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ORIGINAL RESEARCH

DR-FLASH Score Is Useful for Identifying Patients With Persistent Atrial Fibrillation Who Require Extensive Catheter Ablation Procedures

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BACKGROUND: Modification of arrhythmogenic substrates with extensive ablation comprising linear and/or complex fractional atrial electrogram ablation in addition to pulmonary vein isolation (PVI-plus) can theoretically reduce the recurrence of atrial fibrillation. The DR-FLASH score (score based on diabetes mellitus, renal dysfunction, persistent form of atrial fibrillation, left atrialdiameter >45 mm, age >65 years, female sex, and hypertension) is reportedly useful for identifying patients with arrhythmogenic substrates. We hypothesized that, in patients with persistent atrial fibrillation, the DR-FLASH score can be used to classify patients into those who require PVI-plus and those for whom a PVI-only strategy is sufficient.

METHODS AND RESULTS: This study is a post hoc subanalysis of the a multicenter, randomized controlled, noninferiority trial investigating efficacy and safety of pulmonary vein isolation alone for recurrence prevention compared with extensive ablation in patients with persistent atrial fibrillation (EARNEST-PVI trial). This analysis focuses on the relationship between DR-FLASH score and the efficacy of different ablation strategies. We divided the population into 2 groups based on a DR-FLASH score of 3 points. A total of 469 patients were analyzed. Among those with a DR-FLASH score >3 (N=279), the event rate of atrial arrhythmia recurrence was significantly lower in the PVI-plus arm than in the PVI-only arm (hazard ratio [HR], 0.45 [95% CI, 0.28–0.72]; $P<0.001$). In contrast, among patients with a DR-FLASH score ≤3 (N=217), no differences were observed in the event rate of atrial arrhythmia recurrence between the PVI-only arm and the PVI-plus arm (HR, 1.08 [95% CI, 0.61–1.89]; $P=0.795$). There was significant interaction between patients with a DR-FLASH score >3 and DR-FLASH score ≤3 (P value for interaction=0.020).

CONCLUSIONS: The DR-FLASH score is a useful tool for deciding the catheter ablation strategy for patients with persistent atrial fibrillation.

REGISTRATION: URL: https://clinicaltrials.gov; Unique identifier: NCT03514693.

Key Words: catheter ablation ■ DR-FLASH score ■ persistent atrial fibrillation ■ stratification

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CLINICAL PERSPECTIVE

What Is New?

- This is a post hoc subanalysis of the EARNEST-PVI trial (a multicenter, randomized controlled, noninferiority trial investigating efficacy and safety of pulmonary vein isolation alone for recurrence prevention compared with extensive ablation in patients with persistent atrial fibrillation), focusing on stratification by DR-FLASH score.
- Together with pulmonary vein isolation, an extensive ablation strategy involving linear ablation and complex fractionated atrial ECG ablation was effective in reducing recurrence of atrial fibrillation among patients with a DR-FLASH score >3; in contrast, a pulmonary vein isolation alone strategy was similarly effective to the extensive ablation strategy among those with a DR-FLASH score ≤3.

What Are the Clinical Implications?

- The DR-FLASH score may be useful for stratifying patients into those who do and do not require extensive ablation, thereby reducing cost and complications.
- Further prospective studies are warranted to confirm the clinical utility of the DR-FLASH score in the determination of catheter ablation strategy.

Nonstandard Abbreviations and Acronyms

CFAE	complex fractional atrial electrogram
PV	pulmonary vein
PVI	pulmonary vein isolation
PVI-alone	pulmonary vein isolation only
PVI-plus	extensive ablation comprising linear and/or complex fractional atrial electrogram ablation in addition to pulmonary vein isolation

Catheter ablation is an effective and safe treatment for atrial fibrillation (AF). Pulmonary vein isolation (PVI) is commonly performed on patients with drug-resistant AF in clinical settings.[1,2] However, PVI is less effective for maintaining sinus rhythm in patients with persistent AF than in those with paroxysmal AF. Extensive catheter ablation, comprising linear ablation and complex fractional atrial electrogram (CFAE) ablation in addition to PVI, is also performed on patients with persistent AF.[3] The efficacy of the extensive ablation strategy, however, remains controversial. In patients with persistent AF, the Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial Part 2 (STAR-AF2 trial) did not show the superiority of extensive catheter ablation strategy to PVI alone with regard to freedom from AF.[4] In contrast, the EARNEST-PVI trial, which was a prospective, multicenter, randomized, and open-label noninferiority trial of patients with persistent AF, did not show the noninferiority of PVI alone to extensive catheter ablation in patients with persistent AF in freedom from AF.[5] Theoretically, an extensive ablation strategy should be effective in patients with non–pulmonary vein (PV) arrhythmogenic substrates, whereas a PVI alone strategy should be sufficient in those without non-PV arrhythmogenic substrates.

The presence of non-PV arrhythmogenic substrates, which is more commonly observed in patients with persistent AF than paroxysmal AF,[6] has been reported to be a strong predictor of AF recurrence after PVI.[7,8] Although detection of arrhythmogenic substrates is generally done by voltage mapping, Kosiuk et al reported that the DR-FLASH score is a noninvasive measure for predicting the presence of low-voltage areas, which are a type of arrhythmogenic substrate.[9] The DR-FLASH score accounts for the following clinical factors: diabetes, renal dysfunction, persistent form of AF, left atrial diameter, age, sex, and hypertension. The recurrence rate of AF after PVI is significantly higher among patients with a DR-FLASH score >3 than a score ≤3.[9]

In this study, we examined whether the DR-FLASH score is useful in identifying patients who do or do not require extensive substrate ablation in addition to PVI in patients with persistent AF. Our hypothesis was that an extensive ablation strategy would be effective among those with higher DR-FLASH scores, whereas a PVI-only (PVI-alone) strategy would be sufficient among those with lower DR-FLASH scores.

METHODS

Our study data will not be made available to other researchers for purposes of reproducing the results because of institutional review board restrictions.

Study Design

This study was conducted as a post hoc subanalysis of the EARNEST-PVI trial, registered at ClinicalTrials.gov (NCT03514693),[5,10–12] which focused on the relationship between DR-FLASH score and the efficacy of different ablation strategies. The EARNEST-PVI trial is a prospective, multicenter, randomized, and open-label noninferiority trial of patients with persistent AF undergoing an initial catheter ablation procedure. The study was performed by the Osaka Cardiovascular Conference Arrhythmia Investigators. All patients

provided written informed consent to participate, and the study was approved by the ethics committee of each hospital. After informed consent was provided, patients were randomized to receive either PVI-alone or extensive ablation comprising linear and/or CFAE ablation in addition to PVI (PVI-plus). This study conformed to the ethical guidelines outlined in the Declaration of Helsinki and was approved by the Institutional Review Boards of all hospitals.

Patients with persistent AF were enrolled in 8 hospitals with extensive experience of catheter ablation therapy. A sustained episode of AF lasting for ≥7 days and <5 years was defined as persistent AF at enrollment. Exclusion criteria were as follows: aged <20 or ≥80 years; sinus rhythm at enrollment; history of catheter ablation; left atrial diameter >50 mm in the parasternal long-axis view on echocardiography; AF with mitral stenosis or artificial heart valve; history of cardiac surgery; hemodialysis; left ventricular ejection fraction <30%; and New York Heart Association functional classification 3 or 4.

