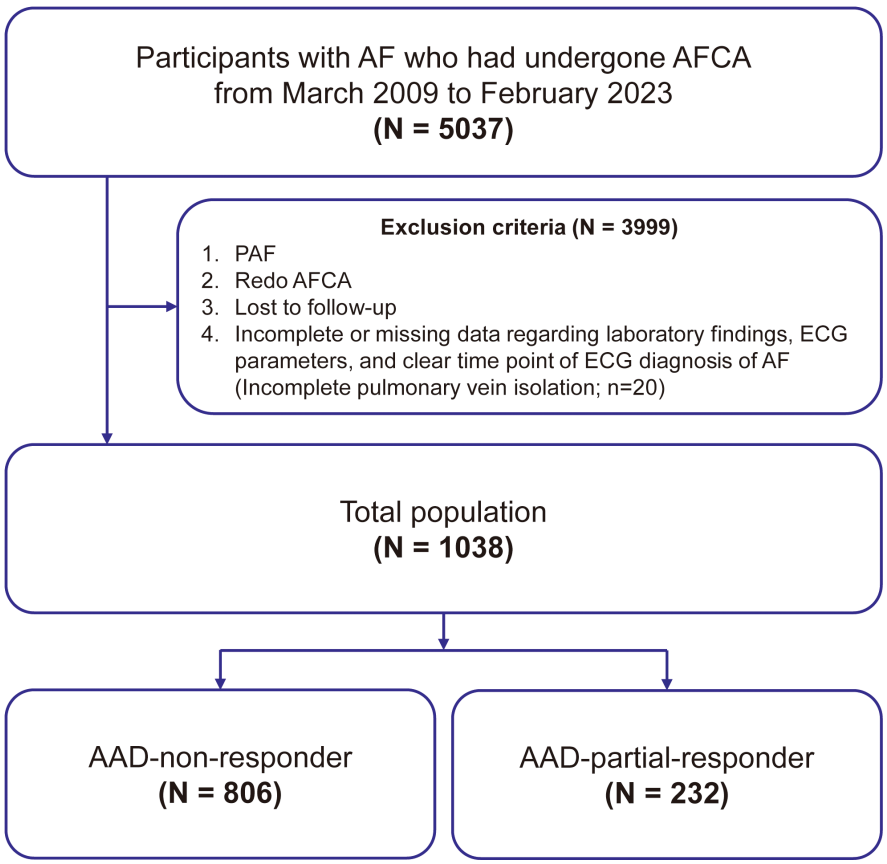

FIGURE 1 Study population and flowchart of the selection of participants. AAD, antiarrhythmic drug; AF, atrial fibrillation; AFCA, atrial fibrillation catheter ablation; ECG, electrocardiographic; PAF, paroxysmal atrial fibrillation.

This study was conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent was obtained from all participants who were included in the Yonsei AF Ablation Cohort Database (NCT02138695) for the final data analysis.

2.2 | Electroanatomical mapping and atrial fibrillation catheter ablation

Before the AFCA, all participants underwent transthoracic echocardiography. Additionally, either transesophageal echocardiography or intracardiac echocardiography was performed to exclude intracardiac thrombi. Intracardiac electrograms were obtained using the Prucka Cardio Lab electrophysiology system (General Electric Medical Systems Inc., Milwaukee, WI, USA). For participants who underwent radiofrequency catheter ablation, three-dimensional electroanatomic mapping was performed (NavX, St. Jude Medical, Inc., Minnetonka, Minnesota; and CARTO, Biosense-Webster, Inc., Diamond Bar, California), using a circumferential pulmonary vein (PV) mapping catheter (AFocus, Abbott, Inc., Chicago, IL, USA; Lasso, Biosense-Webster Inc., Diamond Bar, CA, USA). An open-irrigated tip catheter (Celsius, Johnson & Johnson Inc., Diamond Bar, CA, USA; NaviStar ThermoCool, Biosense Webster Inc.; ThermoCool SF, Biosense Webster Inc.; ThermoCool SmartTouch, Biosense Webster Inc.; Coolflex, Abbott Inc.; TactiCath, Abbott Inc.; and FlexAbility, Abbott Inc.) was used. Circumferential PVI was achieved through the creation of continuous circumferential lesions at the antral level of the left atrium (LA), encircling both the left and right PVs. For participants who underwent cryoballoon ablation, the AFCA procedures were performed using a 28-mm cryoballoon (Arctic Front Advance or Arctic Front Advance Pro, Medtronic, Minneapolis, MN, USA) and a 12 Fr deflectable transseptal sheath (Flex Cath Advance, Medtronic). The 28-mm cryoballoon was used in conjunction with a multipolar spiral catheter (Achieve, 20 mm, Medtronic), which allowed the registration of PV conduction and the determination of time to isolation. To ensure optimal PV occlusion, we confirmed proper sealing by injecting a contrast medium through the distal catheter lumen. Each PV ostium or antrum was frozen for 4 min. During the right-sided PV ablation, we stimulated the right phrenic nerve (PN) with a quadripolar catheter (5 F, Laon Med, Inc., Republic of Korea, 4–10 V, 2 ms, 1500 ms), at the junction between the superior vena cava and right subclavian vein. Furthermore, we monitored the compound motor action potentials to immediately identify right PN damage. In cases of >30% reduction or weakness in the compound motor action potential amplitude, or cases due to the loss of PN capture, the freezing process was instantly terminated.

