BMJ Open New-onset paroxysmal atrial fibrillation in acute myocardial infarction: increased risk of stroke

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ABSTRACT

Objective To investigate the long-term prognostic implications of transient new-onset atrial fibrillation (AF) in patients with acute myocardial infarction (AMI).

Design Retrospective observational study.

Setting Single tertiary centre.

Participants This study included 2523 patients who presented with AMI from 3 June 2003 to 24 February 2015, after the exclusion of those with prior AF or in-hospital death.

Outcome measures Patients were divided into three groups according to the occurrence and type of new-onset AF: (1) sinus rhythm (SR) group; (2) paroxysmal AF (PaAF: AF converted to SR prior to discharge) group and (3) persistent AF (PeAF: AF persisted during the hospitalisation) group. Post-discharge all-cause mortality and stroke incidences were compared between the groups.

Results New-onset AF was observed in 271 patients (10.7%; PaAF: 230, PeAF: 41). The median follow-up period was 7.2 years (IQR: 5.2–9.4). The incidence of all-cause death and stroke was highest in the PeAF group, followed by the PaAF and SR groups (all-cause mortality: 48.8% vs 26.5% vs 14.7%, $p<0.001$; stroke 22.0% vs 8.3% vs 4.4%, $p<0.001$). In the multivariable analysis, PaAF and PeAF were associated with an increased risk of stroke (PaAF, HR: 1.972, 95% CI: 1.162–3.346; PeAF, HR: 5.160, CI: 2.242–11.873) compared with SR. The PaAF group showed a higher incidence of post-discharge AF than the SR group (29.1% vs 4.2%, $p<0.001$).

Conclusions New-onset AF following AMI is associated with poor long-term outcomes. Even when AF episodes are brief and are converted to SR, new-onset AF remains associated with an increased risk of recurrent AF and stroke.

INTRODUCTION

Acute coronary syndrome (ACS) is often accompanied by atrial fibrillation (AF). Based on recently published data, the incidence of new-onset AF among ACS events varied from 4.5%–10.9% in clinical settings of ACS.^{1–5} Regardless of whether AF was

Strengths and limitations of this study

- The present study was conducted with a relatively large number of patients with acute myocardial infarction who were followed up for a long-term period.
- All events of all-cause death were validated with data from the Korean Ministry of the Interior and Safety.
- This study was performed in a single centre and has the intrinsic limitations of a retrospective observational study.

newly developed or pre-existent, it was associated with over a twofold increased risk of mortality.^{1–4 6} However, it remains unclear whether new-onset paroxysmal AF (PaAF), which was transient during the admission, is related to long-term adverse events, including mortality, and particularly, stroke in this population. We assessed the clinical impact of new-onset AF on post-discharge mortality and stroke according to the presence and features of AF in hospitalised patients with acute myocardial infarction (AMI).

METHODS

Study population and design

We retrospectively selected consecutive patients who underwent coronary angiography for AMI from 3 June 2003 to 24 February 2015 in Seoul National University Bundang Hospital. Patients with a history of any AF type (paroxysmal, persistent and permanent) or those with in-hospital death were excluded through an in-depth review of the medical records.

AF diagnosis was based on electrocardiogram (ECG) findings characterised by the absence of discrete P waves and an irregular ventricular rate. The AF was defined as any documented episode of AF on 12-lead ECG

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or lasting >30 s on continuous ECG monitoring. New-onset AF was defined as newly detected AF during the index hospitalisation without a history of AF.

The study population was divided into three groups: the sinus rhythm (SR) group (subjects with no AF), the PaAF group (patients with AF that was converted to SR prior to discharge) and the persistent AF (PeAF) group. If AF was resolved and recurred repeatedly, the patient was classified according to the rhythm status at discharge. The demographic, clinical, laboratory and echocardiographic data of the patients were obtained.

Patient and public involvement

Patients or the public were not involved in the designing, participation, reporting, or dissemination of our research.