Prediction of Low-Voltage Area

In the present study, we selected patients based on DR-FLASH score because the predictive value of this score is high[9] and has been validated in East Asian populations.[6] The DR-FLASH score was calculated by adding 1 point each for the presence of diabetes, renal dysfunction (estimated glomerular filtration rate <90 mL/min per 1.73 m^2), persistent form of AF, left atrial diameter >45 mm, aged >65 years, female sex, and hypertension.[9] Given that all subjects in the current study had persistent AF, the minimum score was 1 point. We divided the study population into 2 groups based on a DR-FLASH score of 3 points, as first reported in a previous study.[9] Analysis of the receiver operating characteristic curves with an area under the curve of 0.801 (95% CI, 0.738–0.865; P<0.001) revealed that a DR-FLASH score of 3 points was the optimal cutoff value for predicting low-voltage areas. A DR-FLASH score of 3 points had a sensitivity of 76% (95% CI, 64%–85%), a specificity of 73% (95% CI, 65%–79%), a negative predictive value of 88% (95% CI, 82%–93%), and a positive predictive value of 53% (95% CI, 42%–63%).[9]

Study Procedure

At the beginning of the procedure, direct current cardioversion was performed to identify AF triggers. Origins of the AF triggers were identified using an electrophysiological study before performing the ablation procedures. An AF trigger was defined as an arrhythmogenic focus initiating AF ≥2 times with the same sequence. AF triggers of PV origin were defined as those from PVs, whereas triggers of non-PV origin were defined as those from sites other than PVs. Mapping catheters with at least 4 electrodes were used to record the electrogram from PVs and other sites to detect the location of AF triggers. A total of 1 or 2 circular catheters, in addition to an ablation catheter, were located at each ostium of 2 or 3 PVs simultaneously. If AF was induced, direct current cardioversion was performed to confirm the reproducibility of AF initiation. If spontaneous recurrence of AF was not observed for 5 minutes after cardioversion, administration of isoproterenol in incremental doses up to 0.4 mg/kg per minute was performed. The end point of isoproterenol administration was systolic blood pressure of ≤80 mm Hg, heart rate in sinus rhythm of ≥130 beats per minute, or isoproterenol administration at 0.4 mg/kg per minute for 5 minutes. In the EARNEST-PVI trial, operators performed large antral encircling of ipsilateral PVs with complete antral disconnection as PVI. The end point of PVI was bidirectional conduction block at the end of the initial PVI procedure after a waiting period of at least 20 minutes. Additional ablations, such as focal ablation for superior vena cava isolation, ablation for paroxysmal supraventricular tachycardia, and cavotricuspid isthmus linear ablation for common atrial flutter induced by burst pacing, were acceptable in both the PVI-alone and PVI-plus arms, as was ablation for non-PV AF triggers. All procedures were performed by radiofrequency catheter ablation, with a recommended radiofrequency energy of 25 to 35 W in the EARNEST-PVI trial. In patients allocated to the PVI-plus arm, CFAE ablation, linear ablation, or both ablations were performed at the physician's discretion. For linear ablation, ablation of at least 2 left atrial linear lesions was required. The first ablation line was a mitral isthmus or an anterior line connecting the mitral annulus to a line of PVI. The second ablation line was a roof line connecting the superior aspect of encircling lesions for PVI. Ablation of a bottom line connecting the inferior aspect of encircling lesions for PVI was permitted, which, in turn, meant that electrical isolation of the left atrial posterior wall was accepted. The end point of linear ablation was a bidirectional conduction block at the end of the initial procedure after a waiting period of at least 20 minutes. For CFAE ablation, CFAE mapping was performed during AF using a high-density mapping catheter. Automated algorithms of the 3-dimensional mapping system identified sites of CFAE. The online CFAE software module was used to evaluate a 2.5-second window of bipolar electrograms at each mapping site when the CARTO system (Biosense Webster Inc.) was used as a 3-dimensional mapping system. Voltage peaks were set as a higher potential than the noise threshold but a lower potential than the upper threshold (0.05–0.15 mV). The intervals between successive peaks falling within 60 to 120 ms was counted, and the total interval was defined as the interval confidence level. All sites with an interval

confidence level >7 were targets for CFAE ablation. Cycle length of AF was measured from a predetermined pair of recording electrodes in the coronary sinus and vein, as reported in a previous study.[13] The Ensite Complex Fractionated Electrograms Algorithm was used to measure the interval between multiple discrete deflections in a local electrogram during AF recording of >5 seconds when the Ensite NavX system was used in the procedure. These interdeflection time intervals were then averaged to calculate the mean cycle length of the local AF electrogram. The P-P sensitivity, refractory value, and width had to be 0.03 to 0.05 mV, 35 to 45 ms, and 15 to 20 ms, respectively. The average of cycle length was projected on an anatomical shell of the left atrium as a color-coded display. Electrograms of areas with a mean cycle length <120 ms were defined as "CFAE" based on a previous study.[14] The end point of CFAE ablation was elimination of sites where CFAE was recorded, or a rhythm change from AF to sinus rhythm, organized atrial tachycardia, or atrial flutter was seen.

Data Collection and Follow-Up

Before catheter ablation, we collected patients' clinical data, including patient history, laboratory data, and transthoracic echocardiography. A 12-lead ECG was obtained before the procedure, at discharge, and at 1, 3, 6, 9, and 12 months. A 24-hour Holter ECG was obtained at 6 and 12 months. The study patients were allowed to visit their clinic or hospital on nonscheduled days. A 12-lead ECG was obtained at each additional visit. In patients with symptoms suggestive of recurrence, an additional Holter ECG or event monitor recording was obtained.

Study End Points

The primary end point was recurrence of AF demonstrated by ECGs within the 1-year follow-up period after the initial procedure. Recurrence of AF was defined as AF, atrial flutter, or atrial tachycardia lasting for >30 seconds in an ECG, including a 12-lead ECG, a 24-hour Holter ECG, or an event recorder. A blanking period of 3 months was implemented. Use of antiarrhythmic drugs was acceptable during the blanking period, but was not recommended thereafter. A second ablation was allowed in patients with recurrence of AF after the blanking period.

Statistical Analysis

Statistical analysis was conducted using R software (version 4.0.5; R Foundation for Statistical Computing). In the present study, intention-to-treat analysis was performed. Continuous variables are presented as medians with interquartile range (median [25th–75th percentile]), and categorical data are presented as counts and percentages. Demographic and procedural differences were analyzed using the Mann-Whitney *U* test for continuous variables and Fisher exact test for categorical variables. The cumulative event rate was calculated using the Kaplan-Meier method with the log-rank test. The hazard ratio (HR), 95% CI, and *P* value for interaction were calculated using the Cox proportional hazards model. The proportional hazards assumption of the treatment strategy for the primary end point was confirmed using Schoenfeld residuals ($P>0.05$). $P<0.05$ indicated statistical significance. The Bonferroni method was used in multiple comparison.

RESULTS

Study Subjects

A total of 512 patients were enrolled between March 2016 and September 2017. After excluding 9 patients for protocol violation, 5 for errors in the electronic data collection system, and 1 for withdrawal of consent, 497 patients were analyzed in the EARNEST-PVI trial. The median of age (interquartile range) was 67 (59–72) years. In the present study, 1 patient was excluded because of missing data required to calculate the DR-FLASH score. Thus, 496 patients were analyzed in the present study. A histogram of the distribution of DR-FLASH scores is shown in Figure S1. The numbers of patients with DR-FLASH scores of >3 and ≤3 were 279 and 217, respectively. Among those with a score >3, 137 patients were allocated to the PVI-plus arm and 142 were allocated to the PVI-alone arm. Among those with a DR-FLASH score ≤3, 111 patients were allocated to the PVI-plus arm and 106 were allocated to the PVI-alone arm. (Figure 1). Patient characteristics are summarized in Table 1. There were no significant differences between the PVI-alone arm and PVI-plus arm by a DR-FLASH score of >3 or ≤3, except in hemoglobin by a DR-FLASH score ≤3.