PVI was performed in all the participants. After achieving PVI, we did not use the isoproterenol and adenosine triphosphate testing for dormant conduction testing; instead, the procedure was finished after a 20-min observation period in accordance with expert consensus.[15] Moreover, at their discretion and when deemed necessary, the operators opted to perform cavotricuspid isthmus and other additional ablations, such as the roof, posterior–inferior, and anterior lines, as well as complex fractionated atrial electrograms in the superior vena cava or other non-PV foci.

2.3 | Follow-up and study endpoints

All participants who had undergone AFCA attended regular follow-up consultations at the outpatient clinic at 1, 3, 6, and 12 months, and thereafter every 6 months, or when symptoms occurred. In accordance with the 2012 Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society (HRS/EHRA/ECAS) Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation Guidelines, participants underwent an ECG at each outpatient consultation, as well as a 24 h Holter recording at 3 and 6 months subsequent to AFCA and every 6 months thereafter.[20] The clinical outcome was set to clinical recurrence, defined as any atrial arrhythmias, including atrial tachycardia, atrial flutter, and AF, lasting for 30 sec or more, beyond the 90-day blanking period subsequent to AFCA.

2.4 | Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SDs) or medians with interquartile ranges (IQRs), and categorical variables were reported as counts (percentages). The Kaplan–Meier analysis with the log-rank test was used to analyze the cumulative incidence of clinical recurrences subsequent to AFCA. The Cox proportional hazards regression model was used to examine the correlation between DAT and clinical recurrence subsequent to AFCA, and factors significant in the univariable analyses ($p < .1$) were entered into the multivariable analyses. The results were reported as hazard ratios (HRs) and 95% confidence intervals (CIs). In this study, we utilized Cox proportional hazards regression models for each potential DAT cutoff value. The maximum log-likelihood estimation method, a standard statistical approach for estimating the parameters of a probability distribution from the observed data, was employed to determine the time at which the disparity between the two cohorts was the most statistically significant. Consequently, the cutoff value with the highest likelihood estimation was chosen as the optimal timing for DAT. Two-sided p-values <.05 were considered statistically significant. Statistical analyses were conducted using R statistical software (version 4.1.2, R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/).

3 | RESULTS

3.1 | Baseline characteristics of participants

In this study, 1038 participants with PeAF were included, with a median age of 61 years (IQR: 54–68 years), and 79.8% of the participants were male. Cryoablation was performed in 20.9% ($n = 217$) of

the participants, and the median DAT was 24 months (IQR: 11–51) (Table 1).

3.2 | Comparison of the antiarrhythmic rhythm outcomes between drug-non-responders and partial-responders

We compared the two cohorts of participants: the AAD-non-responders and the AAD-partial-responders (Table 1). The proportion of males ($p = .001$), body mass index ($p = .007$), LA diameter ($p < .001$), and pericardial fat volume ($p < .001$) were higher in the AAD-non-responders than in the AAD-partial-responders. Redo procedures were performed more in AAD-non-responders than in AAD-partial responders. Regarding rhythm outcomes during the median of the 27-month follow-up (IQR: 16–46 months), the AAD-non-responders demonstrated a higher incidence of clinical recurrences subsequent to AFCA than did the AAD-partial-responders (log-rank $p < .001$; adjusted HR [aHR] 1.75; 95% CI 1.33–2.30) (Figure 2A).

3.3 | Cutoff values of diagnosis-to-ablation time, with post-ablation rhythm outcomes

In the multivariate Cox proportional hazards regression analysis, a longer DAT was correlated with a high risk of clinical recurrence subsequent to AFCA (per year increase, aHR = 1.03, 95% CI: 1.01–1.06, $p = .008$, Table 2 and Table S1). The log-likelihood graphs of the Cox proportional hazards regression models showed bimodal morphology for the cutoff values of 22 and 40 months (Figure 3A). The cutoff value of DAT that most optimally discriminated between rhythm outcomes was 22 months, using the maximum log-likelihood estimation method.

Table 3 presents the characteristics of the participants with a DAT ≤22 months and with a DAT > 22 months. Although empirical linear ablations were more frequently performed and the procedure times were longer, the risk of clinical recurrence subsequent to AFCA was statistically significantly higher in the DAT > 22 months sub-cohort than that in the DAT ≤22 months sub-cohort (log-rank $p = .001$; aHR 1.34, 95% CI 1.09–1.64) (Figure 2C and Table 2). The DAT >40 months showed a similar discrimination power for worse rhythm outcomes (log-rank $p = .001$; aHR 1.34, 95% CI 1.09–1.65) (Figure 2D and Table 2). In contrast, the DAT >12 months did not discriminate against the risk of recurrence subsequent to AFCA (log-rank $p = .290$; aHR 1.09, 95% CI 0.88–1.36) (Figure 2B and Table 2).

3.4 | Optimal timing of ablation depending on antiarrhythmic drug responsiveness

We examined the log-likelihood function for Cox proportional hazards regression models at each possible cutoff value for DAT in the cohorts of the AAD-partial-responders and AAD-non-responders. The cutoff values for DAT, calculated using the maximum likelihood estimation method, were 22 and 40 months in the cohorts of the AAD-partial-responders and AAD-non-responders, respectively (Figure 3B,C). In the cohort of the AAD-partial-responders, the DAT cutoff value of 22 months demonstrated a higher discriminative power for rhythm outcomes (DAT >22 months: aHR 1.96, 95% CI 1.16–3.31, $p = .012$) than that of 40 months (DAT >40 months: aHR 1.69, 95% CI 1.02–2.80, $p = .040$) (Figure 4; Table S2). In the cohort of the AAD-non-responders, the DAT cutoff values of 22 and 40 months exhibited comparable discrimination powers for clinical recurrences subsequent to AFCA (DAT >22 months: aHR 1.24, 95% CI 0.99–1.55, $p = .056$; DAT >40 months: aHR 1.28, 95% CI 1.02–1.60, $p = .031$) (Figure 5; Table S3).

