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Transient New-Onset Atrial Fibrillation Is Associated With Poor Clinical Outcomes in Patients With Acute Myocardial Infarction

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Background: Atrial fibrillation (AF) is considered to be associated with poor clinical outcomes in patients with acute myocardial infarction (AMI). However, it remains uncertain whether transient new-onset AF (NOAF) during AMI has a subsequent increased risk of poor clinical outcomes.

Methods and Results: Transient NOAF was defined as AF that developed during AMI without a prior history and not documented for 1 month after discharge. The primary endpoints were major adverse cardiac events (MACE) and all-cause death. We enrolled 2,105 consecutive AMI patients. Overall, AF was observed in 209 (9.9%) and transient NOAF occurred in 102 (4.8%) among 150 patients (7.1%) with NOAF. The transient NOAF group showed higher 1-month (21.8 vs. 7.0%, P<0.001), 2-year (37.8 vs. 20.7%, P<0.001), and 5-year MACE rates (51.8 vs. 28.0%, P<0.001) than the group without AF. In-hospital (16.7 vs. 5.2%, P<0.001), 1-month (17.9 vs. 5.7%, P<0.001), 2-year (30.0 vs. 11.6%, P<0.001), and 5-year mortality rates (36.9 vs. 14.0%, P<0.001) were also higher in patients with transient NOAF. Transient NOAF was a significant independent predictor of both MACE (hazard ratio [HR] 1.55, 95% confidence interval [CI] 1.10–2.18, P=0.013) and death (HR 1.87, 95% CI 1.22–2.85, P=0.004).

Conclusions: Transient NOAF was associated with the poorer clinical outcomes and was an important independent predictor of MACE and death in AMI patients. (*Circ J* 2016; **80:** 1615–1623)

Key Words: Acute myocardial infarction; Atrial fibrillation; Major adverse cardiovascular event; Mortality

Cardiac arrhythmia is one of the most common complications of acute myocardial infarction (AMI).[1] Atrial fibrillation (AF) is the most common supraventricular tachyarrhythmia in the general population and also in patients with AMI, with a reported incidence between 5% and 23%.[2–4] Compared with ventricular tachyarrhythmias, severe heart failure, or sudden cardiac arrest, AF has been commonly regarded as a benign, transient, and self-limited complication and not considered a critical event during AMI. In recent studies, however, AF has been reported to be associated with poor clinical outcomes in patients with AMI.[5–9] In particular, new-onset AF (NOAF) with no history of AF before AMI remains associated with markedly higher rates of adverse events and mortality.[5] Nonetheless, it still remains unclear whether NOAF that develops and is maintained only during hospitalization for AMI, namely transient NOAF, is also associated with a subsequent increased risk of poor clinical outcomes.

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Methods

Study Protocol

We enrolled all consecutive AMI patients aged 20 years of or older who were admitted to Severance Cardiovascular Hospital, Seoul, Korea, between May 2005 and December 2012. The present study was approved by the hospital's institutional review board and performed in accordance with the Declaration of Helsinki. Written informed consent was given by each patient before enrollment. Patients who had known diseases, such as malignancy or severe infection, making 3-month survival unlikely or who did not want aggressive treatment, including vasopressor and/or inotropic medication, mechanical ventilation, mechanical circulatory support, or cardiopulmonary resuscitation, were excluded. Demographic, clinical, biochemical and echocardiographic data were obtained.

Patients were treated according to the international AMI treatment guidelines.[10,11] All patients received standard pharmacological therapies, and revascularization and mechanical circulatory support were left to the discretion of the attending

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Table 1. Comparison of Baseline Clinical Characteristics According to Presence or Absence of AF

	Total (n=2,105)	AF (n=209)	No AF (n=1,896)	P value
Men	1,530 (73%)	130 (62%)	1,400 (74%)	<0.001
Age, years	63.8±12.6	70.9±11.4	63.1±12.5	<0.001
>75 years	441 (21%)	86 (41%)	355 (19%)	<0.001
Smoker	882 (42%)	69 (33%)	813 (43%)	0.006
Diabetes mellitus	649 (31%)	63 (30%)	586 (31%)	0.821
Hypertension	1,163 (55%)	136 (65%)	1,027 (54%)	0.003
ESRD	50 (2%)	9 (4%)	41 (2%)	0.087
Previous stroke	127 (6%)	16 (8%)	111 (6%)	0.299
Previous CAD	387 (18%)	49 (23%)	338 (18%)	0.047
Previous MI	150 (7%)	19 (9%)	131 (7%)	0.245
Previous PCI	284 (14%)	32 (15%)	252 (13%)	0.417
Previous CABG	65 (3%)	10 (5%)	55 (3%)	0.135
STEMI	966 (46%)	91 (44%)	875 (46%)	0.473
MI location				0.006
Anterior	1,253 (59%)	101 (48%)	1,152 (61%)	
Inferior	600 (29%)	81 (39%)	519 (27%)	
Lateral	252 (12%)	27 (13%)	225 (12%)	
Killip class ≥2	667 (32%)	103 (49%)	564 (30%)	<0.001
Cardiogenic shock	319 (15%)	52 (25%)	268 (14%)	<0.001
Use of IABP	118 (6%)	17 (8%)	102 (5%)	0.102
Cardiac arrest	101 (5%)	24 (12%)	77 (4%)	<0.001
LVEF, %	48.4±13.4	43.7±13.9	48.9±13.3	<0.001
LV systolic dysfunction	545 (26%)	80 (39%)	465 (25%)	<0.001
E/E' ratio	14.7±7.0	17.8±8.2	14.4±6.8	<0.001
LV diastolic dysfunction	770 (37%)	121 (63%)	649 (35%)	<0.001
LAVI, ml/m^2	30.5±18.0	42.8±22.0	29.0±16.9	<0.001
Multivessel disease	1,314 (63%)	128 (65%)	1,186 (64%)	0.809
Atrial branch disease	279 (13%)	54 (26%)	225 (12%)	<0.001
Baseline eGFR, ml/min/1.73 m^2	70.9±25.7	56.3±26.0	72.6±25.2	<0.001
Baseline renal dysfunction	615 (29%)	120 (57%)	495 (26%)	<0.001
Hemoglobin, g/dl	13.7±2.2	13.1±2.1	13.8±2.2	<0.001
Anemia	538 (26%)	76 (36%)	462 (24%)	<0.001
hs-CRP, mg/L	24.7±46.8	33.1±55.5	23.0±44.8	0.005
Medications				
Aspirin	2,043 (97%)	204 (97%)	1,839 (97%)	1.000
Thienopyridine	1,872 (89%)	185 (88%)	1,687 (89%)	0.913
β-blocker	1,663 (79%)	155 (73%)	1,508 (79%)	0.163
ACEI/ARB	1,745 (83%)	171 (81%)	1,574 (83%)	0.638
Statin	1,831 (87%)	180 (85%)	1,651 (87%)	0.532
Antiarrhythmic drug	9 (0.4%)	9 (4.3%)	0 (0%)	<0.001

