

# Long-term impact of new-onset atrial fibrillation complicating acute myocardial infarction on heart failure

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## Abstract

**Aims** New-onset atrial fibrillation (NOAF) complicating acute myocardial infarction (AMI) has been associated with poor survival, but the clinical implication of NOAF on heart failure (HF) is still not well characterized. We aimed to investigate the relationship between NOAF complicating AMI and HF hospitalization.

**Methods and results** Adult AMI patients identified in the New-Onset Atrial Fibrillation Complicating Acute Myocardial Infarction in Shanghai registry who, discharged alive, had complete echocardiography and follow-up data from February 2014 to March 2018 were included. Patients were divided according to the presence of NOAF. The outcome measures were HF hospitalization and death during the observational period (until 10 April 2019). Cox proportional hazard models were performed in the whole population and propensity score-matched (PSM) cohort to assess the adjusted hazard ratio (HR) and 95% confidence interval (CI). Overall, 2075 patients (mean age:  $65.2 \pm 12.3$  years, 77.3% were men) with AMI were analysed, of whom 228 (11.0%) developed NOAF. Advanced age, admission HF (Killip II–IV), impaired renal function, decreased left ventricular ejection fraction, increased heart rate, and left atrial enlargement were independent predictors of NOAF. Over a median observational period of 2.7 years, the annual incidence rates of HF hospitalization were 18.4% and 2.8% for patients with NOAF and sinus rhythm, respectively. After adjustment for confounders, NOAF was significantly associated with HF hospitalization (HR: 3.14, 95% CI: 2.30–4.28,  $P < 0.001$ ). Similar results were obtained when accounting for the competing risk of all-cause death (subdistribution HR: 3.06, 95% CI: 2.18–4.30,  $P < 0.001$ ) or from the PSM cohort (HR: 2.82, 95% CI: 1.99–4.00,  $P < 0.001$ ). Patients with persistent NOAF (HR: 5.81, 95% CI: 3.59–9.41) were at significantly higher risk of HF hospitalization when compared with those with transient one (HR: 2.61, 95% CI: 1.84–3.70,  $P$  interaction = 0.008). Although post-MI NOAF was significantly related to cardiovascular death (annual incidence rates for NOAF and sinus rhythm were 9.4% and 2.3%, respectively; HR: 1.97, 95% CI: 1.36–2.85,  $P < 0.001$ ), such an association was attenuated when HF hospitalization (modelled as a time-varying covariate) and antithrombotic treatment were adjusted (HR: 1.37, 95% CI: 0.92–2.02,  $P = 0.121$ ).

**Conclusions** In patients with AMI, NOAF is strongly associated with an increased long-term risk of HF hospitalization. Our findings suggest that strengthened secondary prevention of HF should be considered in this high-risk population.

**Keywords** Acute myocardial infarction; Atrial fibrillation; Heart failure; Mortality; Risk factor

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## Introduction

Heart failure (HF) is a common finding after acute myocardial infarction (AMI) and has been associated with excess mortality and morbidity.<sup>1</sup> Owing to the effective utilization of

invasive strategies and intensive pharmacotherapy, the incidence rate of HF after AMI has markedly decreased during the last decades, but the long-term survival after HF complicating AMI remains poor.<sup>2–4</sup> Therefore, a better understanding of risk factors involving in the development of HF in

long-term AMI survivors will help identify individuals expected to benefit from the preventive measures.

New-onset atrial fibrillation (NOAF) is a frequent complication during the acute phase of MI, and the incidence rate of which ranges from 5% to 21%.<sup>5</sup> Previous studies have shown that the presence of NOAF in the setting of AMI is independently associated with increased risks of death and ischemic stroke.<sup>6,7</sup> Given the fact that a transient NOAF episode is even related to poor outcome, NOAF during AMI should not be perceived as a benign event anymore.<sup>8</sup> AF and HF often coincide in clinical practice, and the reciprocal impact of both conditions on patients' prognosis has been validated in various settings.<sup>9,10</sup> However, until now, there remains a paucity of evidence regarding the association of NOAF with long-term risk of HF in a contemporary AMI cohort.

Accordingly, in this analysis using data from the New-Onset Atrial Fibrillation Complicating Acute Myocardial Infarction in Shanghai (NOAFCAMI-SH) registry (ClinicalTrials.gov Identifier: NCT03533543), we aimed to investigate the relationship between NOAF and the long-term risk of HF hospitalization, as well as the risk factors of NOAF during AMI hospitalization.

## Methods

### Data source

The NOAFCAMI-SH registry was a retrospective hospital-based AMI registry designed to investigate the association of NOAF-related characteristics [including atrial fibrillation (AF) pattern, burden, duration, frequency, and with or without symptoms; details in Supporting Information, *Table S1*] with long-term cardiovascular outcomes after AMI. The electronic medical records of 2698 patients who were over 18 years old and diagnosed with AMI at the coronary care unit of Shanghai Tenth People's Hospital between February 2014 and March 2018 had been reviewed for eligibility. AMI was diagnosed as an increase in serum troponin T ( $2 \times$  upper limit of the normal range) associated with symptoms of ischemia and/or characteristic electrocardiogram (ECG) signs (ST-segment-T wave changes, left bundle branch block, or presence of pathological Q waves).<sup>11</sup> After excluding patients whose clinical characteristics were not available ( $N = 157$ ), those with a documented history of AF ( $N = 89$ ), those with a rheumatic valvular disease ( $N = 4$ ) or sick sinus syndrome ( $N = 2$ ), those without heart rhythm data ( $N = 14$ ), and those underwent emergent coronary artery bypass grafting surgery ( $N = 33$ ), 2399 patients were included. Data within the NOAFCAMI-SH registry included patient demographics, cardiovascular risk factors, medical history, laboratory tests, procedures, and medications.