Procedure Data

Procedure data, such as the number and site of non-PV triggers, extensive catheter ablation, and total procedure time, are summarized in Table 2. In the DR-FLASH score >3 group, the number and frequency of patients with non-PV triggers was 6 (4.4%) in PVI-plus arm and 14 (9.8%) in PVI-alone arm, whereas in the DR-FLASH score ≤3 group, the number and frequency of patients with non-PV triggers was 2 (1.8%) and 6 (5.6%), respectively. Among patients with a DR-FLASH score ≤3 and PVI-plus, 2 non-PV triggers from unknown origins were observed in 1 patient, and data for 1 non-PV trigger were missing in 1 patient. Among patients with a DR-FLASH score ≤3 and PVI-alone, 2 non-PV triggers

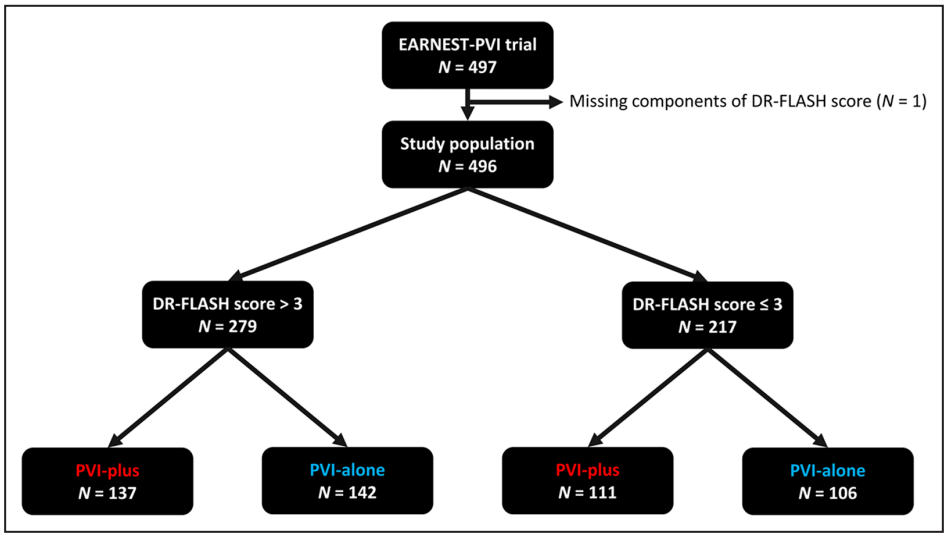

Figure 1. Patient tree.
PVI-alone indicates pulmonary vein isolation only; and PVI-plus, extensive ablation comprising linear and/or complex fractional atrial electrogram ablation in addition to pulmonary vein isolation. EARNEST-PVI trial indicates a multicenter, randomized controlled, noninferiority trial investigating efficacy and safety of pulmonary vein isolation alone for recurrence prevention compared with extensive ablation in patients with persistent atrial fibrillation.

from unknown origins were seen in 1 patient. Among all types of extensive catheter ablation, linear ablation for block lines at the roof, bottom, and mitral isthmus in addition to PVI was most commonly performed in both cohorts. In the DR-FLASH score >3 cohort, median total procedure time (interquartile range) was 180 (130–230) minutes in the PVI-plus arm and 145 (113–200) minutes in the PVI-alone arm. In the DR-FLASH score ≤3 cohort, median total procedure time (interquartile range) was 185 (147–229) minutes in the PVI-plus arm and 143 (113–167) minutes in the PVI-alone arm. In other words, procedure time was longer in the PVI-plus arm than in the PVI-alone arm in both cohorts.

Clinical End Points

Kaplan-Meier analysis with the log-rank test for the primary end point is shown in Figure 2. Among patients with a DR-FLASH score >3, the event rate of the primary end point was significantly lower in the PVI-plus arm than in the PVI-alone arm (PVI-plus versus PVI-alone, 25/137 [18.2%] versus 53/142 [37.3%]; HR, 0.45 [95% CI, 0.28–0.72]; $P<0.001$). In contrast, among patients with a DR-FLASH score ≤3, no differences were observed in the event rate of the primary end point between the 2 arms (PVI-plus versus PVI-alone, 26/111 [23.4%] versus 23/106 [21.7%]; HR, 1.08 [95% CI, 0.61–1.89]; $P=0.795$). There was significant interaction between the DR-FLASH score >3 group and DR-FLASH score ≤3 group (P value for interaction=0.020) (Figure 3).

Among those with a DR-FLASH score >3, each extensive catheter ablation tended to decrease the rate of AF recurrence (Figure 4). Figure 4 illustrates the recurrence rates following each type of extensive ablation procedure versus PVI-alone. In Figure 4, $P<0.01$ indicates significance level as calculated with the Bonferroni method. In the PVI-plus arm with DR-FLASH score >3, the recurrence rate in patients with extensive procedures of roof line, bottom line, and mitral isthmus ablation; with procedures of roof line and mitral isthmus ablation; with procedures of CFAE ablation; with procedures of roof line and anterior line ablation; and with others was 7 of 54 (13.0%), 7 of 33 (21.2%), 3 of 16 (18.8%), 5 of 20 (25.0%), and 3 of 14 (21.4%), respectively. Patients with other procedures in the DR-FLASH score >3 consisted of those with roof line, anterior line, and mitral isthmus ablation; with roof line and bottom line ablation; with roof line, bottom line, and anterior line ablation; with roof line, bottom line, anterior line, and mitral isthmus ablation; with roof line and CFAE ablation; with roof line, bottom line, and CFAE ablation; and with no extensive catheter ablation. In the PVI-alone arm with a DR-FLASH score >3, recurrence rate in patients who underwent PVI-alone was 53 of 142 (37.3%). In patients with a DR-FLASH score >3, recurrence rate was significantly lower in patients with extensive procedures of roof line, bottom line, and mitral isthmus ablation than in those with PVI-alone. All types of extensive ablation procedures, except for the extensive procedures of roof line, bottom line, and mitral isthmus ablation, led to numerically lower recurrence rates, albeit