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin-receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; hs-CRP, high sensitivity C-reactive protein; IABP, intra-aortic balloon pump; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI.

physician. All patients had in-hospital continuous ECG monitoring for at least 48 h in a coronary care unit after hospital admission and underwent 12-lead ECG twice daily during the hospital stay. Echocardiographic evaluation was performed within 24 h of hospital admission and relevant baseline and follow-up laboratory and clinical data were recorded.

After hospital discharge, all patients were clinically followed up in the outpatient clinic at 2 and 4 weeks and thereafter every 2 months with ECG and additional 24-h ambulatory Holter monitoring in those with NOAF. Patients were asked to visit the clinic or the emergency room at any time if they had any symptoms suspicious of arrhythmia, such as palpitation or irregular heartbeats, and were checked by 12-lead ECG and 24-h Holter monitoring.

Definitions

AMI was diagnosed if a patient had a cardiac troponin-T level above the 99th centile for our population with at least one of the following: characteristic chest pain lasting >20 min or diagnostic serial ECG changes consisting of new pathologic

Table 2. Comparison of Baseline Clinical Characteristics According to Type of AF

	Chronic AF (n=59)	Persistent NOAF (n=48)	Transient NOAF (n=102)	No AF (n=1,896)	P value
Men	36 (61%)	29 (60%)	65 (64%)	1,400 (74%)	0.004*
Age, years	72.1±8.8	75.2±10.0	68.2±12.8	63.1±12.5	<0.001*
>75 years	22 (37%)	30 (63%)	34 (33%)	355 (19%)	<0.001*
Smoker	15 (25%)	13 (27%)	41 (40%)	813 (43%)	0.008
Diabetes mellitus	18 (31%)	13 (27%)	32 (31%)	586 (31%)	0.953
Hypertension	44 (75%)	29 (60%)	63 (62%)	1,027 (54%)	0.007
ESRD	4 (7%)	1 (2%)	4 (4%)	41 (2%)	0.072
Previous stroke	6 (10%)	2 (4%)	8 (8%)	111 (6%)	0.377
Previous CAD	15 (25%)	12 (25%)	22 (22%)	338 (18%)	0.219
Previous MI	6 (10%)	4 (8%)	9 (9%)	131 (7%)	0.538
Previous PCI	10 (17%)	8 (17%)	14 (14%)	252 (13%)	0.780
Previous CABG	5 (9%)	2 (4%)	3 (3%)	55 (3%)	0.097
STEMI	11 (19%)	20 (42%)	60 (59%)	875 (46%)	<0.001*
MI location					0.015*
Anterior	34 (57%)	26 (54%)	41 (40%)	1,152 (61%)	
Inferior	18 (31%)	17 (35%)	46 (45%)	519 (27%)	
Lateral	7 (12%)	5 (11%)	15 (15%)	225 (12%)	
Killip class ≥2	30 (51%)	21 (44%)	52 (51%)	564 (30%)	<0.001*
Cardiogenic shock	11 (19%)	9 (19%)	32 (31%)	268 (14%)	<0.001*
Use of IABP	4 (7%)	1 (2%)	12 (12%)	102 (5%)	0.045*
Cardiac arrest	6 (10%)	1 (2%)	17 (17%)	77 (4%)	<0.001*
LVEF, %	43.7±13.4	46.0±12.3	42.6±14.9	48.9±13.3	<0.001*
LV systolic dysfunction	21 (36%)	14 (29%)	45 (46%)	465 (25%)	<0.001*
E/E' ratio	19.3±7.7	18.2±8.4	16.8±8.4	14.4±6.8	<0.001*
LV diastolic dysfunction	37 (71%)	30 (68%)	54 (56%)	649 (35%)	<0.001*
LAVI, ml/m^2	57.0±25.3	46.6±21.3	32.2±13.4	29.0±16.9	<0.001
Multivessel disease	37 (66%)	32 (68%)	59 (63%)	1,186 (64%)	0.922
Atrial branch disease	9 (15%)	12 (25%)	33 (32%)	225 (12%)	<0.001*
Baseline eGFR, ml/min/1.73 m^2	52.8±23.9	57.5±26.5	57.5±26.8	72.6±25.2	<0.001*
Baseline renal dysfunction	34 (58%)	28 (58%)	58 (57%)	495 (26%)	<0.001*
Hemoglobin, g/dl	12.7±2.2	13.2±2.1	13.2±2.0	13.8±2.2	<0.001*
Anemia	25 (42%)	17 (35%)	34 (33%)	462 (24%)	0.001*
hs-CRP, mg/L	26.3±38.9	26.9±47.3	40.1±66.1	23.0±44.8	0.006*
Medications					
Aspirin	54 (91%)	48 (100%)	102 (100%)	1,839 (97%)	0.259
Thienopyridine	51 (87%)	42 (88%)	99 (90%)	1,687 (89%)	0.894
β-blocker	40 (68%)	33 (69%)	82 (80%)	1,508 (79%)	0.262
ACEI/ARB	47 (79%)	36 (75%)	88 (86%)	1,574 (83%)	0.669
Statin	47 (79%)	45 (94%)	88 (86%)	1,651 (87%)	0.501
Antiarrhythmic drugs	5 (8.5%)	4 (8.3%)	0 (0%)	0 (0%)	<0.001*

*P<0.05 for the comparison between transient NOAF and no AF. NOAF, new-onset AF. Other abbreviations as in Table 1.