3.5 | Sensitivity analysis

We conducted sensitivity analyses, limiting the maximal follow-up duration to 3 years. The results were consistent with the main analyses in the overall population (Figure S1). Additionally, in subgroup analyses based on AAD responsiveness, both DAT cutoffs of 22 and 40 months exhibited greater distinctiveness compared to the main analyses (Figures S2 and S3). This further strengthens our initial observation that the DAT cutoff value of 22 months possesses high discriminative power for long-term rhythm outcomes in the overall population.

4 | DISCUSSION

The main findings of our study are as follows. First, in the cohort of the AAD-partial-responders, the incidence of recurrence subsequent to AFCA was lower than that in the cohort of the AAD-non-responders. Second, in participants with PeAF, a longer DAT was correlated with a higher risk of recurrence, with a cutoff value of 22 months, as estimated using the maximum log-likelihood estimation method. Third, these results suggest that in participants with PeAF, the implementation of AFCA should not be postponed until 22 months of DAT, particularly in those who had responded to AADs.

Recent studies have emphasized the importance of an early rhythm control strategy, which includes not only AFCA but also AADs. However, clear evidence for the early implementation of AFCA is still lacking.[17,21] Several studies, including retrospective observational studies and meta-analyses, have shown that a shorter duration from diagnosis to ablation (DAT) is associated with higher procedural success rates and improved clinical outcomes.[16,22–24] However, a recent RCT indicated similar success rates between early and delayed AFCA.[25] It is worth noting that in this trial, the distinction between "early" and "delayed" centers on referral periods rather than the duration of DAT. Furthermore, the trial encompassed both PAF and PeAF. In this study, we conducted Cox proportional hazards regression analysis, focusing on

TABLE 1 A comparison of the baseline characteristics of participants divided into the two cohorts of AAD-non-responders and AAD-partial-responders.

	Overall (*N* = 1038)	AAD-non-responders (*N* = 806)	AAD-partial-responders (*N* = 232)	*p*-value
Age, yr	61 (54–68)	61 (54–68)	62 (55–69)	.194
Male sex, *n* (%)	828 (79.8%)	662 (82.1%)	166 (71.6%)	.001
BMI, kg/m^2	25.3 (23.4–27.3)	25.3 (23.5–27.4)	24.9 (22.8–26.6)	.007
BSA, m^2	1.9 (1.7–2.0)	1.9 (1.8–2.0)	1.8 (1.7–1.9)	<.001
Cryoablation, *n* (%)	217 (20.9%)	185 (23.0%)	32 (13.8%)	.003
DAT, mo	24 (11–51)	24 (10–51)	24 (12–48)	.493
Follow-up, mo	27 (16–46)	26 (15–42)	35 (21–57)	<.001
Comorbidities, *n* (%)				
Congestive heart failure	261 (25.1%)	202 (25.1%)	59 (25.4%)	.977
Hypertension	538 (51.8%)	420 (52.1%)	118 (50.9%)	.795
Diabetes mellitus	188 (18.1%)	149 (18.5%)	39 (16.8%)	.626
Stroke or TIA	139 (13.4%)	104 (12.9%)	35 (15.1%)	.453
Vascular disease	80 (7.7%)	57 (7.1%)	23 (9.9%)	.197
CHA_2DS_2-VASc score	2 (1–3)	2 (1–3)	2 (1–3)	.181
Echocardiography				
LA diameter, mm	44 (40–47)	44 (41–48)	41 (37–46)	<.001
LA volume index, mL/m^2	42.0 (35.2–51.1)	43.0 (36.4–52.9)	38.0 (31.6–45.9)	<.001
LVEF, %	62 (58–67)	62 (57–67)	63 (59–68)	.004
E/e' ratio	9.2 (7.5–12.0)	9.1 (7.4–11.7)	9.3 (7.8–12.4)	.140
E velocity, m/s	0.8 (0.6–0.9)	0.8 (0.7–0.9)	0.7 (0.6–0.8)	<.001
Peak TRV, m/s	2.3 (2.1–2.5)	2.3 (2.1–2.5)	2.3 (2.1–2.5)	.352
RVSP, mmHg	26 (22–30)	26 (23–31)	25 (22–30)	.169
Laboratory findings				
BUN, mg/dL	16.4 (13.9–19.4)	16.5 (14.0–19.8)	15.6 (13.1–18.4)	.001
Creatinine, mg/dL	1.0 (0.8–1.1)	1.0 (0.8–1.1)	0.9 (0.8–1.0)	<.001
Serum albumin, g/dL	4.4 (4.2–4.6)	4.4 (4.2–4.6)	4.4 (4.1–4.6)	.014
GFR, ml/min/1.73 m^2	78.0 (68.0–87.0)	77.0 (68.0–86.0)	80.0 (67.5–93.0)	.039
Hb, g/dL	14.8 (13.8–15.8)	14.9 (14.0–15.8)	14.2 (13.2–15.4)	.000
RDW, %	12.8 (12.3–13.3)	12.8 (12.3–13.3)	12.8 (12.4–13.3)	.990
Lymphocyte count, 10^3/uL	2.0 (1.7–2.5)	2.0 (1.7–2.6)	2.0 (1.7–2.5)	.940
Total cholesterol, mg/dL	167 (138–194)	169 (138–196)	164 (138–188)	.261
HDL-cholesterol, mg/dL	47 (41–53)	46 (41–53)	48 (41–55)	.199
LDL-cholesterol, mg/dL	96 (70–121)	98 (72–122.0)	91 (68–117)	.103
Triglycerides, mg/dL	112 (82–158)	114.0 (83.2–158.0)	108 (79–156)	.218
Serum glucose, mg/dL	102 (95–112.5)	102 (95–113)	103 (95–112)	.979
HbA1c, %	6.3 (6.0–6.9)	6.4 (6.0–6.9)	6.2 (5.9–7.0)	.392
PFV				
Total PFV, cm^3	119.2 (91.4–152.0)	123.4 (96.4–156.3)	105.8 (77.3–136.5)	<.001
Atrial PFV, cm^3	50.4 (37.6–65.9)	52.1 (39.7–68.2)	42.9 (30.8–56.3)	<.001
Ventricular PFV, cm^3	68.7 (51.3–87.1)	70.1 (53.2–88.5)	61.7 (45.9–79.7)	<.001
AADs				.495
Class Ic, *n* (%)[a]	313 (30.3%)	248 (30.9%)	65 (28.3%)	
Class III, *n* (%)[b]	720 (69.7%)	555 (69.1%)	165 (71.1%)	