Table 1. Patient Characteristics

Characteristic	DR-FLASH score >3 and PVI-plus	DR-FLASH score >3 and PVI-alone	*P* value*	DR-FLASH score ≤3 and PVI-plus	DR-FLASH score ≤3 and PVI-alone	*P* value*
Total No.	137	142		111	106	
Age, y	69 (66–74)	71 (67–75)	0.062	60 (54–65)	60 (56–65)	0.829
Aged >65 y	103 (75.2)	118 (83.1)	0.108	27 (24.3)	26 (24.5)	1.000
Female sex	51 (37.2)	56 (39.4)	0.714	7 (6.3)	6 (5.7)	1.000
Height, cm	164 (156–169)	162 (154–169)	0.313	170 (165–174)	170 (165–174)	0.882
Weight, kg	64.8 (58.5–72.0)	64.8 (55.9–72.6)	0.827	69.6 (61.0–76.0)	70.3 (60.7–77.0)	0.957
Body mass index, kg/m^2	24.4 (22.5–27.0)	24.6 (22.4–27.1)	0.659	23.7 (21.9–25.8)	24.0 (21.6–26.7)	0.691
Family history	10 (7.3)	11 (7.7)	1.000	5 (4.5)	12 (11.3)	0.078
Long-standing persistent AF	37 (27.0)	34 (23.9)	0.584	28 (25.2)	24 (22.6)	0.751
AF duration before the procedure, d	312 (104–1038)	291 (85–791)	0.326	305 (123–820)	215 (85–620)	0.172
Hypertension	115 (83.9)	117 (82.4)	0.752	34 (30.6)	33 (31.1)	1.000
Diabetes	43 (31.4)	34 (23.9)	0.182	4 (3.6)	4 (3.8)	1.000
Dyslipidemia	65 (47.4)	66 (46.5)	0.905	50 (45.0)	46 (43.4)	0.891
Heart failure	29 (21.2)	33 (23.2)	0.774	17 (15.3)	13 (12.3)	0.559
Coronary artery disease	12 (8.8)	16 (11.3)	0.553	8 (7.2)	4 (3.8)	0.376
Peripheral artery disease	3 (2.2)	4 (2.8)	1.000	1 (0.9)	1 (0.9)	1.000
History of stroke or transient ischemic attack	19 (13.9)	13 (9.2)	0.261	5 (4.5)	7 (6.6)	0.563
History of systemic thromboembolism	4 (2.9)	1 (0.7)	0.207	1 (0.9)	0 (0.0)	1.000
eGFR, mL/min per 1.73 m^2	59.8 (52.3–67.1)	60.0 (50.4–70.2)	0.842	67.6 (60.6–77.6)	69.2 (61.9–76.8)	0.736
eGFR <90 mL/min per 1.73 m^2	135 (98.5)	140 (98.6)	1.000	102 (91.9)	99 (93.4)	0.797
Hemoglobin, g/dL	14.3 (13.4–15.1)	14.5 (13.2–15.4)	0.437	14.7 (14.1–15.3)	15.2 (14.2–15.8)	0.043
CRP, mg/dL	0.10 (0.08–0.21)	0.10 (0.06–0.20)	0.338	0.10 (0.05–0.12)	0.10 (0.06–0.14)	0.537
B-type natriuretic peptide, pg/mL	160 (112–242)	162 (115–246)	0.899	143 (82–194)	111 (77–157)	0.064
CHA2DS2-VASc score			0.516			0.370
0	0 (0.0)	0 (0.0)		36 (32.4)	37 (34.9)	
1	13 (9.5)	8 (5.6)		49 (44.1)	49 (46.2)	
2	42 (30.7)	48 (33.8)		20 (18.0)	12 (11.3)	
3	42 (30.7)	46 (32.4)		4 (3.6)	8 (7.5)	
4	26 (19.0)	25 (17.6)		1 (0.9)	0 (0.0)	
5	10 (7.3)	11 (7.7)		1 (0.9)	0 (0.0)	
6	0 (0.0)	3 (2.1)		0 (0.0)	0 (0.0)	
7	3 (2.2)	1 (0.7)		0 (0.0)	0 (0.0)	
8	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
9	1 (0.7)	0 (0.0)		0 (0.0)	0 (0.0)	
Anticoagulant			0.322			0.531
None	1 (0.7)	0 (0.0)		0 (0.0)	0 (0.0)	
Warfarin	13 (9.5)	9 (6.3)		4 (3.6)	6 (5.7)	
DOAC	123 (89.8)	133 (93.7)		107 (96.4)	100 (94.3)	

(*Continued*)

Table 1. Continued

Characteristic	DR-FLASH score >3 and PVI-plus	DR-FLASH score >3 and PVI-alone	*P* value*	DR-FLASH score ≤3 and PVI-plus	DR-FLASH score ≤3 and PVI-alone	*P* value*
DOAC			0.323			0.191
Dabigatran	24 (17.5)	16 (11.3)		10 (9.0)	21 (19.8)	
Rivaroxaban	40 (29.2)	44 (31.0)		42 (37.8)	33 (31.1)	
Apixaban	33 (24.1)	45 (31.7)		17 (15.3)	15 (14.2)	
Edoxaban	26 (19.0)	28 (19.7)		38 (34.2)	31 (29.2)	
Antiplatelets	17 (12.4)	22 (15.5)	0.493	8 (7.2)	6 (5.7)	0.784
Angiotensin-converting enzyme or angiotensin receptor blockers	51 (37.2)	62 (43.7)	0.329	24 (21.6)	22 (20.8)	1.000
Calcium channel blockers	65 (47.4)	80 (56.3)	0.151	27 (24.3)	22 (20.8)	0.626
β Blockers	65 (47.4)	71 (50.0)	0.720	41 (36.9)	38 (35.8)	0.889
Ineffective antiarrhythmic drugs before the procedure			0.162			0.904
0	110 (80.3)	100 (70.4)		87 (78.4)	81 (76.4)	
1	18 (13.1)	31 (21.8)		20 (18.0)	21 (19.8)	
2	8 (5.8)	7 (4.9)		4 (3.6)	3 (2.8)	
3	1 (0.7)	2 (1.4)		0 (0.0)	1 (0.9)	
4	0 (0.0)	2 (1.4)		0 (0.0)	0 (0.0)	
Mitral regurgitation	102 (74.5)	112 (79.4)	0.393	73 (65.8)	59 (55.7)	0.164
Left atrial diameter, mm	44.0 (40.0–47.0)	43.0 (40.4–46.4)	0.694	41.0 (38.0–44.0)	40.0 (38.0–43.2)	0.834
Left atrial diameter >45 mm	57 (41.6)	53 (37.3)	0.540	10 (9.0)	8 (7.5)	0.807
Left ventricular ejection fraction, %	64.0 (59.0–68.5)	64.4 (59.1–70.3)	0.361	63.0 (54.6–66.4)	62.5 (57.2–68.0)	0.334
Antiarrhythmic drugs in the blanking period			0.797			0.277
Overall	42 (30.7)	46 (32.4)		57 (51.4)	46 (43.4)	
Mexiletine	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Procainamide	1 (0.7)	0 (0.0)		0 (0.0)	0 (0.0)	
Disopyramide	1 (0.7)	1 (0.7)		0 (0.0)	1 (0.9)	
Quinidine	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Propafenone	0 (0.0)	1 (0.7)		0 (0.0)	0 (0.0)	
Aprindine	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Cibenzoline	0 (0.0)	2 (1.4)		1 (0.9)	0 (0.0)	
Pirmenol	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Flecainide	3 (2.2)	5 (3.5)		2 (1.8)	6 (5.7)	
Pilsicainide	6 (4.4)	6 (4.2)		6 (5.4)	6 (5.7)	
Bepridil	31 (22.6)	29 (20.4)		48 (43.2)	31 (29.2)	
Sotalol	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Amiodarone	0 (0.0)	2 (1.4)		0 (0.0)	2 (1.9)	

Continuous values are given as median with interquartile range (25th–75th percentile). Categorical values are given as number with percentage of positive findings per number of studied patients. AF indicates atrial fibrillation; CRP, C-reactive protein; DOAC, direct oral anticoagulant; DR-FLASH, score based on diabetes mellitus, renal dysfunction, persistent form of atrial fibrillation, left atrialdiameter >45 mm, age >65 years, female sex, and hypertension; eGFR, estimated glomerular filtration rate; PVI-alone, pulmonary vein isolation only; and PVI-plus, extensive ablation comprising linear and/or complex fractional atrial electrogram ablation in addition to pulmonary vein isolation.

*Comparison between PVI-alone and PVI-plus in each group of DR-FLASH score >3 and DR-FLASH score ≤3. The CHA2DS2-VASc score consisted of the following: 2 points each for aged ≥75 years, and history of stroke, transient ischemic attack, or systemic thromboembolism; 1 point each for congestive heart failure, hypertension, aged 65 to 74 years, diabetes, vascular disease, and female sex.

