Supplemental Material

Data S1.

Supplemental Methods

Electrophysiological study and RFCA procedures

The RFCA was performed under the guidance of three-dimensional electroanatomic mapping systems (CARTO 3, Biosense Webster, Diamond Bar, CA, USA; or EnSite Velocity, Abbott, St. Paul, MN, USA). We incorporated CARTOMERGE (Biosense Webster) computed tomography integration with CARTO 3. We administered 10 μg of isoproterenol and 10 mg of adenosine triphosphate intravenously to elicit AF and identify its origin. Circumferential PVI was performed by double-Lasso technique using two circular mapping catheters (CARTO, Lasso, Biosense Webster; EnSite, Inquiry, Abbott) or a combination of a circular mapping catheter and an multielectrode mapping catheter (CARTO, PENTARAY, Biosense Webster, EnSite; Advisor HD Grid, Abbott), whichever was applicable. We used an open-irrigated 3.5-mm-tip deflectable catheter (CARTO, THERMOCOOL SMARTTOUCH, Biosense Webster. EnSite; Flexibility, Abbott) with the radiofrequency power set at 30 W on the anterior left atrial (LA) wall and 25 W on the posterior LA wall. We confirmed successful PVI by the disappearance of PV potentials and exit block. After successful PVI, 10 μg of isoproterenol and 10 mg of adenosine triphosphate were again infused intravenously. If AF was triggered by non-PV foci, which were identified as being the earliest ectopic sites where the ectopic beats were initiated in AF, a non-PV foci ablation was added. The endpoint of RFCA was the disconnection of all PVs and elimination of all non-PV foci. In patients with documentation of a typical atrial flutter before or during RFCA, a cavotricuspid isthmus ablation was also performed. The RFCA was followed by an electrophysiological study while the sinus rhythm was stable. During the electrophysiological study, we measured the atrial signal–to–His bundle interval, His bundle–to–the first ventricular activation interval, sinus node recovery time, and atrioventricular nodal conduction at a maximal rate of 1:1.

Table S1. Antiarrhythmic drugs, RFCA procedures, complications, and electrophysiological study between treatment and nontreatment groups

	Treatment (n = 97)	Nontreatment (n = 191)	*P* value
Antiarrhythmic drugs (pre-RFCA)			
Ia, n (%)	15 (15%)	26 (14%)	0.67
Ic, n (%)	1 (1%)	0 (0%)	0.14
II, n (%)	47 (48%)	90 (47%)	0.83
III, n (%)	2 (2%)	3 (2%)	0.77
Bepridil, n (%)	10 (10%)	16 (8%)	0.59
Antiarrhythmic drugs (post-RFCA)			
Ia, n (%)	16 (16%)	29 (15%)	0.77
Ic, n (%)	0 (0%)	2 (1%)	0.20
II, n (%)	29 (30%)	57 (30%)	0.99
III, n (%)	4 (4%)	13 (7%)	0.35
Bepridil, n (%)	72 (74%)	139 (73%)	0.79
RFCA procedures			
CARTO, n (%)	49 (51%)	104 (54%)	0.53
EnSite, n (%)	48 (49%)	87 (46%)	0.53
Operator A, n (%)	37 (38%)	80 (42%)	0.54
Operator B, n (%)	28 (29%)	50 (26%)	0.63
Operator C, n (%)	14 (14%)	27 (14%)	0.95
Operator D, n (%)	18 (19%)	34 (18%)	0.88
CTI linear ablation, n (%)	16 (16%)	22 (12%)	0.25
SVC isolation, n (%)	2 (2%)	9 (5%)	0.24
Periprocedural complications*			