(Continues)

TABLE 1 (Continued)

	Overall (*N* = 1038)	AAD-non-responders (*N* = 806)	AAD-partial-responders (*N* = 232)	*p*-value
Procedures				
CPVIs, *n* (%)	1038 (100.0%)	806 (100.0%)	232 (100.0%)	1.000
CTI ablations, *n* (%)	848 (81.7%)	638 (79.2%)	210 (90.5%)	<.001
Other linear ablations, *n* (%)	809 (77.9%)	603 (74.8%)	206 (88.8%)	<.001
Use of a contact force-sensing catheter, *n* (%)	93 (9.0%)	67 (8.3%)	26 (11.2%)	.219
Procedure time, min	129 (93–173)	123 (88–170)	143 (108–180)	<.001
Ablation time, s	2606 (1808–4441)	2512 (1749–4132)	3298 (1964–5038)	.001
Performance of repeat ablation during follow-up, *n* (%)	70 (6.7%)	67 (8.3%)	3 (1.3%)	<.001

Abbreviations: AADs, antiarrhythmic drugs; BMI, body mass index; BSA, body surface area; BUN, blood urea nitrogen; CHA2DS2-VASc score, congestive cardiac failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex category (female) score; CPVIs, circumferential pulmonary vein isolations; CTI, cavotricuspid isthmus; DAT, diagnosis-to-ablation time; E velocity, early filling velocity; E/e' ratio: the ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity; GFR, glomerular filtration rate; Hb, hemoglobin; HbA1c, glycated hemoglobin; HDL-cholesterol, high-density lipoprotein-cholesterol; LA: left atrial; LDL-cholesterol, low-density lipoprotein-cholesterol; LVEF, left ventricular ejection fraction; PFV, pericardial fat volume; RDW, red blood cell distribution width; RSVP, right ventricular systolic pressure; TIA, transient ischemic attack; TRV, tricuspid regurgitation velocity.

[a]Class Ic antiarrhythmic drugs: flecainide, propafenone, pilsicainide.

[b]Class III antiarrhythmic drugs: amiodarone, dronedarone, sotalol.