Q waves or ST-segment and T-wave changes.[12] ST-segment elevation MI (STEMI) was defined as ST-segment elevation ≥0.2 mV in ≥2 contiguous leads or new-onset left bundle branch block observed on ECG. Non-STEMI (NSTEMI) was defined as MI without ST-segment elevation.

AF was defined as the absence of P waves, coarse or fine fibrillatory waves, and irregular RR intervals. NOAF was defined as AF newly developed during hospitalization for AMI without a prior history. Transient NOAF was defined as AF documented only during hospitalization and not documented for at least 1 month after hospital discharge. In patients who died during hospitalization or within 1 month after hospital discharge, transient NOAF was defined as AF not documented for at least 48 h before death. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease formula. Baseline renal dysfunction was defined as eGFR <60 ml/min/1.73 m^2 on admission. Anemia was defined as hemoglobin <13 g/dl for men and <12 g/dl for women. Left ventricular systolic and diastolic dysfunction were respectively defined as the left ventricular ejection fraction (LVEF) <40% and E/E' ratio >15 on echocardiogram.

The primary endpoint, major adverse cardiovascular events (MACE), was defined as a composite of all-cause death, nonfatal AMI, target-vessel revascularization, heart failure requiring hospital admission, and cerebrovascular events. For patients who experienced multiple events, the first episode was taken as the standard. In addition, we also investigated the outcome of all-cause death.

Table 3. Cause of Death According to Type of AF

	All	Chronic AF	Persistent NOAF	Transient NOAF	No AF
Cardiogenic	215 (65%)	14 (61%)	9 (69%)	21 (60%)	171 (65%)
Cerebrovascular	13 (4%)	3 (13%)	1 (8%)	1 (3%)	8 (3%)
Non-cardiogenic	67 (20%)	4 (17%)	2 (15%)	11 (31%)	50 (19%)
Unknown	38 (11%)	2 (9%)	1 (8%)	2 (6%)	33 (13%)
Total	333 (100%)	23	13	35	262

Abbreviations as in Tables 1,2.

Table 4. Major Adverse Cardiovascular Events According to Type of AF

	All	Chronic AF	Persistent NOAF	Transient NOAF	No AF (n=1,896)
Death	276 (45%)	15 (42%)	10 (40%)	31 (66%)	220 (44%)
Re-infarction	87 (14%)	3 (8%)	3 (12%)	2 (4%)	79 (16%)
TVR	88 (14%)	1 (3%)	1 (4%)	2 (4%)	84 (16%)
Heart failure	112 (19%)	9 (25%)	8 (32%)	9 (19%)	86 (17%)
CVA	50 (8%)	8 (22%)	3 (12%)	3 (7%)	36 (7%)
Total	613 (100%)	36	25	47	505

CVA, cerebrovascular accident; TVR, target-vessel revascularization. Other abbreviations as in Tables 1,2.

Statistical Analysis

Continuous data are expressed as mean±SD and normality tests were performed for each variable to determine whether or not a data set was well-modeled by normal distribution. The baseline characteristics of the groups were compared using Student's t-test or ANOVA for continuous variables, and the chi-square test and Fisher's exact test for categorical variables. The cumulative incidence of clinical events was estimated using the Kaplan-Meier method and the significance of curves was tested using the log-rank test. Univariate and multivariate Cox regression analyses using forward stepwise selection were performed to identify independent predictors of MACE and mortality. Variables with P<0.10 in the univariate analysis were entered into the multivariate logistic regression model. Statistical significance was established at P<0.05. Statistical analysis was performed by SPSS version 18.0 (SPSS Inc, Chicago, IL, USA).

Results

Baseline Characteristics

We enrolled a total of 2,188 consecutive AMI patients. Patients with terminal-stage cancer (n=6) or severe infection (n=13), and those refusing aggressive treatment (n=64) were excluded. Finally, the study population included 2,105 patients [1,530 men (72.7%), mean age 63.8±12.6 years]. STEMI and NSTEMI were observed in 966 (45.9%) and 1,139 (54.1%) patients, respectively. Overall, AF was observed in 209 (9.9%). Chronic AF and NOAF occurred in 59 (2.8%) and 150 patients (7.1%), respectively. Among the patients with NOAF, transient NOAF was observed in 102 patients (4.8%) and 48 patients (2.3%) had persistent AF after hospital discharge.

Table 1 shows the baseline clinical characteristics of patients with and without AF. There were notable significant clinical differences between the groups. Patients with AF were older (70.9±11.4 vs. 63.1±12.5 years, P<0.001) and more likely to be female (38 vs. 26%, P<0.001) than those without AF. They also had lower LVEF (43.7±13.9% vs. 48.9±13.3%, P<0.001), baseline eGFR (56.3±26.0 vs. 72.6±25.2 ml/min/1.73 m^2, P<0.001), and hemoglobin (13.1±2.1 vs. 13.8±2.2 g/dl, P<0.001), but higher E/E' ratio (17.8±8.2 vs. 14.4±6.8, P<0.001), left atrial volume index (LAVI, 42.8±22.0 vs. 29.0±16.9 ml/m^2, P<0.001), and high sensitivity C-reactive protein (hs-CRP, 33.1±55.5 vs. 23.0±44.8 mg/L, P=0.005) than those without AF. Inferior AMI (39% vs. 27%, P=0.006), cardiogenic shock (25% vs. 14%, P<0.001), higher Killip class (≥2, 49% vs. 30%, P<0.001), cardiac arrest (12% vs. 4%, P<0.001), systolic (39% vs. 25%, P<0.001) and diastolic LV dysfunction (63% vs. 35%, P<0.001), atrial branch disease (26% vs. 12%, P<0.001), and baseline renal dysfunction (57% vs. 26%, P<0.001) were also observed more frequently in the AF group.