### Study population

All NOAFCAMI-SH registry participants were included in the present analysis, except those who died during hospitalization or did not have transthoracic echocardiographic data within 7 days after AMI admission ( $N = 252$ ), or those lost to follow-up ( $N = 72$ ). A total of 2075 patients were included in the final analysis. The study was performed following the Declaration of Helsinki, and the ethics committee of the Shanghai Tenth People's Hospital approved the study protocol (SHSY-IEC-KY-4.1/18-199/01). Informed consent was waived as information was extracted anonymously and participants were assigned to a code number.

### New-onset atrial fibrillation ascertainment

Atrial fibrillation was diagnosed in accordance with the consensus guidelines as the absence of P waves with irregular RR intervals lasting at least 30 s.<sup>12</sup> NOAF was defined as patients with no prior history of AF who developed the first documented AF episode. Continuous electronic monitoring (IntelliVue MP40, Philips, Netherlands) was started immediately after admission and continued throughout the hospitalization. All participants' electronic monitoring data were reviewed to adjudicate the occurrence of NOAF. Patients were divided into two groups according to the presence of NOAF.

### Data collection

A detailed review of the electronic medical records was performed to collect patients' demographic characteristics, cardiovascular risk factors, baseline comorbidities, biological, echocardiography, and angiography data, as well as medications. Blood samples were obtained after 12 h of fasting and were examined in a central laboratory. Left atrial diameter, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, and left ventricular ejection fraction (LVEF) were measured according to standardized criteria.<sup>13</sup> Definitions of essential clinical characteristics were described in *Table S2*.

### Outcome measures

The primary outcome was HF hospitalization, defined as a minimum of an overnight hospital stay of a participant who presented with symptoms and signs of HF or received intravenous diuretics. The secondary outcomes included cardiovascular and all-cause death. All deaths without a clear non-cardiovascular cause would be classified as cardiovascular deaths. Each patient was followed from the index AMI

discharge to the date of HF hospitalization, death, or the end of the observational period (as of the censoring date of 10 April 2019), whichever came first. Clinical outcomes that occurred during the observational period were evaluated either by telephone interview or by a comprehensive review of the patient's inpatient and outpatient records.

## Statistical analysis

Baseline characteristics were compared between patients with sinus rhythm (SR) and NOAF during index AMI hospitalization. Statistical significance for categorical variables was tested using the  $\chi^2$  or Fisher's exact test and the analysis of Student's *t*-test or Mann–Whitney *U* test for continuous variables, as appropriate. Independent predictors of in-hospital NOAF were identified using a logistic regression model (details in Supporting Information).

Incidence rates were calculated using the total number of HF hospitalization and death during the observational period divided by person-years at risk. Kaplan–Meier method was used to calculate the cumulative incidence of HF hospitalization and death stratified by rhythm status, and the difference was compared using the log-rank test. Cox proportional hazard regression analysis was used to investigate the association of post-MI NOAF and HF hospitalization and death. Baseline covariates incorporated in the multivariable models were selected on the basis of clinical plausibility and previous literature<sup>14</sup> including *age, sex, current smoking, comorbidity [hypertension, diabetes, hyperlipidaemia, chronic kidney disease (CKD), HF, MI, and stroke/transient ischemic attack (TIA), initial presentation (Killip class on arrival > 1, heart rate, systolic blood pressure) in-hospital percutaneous coronary intervention (PCI) with stent, LVEF, and medications at discharge (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, statin,  $\beta$ -blocker, and diuretic)*. No missing data existed in the abovementioned covariates. The assumption of proportional hazards was validated by a visual examination of the log (minus log) curves. In addition, we performed an exploratory analysis to demonstrate the association of NOAF pattern with HF hospitalization; patients with NOAF who discharged with SR were considered as with transient NOAF, while those remained with AF at discharge were considered as with persistent NOAF.<sup>8</sup>

## Propensity score matching analysis

We used a propensity score matching (PSM) method to balance important patient characteristics between groups. A logistic regression model was used to calculate the propensity score that represented each participants' probability of developing NOAF during the index AMI hospitalization. The covariates introduced in the logistic regression model were

selected based on the measured baseline characteristics, including age, sex, smoking status, comorbidity (hypertension, diabetes, hyperlipidaemia, CKD, HF, MI, PCI, stroke/TIA), initial presentation [ST-segment elevation myocardial infarction (STEMI), Killip class, heart rate, systolic blood pressure, and out-of-hospital cardiac arrest], and LVEF. A 1:2 (exposed to unexposed) nearest-neighbour matching without replacement algorithm was performed using a caliper of 0.05 to ensure adequate matches.

## Subgroup and sensitivity analysis

The relationship between NOAF and HF hospitalization was evaluated in several subgroups: age (< or  $\geq$  65 years), sex, hypertension, diabetes, Killip class (II–IV vs. I), estimated glomerular filtration rate (eGFR; < or  $\geq$  60 mL/min/1.73m<sup>2</sup>), MI category (STEMI vs. NSTEMI), and the use of PCI with stent.