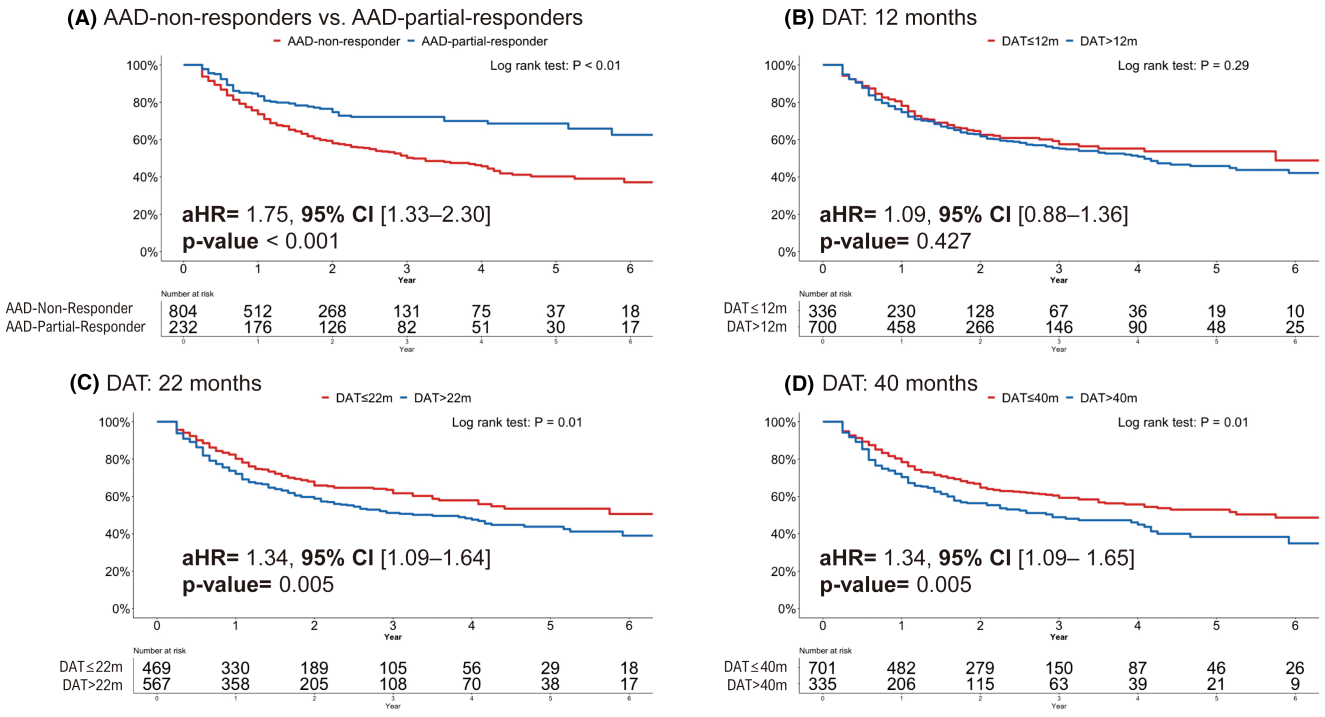

FIGURE 2 Kaplan–Meier analyses of the recurrence-free survival of PeAF subsequent to AFCA. (A) Kaplan–Meier analysis of the recurrence-free survival of PeAF subsequent to AFCA between AAD-partial-responders and AAD-non-responders. Kaplan–Meier analysis of the recurrence-free survival of PeAF subsequent to AFCA between the DAT (B) ≤12 and >12 months, (C) ≤22 and >22 months, and (D) ≤40 and >40 months. AAD, antiarrhythmic drug; aHR, adjusted hazards ratio; AFCA, atrial fibrillation catheter ablation; CI, confidence interval; DAT, diagnosis-to-ablation time; PeAF, persistent atrial fibrillation.

participants with PeAF, to investigate the impact of DAT on clinical recurrences following AFCA. Subsequently, we employed the maximum likelihood estimation method to determine the optimal DAT cutoff value. Our findings revealed that the greatest disparity in clinical recurrences occurred when comparing DATs before and after 22 months. This underscores the significance of performing

the procedure within 22 months to mitigate clinical recurrences in the overall population with PeAF.

An extended period of AF leads to pronounced atrial remodeling, and the maintenance of sinus rhythm (SR) is essential in mitigating this remodeling process.[26] Furthermore, the extent of atrial remodeling significantly affects the prognosis of AF following rhythm control.[27] In this study, the observation that the LA size and pericardial fat volume are significantly larger in the AAD-non-responder group than in the AAD-partial-responder group suggests an association with LA remodeling. Based on these considerations, studies investigating early rhythm control have been in focus. Current findings indicate a positive correlation between early rhythm control and improved clinical outcomes.[17,21] AFCA performed in the early disease state of AF, such as PAF, is approximately more effective than ablations that are performed in a later disease state of AF, such as long-standing PeAF.[28] The success rate of PVI for PeAF is approximately 54%, which is a consistent observation in two recent large RCTs using contemporary ablation technology.[29,30] While the 2020 ESC guidelines recommend AFCA for patients with an AF unresponsive to AADs, there is limited evidence on rhythm outcomes subsequent to AFCA based on the responsiveness to AADs. In a study by Igarashi et al., the data of 51 patients with long-standing PeAF were analyzed to compare AFCA outcomes after extensive AAD therapy. Those with a restored SR showed better AFCA outcomes than those remaining in AF, with AF-free rates of 61% and 22% at 14 months, respectively.[31] In this study, the proportion of patients undergoing additional non-PV ablation, such as linear ablation, was lower in the AAD-non-responder group despite having a larger LA size than in the AAD-partial-responder group (Table 1). Conversely, additional ablation was more frequently performed in the DAT > 22-month group than in their counterpart, while there was no difference in LA size between the groups (Table 3). These findings suggest that LA size, AAD response, or AF duration are not strongly related to the decision to perform additional ablation beyond PV isolation. Moreover, the observation that the rhythm outcome was not favorable in the DAT > 22-month group, despite the performance of linear ablation, aligns with the findings of the previous RCTs.[29,32]

The interval from AF diagnosis to deciding on AFCA is influenced by the response to AADs. In real clinical practice, the decision to continue AAD therapy or to opt for AFCA in patients with PeAF who responded to AAD therapy makes a dilemma, influenced by the cost and risk–benefit considerations and the fact that AFCA is not the first-line treatment for PeAF. Consequently, our aim was to conduct an analysis that focused on the response to AAD. To reiterate, in this study, AAD-partial-responders were defined as participants who experienced paroxysmal recurrence after the use of AADs. AAD-partial-responders exhibited more favorable rhythm outcomes than AAD-non-responders. Sub-cohort analyses based on AAD responsiveness were conducted to determine the optimal DAT cutoff value. In the cohort of AAD-partial-responders, the lesser extent of atrial remodeling indicated a favorable response to the AADs, suggesting

TABLE 2 Multivariable Cox proportional hazards regression analyses of the clinical recurrences subsequent to atrial fibrillation catheter ablation in persistent atrial fibrillation.

	Multivariate analysis		
	HR	95% CI	*p*-value
DAT as a continuous variable			
DAT, per 12 months increase	1.03	1.01–1.06	.008
DAT as a categorical variable			
DAT >12 months	1.09	0.88–1.36	.427
DAT >22 months	1.34	1.09–1.64	.005
DAT >40 months	1.34	1.09–1.65	.005

Note: Factors significant in the univariable analyses ($p < .1$), including left atrial volume index, left ventricular ejection fraction, E velocity, atrial pericardial fat volume, and antiarrhythmic drug responsiveness, were entered into the multivariable analyses. Detailed univariable and multivariable Cox regression models were presented in Table S1.

Abbreviations: CI, confidence interval; DAT, diagnosis-to-ablation time; HR, hazard ratio.