Table 2. Procedure Data

Variable	DR-FLASH score >3 and PVI-plus	DR-FLASH score >3 and PVI-alone	DR-FLASH score >3	DR-FLASH score ≤3 and PVI-plus	DR-FLASH score ≤3 and PVI-alone	DR-FLASH score ≤3
Total No.	137	142	279	111	106	217
No. of non-PV triggers						
0	131 (95.6)	128 (90.1)	259 (92.8)	109 (98.2)	100 (94.3)	209 (96.3)
1	3 (2.2)	7 (4.9)	10 (3.6)	1 (0.9)	5 (4.7)	6 (2.8)
2	2 (1.5)	5 (3.5)	7 (2.5)	1 (0.9)	1 (0.9)	2 (0.9)
3	0 (0.0)	2 (1.4)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
4	1 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Location of non-PV trigger						
Superior vena cava	0 (0.0)	4 (2.8)	4 (1.4)	1 (0.9)	1 (0.9)	2 (0.9)
High right atrium	1 (0.7)	4 (2.8)	5 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Lateral right atrium	0 (0.0)	1 (0.7)	1 (0.4)	0 (0.0)	1 (0.9)	1 (0.5)
Atrial septum of the right side	1 (0.7)	2 (1.4)	3 (1.1)	2 (1.8)	1 (0.9)	3 (1.4)
Atrial septum of the left side	1 (0.7)	3 (2.1)	4 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Posterior left atrium	1 (0.7)	2 (1.4)	3 (1.1)	0 (0.0)	2 (1.9)	2 (0.9)
Anterior left atrium	0 (0.0)	1 (0.7)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Lateral left atrium	1 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Mitral annulus	0 (0.0)	1 (0.7)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Coronary sinus	3 (2.2)	1 (0.7)	4 (1.4)	0 (0.0)	1 (0.9)	1 (0.5)
Unknown	1 (0.7)	3 (2.1)	4 (1.4)	0 (0.0)	1 (0.9)	1 (0.5)
Extensive catheter ablation						
Linear ablation	119 (86.9)	0 (0.0)	119 (42.7)	92 (82.9)	0 (0.0)	92 (42.2)
Roof line ablation	119 (86.9)	0 (0.0)	119 (42.7)	91 (82.0)	0 (0.0)	91 (41.7)
Bottom line ablation	63 (46.0)	0 (0.0)	63 (22.6)	47 (42.3)	0 (0.0)	47 (21.6)
Anterior line ablation	28 (20.4)	0 (0.0)	28 (10.0)	12 (10.8)	0 (0.0)	12 (5.5)
Mitral isthmus ablation	90 (65.7)	0 (0.0)	90 (32.3)	81 (73.0)	0 (0.0)	81 (37.2)
CFAE ablation	19 (13.9)	0 (0.0)	19 (6.8)	19 (17.1)	0 (0.0)	19 (8.7)
Combinations of procedures						
Roof line and anterior line ablation+PVI	20 (14.6)	0 (0.0)	20 (7.2)	10 (9.0)	0 (0.0)	10 (4.6)
Roof line, anterior line, and mitral isthmus ablation+PVI	1 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Roof line and bottom line ablation+PVI	1 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Roof line, bottom line, and anterior line ablation+PVI	5 (3.6)	0 (0.0)	5 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Roof line, bottom line, anterior line, and mitral isthmus ablation+PVI	2 (1.5)	0 (0.0)	2 (0.7)	1 (0.9)	0 (0.0)	1 (0.5)
Roof line, bottom line, and mitral isthmus ablation+PVI	54 (39.4)	0 (0.0)	54 (19.4)	45 (40.5)	0 (0.0)	45 (20.7)

(*Continued*)

Table 2. Continued

Variable	DR-FLASH score >3 and PVI-plus	DR-FLASH score >3 and PVI-alone	DR-FLASH score >3	DR-FLASH score ≤3 and PVI-plus	DR-FLASH score ≤3 and PVI-alone	DR-FLASH score ≤3
Roof line and mitral isthmus ablation+PVI	33 (24.1)	0 (0.0)	33 (11.8)	34 (30.6)	0 (0.0)	34 (15.7)
Anterior line and mitral isthmus ablation+PVI	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.5)
CFAE ablation+PVI	16 (11.7)	0 (0.0)	16 (5.7)	18 (16.2)	0 (0.0)	18 (8.3)
Roof line and CFAE ablation+PVI	2 (1.5)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Roof line, bottom line, and CFAE ablation+PVI	1 (0.7)	0 (0.0)	1 (0.4)	1 (0.9)	0 (0.0)	1 (0.5)
No extensive catheter ablation+PVI	2 (1.5)	142 (100.0)	144 (51.6)	1 (0.9)	106 (100.0)	107 (49.3)
Total procedure time, min	180 (130–230)	145 (113–200)	160 (124–216)	185 (147–229)	143 (113–167)	160 (125–200)

Continuous values are given as median with interquartile range (25th–75th percentile). Categorical values are given as number with percentage of positive findings per number of studied patients. CFAE, complex fractional atrial electrogram; DR-FLASH, score based on diabetes mellitus, renal dysfunction, persistent form of atrial fibrillation, left atrialdiameter >45 mm, age >65 years, female sex, and hypertension; PV, pulmonary vein; PVI, PV isolation; PVI-alone, PVI only; and PVI-plus, extensive ablation comprising linear and/or CFAE ablation in addition to PVI.

that statistical significance was not observed because of the small sample sizes. In the PVI-plus arm with a DR-FLASH score ≤3, recurrence rate in patients with procedures of roof line, bottom line, and mitral isthmus ablation; with procedures of roof line and mitral isthmus ablation; with procedures of CFAE ablation; with procedures of roof line and anterior line ablation; and with the others was 8 of 45 (17.8%), 10 of 34 (29.4%), 5 of 18 (27.8%), 1 of 10 (10.0%), and 2 of 4 (50.0%), respectively. Patients with other procedures and a DR-FLASH score ≤3 consisted of those with roof line, bottom line, anterior line, and mitral isthmus ablation; with anterior line and mitral isthmus ablation; with roof line, bottom line, and CFAE ablation; and with no extensive catheter ablation. In the PVI-alone arm with a DR-FLASH score ≤3, the recurrence rate in patients who underwent PVI-alone was 23 of 106 (21.7%). There were no significant differences in recurrence rate between types of extensive ablation procedures and PVI-alone in patients with a DR-FLASH score ≤3.

Complications

Complications are summarized in Table 3. During the follow-up period, 1 patient in the PVI-plus arm with a DR-FLASH score >3 experienced a massive ischemic stroke of the left midcerebral artery 3 days after the index catheter ablation. Although promptly hospitalized and treated by intensive care, the patient died 7 days after the index catheter ablation. In the DR-FLASH score >3 patients allocated to the PVI-alone arm, 2 patients experienced symptomatic ischemic strokes. Numerically more complications were seen in patients with a DR-FLASH score >3 than in those with a score ≤3.

DISCUSSION

Main Findings

In this post hoc analysis of randomized controlled trial data, we found that an extensive ablation strategy, such as linear ablation and/or CFAE ablation, in addition to PVI was effective in reducing the recurrence of AF among patients with a DR-FLASH score >3, whereas a PVI-alone strategy showed similar effectiveness to PVI-plus among those with a DR-FLASH score ≤3. These findings suggest that the DR-FLASH score is a useful noninvasive means of identifying patients who do or do not need extensive substrate ablation in addition to PVI in patients with persistent AF.

Relationship Between Arrhythmogenic Substrates and DR-FLASH Score

Differences in the efficacy of catheter ablation strategies among patients with higher and lower DR-FLASH scores might be linked to arrhythmogenic substrates. This is because the 7 clinical factors for which the DR-FLASH score accounts, (1) diabetes, (2) renal dysfunction, (3) persistent form of AF, (4) left atrial diameter, (5) age, (6) sex, and (7) hypertension, are all linked to atrial fibrosis and/or remodeling.