Calculation of CHA₂DS₂-VASc score

The CHA₂DS₂-VASc score for stroke prediction was calculated based on the clinical characteristics at discharge.⁷ The score was calculated by summing all assigned points for each certain medical condition: 1 point for ages between 65 and 74 years, female sex, hypertension, diabetes mellitus, heart failure and vascular disease (prior myocardial infarction or peripheral artery disease); 2 points each for a history of stroke/transient ischaemic attack/thromboembolism or age of ≥75 years.⁸ Because the participants were hospitalised patients with AMI, they received at least 1 point on the CHA₂DS₂-VASc score.

Study endpoint

The primary endpoint was all-cause death after discharge. All cases of all-cause death were confirmed using the institutional medical records and data from the Korean Ministry of the Interior and Safety. The secondary endpoints were stroke and post-discharge AF. The incidence of all-cause mortality and stroke was compared between the three groups and post-discharge AF was compared between the PaAF and SR groups. As a study endpoint, the post-discharge AF was defined as any

documented episode of AF on 12-lead ECG or lasting >30 s on Holter monitoring during follow-up. ECG screening and 24-hour Holter monitoring were performed at the physician's discretion during follow-up unless the patient had any cardiac symptom.

Stroke included acute ischaemic and haemorrhagic stroke. Both were defined as the sudden development of neurological deficits that corresponded with brain imaging studies (CT or MRI).

Statistical analysis

Categorical variables are presented as numbers and frequencies, whereas continuous variables are presented as means±SD. The Student's t-test, analysis of variance and the Kruskal-Wallis test were used to compare continuous variables depending on the presence of a normal distribution of variables. The χ^2 test was used to compare categorical variables.

Kaplan-Meier curves were plotted and compared using the log-rank test. To adjust for covariates, a multivariable Cox proportional-hazards regression model was used to predict the study endpoint. Covariables of age, sex, body mass index, ST-segment elevation myocardial infarction (STEMI), Killip class, diabetes, hypertension, a history of myocardial infarction, left ventricular ejection fraction (LVEF), serum creatinine level, percutaneous coronary intervention, beta blocker use, renin-angiotensin system inhibitor use, statin, and pro-brain natriuretic peptide (proBNP) level were included in the multivariable model for the primary endpoint. For the analysis of stroke, the variables of age, sex, body mass index, STEMI, hypertension, diabetes, a history of stroke, serum creatinine level, proBNP level and warfarin use were included in the multivariable model.

Statistical tests were performed using SPSS V.22 and R programming V.3.5.1 (<http://www.R-project.org>; R Foundation for Statistical Computing, Vienna, Austria).

Figure 1 Flowchart of the study population. AF, atrial fibrillation; AMI, acute myocardial infarction.