All complications, n (%)	2 (2%)	7 (4%)	0.45
Cerebral infarction, n (%)	0 (0%)	1 (0.5%)	0.48
Puncture-site hematoma, n (%)	1 (1%)	2 (1%)	0.99
Pericarditis, n (%)	0 (0%)	3 (2%)	0.21
Phrenic nerve paralysis, n (%)	1 (1%)	1 (0.5%)	0.62
Electrophysiological study			
Maximum SNRT (ms)	1615.9 ± 337.0	1741.1 ± 638.7	0.09
Corrected SNRT (ms)	645.9 ± 275.9	726.8 ± 549.6	0.20
1:1 AV nodal conduction (beats/min)	130.1 ± 22.8	127.5 ± 22.5	0.37
AH interval (ms)	107.5 ± 26.9	106.5 ± 30.5	0.80
HV interval (ms)	43.0 ± 10.7	44.4 ± 11.8	0.34

*Two cases of intraoperative cardiac tamponade were excluded from the analyses and not included in this table. AH, atrial signal–to–His bundle; AV nodal conduction, atrioventricular nodal conduction; CTI, cavotricuspid isthmus; HV, his bundle–to–the first ventricular activation; RFCA, radiofrequency catheter ablation; SNRT, sinus node recovery time; SVC, superior vena cava.

Table S2. Cox regression analyses for AF recurrence (undichotomized version)

	Univariable			Multivariable		
Variable	Unadjusted HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value
Age, years	1.019	0.994–1.046	0.16			
BMI, kg/m^2	1.051	0.980–1.123	0.15			
Female (yes or no)	1.777	1.028–3.070	0.04	2.139	1.187–3.821	0.01
Nonparoxysmal AF (yes or no)	2.138	1.247–3.665	0.006	1.562	0.838–2.942	0.16
AF duration, months	1.004	1.0005–1.007	0.01	1.005	1.002–1.009	0.002
Left atrial volume, mL	1.019	1.008–1.029	0.0005	1.013	1.0005–1.025	0.04
Smoking (yes or no)	0.724	0.424–1.238	0.24			
Habitual drinking (yes or no)	0.621	0.332–1.162	0.14			
Hypertension (yes or no)	1.703	0.957–3.031	0.07			
Diabetes mellitus (yes or no)	1.088	0.532–2.227	0.82			
Dyslipidemia (yes or no)	1.084	0.633–1.855	0.77			
Previous cerebral infarction (yes or no)	1.093	0.464–2.572	0.84			
NT-proBNP, pg/mL	1.00005	0.9998–1.0003	0.66			

Hs-CRP, mg/dL	1.222	0.501–1.942	0.52			
Nonpulmonary vein foci (yes or no)	1.548	0.798–3.003	0.20			
Number of remaining teeth	1.021	0.988–1.059	0.24			
PISA, mm^2	1.0009	1.0001–1.002	0.02	1.0009	1.0001–1.002	0.02

Univariable and multivariable Cox regression analyses were applied among the nontreatment group (n = 191). Continuous variables were not dichotomized in this analysis. Variables with $P < 0.05$ in the univariable analysis were included in the multivariable model. AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PISA, periodontal inflamed surface area.

Table S3. Cox regression analyses for AF recurrence (sensitivity analysis)

	Univariable			Multivariable		
Variable	Unadjusted HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value
Age >75 years (yes or no)	0.967	0.547–1.705	0.91			
BMI >25.0 kg/m^2 (yes or no)	1.073	0.621–1.856	0.80			
Female (yes or no)	1.777	1.028–3.070	0.04	2.284	1.259–4.099	0.006
Nonparoxysmal AF (yes or no)	2.138	1.247–3.665	0.006	1.559	0.838–2.935	0.16
AF duration >2 years (yes or no)	2.356	1.368–4.058	0.002	2.236	1.277–3.914	0.005
Left atrial volume >70 mL (yes or no)	2.784	1.580–4.905	0.0004	2.121	1.093–4.117	0.03
Smoking (yes or no)	0.724	0.424–1.238	0.24			
Habitual drinking (yes or no)	0.621	0.332–1.162	0.14			
Hypertension (yes or no)	1.703	0.957–3.031	0.07			
Diabetes mellitus (yes or no)	1.088	0.532–2.227	0.82			
Dyslipidemia (yes or no)	1.084	0.633–1.855	0.77			
Previous cerebral infarction (yes or no)	1.093	0.464–2.572	0.84			
NT-proBNP >100 pg/mL (yes or no)	2.725	1.164–6.378	0.02	1.334	0.521–3.414	0.55