Table 2 compares the baseline clinical characteristics of the patients according to type of AF. It shows aspects similar to the comparison between patients with and without AF. Compared with the patients without AF, those with transient NOAF were more likely to be female (36% vs. 26%, P=0.024) and older (68.2±12.8 vs. 63.1±12.5 years, P<0.001). They also had lower LVEF (42.6±14.9 vs. 48.9±13.3 %, P<0.001), baseline eGFR (57.5±26.8 vs. 72.6±25.2 ml/min/1.73 m^2, P<0.001), and hemoglobin (13.2±2.0 vs. 13.8±2.2 g/dl, P=0.008), but higher E/E' ratio (16.8±8.4 vs. 14.4±6.8, P=0.001), and hs-CRP (40.1±66.1 vs. 23.0±44.8 mg/L, P=0.001) than those without AF. Cardiogenic shock (31% vs. 14%, P<0.001), Killip class ≥2 (51% vs. 30%, P<0.001), cardiac arrest (17% vs. 4%, P<0.001), STEMI (59% vs. 46%, P=0.012), inferior AMI (45% vs. 27%, P<0.001), atrial branch disease (32% vs. 12%, P<0.001), baseline renal dysfunction (57% vs. 26%, P<0.001), and systolic (46% vs. 25%, P<0.001) and diastolic LV dysfunction (56% vs. 35%, P<0.001) were also observed more frequently in the transient NOAF group.

Clinical Outcomes

Patients were clinically followed up for a median duration of 50.4 months (0–121.6 months). In the overall population, all-cause death occurred in 333 patients (15.8%). The causes of

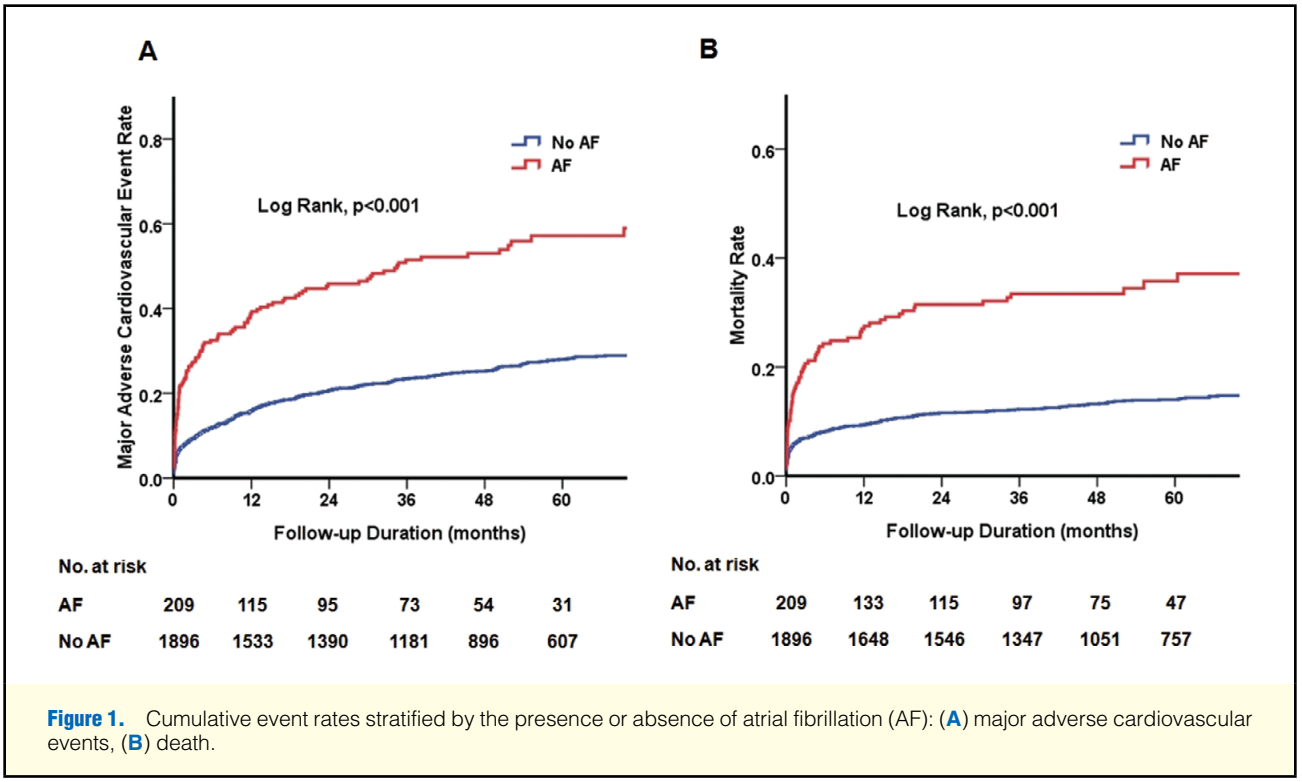

Figure 1. Cumulative event rates stratified by the presence or absence of atrial fibrillation (AF): (**A**) major adverse cardiovascular events, (**B**) death.