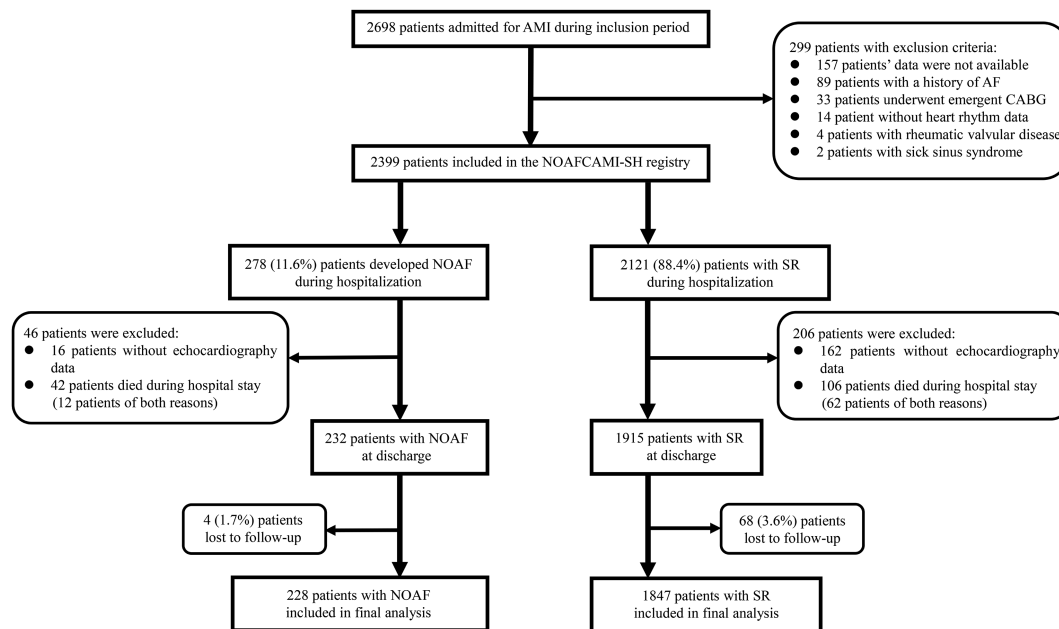
Several sensitivity analyses were also performed. First, we further adjusted for LDL-c, HDL-c, peak TnT, and peak NT-proBNP (N terminal pro brain natriuretic peptide). Second, we repeated the analysis after excluding all patients with a history of HF or developed acute HF during the index AMI hospitalization. Third, we repeated the analysis after excluding patients with an LVEF level of  $\leq$ 40%. Fourth, HF hospitalization that occurred within the first month after discharge was censored. Fifth, a competing risk analysis using the method of Fine and Gray was conducted to treat all-cause death as a competing event for the outcomes of interest.<sup>15</sup> Besides, we further adjusted the HF hospitalization during the observational period (modelled as a time-varying covariate) as well as the use of dual-antiplatelet therapy (DAPT) and oral anticoagulation at discharge to evaluate the association of post-MI NOAF with long-term mortality. All tests were two sided at the 0.05 significance level. All analyses were performed using Stata 14.0 (StataCorp, College Station, Texas).

## Results

### Patient characteristics

The flow diagram of patient inclusion was illustrated in *Figure 1*. Of 2075 analysed patients, 228 (11.0%) developed NOAF during hospitalization. Baseline characteristics were summarized in *Table 1*. The mean age was  $65.2 \pm 12.3$  years, and 77.3% were men. Patients with NOAF were older, less likely to be female and current smokers, more likely to have a history of hypertension, CKD, HF, and stroke/TIA, were more likely to present with a higher Global Registry of Acute Coronary Events risk score compared with those with SR. In addition, patients with NOAF had higher levels of serum creatinine and peak NT-proBNP, while lower total and LDL cholesterol and LVEF values when compared with those with

**Figure 1** Flow diagram depicting the study population. AF, atrial fibrillation; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; NOAF, new-onset atrial fibrillation; NOAF-CAMI-SH, New-Onset Atrial Fibrillation Complicating Acute Myocardial Infarction in Shanghai; SR, sinus rhythm.



**Table 1** Baseline characteristics

Characteristics	Overall (n = 2075)	Sinus rhythm (n = 1847)	NOAF (n = 228)	P value
Age (years)	65.2 ± 12.3	64.1 ± 12.1	74.1 ± 10.6	<0.001
Male, n (%)	1605 (77.3)	1451 (78.6)	154 (67.5)	<0.001
BMI (kg/m <sup>2</sup> )	24.6 ± 3.3	24.6 ± 3.3	24.3 ± 3.4	0.282
Smoking status				<0.001
Never	946 (45.6)	817 (44.2)	129 (56.6)	
Former	202 (9.7)	171 (9.3)	31 (13.6)	
Current	927 (44.7)	859 (46.5)	68 (29.8)	
Comorbidity				
Hypertension	1307 (63.0)	1149 (62.2)	158 (69.3)	0.036
Diabetes	763 (36.8)	675 (36.5)	88 (38.6)	0.545
Hyperlipidaemia	547 (26.4)	497 (26.9)	50 (21.9)	0.107
Chronic kidney disease	174 (8.4)	147 (8.0)	27 (11.8)	0.046
History of heart failure	109 (5.3)	79 (4.3)	30 (13.2)	<0.001
Prior MI	135 (6.5)	117 (6.3)	18 (7.9)	0.367
Prior PCI	183 (8.8)	155 (8.4)	28 (12.3)	0.051
Prior TIA	235 (11.3)	196 (10.6)	39 (17.1)	0.004
Initial presentation				
Out-of-hospital cardiac arrest	44 (2.1)	35 (1.9)	9 (4.0)	0.042
STEMI	1262 (60.8)	1122 (60.7)	140 (61.4)	0.848
Anterior location	654 (51.8)	585 (52.1)	69 (49.3)	0.429
Inferior location	552 (43.7)	485 (43.2)	67 (47.9)	
Other	56 (4.4)	52 (4.6)	4 (2.9)	
Heart rate (bpm)	79.7 ± 16.7	79.1 ± 15.6	84.7 ± 23.5	<0.001
SBP (mmHg)	138.1 ± 24.2	138.2 ± 23.8	137.1 ± 26.9	0.563
Killip class >I	288 (13.9)	221 (12.0)	67 (29.4)	<0.001
GRACE risk score	119.5 ± 27.3	116.6 ± 25.9	142.7 ± 27.0	<0.001

BMI, body mass index; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction; NOAF, new-onset atrial fibrillation; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack.