First, diabetes, which leads to electrical remodeling, causes structural remodeling in the left atrium. Hyperglycemia may lead to the production of inflammatory cytokines that induce fibroblast proliferation. Second, renal dysfunction is linked to arrhythmogenic substrates.[15] Increased levels of uremic toxins have

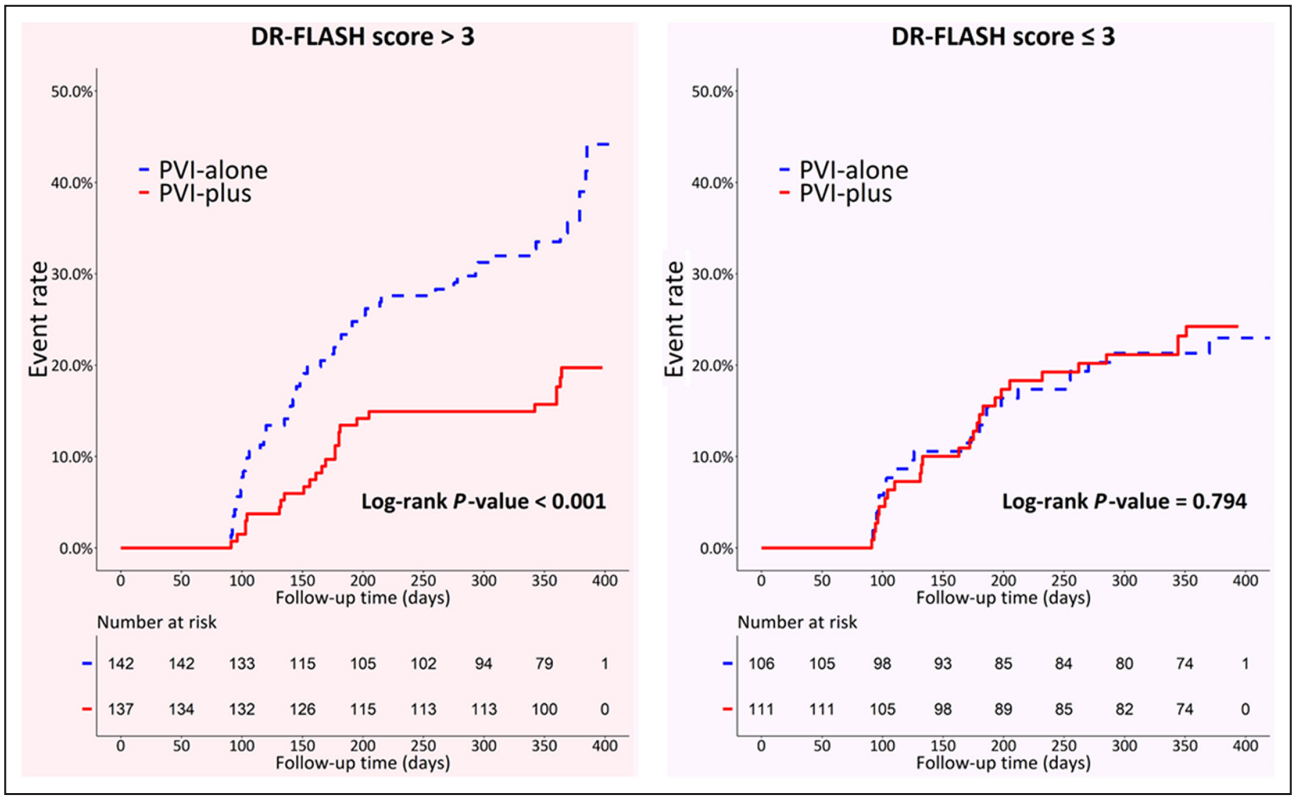

Figure 2. Kaplan-Meier analysis with a log-rank test for the primary end point in patients with a DR-FLASH score >3 (left panel) and DR-FLASH score ≤3 (right panel).
PVI-alone indicates pulmonary vein isolation only; and PVI-plus, extensive ablation comprising linear and/or complex fractional atrial electrogram ablation in addition to pulmonary vein isolation; DR-FLASH, score based on diabetes mellitus, renal dysfunction, persistent form of atrial fibrillation, left atrialdiameter >45 mm, age >65 years, female sex, and hypertension.

cytotoxic effects, which cause necrosis and fibrosis.[16] Third, AF itself leads to atrial fibrosis, which, in turn, causes sustained AF.[17,18] A previous study using cardiac magnetic resonance imaging showed that more late-gadolinium–enhanced segments were observed in patients with persistent AF than in those with paroxysmal AF.[19] Fourth, dilation of the left atrium is associated with conduction disturbance,[20,21] which leads to triggered activity and reentry. Fifth, aging is related to atrial remodeling and fibrosis. Advancing age is associated with interstitial fibrosis and atrial diastolic function decline. Sixth, female sex is associated with non-PV arrhythmogenic substrates[22,23] and poor AF ablation outcomes.[24] Sex differences in hormones, inflammation, and autonomic nerve system function may influence AF development.[25] Seventh, hypertension, which leads to enlargement and fibrosis of the left atrium, plays an important role in the development of AF.[26–28] Furthermore, hypertension reportedly induces heterogeneous left atrial wall hypertrophy, which is also linked to the reentrant circuit.[28,29] Therefore, the association between DR-FLASH score and increased arrhythmogenic substrates may be explained by the effects of its 7 component items.[30]

Effectiveness of Extensive Catheter Ablation

Combination of roof line, bottom line, and mitral isthmus ablation seemed to be effective in patients with a DR-FLASH score >3, although in the other types of extensive catheter ablation, recurrence rate was numerically, but not significantly, lower than with PVI-alone because of the small sample size (Figure 4). For linear ablation in the present study, at least 2 lines in the left atrium were required. The first mandatory line was a mitral isthmus or anterior line. The second mandatory line was a roof line. Bottom line ablation was performed at the operator's discretion. Given that most patients in the PVI-plus arm underwent roof line and mitral isthmus ablation, and that PVI-plus was effective in those with a DR-FLASH score >3 in this study, it appears reasonable that ablation of at least 2 lines, roof line and mitral isthmus, should be recommended for those with a DR-FLASH score >3. In addition, recurrence rate was numerically lower in patients who underwent extensive catheter ablation of roof line, bottom line, and mitral isthmus than in those who underwent extensive catheter ablation of roof line and mitral isthmus. This result suggests that complete isolation of the left atrial posterior wall by adding bottom line ablation in patients with

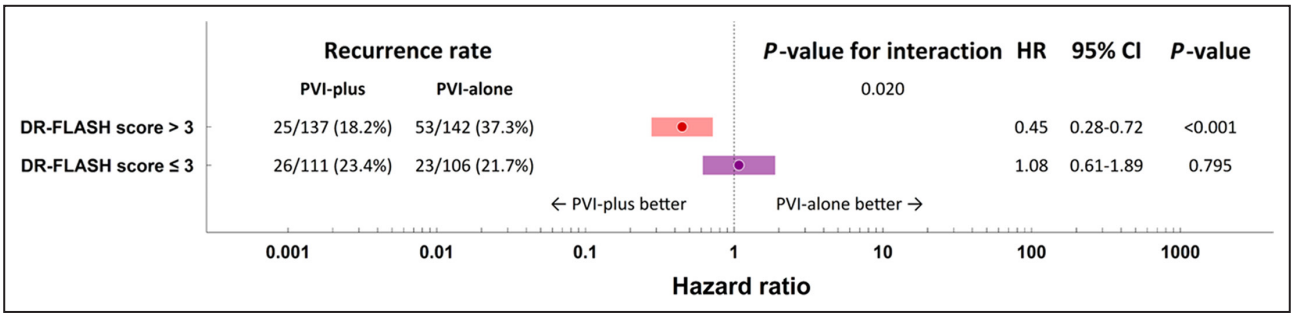

Figure 3. Hazard ratio (HR) for the primary end point using a Cox proportional hazards model.
DR-FLASH indicates score based on diabetes mellitus, renal dysfunction, persistent form of atrial fibrillation, left atrialdiameter >45 mm, age >65 years, female sex, and hypertension; PVI-alone, pulmonary vein isolation only; and PVI-plus, extensive ablation comprising linear and/or complex fractional atrial electrogram ablation in addition to pulmonary vein isolation.

roof line and mitral isthmus ablation might be required to effectively suppress AF, atrial tachycardia, or atrial flutter in patients with a DR-FLASH score >3. The effectiveness of posterior wall isolation is controversial. Lee et al reported that the 12-month freedom from recurrence rate for atrial arrhythmias was significantly lower in patients with posterior wall isolation in addition to PVI for persistent AF than in those with PVI alone.[31] In contrast, Thiyagarajah et al reported that the recurrence rate of atrial arrhythmias did not significantly differ between patients with persistent AF receiving PVI alone and those with posterior wall isolation in addition to PVI.[32] These inconsistent results between our present and these previous studies suggest that posterior wall isolation may not be effective as an empirical procedure. Accordingly, patient selection is an important consideration in the decision to perform posterior wall isolation for patients with persistent AF.