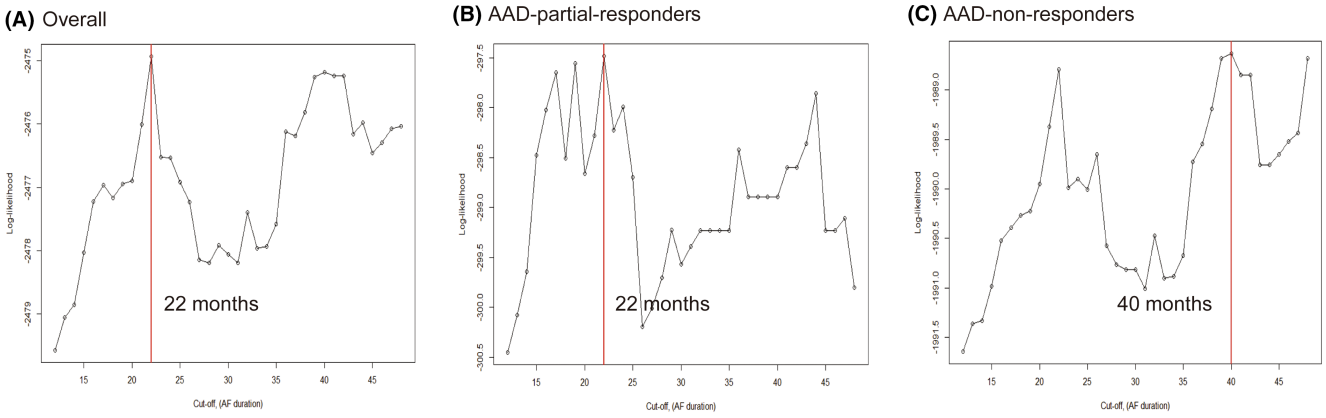

FIGURE 3 Log-likelihood graphs of the Cox proportional hazards regression models of the clinical recurrences subsequent to AFCA. Log-likelihood graph and maximum log-likelihood estimation of the Cox proportional hazards regression model in (A) all participants, (B) AAD-partial-responders, and (C) AAD-non-responders. AAD, antiarrhythmic drug; AFCA, atrial fibrillation catheter ablation.

TABLE 3 A comparison of the baseline characteristics of participants divided into sub-cohorts, as determined by the DAT ≤22 and >22 months.

	DAT ≤22 months (*N* = 470)	DAT >22 months (*N* = 568)	*p*-value
Age, y	60 (53–67)	61 (55–68)	.151
Male sex, *n* (%)	376 (80.0%)	452 (79.6%)	.927
BMI, kg/m^2	25.1 (23.2–27.4)	25.3 (23.5–27.1)	.902
BSA, m^2	1.9 (1.7–2.0)	1.9 (1.7–2.0)	.885
Cryoablation, *n* (%)	111 (23.6%)	106 (18.7%)	.060
DAT, mo	10 (7–14)	48 (32–84)	<.001
Follow-up, mo	27 (16–44)	28 (16–50)	.320
Comorbidities, *n* (%)			
Congestive heart failure	112 (23.8%)	149 (26.2%)	.414
Hypertension	260 (55.3%)	278 (48.9%)	.047
Diabetes mellitus	88 (18.7%)	100 (17.6%)	.701
Stroke or TIA	68 (14.5%)	71 (12.5%)	.404
Vascular disease	41 (8.7%)	39 (6.9%)	.317
CHA_2DS_2-VASc score	2 (1–3)	2 (1–3)	.227
Echocardiography			
LA diameter, mm	43 (40–47)	44 (40–48)	.080
LA volume index, mL/m^2	41.2 (34.9–51.0)	42.2 (35.5–51.2)	.239
LVEF, %	62.0 (57.0–67.0)	62.0 (58.0–67.0)	.036
E/e' ratio	9.1 (7.7–11.4)	9.2 (7.4–12.2)	.342
E velocity, m/s	0.8 (0.6–0.9)	0.8 (0.7–0.9)	.393
Peak TR velocity, m/s	2.3 (2.1–2.5)	2.3 (2.1–2.5)	.359
RVSP, mmHg	26 (22–30)	26 (23–31)	.395
Laboratory findings			
BUN	16.4 (13.8–19.4)	16.4 (13.9–19.5)	.976
Creatinine	1.0 (0.8–1.1)	1.0 (0.8–1.1)	.696
Serum albumin	4.4 (4.2–4.6)	4.4 (4.2–4.6)	.954
GFR	78.0 (68.0–88.0)	77.0 (68.0–86.5)	.323
Hb	14.7 (13.6–15.8)	14.9 (13.9–15.8)	.172
RDW	12.8 (12.3–13.2)	12.9 (12.4–13.3)	.288
Lymphocyte count	2.0 (1.7–2.6)	2.1 (1.7–2.5)	.648
Total cholesterol	164.0 (135.0–195.0)	168.0 (141.0–193.0)	.469
HDL-cholesterol	46.0 (39.8–53.0)	47.0 (42.0–54.0)	.038
LDL-cholesterol	93.0 (66.5–122.2)	97.0 (72.7–120.8)	.311
Triglycerides	115.5 (84.0–164.0)	109.0 (81.0–151.0)	.092
Serum glucose	103.0 (95.0–114.0)	101.5 (94.0–111.0)	.067
HbA1c	6.2 (6.0–7.0)	6.3 (5.9–6.9)	.960
PFV			
Total PFV, cm^3	117.3 (90.4–150.4)	121.9 (91.6–154.6)	.351
Atrial PFV, cm^3	50.2 (37.1–63.6)	50.6 (38.0–67.1)	.378
Ventricular PFV, cm^3	68.6 (51.7–86.2)	68.8 (51.2–87.7)	.433
AADs, *n* (%)			.786
Class Ic[a]	144 (30.8%)	169 (29.9%)	
Class III[b]	323 (69.2%)	397 (70.1%)	