Hs-CRP >0.10 mg/dL (yes or no)	1.681	0.962–2.904	0.06			
Nonpulmonary vein foci (yes or no)	1.548	0.798–3.003	0.20			
Number of remaining teeth <20 (yes or no)	0.688	0.354–1.336	0.27			
High PISA (>500 mm^2)[a] (yes or no)	2.339	1.304–4.196	0.004	1.992	1.094–3.628	0.02

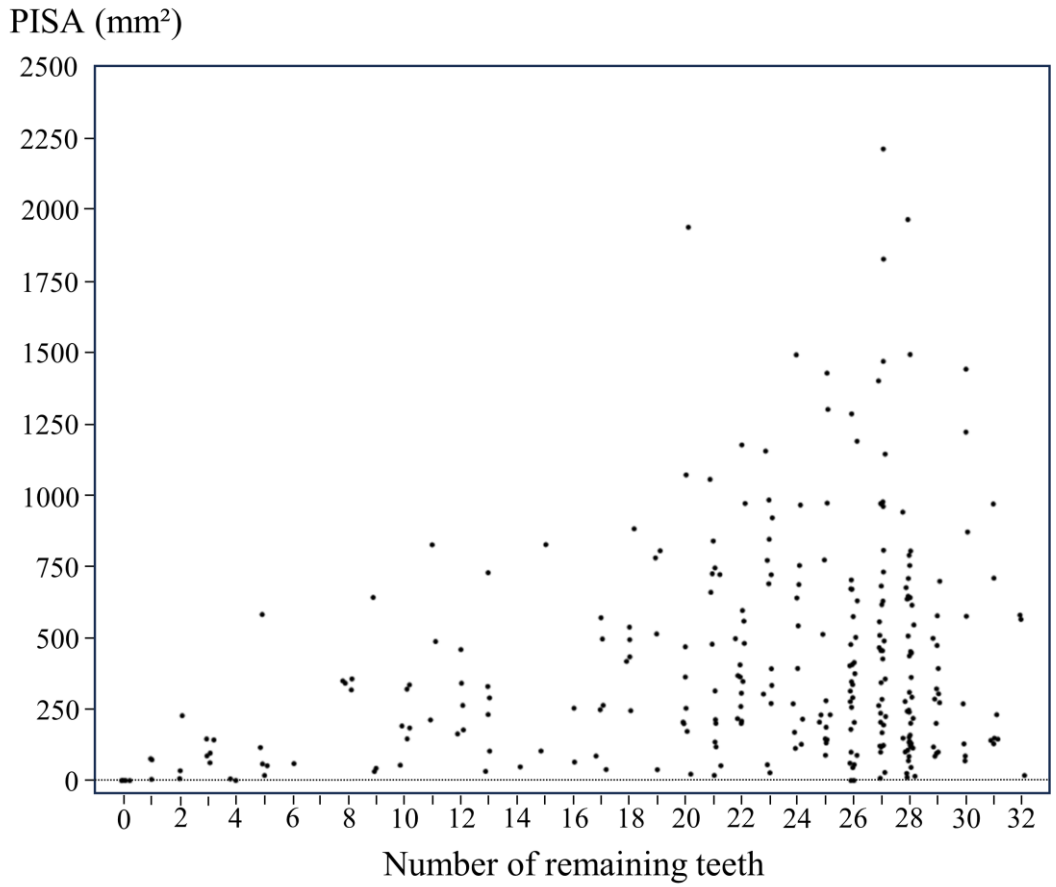
Univariable and multivariable Cox regression analyses were applied among the nontreatment group (n = 191). Variables with $P < 0.05$ in the univariate analysis were included in the multivariate model. [a]For the sensitivity analysis, 500 mm^2 was used as the cutoff value of PISA. AF, atrial fibrillation; BMI, body mass index; CI, confidence interval; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PISA, periodontal inflamed surface area.