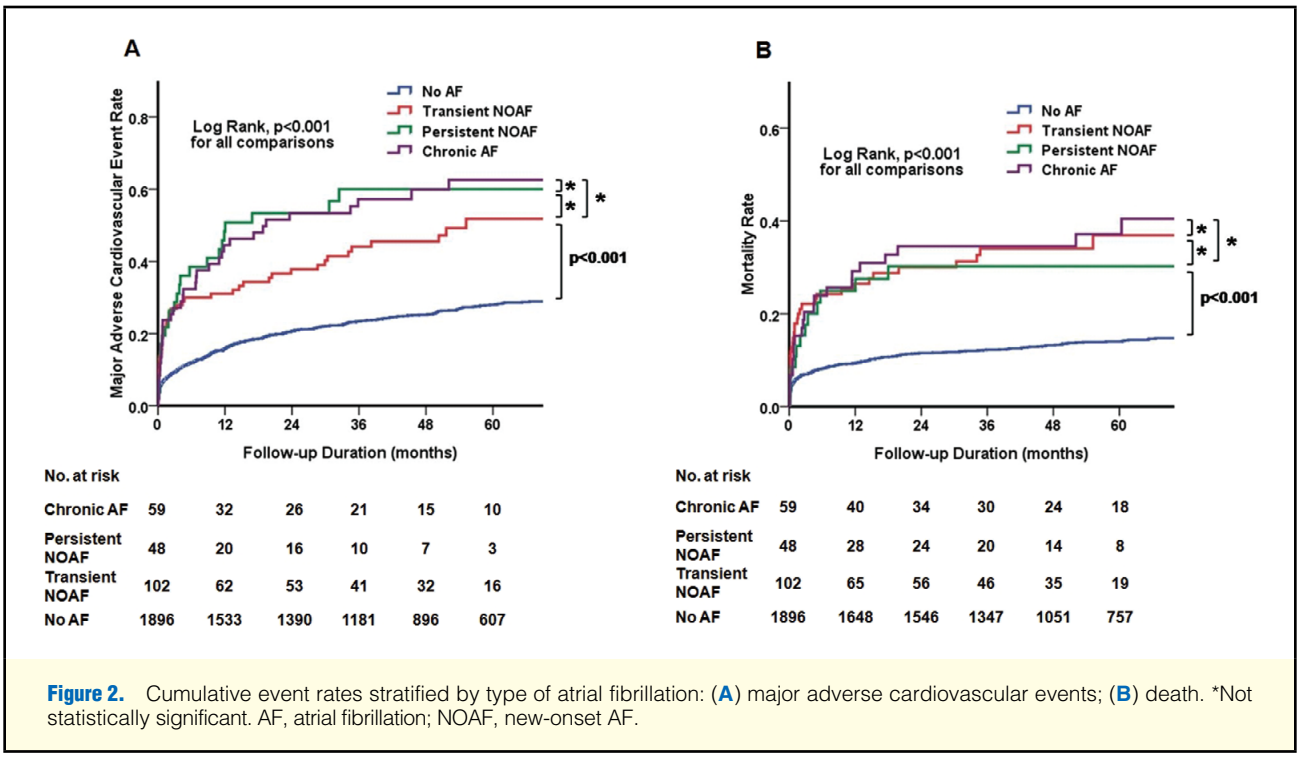

Figure 2. Cumulative event rates stratified by type of atrial fibrillation: (**A**) major adverse cardiovascular events; (**B**) death. *Not statistically significant. AF, atrial fibrillation; NOAF, new-onset AF.

death were cardiogenic in 215 patients (64.6%), cerebrovascular in 13 (3.9%), non-cardiogenic in 67 (20.1%), and unknown in 38 (11.4%). MACE occurred in 613 patients (29.1%) as follows: death in 276 (45.0%), re-infarction in 87 (14.2%), target-vessel revascularization in 88 (14.3%), heart failure requiring hospital admission in 112 (18.3%), and cerebrovascular events in 50 (8.2%). The cause of death and MACE according to type of AF are shown in **Table 3** and **Table 4**, respectively.

Patients with AF demonstrated higher MACE and mortality

Table 5. Independent Predictors of MACE: Multivariate Cox Regression Analysis Using Forward Stepwise Selection

	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
LV systolic dysfunction	2.67	2.27–3.15	<0.001	1.86	1.55–2.24	<0.001
Age >75 years	2.55	2.16–3.02	<0.001	1.78	1.46–2.17	<0.001
Cardiogenic shock	3.02	2.53–3.61	<0.001	1.62	1.30–2.01	<0.001
Baseline renal dysfunction	3.06	2.61–3.59	<0.001	1.61	1.32–1.96	<0.001
AF			<0.001			<0.001
Transient NOAF	2.23	1.65–3.01	<0.001	1.55	1.10–2.18	0.013
Persistent NOAF	3.13	2.10–4.69	<0.001	2.00	1.31–3.08	0.002
Chronic AF	3.00	2.14–4.21	<0.001	2.24	1.54–3.25	<0.001
Multivessel disease	1.79	1.48–2.15	<0.001	1.51	1.24–1.84	<0.001
Anemia	2.40	2.04–2.83	<0.001	1.36	1.11–1.65	0.002
Killip class ≥2	2.59	2.21–3.03	<0.001			
LV diastolic dysfunction	1.99	1.68–2.35	<0.001			
Previous stroke	1.80	1.36–2.37	<0.001			
Female sex	1.56	1.32–1.85	<0.001			
Hypertension	1.49	1.27–1.76	<0.001			
Previous MI	1.47	1.12–1.93	0.005			
Previous CAD	1.45	1.20–1.74	<0.001			
Diabetes mellitus	1.44	1.22–1.70	<0.001			

CI, confidence interval; HR, hazard ratio. Other abbreviations as in Tables 1,2.

Table 6. Independent Predictors of Death: Multivariate Cox Regression Analysis Using Forward Stepwise Selection

	Univariate			Multivariate		
	HR	95% CI	P value	HR	95% CI	P value
Baseline renal dysfunction	5.71	4.56–7.16	<0.001	2.48	1.86–3.31	<0.001
Cardiogenic shock	5.31	4.26–6.61	<0.001	2.27	1.72–2.99	<0.001
Age >75 years	3.68	2.96–4.57	<0.001	2.20	1.69–2.87	<0.001
LV systolic dysfunction	3.77	3.01–4.72	<0.001	2.10	1.61–2.73	<0.001
AF						0.001
Transient NOAF	3.10	2.18–4.42	<0.001	1.87	1.22–2.85	0.004
Persistent NOAF	2.49	1.43–4.35	0.001	1.55	0.86–2.79	0.149
Chronic AF	3.20	2.09–4.90	<0.001	2.19	1.36–3.53	0.001
Anemia	3.93	3.17–4.88	<0.001	1.76	1.34–2.32	0.002
Multivessel disease	1.94	1.48–2.53	<0.001	1.49	1.10–2.01	0.010
Killip class ≥2	4.54	3.63–5.68	<0.001			
LV diastolic dysfunction	3.14	2.47–3.99	<0.001			
Previous stroke	2.13	1.51–3.02	<0.001			
Hypertension	1.72	1.37–2.16	<0.001			
Diabetes mellitus	1.60	1.28–1.99	<0.001			
Female sex	1.54	1.23–1.92	<0.001			
Previous MI	1.39	0.96–2.01	0.081			
Previous CAD	1.28	0.99–1.66	0.060			