Values are presented as number (percentage) or mean ± SD, as appropriate.

SR. Out of 228 patients with NOAF, SR was restored during hospitalization in 188 (82.5%) patients of whom only one had undergone direct current cardioversion. Amiodarone (146/228) was the most commonly applied antiarrhythmic agent for cardioversion, as well as maintaining SR. NOAF individuals were more likely to be prescribed with amiodarone, diuretic, oral anticoagulants, and aldosterone antagonist, but less likely to receive DAPT and  $\beta$ -blocker at discharge compared with SR (Table 2). Baseline characteristics stratified by NOAF pattern were shown in Table S3.

### Predictors of new-onset atrial fibrillation development

Findings from a multivariable logistic model identifying predictors of NOAF were shown in Table 3. Every 10 year increase in age was the strongest predictor of the occurrence of NOAF [odds ratio: 1.88, 95% confidence interval (CI): 1.60–2.19]. Other significant predictors (in decreasing order) included admission Killip > I, impaired kidney function

(eGFR < 60 mL/min/1.73m<sup>2</sup>), decreased LVEF value, elevated admission heart rate, and left atrial enlargement.

### New-onset atrial fibrillation complicating acute myocardial infarction and heart failure hospitalization

During a median observational period of 2.7 years (interquartile range: 1.6–3.9), a total of 72 (3.5%) patients lost to follow-up and were excluded from this analysis. Overall, 205 patients (9.9%) experienced HF hospitalization, with an annual incidence rate of 18.4% and 2.8% for patients with NOAF and SR, respectively (Figure 2A). After adjustment for confounding factors, NOAF remained a predictor of HF hospitalization [hazard ratio (HR): 3.14, 95% CI: 2.30–4.28,  $P < 0.001$ ] (Table 4). Results were similar when accounting for the competing risk of all-cause death [subdistribution HR (sHR): 3.06, 95% CI: 2.18–4.30,  $P < 0.001$ ]. In our exploratory analyses, the risk of HF hospitalization was significantly higher in patients with persistent NOAF (HR: 5.81, 95% CI: 3.59–9.41)

**Table 2** In-hospital examination and medications at discharge

	Overall (n = 2075)	Sinus rhythm (n = 1847)	NOAF (n = 228)	P value
<b>Laboratory indices</b>				
Total cholesterol (mmol/L)	4.38 (3.76–5.07)	4.42 (3.79–5.10)	4.18 (3.53–4.94)	0.002
LDL-c (mmol/L)	2.64 (2.12–3.24)	2.66 (2.15–3.25)	2.44 (1.89–3.08)	0.002
HDL-c (mmol/L)	0.99 (0.83–1.17)	0.99 (0.84–1.17)	1.02 (0.83–1.23)	0.234
Serum creatinine (mg/dL)	0.88 (0.75–1.05)	0.88 (0.75–1.03)	0.96 (0.82–1.27)	<0.001
eGFR (mL/min/1.73 m <sup>2</sup> )	86.0 (67.7–97.3)	88.0 (70.4–98.3)	69.8 (48.6–84.4)	<0.001
Peak TnT (ng/mL)	3.02 (0.80–8.06)	2.91 (0.79–7.76)	3.86 (0.76–10.0)	0.051
Log peak NT-proBNP (pg/mL)	3.18 (2.86–3.53)	3.14 (2.83–3.47)	3.64 (3.34–3.98)	<0.001
<b>Angiographic data</b>				
In-hospital PCI with stent	1750 (84.3)	1577 (85.4)	173 (75.9)	<0.001
Infarct-related artery <sup>a</sup>				0.132
Left anterior descending	618 (51.5)	561 (52.5)	57 (43.5)	
Right coronary artery	451 (37.6)	392 (36.7)	59 (45.0)	
Left circumflex	130 (10.8)	115 (10.8)	15 (11.5)	
Left main disease	89 (4.7)	68 (4.0)	21 (10.3)	<0.001
<b>Echocardiographic data</b>				
Left atrial diameter (mm)	38.1 ± 4.6	37.9 ± 4.5	40.2 ± 5.0	<0.001
LVEDD (mm)	45.6 ± 4.8	45.5 ± 4.6	46.1 ± 5.8	0.115
LVESD (mm)	31.0 ± 5.5	30.8 ± 5.4	32.1 ± 6.5	<0.001
LVEF (%)	50.4 ± 10.6	50.9 ± 10.3	46.5 ± 11.6	<0.001
<b>Medications at discharge</b>				
Aspirin	1908 (92.0)	1708 (92.5)	200 (87.7)	0.013
P2Y <sub>12</sub> receptor inhibitor	1994 (96.1)	1782 (96.5)	212 (93.0)	0.010
DAPT	1843 (88.8)	1655 (89.6)	188 (82.5)	0.001
Oral anticoagulation	12 (0.6)	2 (0.1)	10 (4.4)	<0.001
ACEI/ARB	1227 (59.1)	1104 (59.8)	123 (53.9)	0.091
$\beta$ -blocker	1502 (72.4)	1367 (74.0)	135 (59.2)	<0.001
Aldosterone antagonist	379 (18.3)	325 (17.6)	54 (23.7)	0.009
Statin	1989 (95.9)	1775 (96.1)	214 (93.9)	0.109
Diuretic	303 (14.6)	236 (12.8)	67 (29.4)	<0.001
Amiodarone	54 (2.6)	24 (1.3)	30 (13.2)	<0.001

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; DAPT, dual-antiplatelet therapy; eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-c, low-density lipoprotein cholesterol; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; NOAF, new-onset atrial fibrillation; NT-proBNP, N terminal pro brain natriuretic peptide; PCI, percutaneous coronary intervention.