Table S4. Cox regression analysis of periodontal treatment and AF recurrence (sensitivity analysis)

	Univariable			Multivariable		
Variable	Unadjusted HR	95% CI	*P* value	Adjusted HR	95% CI	*P* value
Female (yes or no)	1.894	1.174–3.035	0.008	2.311	1.402–3.797	0.0009
Nonparoxysmal AF (yes or no)	1.974	1.231–3.200	0.005	1.672	0.955–2.972	0.08
AF duration >2 years (yes or no)	2.067	1.277–3.346	0.003	1.970	1.206–3.218	0.007
Left atrial volume >70 mL (yes or no)	2.157	1.332–3.492	0.002	1.539	0.876–2.703	0.13
NT-proBNP >100 pg/mL (yes or no)	2.461	1.220–4.963	0.01	1.316	0.597–2.901	0.50
High PISA (>500 mm^2)* (yes or no)	1.795	1.103–2.923	0.02	1.992	1.173–3.383	0.01
Periodontal treatment (yes or no)	0.614	0.350–1.076	0.09	0.376	0.204–0.694	0.002

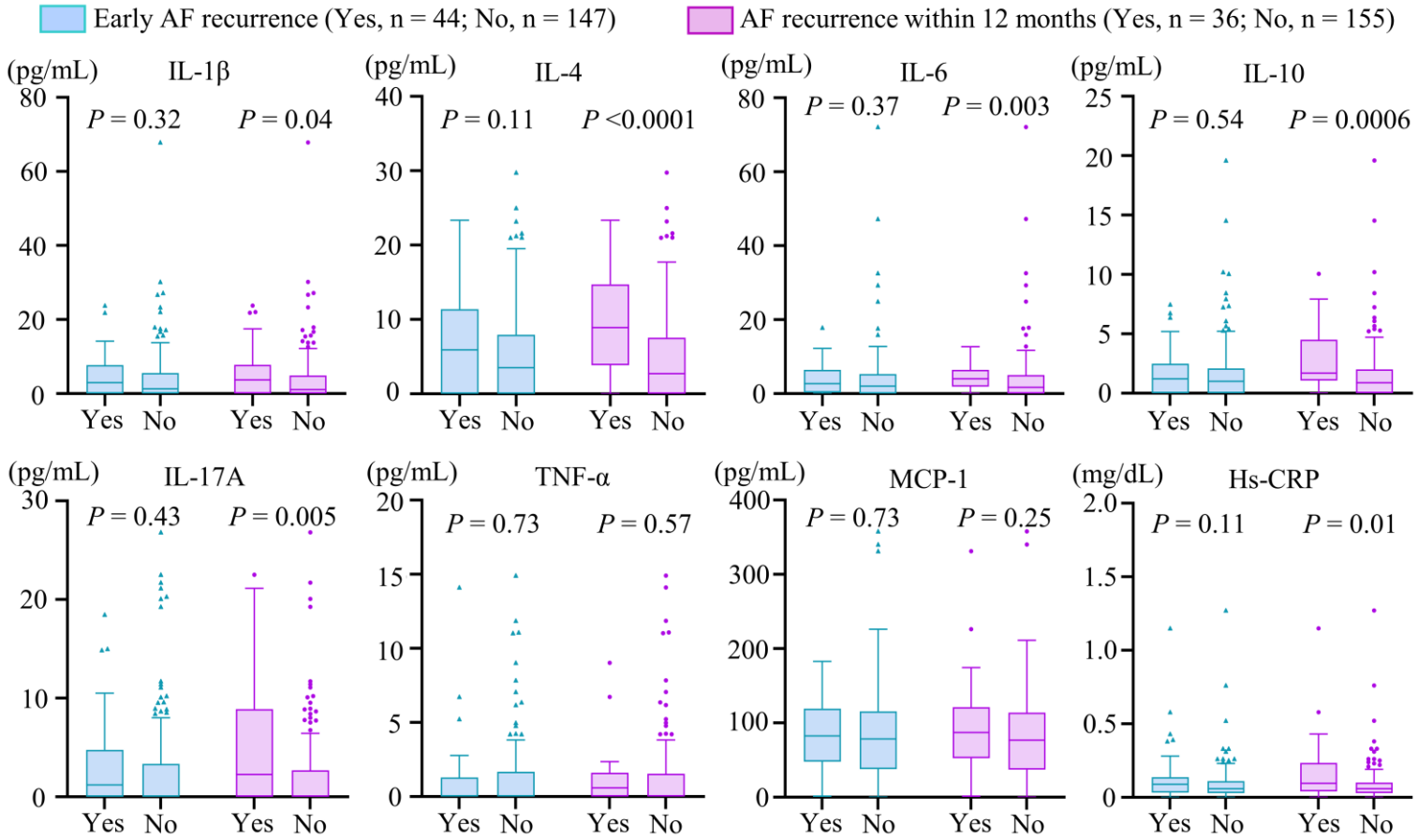
Periodontal treatment and other confounders ($P < 0.05$ in Table 2) were included in the multivariable Cox regression model. *For the sensitivity analysis, 500 mm^2 was used as the cutoff value of PISA. AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PISA, periodontal inflamed surface area.