Abbreviations as in Tables 1,2,5.

rates than those without AF (Figure 1). The AF group demonstrated higher 1-month (21.9% vs. 7.0%, log-rank, P<0.001), 2-year (45.85 vs. 20.7%, log-rank, P<0.001), and 5-year MACE rates (57.25 vs. 28.0%, log-rank, P<0.001) than the group without AF. In-hospital (13.95 vs. 5.2%, P<0.001), 1-month (15.15 vs. 5.7%, log-rank, P<0.001), 2-year (31.55 vs. 11.6%, log-rank, P<0.001), and 5-year mortality rates (37.15 vs. 14.0%, log-rank, P<0.001) were also significantly higher in patients with AF.

Each AF group, including chronic AF and transient and persistent NOAF, also presented markedly higher MACE and mortality rates than those without AF (Figure 2). However, there were no differences in the long-term clinical outcomes for each type of AF. The transient NOAF group demonstrated higher 1-month (21.8% vs. 7.0%, log-rank, P<0.001), 2-year (37.8% vs. 20.7%, log-rank, P<0.001), and 5-year MACE rates (51.8% vs. 28.0%, log-rank, P<0.001) than the group without AF. In-hospital (16.7% vs. 5.2%, P<0.001), 1-month (17.9% vs. 5.7%, log-rank, P<0.001), 2-year (30.0% vs. 11.6%, log-rank, P<0.001), and 5-year mortality rates (36.9% vs. 14.0%,

log-rank, P<0.001) were also significantly higher in patients with transient NOAF.

Multivariate Cox regression analysis revealed that transient NOAF was a significant independent predictor of both MACE (hazard ratio [HR] 1.55, 95% confidence interval [CI] 1.10–2.18, P=0.013) and death (HR 1.87, 95% CI 1.22–2.85, P=0.004) after adjusting for confounding variables such as age, sex, hemodynamic status, LV systolic and diastolic function, baseline renal function, and comorbidities (Tables 5,6). Left ventricular systolic dysfunction (HR 1.86, 95% CI 1.55–2.24, P<0.001), age >75 years (HR 1.78, 95% CI 1.46–2.17, P<0.001), cardiogenic shock (HR 1.62, 95% CI 1.30–2.01, P<0.001), baseline renal dysfunction (HR 1.61, 95% CI 1.32–1.96, P<0.001), multivessel coronary artery disease (HR 1.51, 95% CI 1.24–1.84, P<0.001), and anemia (HR 1.36, 95% CI 1.11–1.65, P=0.002) were other independent predictors of MACE. Baseline renal dysfunction (HR 2.48, 95% CI 1.86–3.31, P<0.001), cardiogenic shock (HR 2.27, 95% CI 1.72–2.99, P<0.001), age >75 years (HR 2.20, 95% CI 1.69–2.87, P<0.001), LV systolic dysfunction (HR 2.10, 95% CI 1.61–2.73, P<0.001), anemia (HR 1.76, 95% CI 1.34–2.32, P=0.002), and multivessel coronary artery disease (HR 1.49, 95% CI 1.10–2.01, P=0.010) were other independent predictors of death.

Discussion

The major findings of the present study were that patients with AMI who developed transient NOAF, as well as chronic AF and persistent NOAF, had poorer short-, mid-, and long-term clinical outcomes for MACE and all-cause death than those without AF. Transient NOAF was an important independent predictor of the long-term occurrence of MACE and death in AMI patients. However, there were no significant differences in the clinical outcomes of each type of AF. An additional finding of our study was an incidence of AF of 9.9%, comparable with previous studies, and 4.8% of patients developed transient NOAF.

Cardiac arrhythmia, including supraventricular and ventricular tachyarrhythmias and conduction abnormalities, is one of the most common complications of AMI.[1,13] Death from ventricular fibrillation in the setting of AMI has historically been one of the most frequent causes of sudden cardiac death, and sustained ventricular tachyarrhythmia is the most common reason for close in-hospital cardiac monitoring of patients with AMI.[14,15] Recently, however, Mehta et al reported that sustained ventricular tachyarrhythmia in patients undergoing primary percutaneous coronary intervention for STEMI was not significantly associated with long-term death or MACE.[16] AF is the most common supraventricular tachyarrhythmia in the general population and also in patients with AMI, with a reported incidence as high as 20%.[2,3] Nevertheless, AF often goes unnoticed, and, even if noticed, generally considered by physicians as a mild and benign episode, not a critical event, during AMI, especially when the AF episode is transient, compared with ventricular tachyarrhythmia, severe heart failure, or sudden cardiac arrest. Whereas previous studies have provided conflicting findings concerning the association of AF and mortality,[3,17–19] recent studies, including a meta-analysis, demonstrated that AF carried adverse prognostic implications for both in-hospital and long-term mortality rates in patients with AMI.[5,6,8,9,20,21] Rathore et al reported that patients with NOAF during hospitalization had higher in-hospital, 30-day, and 1-year mortality rates compared with those without AF.[5] They showed that the difference in mortality rates between patients with prior AF and NOAF was significant during hospital stay and at 30 days, but decreased over time and was not significant at 1 year. Crenshaw et al revealed no difference in in-hospital, 30-day, and 1-year mortality rates between patients with AF at entry and after admission.[22] However, there is a lack of study regarding the implications of transient NOAF documented only during AMI, and its relation to clinical outcome has never been evaluated in patients with AMI. Although the 2 studies reported long-term data for patients after AMI complicated by AF, generally only up to 1-year outcomes are shown.[5,22] In the present study, we demonstrated that all types of AF, including transient and persistent NOAF and chronic AF, were associated with poorer long-term (5 years) clinical outcomes as well as short- (1 month) and mid-term (2 years) MACE and all-cause death compared with those without AF. Transient NOAF was an independent risk factor for adverse long-term outcomes. Our study also showed no statistical differences in the clinical outcomes, regardless of time course, between each type of AF. Although the transient AF group had poorer short-term outcomes with higher in-hospital and 1-month mortality rates related to hemodynamic instability, including cardiac shock, cardiac arrest or LV systolic dysfunction, thereafter survivors showed more gradual curves in the rates of death and MACE than did the other AF groups. On the other hand, patients in the other AF groups were older and had more LV diastolic dysfunction and LA enlargement, which may be risk factors for pulmonary congestion and cerebrovascular events, and showed steadily increasing rates of MACE and death as time passed. As a result, the transient AF group had a higher proportion of deaths among MACE, whereas other AF groups had higher proportions of re-infarction, heart failure, and cerebrovascular events. To the best of our knowledge, the present study is the first attempt to evaluate the clinical implications of transient NOAF in the AMI setting. The results of our study indicated that AF unfavorably influences both short and long-term clinical outcomes in patients with AMI, even when it is transient, and should no longer be considered an unimportant event during AMI.