Values are presented as number (percentage), mean ± SD, or median (IQR), as appropriate.

<sup>a</sup>For patients with STEMI undergoing angiography.

**Table 3** Independent predictors of post-MI NOAF

Variables	Multivariable-adjusted risk		
	OR	95% CI	P value
Age (+10 years)	1.88	1.60–2.19	<0.001
Admission Killip > I	1.68	1.14–2.48	0.008
eGFR < 60 mL/min/1.73m <sup>2</sup>	1.60	1.10–2.32	0.014
LVEF < 40%	1.59	1.10–2.31	0.015
Admission heart rate (+10 bpm)	1.19	1.09–1.30	<0.001
Left atrial diameter (+1 mm)	1.07	1.03–1.11	<0.001

Discrimination: C index: 0.77 (95% CI: 0.74–0.81); calibration: H-L test P value: 0.869.

CI, confidence interval; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NOAF, new-onset atrial fibrillation; OR, odds ratio.

compared with that in those with transient NOAF (HR: 2.61, 95% CI: 1.84–3.70, P interaction = 0.008).

### New-onset atrial fibrillation complicating acute myocardial infarction and mortality

A total of 220 patients (10.6%) died during the observational period, of whom 159 were cardiovascular deaths.

The annual incidence rates of all-cause mortality in patients with SR and NOAF were 3.2% and 12.3%, respectively, and of cardiovascular mortality were 2.3% and 9.4%, respectively (Figure 2B,C). Following multivariable adjustment, NOAF was independently associated with the risk of cardiovascular (HR: 1.97, 95% CI: 1.36–2.85, P < 0.001) and all-cause death (HR: 1.90, 95% CI: 1.38–2.61, P < 0.001) (Table 4). Results were similar when performing competing risk analysis for cardiovascular death with non-cardiovascular death as a competing factor (sHR: 1.98, 95% CI: 1.36–2.88, P < 0.001). When we further adjusted for the HF hospitalization (modelled as a time-varying covariate) as well as the use of DAPT and oral anticoagulation at discharge, we found that NOAF was not an independent risk factor of cardiovascular death (HR: 1.37, 95% CI: 0.92–2.02, P = 0.121), and its association with all-cause death was attenuated (HR: 1.43, 95% CI: 1.02–2.00, P = 0.037). In contrast, post-discharge HF hospitalization was determined as the strongest predictor for both cardiovascular death (HR: 7.23, 95% CI: 5.01–10.43, P < 0.001) and all-cause death (HR: 5.21, 95% CI: 3.78–7.18, P < 0.001).

**Figure 2** Kaplan–Meier curves illustrating the cumulative incidence of (A) heart failure (HF) hospitalization, (B) all-cause death, and (C) cardiovascular death according to rhythm status. CI, confidence interval; HR, hazard ratio; NOAF, new-onset atrial fibrillation.