Figure S1. Number of remaining teeth and PISA



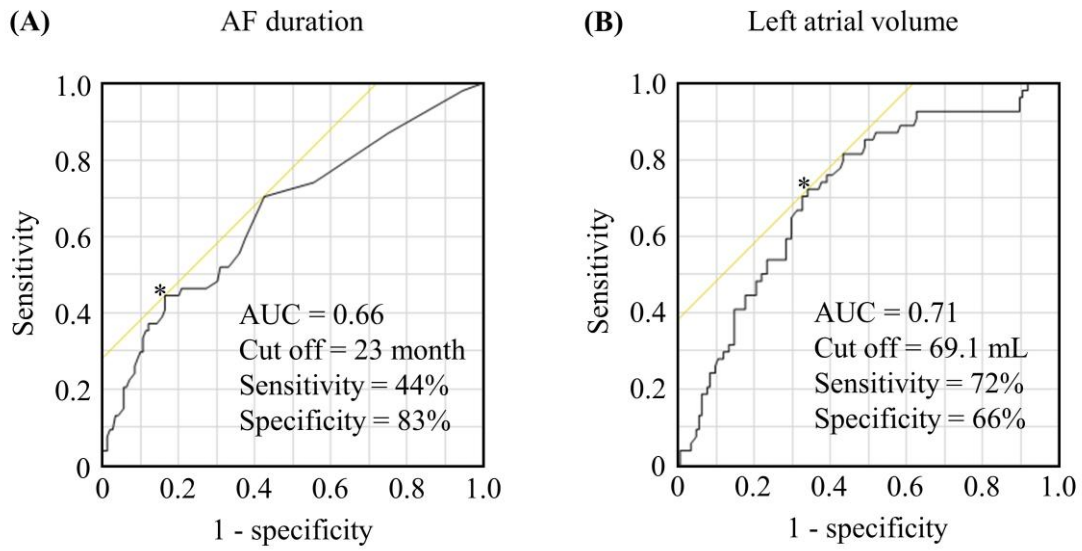
PISA is the sum of all bleeding areas in the epithelia of the periodontal pocket, which reflects the quantification of clinical periodontal inflammation degree. Periodontal pockets at tooth loss sites heal and disappear, and the areas of the periodontal pocket are calculated as 0 mm^2. For patients with an edentulous jaw, PISA is calculated as 0 mm^2. PISA = periodontal inflamed surface area.