TABLE 3 (Continued)

	DAT ≤22 months (*N* = 470)	DAT >22 months (*N* = 568)	*p*-value
Procedures			
CPVIs, *n* (%)	470 (100.0%)	568 (100.0%)	1.000
CTI ablations, *n* (%)	375 (79.8%)	473 (83.3%)	.172
Other linear ablations, *n* (%)	344 (73.2%)	465 (81.9%)	.001
Use of a contact force-sensing catheter, *n* (%)	45 (9.6%)	48 (8.5%)	.602
Procedure time, min, *n* (%)	120 (90–163)	135 (95–181)	.001
Ablation time, s	2486 (1752–4086)	2730 (1858–4852)	.010

Abbreviations: AADs, antiarrhythmic drugs; BMI, body mass index; BSA, body surface area; BUN, blood urea nitrogen; CHA2DS2-VASc score, congestive cardiac failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74, and sex category (female) score; CPVIs, circumferential pulmonary vein isolations; CTI, cavotricuspid isthmus; DAT, diagnosis-to-ablation time; GFR, glomerular filtration rate; E velocity, early filling velocity; E/e' ratio: the ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity; GFR, glomerular filtration rate; Hb, hemoglobin; HbA1c, glycated hemoglobin; HDL-cholesterol, high-density lipoprotein-cholesterol; LA, left atrial; LDL-cholesterol, low-density lipoprotein-cholesterol; LVEF, left ventricular ejection fraction; PFV, pericardial fat volume; RDW, red blood cell distribution width; RSVP, right ventricular systolic pressure; TIA, transient ischemic attack; TRV, tricuspid regurgitation velocity.

[a]Class Ic antiarrhythmic drugs: flecainide, propafenone, pilsicainide.

[b]Class III antiarrhythmic drugs: amiodarone, dronedarone, sotalol.

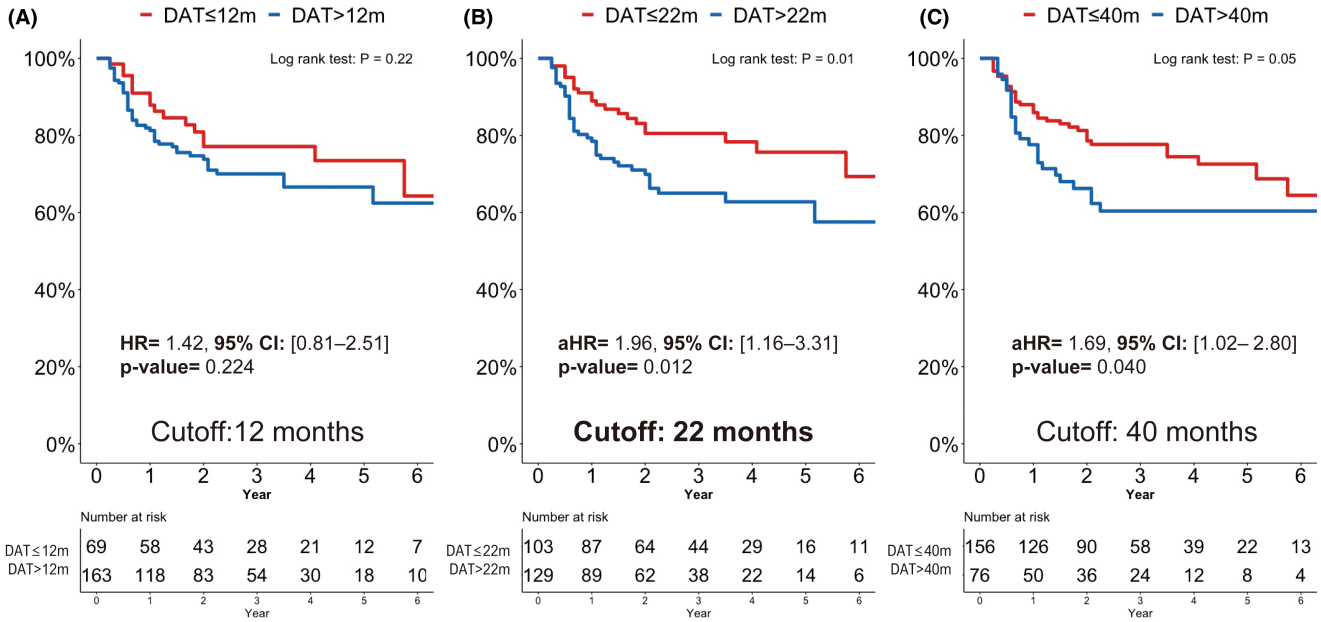

FIGURE 4 Survival analyses by cutoff values for the DAT, in the cohort for AAD-partial-responders. Kaplan–Meier analysis for the recurrence-free survival subsequent to AFCA between the (A) DAT ≤12 and >12 months, (B) ≤22 and >22 months, and (C) ≤40 and >40 months in the cohort of AAD-partial-responders. AAD, antiarrhythmic drug; aHR, adjusted hazards ratio; AFCA, atrial fibrillation catheter ablation; CI, confidence interval; DAT, diagnosis-to-ablation time; HR, hazards ratio.

that the early initiation of AFCA could have resulted in more positive rhythm control outcomes. The optimal cutoff value for AAD-partial-responders was 22 months, whereas the discrimination power of the cutoff value of 22 months for AAD-non-responders was less prominent. This suggests a strong correlation between earlier AFCA and better rhythm outcomes among those for whom the treatment with AADs had worked, partially to a limited extent. In the cohort of AAD-non-responders, the extent of LA remodeling progressed from the time of diagnosis, leading to diminished effectiveness of AFCA, as evidenced by the optimal discrimination power of the cutoff value of 40 months and less prominent discriminating abilities of both cut-off values of 22 and 40 months. These findings suggest that responsiveness to AADs may help predict rhythm outcomes after AFCA and determine the optimal timing of AFCA.