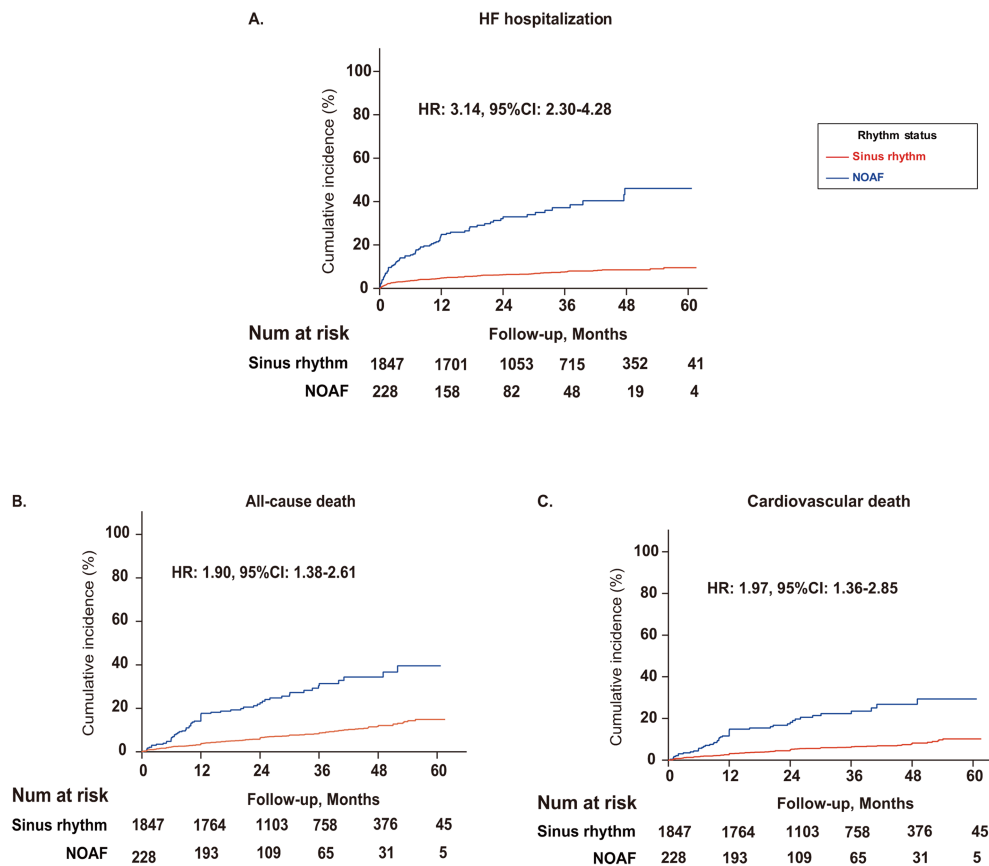


Table 4 Long-term clinical outcomes

Clinical outcome	NOAF development during hospitalization						Unadjusted risk		Multivariable adjusted risk <sup>a</sup>	
	Absent			Present			Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
	Events/Patients	%/Year (95% CI)	Events/Patients	%/Year (95% CI)	Hazard ratio (95% CI)	P value				
HF hospitalization	130/1847	2.8 (2.3–3.3)	75/228	18.4 (14.6–23.0)	5.81 (4.36–7.73)	<0.001	3.14 (2.30–4.28)	<0.001		
All-cause death	158/1847	3.2 (2.8–3.8)	62/228	12.3 (9.6–15.8)	3.76 (2.80–5.05)	<0.001	1.90 (1.38–2.61)	<0.001		
Cardiovascular death	112/1847	2.3 (1.9–2.7)	47/228	9.4 (7.0–12.5)	3.95 (2.81–5.55)	<0.001	1.97 (1.36–2.85)	<0.001		

CI, confidence interval; HF, heart failure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; OR, odds ratio.

<sup>a</sup>Adjusted for age, sex, current smoking, comorbidity (hypertension, diabetes, hyperlipidaemia, chronic kidney disease, HF, myocardial infarction, stroke/transient ischaemic attack), initial presentation (Killip on arrival > 1, heart rate, systolic blood pressure), in-hospital percutaneous coronary intervention with stent, LVEF, and the medications at discharge (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, statin,  $\beta$  blocker, diuretic).

## Propensity score matching analyses

The PSM cohorts were well balanced (Table S4). In the matched cohorts, the annual incidence rate of HF hospitalization was 6.2% for SR and 18.4% for NOAF (HR:2.82, 95% CI:1.99–4.00,  $P < 0.001$ ); of all-cause death was 7.8% for SR and 12.2% for NOAF (HR: 1.73, 95% CI: 1.23–2.45,  $P = 0.002$ ); of cardiovascular death was 5.8% for SR and 9.2% for NOAF (HR: 1.91, 95% CI: 1.27–2.87,  $P = 0.002$ ) (Figure 3A–C).

## Subgroup and sensitivity analyses

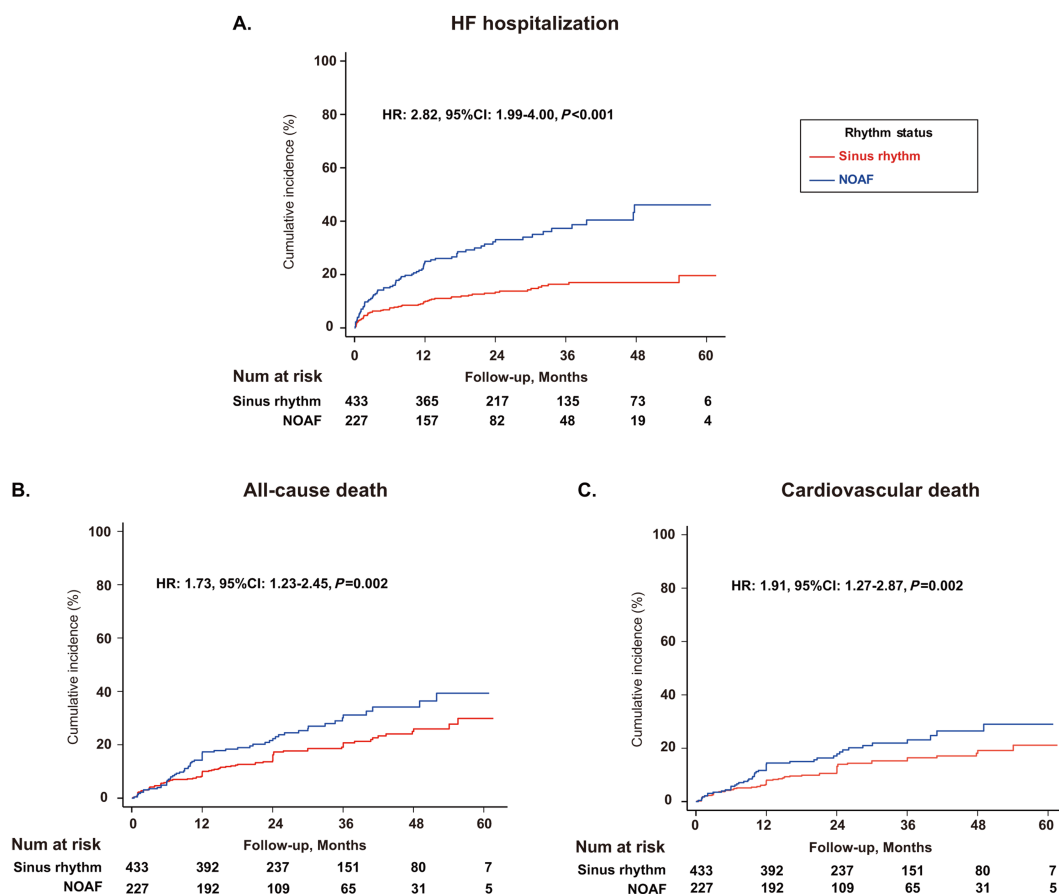
As illustrated in Figure 4, consistent results were observed across all subgroups compared with that in the primary analysis. As for sensitivity analysis, adjusted HR for HF hospitalization was similar after further adjustment for biological data (LDL-c, HDL-c, peak TnT, and peak NT-proBNP; HR: 3.04, 95% CI: 2.18–4.23,  $P < 0.001$ ). Comparable results were also observed after excluding patients who had a history of HF or developed acute HF during AMI hospitalization (HR: 2.05, 95% CI: 1.30–3.21,  $P = 0.002$ ), or after excluding those who had an LVEF value of  $\leq 40\%$  (HR: 4.21, 95% CI: 2.65–6.68,  $P < 0.001$ ). When censoring the HF hospitalization events that occurred within the first month after discharge, the association between NOAF and HF hospitalization remained significant (HR: 3.18, 95% CI: 2.25–4.49,  $P < 0.001$ ).