Relationship Between Complications and DR-FLASH Score

In the present study, patients with DR-FLASH score >3 had more complications than the group with DR-FLASH score ≤3, even for the same type of procedure. This may be explained by the association between several diseases/disorders and each component of DR-FLASH score.

First, each component of the DR-FLASH score is associated with cardiovascular diseases. Diabetes, hypertension, female sex, and higher age are included in the CHA2DS2-VASc score for cerebral infarction in patients with AF (CHA2DS2-VASc score is calculated by adding the following points: 2 points each for age ≥75 years, and history of stroke, TIA or systemic thromboembolism; 1 point each for congestive heart failure, hypertension, age of 65–74 years, diabetes mellitus, vascular disease, and female sex).[33,34] Also, each composite element of the DR-FLASH score is related to heart failure. Diabetes, renal dysfunction, hypertension, female sex, and higher age have a negative impact on the heart.[35–37] Dilated left atrium reflects left ventricular diastolic dysfunction.[38]

Second, patients with some components of the DR-FLASH score (namely, hypertension, renal dysfunction, and higher age) are prone to bleeding. These factors partially compose the HAS-BLED score (Hypertension, Abnormal renal/liver dysfunction, Stroke, Bleeding history, Liable prothrombin time-international normalized ratio, Elderly, Drugs) for bleeding.[39] In our study, more bleeding complications were observed in patients with DR-FLASH score >3. Finally, anatomical structure in patients with a higher DR-FLASH score may linked to a relatively higher rate of complications. Prior studies of catheter ablation for AF reported that more procedural complications were observed in women compared with men.[40,41] These studies explained that catheter control was relatively difficult because cardiac and vascular sizes were smaller, leading to hematoma or cardiac tamponade.[40,41] Moreover, smaller physical size was reportedly associated with periesophageal vagal nerve injury.[42] In the present study, lower height and weight were observed in patients with a DR-FLASH score >3 than in those with a score ≤3. Accordingly, catheter ablation for AF in patients with higher DR-FLASH scores should be performed with particular care.

Clinical Implications

This is the first report to demonstrate that patients with persistent AF with a higher probability of arrhythmogenic substrates, as estimated using the DR-FLASH score, benefit from extensive catheter ablation. Several randomized controlled trials have failed to prove the superiority of extensive catheter ablation strategies over PVI alone in patients with persistent AF.[4,43] A meta-analysis analyzing the efficacy of CFAE and/or linear ablation reported that there was no significant improvement in the AF-free rate.[44] Despite the noninferiority design of the EARNEST-PVI trial, this study found that an extensive strategy comprising PVI plus linear ablation or CFAE ablation may in fact be superior to PVI alone in patients with persistent AF. These inconsistent findings might be attributed to the heterogeneity of patients with persistent

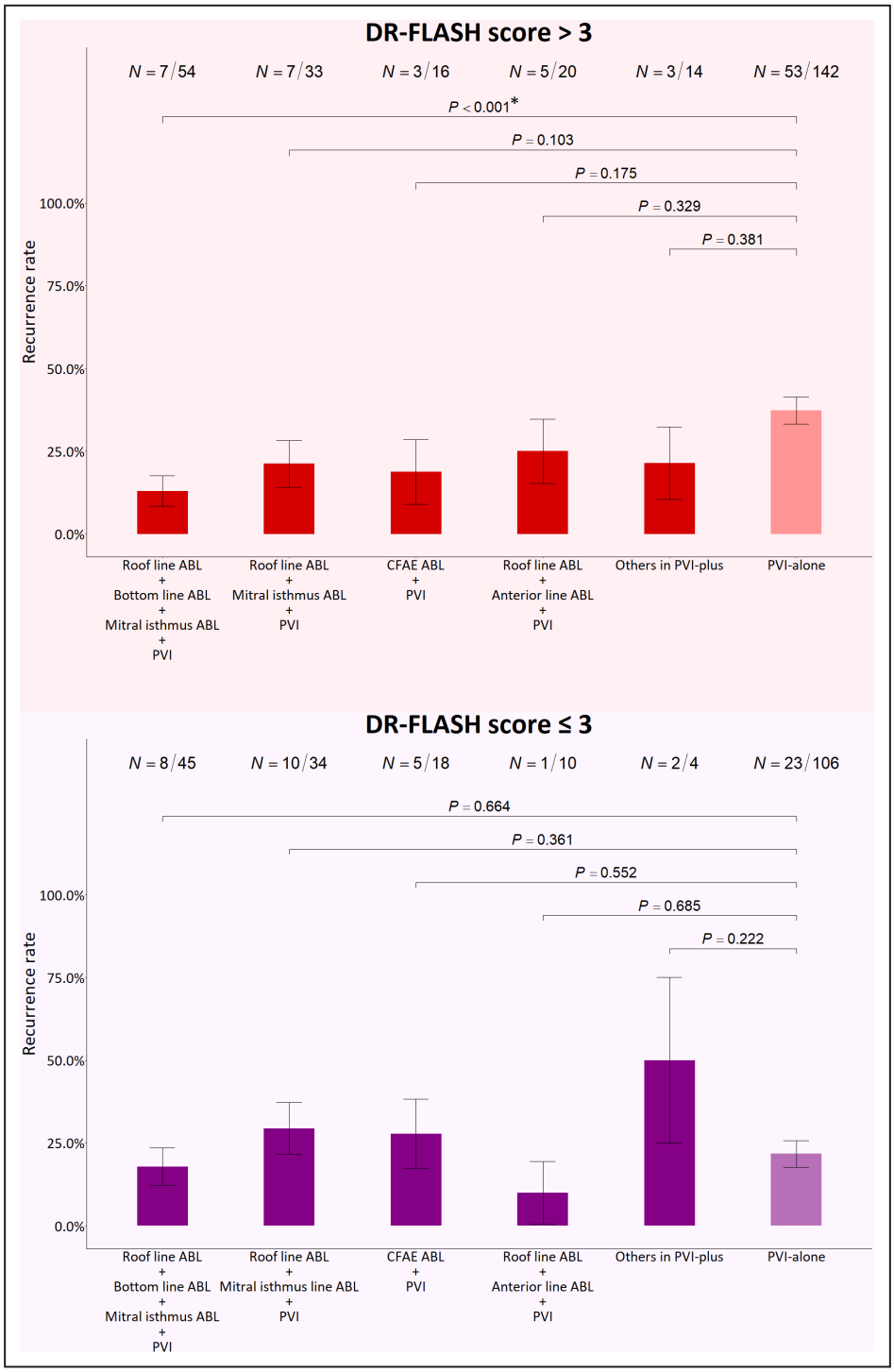

Figure 4. Recurrence rate of atrial fibrillation, atrial flutter, and atrial tachycardia, according to procedures in patients with a DR-FLASH score >3 (top panel) and DR-FLASH score ≤3 (bottom panel).