4.1 | Limitations

This study had several limitations. First, being a single-center, retrospective, observational cohort study introduced a potential

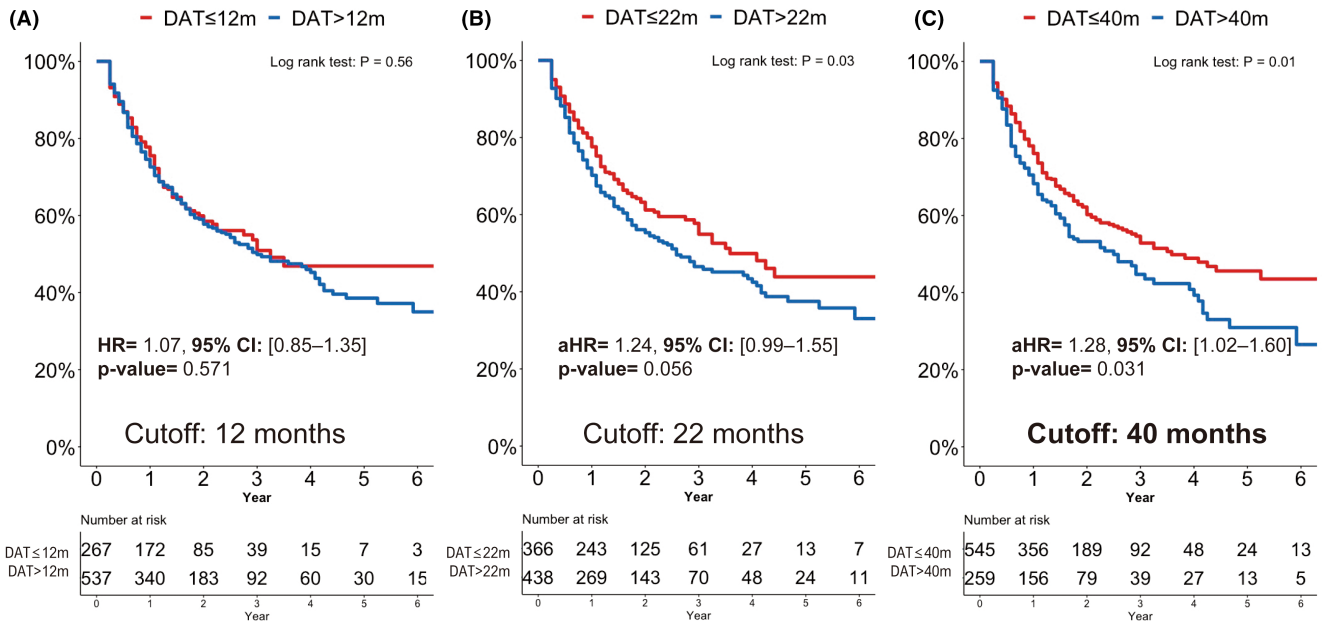

FIGURE 5 Survival analyses by cutoff values for DAT in the cohort of AAD-non-responders. Kaplan–Meier analysis for the recurrence-free survival subsequent to AFCA between the DAT (A) ≤12 and >12 months, (B) ≤22 and >22 months, and (C) ≤40 and >40 months in the cohort of AAD-non responders. AAD, antiarrhythmic drug; aHR, adjusted hazards ratio; AFCA, atrial fibrillation catheter ablation; CI, confidence interval; DAT, diagnosis-to-ablation time; HR, hazards ratio.

selection bias between cohorts, justifying subsequent multi-center, prospective studies. Second, gauging the duration of PeAF and rhythm control outcomes subsequent to AFCA is challenging. We employed the DAT to assess AF progression and post-ablation rhythm outcomes; however, this may not have precisely represented the disease progression of AF, particularly in asymptomatic participants, where potential detection bias may have arisen from delayed diagnoses. Third, variations in the timing of AF diagnosis and administration of AADs may have influenced the AAD responsiveness. Fourth, the participants may exhibit heterogeneity because of the extended period over which the patients were analyzed. Fifth, the proportion of cases using contact force was relatively low. Nevertheless, we believe that our findings provided valuable insights for determining the optimal timing of AFCA in participants.

5 | CONCLUSIONS

Both DAT and AAD responsiveness affected the rhythm outcomes of AFCA. Delaying AFCA to a DAT of longer than 22 months proved not to be advisable, particularly in participants in whom PeAF was changed to PAF during AAD therapy.

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CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interests for this article.

DATA AVAILABILITY STATEMENT

The data and statistical methods are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This study was conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent was obtained from all participants who were included in the Yonsei AF Ablation Cohort Database (NCT02138695) for the final data analysis.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from all participants who were included in the Yonsei AF Ablation Cohort Database (NCT02138695).

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

N/A.

CLINICAL TRIAL REGISTRATION

Yonsei AF Ablation Cohort Database (NCT02138695).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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