Table 1 Baseline characteristics of study population

	Sinus rhythm (n=2252)	Paroxysmal AF (n=230)	Persistent AF (n=41)	P value
Age	61.6±13.2	67.5±14.0	74.6±11.6	<0.001
Male	1747 (77.6)	161 (70.0)	20 (48.8)	<0.001
Discharge SBP (mm Hg)	115.5±17.3	114.9±16.4	117.9±16.3	0.400
Discharge DBP (mm Hg)	66.3±10.3	64.3±10.1	66.0±10.2	0.019
Heart rate (bpm)	72.8±13.8	76.0±13.9	88.9±18.7	<0.001
BMI (kg/m ²)	24.4±3.4	23.6±3.6	24.3±6.0	0.017
STEMI	1142 (50.7)	136 (59.1)	22 (53.7)	0.050
Killip 3–4	235 (10.4)	59 (25.7)	7 (17.1)	<0.001
History				
Hypertension	1133 (50.3)	137 (59.6)	25 (61.0)	0.013
Diabetes	619 (27.5)	72 (31.3)	17 (41.5)	0.074
MI	131 (5.8)	21 (9.1)	2 (4.9)	0.128
PCI	206 (9.1)	26 (11.3)	3 (7.3)	0.510
Dyslipidaemia	536 (23.8)	39 (17.0)	7 (17.1)	0.042
Stroke	120 (5.3)	23 (10.0)	3 (7.3)	0.014
CKD	62 (2.8)	11 (4.8)	1 (2.4)	0.217
Current smoker	982 (43.6)	85 (37.0)	12 (29.3)	0.032
CHA ₂ DS ₂ -VASc score	2.9±1.6	3.6±1.8	4.1±1.7	<0.001
Echocardiography				
LVEF (%)	53.8±10.5	48.5±12.9	47.0±11.1	<0.001
LVEDD (mm)	48.8±5.5	48.6±7.3	48.8±5.5	0.872
LVESD (mm)	33.1±6.6	34.8±7.0	34.3±5.5	0.001
Laboratory test at admission				
Creatinine (mg/dL)	1.1±1.0	1.4±1.5	1.0±0.5	<0.001
hs-CRP (mg/dL)	4.6±6.2	6.0±6.9	4.9±6.3	0.050
Total cholesterol (mg/dL)	176.3±42.6	160.2±41.9	156.2±33.6	<0.001
LDL (mg/dL)	108.6±36.7	100.7±38.2	99.4±31.2	0.004
proBNP (pg/L)	190 (49–982)	620 (87–4180)	1224 (364–4675)	<0.001
Troponin I (ng/mL)	31.1 (6.8–96.7)	62.5 (14.6–144.0)	21.7 (6.6–89.5)	<0.001
CK-MB (mg/dL)	11.6 (2.1–77.3)	14.8 (3.5–110.5)	10.7 (3.2–74.1)	<0.001
Initial treatment				
Thrombolysis	99 (4.4)	6 (2.6)	1 (2.4)	0.372
PCI	1946 (86.4)	196 (85.2)	32 (78.0)	0.279
CABG	59 (2.6)	13 (5.7)	0 (0.0)	0.017
Medical treatment	254 (11.3)	27 (11.7)	8 (19.5)	0.258
Discharge medication				
Aspirin	2236 (99.3)	229 (99.6)	39 (95.1)	0.008
P2Y12 inhibitor	2159 (95.9)	220 (95.7)	38 (92.7)	0.598
Warfarin	51 (2.3)	17 (7.4)	14 (34.1)	<0.001
Beta blocker	1667 (74.0)	141 (61.3)	29 (70.7)	<0.001
RAS inhibitor	1796 (79.8)	186 (80.9)	31 (75.6)	0.736
Statin	1997 (88.7)	197 (85.7)	32 (78.0)	0.050

Values are expressed as mean±SD, median (IQR) or number (%).

.AF, atrial fibrillation; BMI, body mass index; bpm, beats per minute; CABG, coronary artery bypass graft; CKD, chronic kidney disease; CK-MB, creatine kinase-MB; DBP, diastolic blood pressure; hs-CRP, high-sensitive C reactive protein; LDL, low-density lipoprotein; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; MI, myocardial infarction; PCI, percutaneous coronary intervention; proBNP, pro-brain natriuretic peptide; RAS, renin-angiotensin system; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction.

Table 2 Incidence of study endpoint during follow-up

	Sinus rhythm (n=2252)	Paroxysmal AF (n=230)	Persistent AF (n=41)	P value
Primary endpoint				
All-cause death	331 (14.7)	61 (26.5)	20 (48.8)	<0.001
Secondary endpoint				
Stroke	100 (4.4)	19 (8.3)	9 (22.0)	<0.001
Ischaemic stroke	76 (3.4)	17 (7.4)	6 (14.6)	<0.001
Haemorrhagic stroke	27 (1.2)	2 (0.9)	3 (7.3)	0.001
Post-discharge AF	94 (4.2)	67 (29.1)	NA	<0.001

Values are expressed as n (%).
AF, atrial fibrillation; NA, not applicable.

RESULTS

Patients

A total of 2523 patients with AMI were selected. A flow-chart of the patient selection is depicted in [figure 1](#). New-onset AF was observed in 271 patients (10.7%). Among the patients with AF, spontaneous sinus conversion occurred in 230 patients (PaAF group, 84.9%) prior to discharge and the remaining 41 patients (PeAF group, 15.1%) showed persistent AF. No direct current cardioversion to convert AF to SR has been tried during the index hospitalisation.