## Discussion

In this analysis, we found that the presence of NOAF during AMI was significantly associated with a nearly three-fold increased long-term risk of HF hospitalization. The consistent results obtained from the PSM cohorts as well as accounting for the competing risk of death further strengthen our findings. The risk of HF hospitalization was more pronounced in patients with persistent AF compared with those with transient AF, which indicated a dose–response relationship. Although patients with NOAF had a higher risk of death compared with those with SR, such an association was attenuated when accounting for the impact of HF hospitalization.

In this study, increasing age, admission HF, impaired kidney function, decreased LVEF level, elevated admission heart rate, and left atrial enlargement were identified as independent predictors of NOAF during AMI. Advanced age is a well-established risk factor of AF.<sup>16</sup> Left atrial enlargement that reflects the adverse structural remodelling in the left atrium has also proven to be a predictor of AF after AMI.<sup>17</sup> Because left ventricular (LV) dysfunction and impaired haemodynamics have been recognized as potential

**Figure 3** Long-term risk of (A) heart failure (HF) hospitalization, (B) all-cause death, (C) cardiovascular death in the propensity score-matched cohorts. CI, confidence interval; HR, hazard ratio; NOAF, new-onset atrial fibrillation.



mechanisms leading to the occurrence of NOAF, it was not surprising to find that patients with admission HF, decreased LVEF, or elevated admission heart rate (a surrogate of LV dysfunction) were at higher risk of AF compared with those with normal cardiac function.<sup>16</sup> In an analysis of the Atherosclerosis Risk in Communities study,<sup>18</sup> the incidence rates of AF in patients with an eGFR of 30 to 59 mL/min/1.73m<sup>2</sup> and 15 to 30 mL/min/1.73m<sup>2</sup> were nearly 1.6-fold and 3.2-fold higher compared with that in patients with an optimal eGFR ( $\geq 90$  mL/min/1.73m<sup>2</sup>), respectively, which supported the predictive value of impaired kidney function for AF occurrence. Taken together, our results suggested that extensive electrical monitoring should be considered in patients with renal or cardiac dysfunction after AMI for underlying NOAF detection.

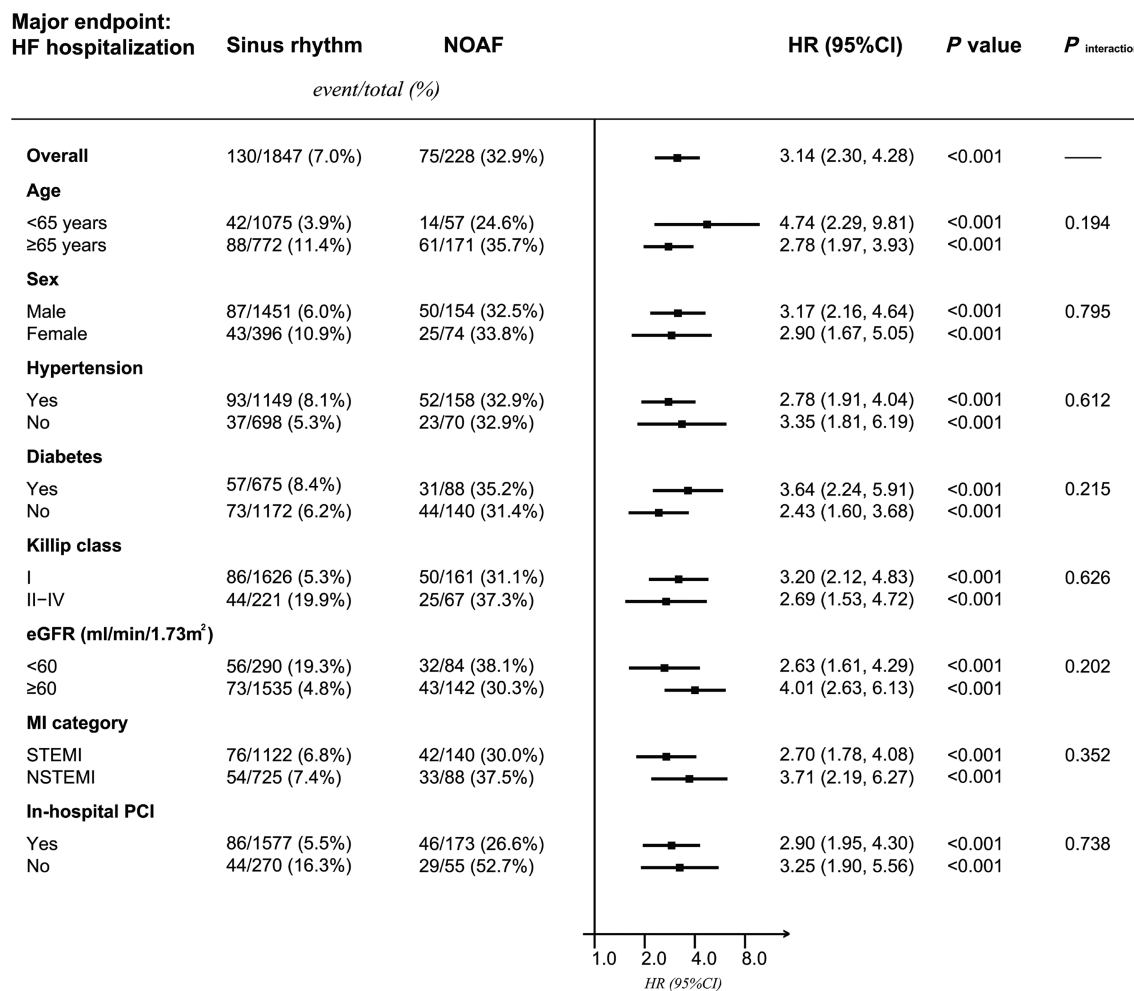
The prognostic impact of NOAF in patients with AMI has been extensively studied. In a previous meta-analysis, Jabre et al. demonstrated that post-MI NOAF was associated with a 37% greater all-cause mortality compared with the SR, but the majority of studies included in their analysis were conducted in the thrombolysis era.<sup>6</sup> Therefore, the clinical implication of post-MI NOAF remains to be validated in