In most studies reporting the clinical implication of AF according to the time of AF onset during AMI, the time of AF onset is classified as AF on arrival and AF during hospitalization after admission.[5,9,22] However, the problem with that classification is that AF on arrival may include chronic AF and early NOAF, and AF after admission may include only late NOAF unless a patient visits a hospital immediately after the clinical manifestation of AMI. Moreover, AF may be first documented at the time of admission for AMI without any medical history of AF, although a patient may have had AF before admission. We also defined NOAF as AF newly documented at the time of admission for AMI without a prior history, but transient NOAF in our study may be the nearest classification to real NOAF during AMI.

Although the precise cause of AF developing in the setting of AMI remains unclear, some proposed mechanisms include abrupt changes of intracardiac hemodynamics, such as deterioration of LV systolic function, increased LV filling pressure, and increased atrial pressure, direct atrial ischemia, increased catecholamines because of the poor hemodynamic status, inflammation, and metabolic abnormalities.[3,7,17,22,23] We noted that patients with transient NOAF had poorer clinical status and significant comorbidities, including cardiogenic shock, cardiac arrest, LV systolic and diastolic dysfunction, impaired renal function, advanced Killip class, and anemia, compared with those without AF. These findings are consistent with previous studies showing that unfavorable changes

in hemodynamic status may influence the development of AF during AMI. Additionally, the present study showed that the group with NOAF, especially transient NOAF, had a higher prevalence of both inferior AMI and coronary artery disease affecting the atrial branches, consistent with prior studies.[24,25] These findings suggested that direct atrial and sinus node ischemia because of impaired blood flow in the sinus node artery or atrioventricular node artery, which is caused mainly by inferior AMI, might be also part of the mechanism of transient NOAF. Inflammation can be considered as associated with promotion of transient NOAF because the hs-CRP level, a typical inflammatory marker, was much higher in the transient NOAF group.[23]

In the present study, patients with transient NOAF more frequently showed STEMI, cardiogenic shock, and atrial branch disease and higher hs-CRP level. On the other hand, we observed that patients with persistent NOAF showed more LA enlargement and LV diastolic dysfunction than those with transient NOAF. The LA dimension was reasonably similar between the transient NOAF and no AF groups. LA dilatation generally represents chronicity of LV diastolic dysfunction over a long period of time and is considered to have an important role in the initiation, perpetuation, and recurrence of AF.[26,27] Therefore, AF might be easily triggered by small stimuli in the setting of AMI and be maintained after hospital discharge in the persistent NOAF group with greater LA dilatation. In the transient NOAF group with less LA dilatation, AF might not be perpetuated after the vulnerable phase of AMI, though AF was induced by large stimuli such as hemodynamic compromise, inflammation, and atrial ischemic insult. This suggests that small stimuli could be enough to trigger and perpetuate AF in a large LA presenting much more electroanatomical substrate, whereas a less dilated LA might require extensive stimuli to initiate AF, but not enough to maintain AF.

Study Limitations

First, it was a moderate-sized study conducted in a single institution. Our findings need to be verified in other larger multicenter trials. Second, because of methodological limitations inherent in retrospective registry analyses, our data cannot establish a definite etiological link between transient NOAF and the increased risk of MACE and death. Third, the period of continuous monitoring during hospitalization was not long enough to confidently verify the development and termination of NOAF. Although all patients had in-hospital continuous ECG monitoring for at least 48 h in a coronary care unit after hospital admission and underwent 12-lead ECG twice daily during their hospital stay, continuous recording for a longer period would have provided more precise information. In addition, we often experience asymptomatic cases of AF and to detect these, 2-week visits with standard ECG and 24-h Holter monitoring after hospital discharge might not be enough.

Conclusions

Transient NOAF was associated with poorer short-, mid-, and long-term clinical outcomes and was an important independent predictor of the long-term occurrence of MACE and death in AMI patients. There were no significant differences in the clinical outcomes of each type of AF.

Disclosures

Nothing to disclose.