Baseline characteristics were different between the groups ([table 1](#)). The mean patient age was highest in the PeAF group, followed by the PaAF and SR groups (74.6 ± 11.6 vs 67.5 ± 14.0 vs 61.6 ± 13.2). Compared with the SR group, patients with AF (PaAF and PeAF groups) generally had a higher comorbidity load and less favourable clinical characteristics such as a higher Killip class, lower LVEF, higher proBNP level and higher CHA₂DS₂-VASc score. Oral anticoagulant (OAC) therapy with warfarin was initiated at discharge in 7.5% and 34.1% of patients in the PaAF and PeAF groups, respectively.

Clinical outcomes

Primary endpoint

During the median follow-up period of 7.2 years (IQR: 5.2–9.4), all-cause death was noted in 16.3% (412 patients) ([table 2](#)). The PeAF group showed the highest incidence of all-cause death, followed by the PaAF and SR groups (48.8% vs 26.5% vs 14.7%, $p<0.001$). In the Kaplan-Meier analysis, the PaAF and PeAF groups showed significantly higher incidence of all-cause death than the SR group ([figure 2A](#)). In the multivariable Cox hazard regression analysis, the PeAF group was associated with an increased risk of all-cause death compared with the SR group (HR: 1.746, 95% CI: 1.030–2.958) whereas the PaAF group was not (HR: 0.993, 95% CI: 0.731–1.349) ([table 3](#)).

Secondary endpoint

The median follow-up period for stroke events was 7.1 years (IQR: 5.1–9.3). During that period, stroke occurred in 128 patients (5.1%) ([table 2](#)). The incidence of stroke was highest in the PeAF group, followed by the PaAF and SR groups (22.0% vs 8.3% vs 4.4%, $p<0.001$). Among the 23 patients with ischaemic stroke in the PaAF and PeAF groups, only one patient was on anticoagulation therapy with warfarin (data now shown). Kaplan-Meier curves demonstrated a higher incidence of stroke and ischaemic stroke in the PeAF and PaAF groups than in the SR group ([figure 2B,C](#)). In the multivariable analysis models, both PaAF and PeAF were consistently associated with an increased risk of stroke (PaAF, HR: 1.972 (1.162–3.346); PeAF, HR: 5.160, CI: 2.242–11.873) and ischaemic stroke (PaAF, HR: 2.209, CI: 1.248–3.910; PeAF, HR: 4.498, CI: 1.713–11.812) ([table 4](#)).

Post-discharge AF was detected more frequently in the PaAF group than in the SR group (29.1% vs 4.2%, $p<0.001$) ([table 1](#)). The Kaplan-Meier curve also demonstrated a higher incidence of AF in the PaAF group than in the SR group ([figure 2D](#)). Among 17 patients who experienced ischaemic stroke in the PaAF group, recurrent AF was detected in 10 patients during follow-up. However, only four patients (23.5%) had recurrent AF prior to an ischaemic stroke event, while the remaining six patients (35.3%) had recurrent AF simultaneously or after the ischaemic stroke event ([figure 3](#)).

DISCUSSION

The present study has several important contributions regarding clinical practice and the treatment of patients with AMI, with the foremost being that the clinical significance of transient AF episodes in AMI should not be neglected. Further, the study demonstrates the clinical implications of new-onset AF in patients with AMI. The major findings can be summarised as follows: (1) new-onset AF is frequently observed in patients with AMI (about 10%), (2) persistent new-onset AF was associated with an increased risk of post-discharge all-cause mortality and (3) new-onset AF, although transient, was associated with an increased risk of AF recurrence, ischaemic stroke and stroke.