Error bars showed SEs. ABL indicates ablation; CFAE, complex fractional atrial electrogram; DR-FLASH score, score based on the presence of diabetes, renal dysfunction, persistent form of AF, left atrial diameter >45 mm, aged >65 years, female sex, and hypertension; PVI, pulmonary vein isolation; PVI-alone, PVI only; and PVI-plus, extensive ablation comprising linear and/or CFAE ablation in addition to PVI. *P<0.01 indicated significance level calculated with the Bonferroni method.

Table 3. Complications

Variable	DR-FLASH score >3 and PVI-plus	DR-FLASH score >3 and PVI-alone	DR-FLASH score >3	DR-FLASH score ≤3 and PVI-plus	DR-FLASH score ≤3 and PVI-alone	DR-FLASH score ≤3
Total No.	137	142	279	111	106	217
Death	1 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebral infarction	1 (0.7)	2 (1.4)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Procedure-related complications	7 (5.1)	4 (2.8)	11 (3.9)	2 (1.8)	1 (0.9)	3 (1.4)
Hematoma	1 (0.7)	1 (0.7)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Systemic thromboembolism	1 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumothorax	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arteriovenous fistula	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pericarditis	1 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac tamponade	1 (0.7)	0 (0.0)	1 (0.4)	1 (0.9)	0 (0.0)	1 (0.5)
Phrenic nerve injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Atrioventricular block	0 (0.0)	1 (0.7)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary hypertension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Left atrial-esophageal fistula	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infection	0 (0.0)	1 (0.7)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Heart failure	1 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Periesophageal vagal nerve injury	2 (1.5)	1 (0.7)	3 (1.1)	1 (0.9)	1 (0.9)	2 (0.9)
Dermatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Allergy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Categorical values are given as number with percentage of positive findings per number of studied patients. DR-FLASH indicates score based on diabetes mellitus, renal dysfunction, persistent form of atrial fibrillation, left atrialdiameter >45 mm, age >65 years, female sex, and hypertension; PVI-alone, pulmonary vein isolation only; and PVI-plus, extensive ablation comprising linear and/or complex fractional atrial electrogram ablation in addition to pulmonary vein isolation.

AF, suggesting the importance of matching the right treatment to the right patients with persistent AF. The present study showed that the DR-FLASH score might be useful for stratifying patients into those who do and do not require extensive ablation, thereby reducing cost and complications. In other words, interest in the DR-FLASH score is based around the goal of avoiding unnecessary ablation in low-score patients. Although all of the extensive ablation strategies tested seemed to be effective in patients with a DR-FLASH score >3 (Figure 4), further studies are needed to determine the most effective extensive ablation strategy. Further prospective studies are also warranted to confirm the clinical utility of the DR-FLASH score in determining catheter ablation strategies.

Limitations

There are several limitations in the present study. First, the primary end point, recurrence of AF, might have been underestimated. Although the study participants underwent ECG tests at every scheduled visit, those with asymptomatic AF may not have undergone additional ECG tests. Second, we did not collect voltage data in the present study. Thus, although the DR-FLASH score appeared to accurately predict the presence of low-voltage areas without voltage mapping, we could not confirm this using the available data. Third, our study was performed in an East Asian population; thus, the generalizability of the results to other populations may be limited. Finally, the additional left atrial ablation protocol for the PVI-plus arm was not specifically prescribed in the EARNEST-PVI trial, which was originally designed to demonstrate the noninferiority of PVI-alone to any extensive catheter ablation for persistent AF.

CONCLUSIONS

The PVI-plus strategy was more effective than the PVI-alone strategy in patients with a DR-FLASH score >3, whereas effectiveness was similar between strategies in those with a DR-FLASH score ≤3. Therefore, the DR-FLASH score may be a useful tool in determining catheter ablation strategy for patients with persistent AF.

APPENDIX

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Disclosures

Dr Hikoso has received grants from Medtronic, Johnson & Johnson, and Abbott during the conduct of the study; personal fees from Bayer, Daiichi Sankyo, Medtronic, Boehringer Ingelheim, Johnson & Johnson, Roche Diagnostics, Fujifilm Toyama Chemical, and Actelion; and nonfinancial support from Actelion, outside the submitted work. Dr Nakatani has received grants from Medtronic, Johnson & Johnson, and Abbott during the conduct of the study; and personal fees from Roche Diagnostics and grants from Daiichi Sankyo, outside the submitted work. Dr Mizuno has received grants from Medtronic, Johnson & Johnson, and Abbott during the conduct of the study; personal fees from Daiichi Sankyo, Bayer, Japan Lifeline, Boehringer Ingelheim, Toa Eiyo, Pfizer, and Medtronic; and acted as an endowed chair lecturer at Terumo, outside the submitted work. Dr Dohi has received grants from Medtronic, Johnson & Johnson, and Abbott during the conduct of the study. Dr Egami has received personal fees from Japan Lifeline and Medtronic, and nonfinancial support from Johnson & Johnson, Abbott, and Medtronic, outside the submitted work. Dr Watanabe has received personal fees from Biosense Webster, Abbott, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Bayer, Daiichi Sankyo, Nihon Kohden, and Fukuda Denshi, outside the submitted work. Dr Minamiguchi has received grants from Medtronic, Johnson & Johnson, and Abbott, during the conduct of the study; and personal fees from Medtronic, Abbott, Johnson & Johnson, Nihon Kohden, Biotronik, Japan Lifeline, Daiichi Sankyo, Bayer, Pfizer, Bristol-Myers Squibb, Boehringer Ingelheim, Kowa, Ono Pharmaceutical, and Otsuka Pharmaceutical, outside the submitted work. Dr Tanaka has received personal fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Johnson & Johnson, Medtronic, and Philips, outside the submitted work. Dr Oka has received personal fees from Medtronic, Biotronik, Abbott, Daiichi Sankyo, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, MSD, and AstraZeneca, outside the submitted work. Dr Okada has received personal fees from Bayer, Bristol-Myers Squibb, Daiichi Sankyo, and Medtronic, outside the submitted work. Dr Kanda has received personal fees from Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Nihon Kohden, Abbott, Medtronic, and Otsuka Pharmaceutical, outside the submitted work. Dr Matsuda has received personal fees from Daiichi Sankyo, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Bayer, Toa Eiyo, MEDICAL VIEW, Medtronic, and Biotronik, outside the submitted work. Dr Kawasaki has received personal fees from Medtronic, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Bristol-Myers Squibb, and Abbott, and grants from Osaka Heart Club, outside the submitted work. Dr Masuda has received personal fees from Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Johnson & Johnson, Boston Scientific, Abbott, Nihon Kohden, Otsuka Pharmaceutical, AstraZeneca, and Medtronic, outside the submitted work. Dr Inoue has received personal fees from Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Johnson & Johnson, and Medtronic, outside the submitted work. Dr Sakata has received grants from Medtronic, Johnson & Johnson, and Abbott during the conduct of the study; and personal fees from Abbott, Sanofi, Johnson & Johnson, Daiichi Sankyo, Terumo, Medtronic, Bayer, Biotronik, Bristol-Myers Squibb, Boehringer Ingelheim, and Boston Scientific, outside the submitted work. Drs Sato, Sotomi, Okada, Sunaga, Kida, Oeun, Miyoshi, and Kitamura have nothing to disclose.

Supplemental Material

Figure S1

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SUPPLEMENTAL MATERIAL

Figure S1. Histogram of DR-FLASH scores