Figure S2. AF recurrence and inflammatory cytokines/chemokines



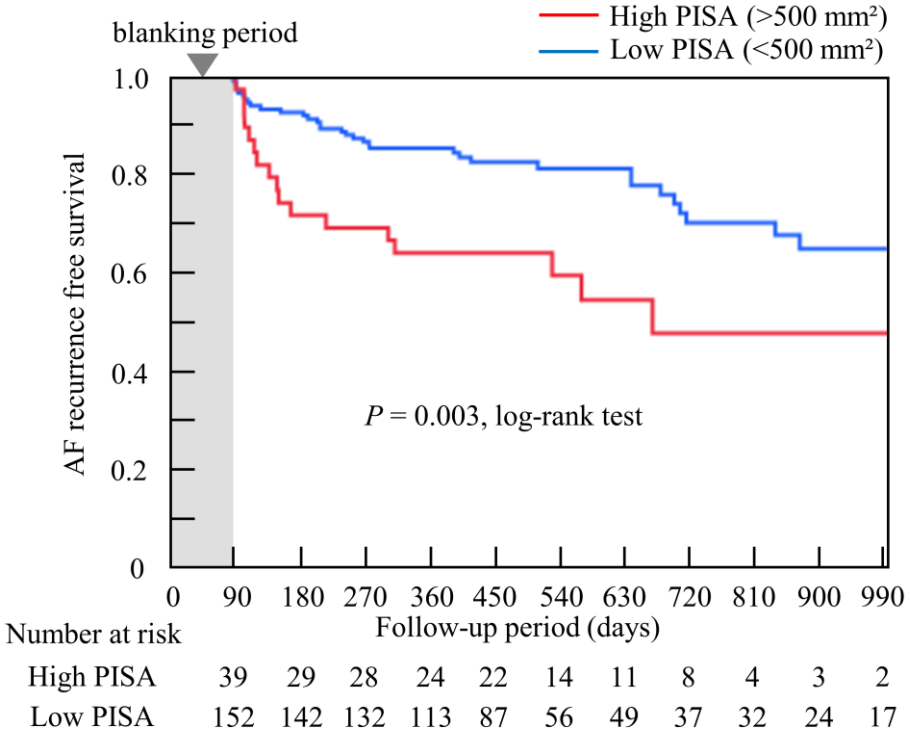
Serum levels of inflammatory cytokines/chemokines and hs-CRP were compared according to the prevalence of early AF recurrence and AF recurrence within 12 months and analyzed using the Wilcoxon rank-sum test. AF, atrial fibrillation; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; TNF-α, tumor necrosis factor-alpha.

Figure S3. Receiver operating characteristic analysis of AF duration and left atrial volume for AF recurrence