The higher incidence of ischaemic stroke as well as recurrent AF in the PaAF group than in the SR group in the present study is notable. Although several previous studies that included patients with AMI showed a higher incidence of stroke in patients with new-onset AF, the mechanism of stroke was not clearly understood because the patients with new-onset AF were older and had a high comorbidity load.^{1 2 4 9} Our study supports the recommendations of current guidelines on the treatment of patients with AF with coronary heart disease.^{10 11} Whenever AF is noted in patients with AMI with CHA₂DS₂-VASc score ≥ 2 , antithrombotic therapy including OAC should be initiated regardless of the occurrence of sinus conversion.^{10 11} The initiation of OAC subsequently, when AF

Figure 2 Cumulative incidence of study endpoints according to the presence and type of new-onset atrial fibrillation. PaAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; SR, sinus rhythm.

is redetected during follow-up, is not a good strategy for stroke prevention unless the patient was on ambulatory ECG monitoring, because recurrent AF was detected in only a limited number of patients prior to the occurrence of ischaemic stroke in this study.

OAC was underutilised in patients with AF in the present study. During the period when the patients were treated for AMI (from June 2003 to February 2015), non-vitamin K antagonist oral anticoagulants (NOACs) were not covered by the national health insurance in our country. Further, there were concerns regarding the use of the triple therapy (dual antiplatelet therapy (DAPT) and warfarin) due to the increased risk of haemorrhagic stroke compared with using DAPT alone in the Korean population.¹² For these reasons, DAPT has been preferred to the triple therapy in patients with AF with AMI. However, we could better analyse the prognosis of

patients with new-onset AF when they were not receiving anticoagulation therapy in this study. In the current era of NOAC, dual therapy with NOAC and P2Y₁₂ receptor inhibitors (mainly clopidogrel) has shown promising results with excellent safety and efficacy in patients with AF undergoing percutaneous coronary intervention.^{13–16}

AMI complicated with AF has been associated with a poor prognosis.^{9 17 18} Ventricular dysfunction caused by myocardial infarction can be aggravated with the development of AF by tachycardia without atrioventricular synchrony.¹⁹ Further, ventricular dysfunction with an irregular ventricular cycle length can lead to fatal ventricular arrhythmia.¹⁹ However, there is no strong evidence that supports the notion that early direct current cardioversion of AF affords survival benefits in patients with AMI. In the present study, among the excluded patients with in-hospital death (n=161), the prevalence of AF was

Table 3 Cox regression analysis for all-cause death

	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.089 (1.080–1.099)	<0.001	1.074 (1.060–1.088)	<0.001
Female	1.432 (1.295–1.583)	<0.001	1.312 (1.025–1.681)	0.031
BMI	0.823 (0.789–0.848)	<0.001	0.924 (0.893–0.957)	<0.001
STEMI	1.157 (1.049–1.276)	0.004	0.942 (0.745–1.190)	0.614
Killip 3, 4	2.914 (2.328–3.647)	<0.001	1.287 (0.980–1.690)	0.069
Diabetes	1.883 (1.547–2.293)	<0.001	1.350 (1.064–1.711)	0.013
Hypertension	1.852 (1.511–2.269)	<0.001	1.098 (0.854–1.413)	0.465
Previous MI	1.791 (1.297–2.473)	<0.001	1.577 (1.101–2.260)	0.013
LVEF	0.963 (0.955–0.971)	<0.001	0.999 (0.989–1.010)	0.896
Creatinine	1.233 (1.182–1.285)	<0.001	1.115 (1.042–1.192)	0.002
PCI	0.547 (0.429–0.697)	<0.001	0.956 (0.706–1.294)	0.771
Beta blocker	0.560 (0.459–0.683)	<0.001	0.822 (0.655–1.033)	0.093
RAS inhibitor	0.688 (0.551–0.859)	0.001	0.948 (0.723–1.243)	0.699
Statin	0.387 (0.309–0.484)	<0.001	0.717 (0.551–0.934)	0.014
Log (proBNP)	2.772 (2.467–3.115)	<0.001	1.481 (1.244–1.764)	<0.001
Sinus rhythm	1	NA	1	NA
Paroxysmal AF	2.039 (1.551–2.680)	<0.001	0.993 (0.731–1.349)	0.963
Persistent AF	4.348 (2.767–6.831)	<0.001	1.746 (1.030–2.958)	0.038

AF, atrial fibrillation; BMI, body mass index; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not applicable; PCI, percutaneous coronary intervention; proBNP, pro-brain natriuretic peptide; RAS, renin–angiotensin system; STEMI, ST-segment elevation myocardial infarction.