References

1. Fluck DC, Olsen E, Pentecost BL, Thomas M, Fillmore SJ, Shillingford JP, et al. Natural history and clinical significance of arrhythmias after acute cardiac infarction. *Br Heart J* 1967; **29:** 170–189.
2. Pizzetti F, Turazza FM, Franzosi MG, Barlera S, Ledda A, Maggioni AP, et al. Incidence and prognostic significance of atrial fibrillation in acute myocardial infarction: The GISSI-3 data. *Heart* 2001; **86:** 527–532.
3. Goldberg RJ, Seeley D, Becker RC, Brady P, Chen ZY, Osganian V, et al. Impact of atrial fibrillation on the in-hospital and long-term survival of patients with acute myocardial infarction: A community-wide perspective. *Am Heart J* 1990; **119:** 996–1001.
4. Pedersen OD, Bagger H, Kober L, Torp-Pedersen C. The occurrence and prognostic significance of atrial fibrillation/-flutter following acute myocardial infarction: TRACE Study group [TRAndolapril Cardiac Evalution]. *Eur Heart J* 1999; **20:** 748–754.
5. Rathore SS, Berger AK, Weinfurt KP, Schulman KA, Oetgen WJ, Gersh BJ, et al. Acute myocardial infarction complicated by atrial fibrillation in the elderly: Prevalence and outcomes. *Circulation* 2000; **101:** 969–974.
6. Behar S, Zahavi Z, Goldbourt U, Reicher-Reiss H. Long-term prognosis of patients with paroxysmal atrial fibrillation complicating acute myocardial infarction: SPRINT Study Group. *Eur Heart J* 1992; **13:** 45–50.
7. Pedersen OD, Abildstrom SZ, Ottesen MM, Rask-Madsen C, Bagger H, Kober L, et al. Increased risk of sudden and non-sudden cardiovascular death in patients with atrial fibrillation/flutter following acute myocardial infarction. *Eur Heart J* 2006; **27:** 290–295.
8. Jabre P, Roger VL, Murad MH, Chamberlain AM, Prokop L, Adnet F, et al. Mortality associated with atrial fibrillation in patients with myocardial infarction: A systematic review and meta-analysis. *Circulation* 2011; **123:** 1587–1593.
9. Rene AG, Genereux P, Ezekowitz M, Kirtane AJ, Xu K, Mehran R, et al. Impact of atrial fibrillation in patients with ST-elevation myocardial infarction treated with percutaneous coronary intervention (from the HORIZONS-AMI [Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction] trial). *Am J Cardiol* 2014; **113:** 236–242.
10. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: Executive summary: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013; **127:** 529–555.
11. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; **130:** e344–e426, doi:10.1161/CIR.0000000000000134. (Erratum in: *Circulation* 2014; **130:** e433–e434. Dosage error in article text.)
12. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction, Jaffe AS, Apple FS, Galvani M, et al. Universal definition of myocardial infarction. *Circulation* 2007; **116:** 2634–2653.
13. Archbold RA, Sayer JW, Ray S, Wilkinson P, Ranjadayalan K, Timmis AD. Frequency and prognostic implications of conduction defects in acute myocardial infarction since the introduction of thrombolytic therapy. *Eur Heart J* 1998; **19:** 893–898.
14. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: Structure, function, and time-dependence of risk. *Circulation* 1992; **85:** I2–I10.
15. Ishihara M, Fujino M, Ogawa H, Yasuda S, Noguchi T, Nakao K, et al. Clinical presentation, management and outcome of Japanese patients with acute myocardial infarction in the troponin era: Japanese Registry of Acute Myocardial Infarction Diagnosed by Universal Definition (J-MINUET). *Circ J* 2015; **79:** 1255–1262.
16. Mehta RH, Yu J, Piccini JP, Tcheng JE, Farkouh ME, Reiffel J, et al. Prognostic significance of postprocedural sustained ventricular tachycardia or fibrillation in patients undergoing primary percutaneous coronary intervention (from the HORIZONS-AMI Trial). *Am J Cardiol* 2012; **109:** 805–812.
17. Eldar M, Canetti M, Rotstein Z, Boyko V, Gottlieb S, Kaplinsky E, et al. Significance of paroxysmal atrial fibrillation complicating acute myocardial infarction in the thrombolytic era: SPRINT and Thrombolytic Survey Groups. *Circulation* 1998; **97:** 965–970.
18. Madias JE, Patel DC, Singh D. Atrial fibrillation in acute myocardial infarction: A prospective study based on data from a consecutive

series of patients admitted to the coronary care unit. *Clin Cardiol* 1996; **19:** 180–186.
19. Serrano CV Jr, Ramires JA, Mansur AP, Pileggi F. Importance of the time of onset of supraventricular tachyarrhythmias on prognosis of patients with acute myocardial infarction. *Clin Cardiol* 1995; **18:** 84–90.
20. Schmitt J, Duray G, Gersh BJ, Hohnloser SH. Atrial fibrillation in acute myocardial infarction: A systematic review of the incidence, clinical features and prognostic implications. *Eur Heart J* 2009; **30:** 1038–1045.
21. Chen LY, Benditt DG, Alonso A. Atrial fibrillation and its association with sudden cardiac death. *Circ J* 2014; **78:** 2588–2593.
22. Crenshaw BS, Ward SR, Granger CB, Stebbins AL, Topol EJ, Califf RM. Atrial fibrillation in the setting of acute myocardial infarction: The GUSTO-I experience [Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries]. *J Am Coll Cardiol* 1997; **30:** 406–413.
23. Harada M, Van Wagoner DR, Nattel S. Role of inflammation in atrial fibrillation pathophysiology and management. *Circ J* 2015; **79:** 495–502.
24. Sakata K, Kurihara H, Iwamori K, Maki A, Yoshino H, Yanagisawa A, et al. Clinical and prognostic significance of atrial fibrillation in acute myocardial infarction. *Am J Cardiol* 1997; **80:** 1522–1527.
25. Alasady M, Abhayaratna WP, Leong DP, Lim HS, Abed HS, Brooks AG, et al. Coronary artery disease affecting the atrial branches is an independent determinant of atrial fibrillation after myocardial infarction. *Heart Rhythm* 2011; **8:** 955–960.
26. Allessie M, Ausma J, Schotten U. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovasc Res* 2002; **54:** 230–246.
27. Zarse M, Deharo JC, Mast F, Allessie MA. Importance of right and left atrial dilation and linear ablation for perpetuation of sustained atrial fibrillation. *J Cardiovasc Electrophysiol* 2002; **13:** 164–171.