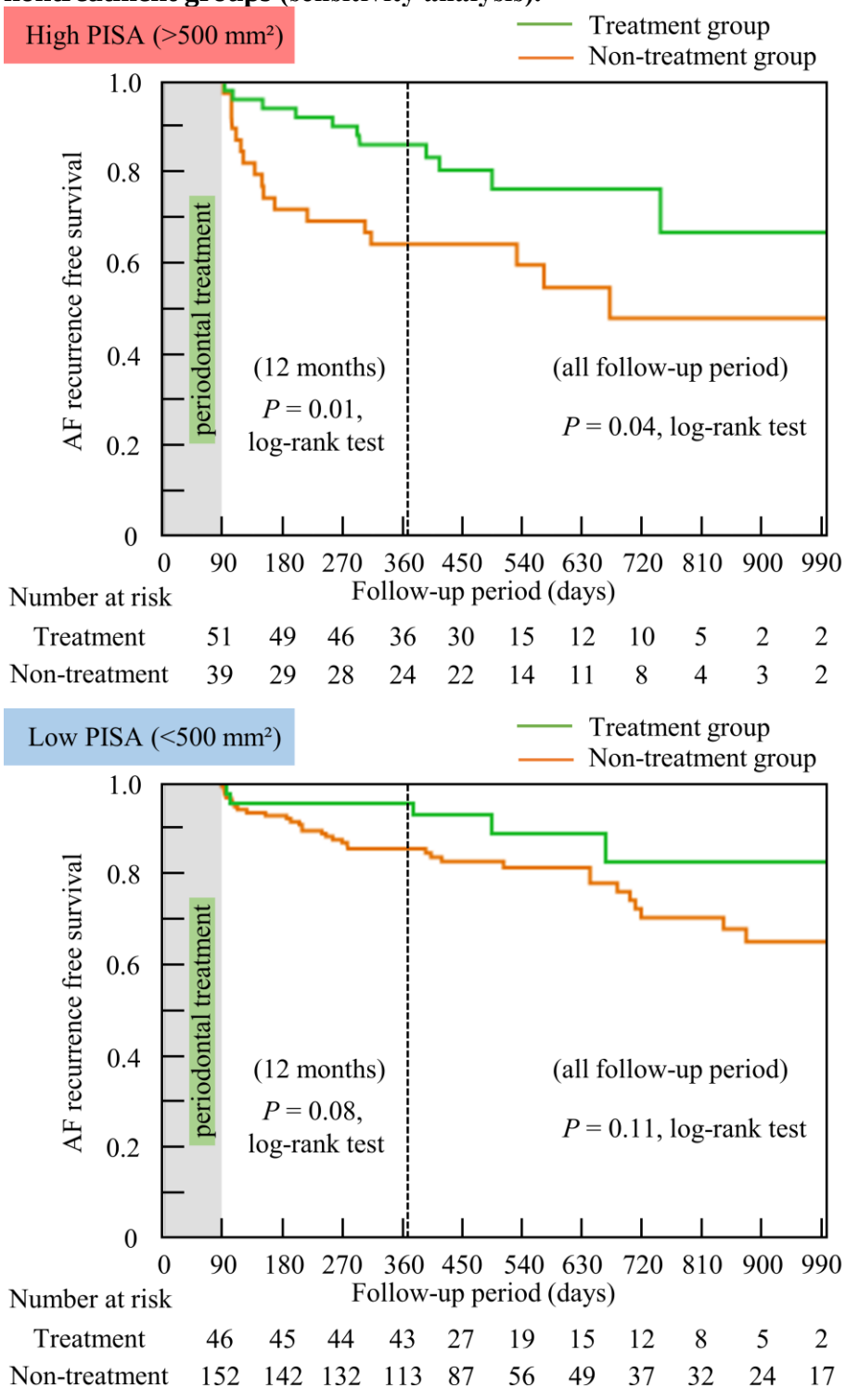
Receiver operating characteristic analysis of AF duration (A) and left atrial volume (B) for AF recurrence. AF, atrial fibrillation; AUC, area under the curve.

Figure S4. Kaplan–Meier analysis of AF recurrence between the high and low PISA groups (sensitivity analysis).