35.4% (data not shown), which is much higher than that in the study subjects (10.7 %).

The mechanism of new-onset AF in ACS is not clearly understood. However, multifactorial mechanisms such as atrial ischaemia, atrial pressure overload, inflammation and neurohormonal activation are considered to be involved in the development of AF in patients with ACS.¹⁷ Accordingly, regarding pressure overload and inflammation, patients with AF had lower LVEF and higher

levels of proBNP and high-sensitive C reactive protein than patients with SR in the present study. Beta blockers may exert protective effects against AF through their anti-adrenergic and anti-ischaemic effects. A previous randomised controlled trial demonstrated the benefits of carvedilol for reducing the risk of AF/atrial flutter (HR 0.41, 95% CI: 0.25–0.68) compared with a placebo among patients with AMI.²⁰ In the present study, beta blocker use at discharge was not associated with a reduced risk of

Table 4 Cox regression analysis for all stroke and ischaemic stroke

	Univariable		Multivariable analysis model 1		Multivariable analysis model 2	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Stroke						
Sinus rhythm	1		1		1	
Paroxysmal AF	2.194 (1.343–3.585)	0.002	1.837 (1.117–3.021)	0.017	1.972 (1.162–3.346)	0.012
Persistent AF	8.297 (4.320–15.935)	<0.001	5.804 (2.986–11.280)	<0.001	5.160 (2.242–11.873)	<0.001
Ischaemic stroke						
Sinus rhythm	1		1		1	
Paroxysmal AF	2.543 (1.502–4.305)	0.001	2.167 (1.270–3.700)	0.005	2.209 (1.248–3.910)	0.006
Persistent AF	6.105 (2.655–14.040)	<0.001	4.396 (1.887–10.243)	0.001	4.498 (1.713–11.812)	0.002

Multivariable analysis model 1: adjusted for age and sex; multivariable analysis model 2: adjusted for age, sex, body mass index, diabetes, hypertension, previous stroke, pro-brain natriuretic peptide, creatinine, ST-elevation myocardial infarction and warfarin. AF, atrial fibrillation.

Figure 3 Detection of recurrent atrial fibrillation in patients who experienced ischaemic stroke in the paroxysmal atrial fibrillation group. Recurrence rate of atrial fibrillation in patients who experienced ischaemic stroke in paroxysmal atrial fibrillation group. AF, atrial fibrillation.

AF (HR: 0.883, 95% CI: 0.565–1.378, data not shown) in the SR group. However, we cannot compare the results directly because the present study was a retrospective observational study and beta blockers were administered to a majority of patients (74%) in the SR group.

Several limitations of the present study should be considered. First, this was a single-centre, retrospective and observational study. Thus, baseline characteristics were different within the groups. Despite statistical adjustments, potential confounders may have remained. Second, some study outcomes might have been underestimated; in particular, rigorous AF surveillance was not attempted in the entire study population. Regarding stroke, a previous substudy of a well-performed randomised controlled trial involving patients with STEMI showed a 5.8% incidence of ischaemic stroke during the 3-year follow-up in patients with new-onset AF.¹ We believe the incidence of ischaemic stroke in our study (8.5% for a median of 7.1 years) corresponds with the results of this previous study. Third, some patients with pre-existing asymptomatic AF may have been erroneously regarded to have had new-onset AF. It is difficult to accurately define new-onset AF because the patients did not undergo ECG monitoring just before the AMI event. Technically, true new-onset AF may only be defined in patients with ambulatory ECG monitoring such as pacemaker and loop recorder. Fourth, some patients in SR group, may have undocumented AF that lasted for a short time. Despite these limitations, the long-term follow-up in the present study is one of its main strengths.

In conclusion, new-onset AF is associated with worse long-term outcomes in patients with AMI. Sinus conversion of new-onset AF does not indicate that it is a transient episode; it is associated with a high risk of AF recurrence and stroke. Appropriate antithrombotic therapy with a combination of OAC and antiplatelet agents should be initiated in these patients according to guidelines.

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