contemporary cohorts. Our results showed that post-MI NOAF was significantly associated with 90% higher all-cause and 97% higher cardiovascular mortality after multivariable adjustment. However, when accounting for the impact of HF hospitalization, NOAF was no longer an independent risk factor of cardiovascular death. Similarly, in Asanin et al., after adjustment for baseline characteristics together with in-hospital HF, NOAF was not associated with long-term mortality (adjusted relative risk: 1.14, 95% CI: 0.72–1.79).<sup>19</sup> As a result, our analysis showed that the association between NOAF during AMI and long-term mortality might be HF-dependent, which underscored the adverse impact of HF after AMI.

The finding that NOAF developing during the acute phase of MI was associated with an increased risk of HF adds to a growing body of published studies highlighting the prognostic importance of post-MI HF. In an analysis of the Coronary Revascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) AMI registry, the onset of HF hospitalization within 1 year after STEMI was independently associated with a 64% increased risk of all-cause death.<sup>4</sup> In a large cohort of 199 851 patients with AMI,



**Figure 4** Subgroup analyses evaluating the association between post-myocardial infarction (MI) new-onset atrial fibrillation (NOAF) and heart failure (HF) hospitalization. CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.



Desta et al. reported nearly two-fold higher mortality in patients with HF compared with those without HF.<sup>2</sup> Finally, in a nationwide analysis of 47 673 patients without a history of HF who were discharged alive after AMI, post-discharge HF during 1 year follow-up accounted for 5.4% of AMI patients but contributed 24.5% and 29.1% of all-cause and cardiovascular death, respectively. After multivariable analysis, post-discharge HF was identified as a strong predictor of cardiovascular (HR: 7.93, 95% CI: 6.84–9.19) and all-cause mortality (HR: 5.98, 95% CI: 5.39–6.64).<sup>20</sup> In line with previous studies, we also demonstrated that HF hospitalization was an independent predictor of mortality after AMI. In this regard, our results were of paramount clinical importance because the identification of NOAF as a strong predictor of long-term HF after AMI would give clinicians a new way to recognize high-risk patients.

Interestingly, in our exploratory analysis, we uncovered a dose–response relationship as patients with persistent NOAF were challenged by a higher risk of HF hospitalization compared with those with transient NOAF. The explicit reasons for such a divergence in NOAF pattern are still elusive, and we postulated that the progression of AF burden might be one of the causes. In a post-hoc analysis of ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) trial, Wong et al. precisely quantified the duration of subclinical AF and demonstrated that the progression of subclinical AF duration from 6 min–24 h to >24 h (or overt AF) was associated with increased risk of HF hospitalization (HR: 4.58, 95% CI: 1.64–12.8).<sup>21</sup> As there were still no data available to address the impact of NOAF pattern on HF after AMI, our study filled this knowledge gap in the literature and indicated that patients with persistent NOAF could

benefit more from the preventive strategies compared with those with transient one.

## Limitations

This was a single-centre retrospective study conducted in a hospital-based setting. Because of the observational design of our study, the observed effects were limited to associations rather than causality given potential unmeasured confounders. Second, although patients with a history of AF had been excluded according to their medical records, some patients who had an undiagnosed AF before admission might be misclassified into the NOAF group. Third, despite the usefulness of ECG parameters (e.g. P-wave duration, axis, etc.) in predicting AF,<sup>22</sup> we could not evaluate their influences on the occurrence of post-MI NOAF because the NOAFCAMI-SH registry specifically focused on the prognostic implication of AF-related characteristics (Table S1) and had not included individuals' ECG data. Similarly, because of the lack of information on angiotensin receptor-neprilysin inhibitor, we could not examine its effect on clinical outcomes.

## Conclusions

Our findings indicate that NOAF during AMI hospitalization is independently associated with increased long-term risk of HF hospitalization. Patients with persistent NOAF are at higher risk of HF hospitalization compared with those with transient NOAF. As a result, NOAF complicating AMI can be a suitable preventive and therapeutic target of post-MI HF.

## Author contributions

JCL and YDW contributed to the conception and design of this work; JCL, SLX, HQL, ZQL, MMG, BXL, BBS, and XMQ

contributed to the acquisition, analysis, and interpretation of data for this work. JCL drafted the manuscript. All authors had critically revised and gave the final approval of the manuscript.

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## Conflict of Interest

None declared.

## Supporting information

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

**Table S1.** Definitions of NOAF-related characteristics in the NOAFCAMI-SH registry

**Table S2.** Definitions of baseline clinical characteristics

**Table S3.** Baseline characteristics of included patients stratified by the pattern of NOAF

**Table S4.** Baseline characteristics of patients with sinus rhythm and NOAF before and after propensity-score matching

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