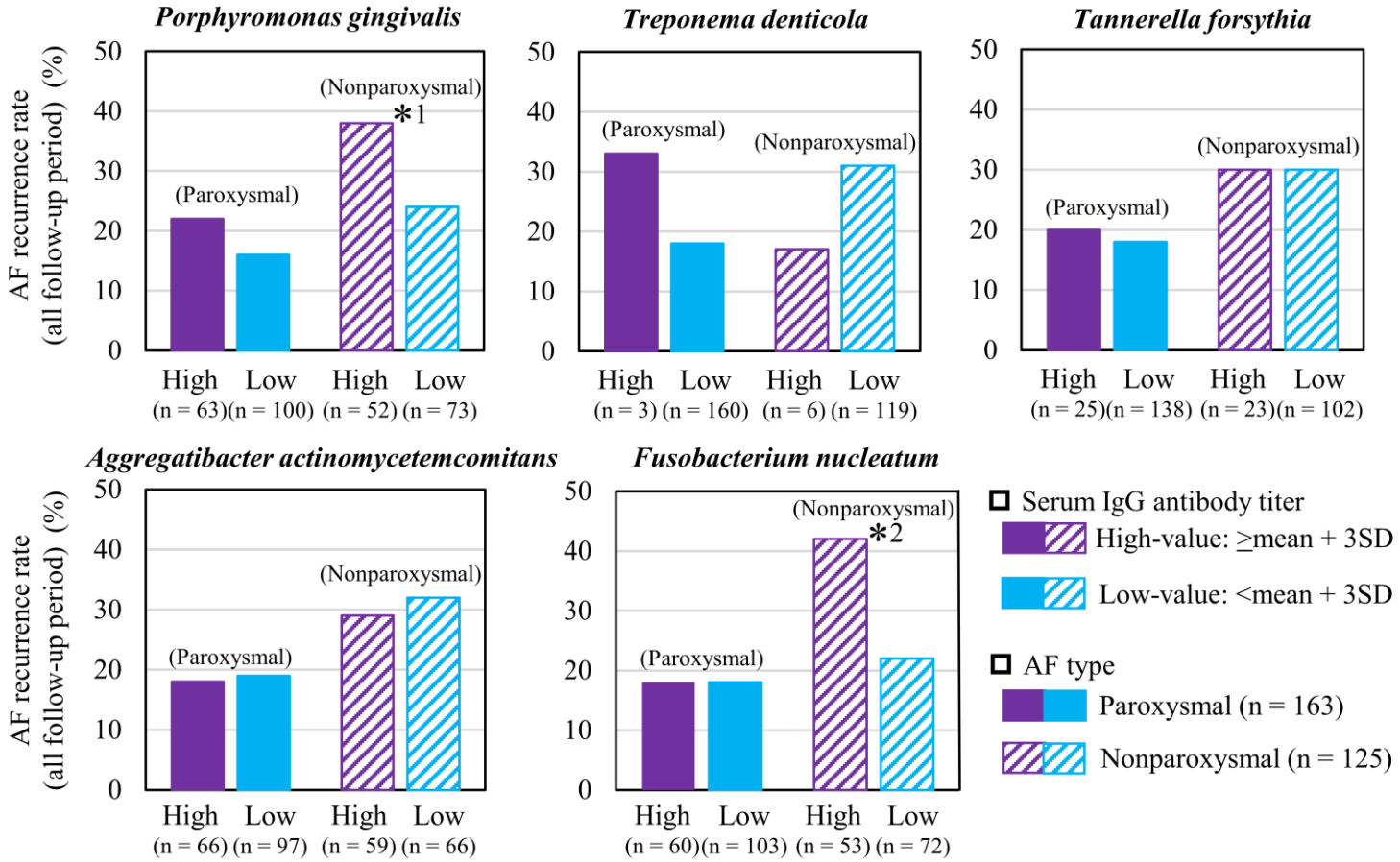
For the sensitivity analysis, patients were divided into high and low PISA groups based on a cutoff value of 500 mm^2. The high PISA group exhibited a significantly lower rate of AF recurrence-free survival than the low PISA group ($P = 0.003$), which was consistent with the primary analysis (Figure 2D).

Figure S5. Kaplan–Meier analysis of AF recurrence between the treatment and nontreatment groups (sensitivity analysis).



For the sensitivity analysis, patients were divided into high and low PISA groups based on a cutoff value of 500 mm^2. The figures show the Kaplan–Meier analysis of AF recurrence between the treatment and nontreatment groups in the high and low PISA value groups. Results of the log-rank tests were presented for AF recurrences within 12 months and the follow-up period. AF, atrial fibrillation; PISA, periodontal inflamed surface area.

Figure S6. Major periodontal pathogen and AF recurrence



AF recurrence rates were compared between the high- and low-value groups of serum IgG antibody titers against each periodontal pathogen, and patients with paroxysmal and nonparoxysmal AF were analyzed separately. *$P < 0.05$ in the univariate Cox regression analyses. Among patients with paroxysmal AF, none of the major periodontal pathogens were related to AF recurrence. Among patients with nonparoxysmal AF, high values serum IgG antibody titer against *P. gingivalis* (HR, 2.06; 95% CI, 1.08–3.94; $P = 0.03$; *1) and *F. nucleatum* (HR, 2.08; 95% CI, 1.09–3.97; $P = 0.03$; *2) were related to AF recurrence. AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; SD, standard deviation.