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ORIGINAL RESEARCH

Newly Diagnosed Atrial Fibrillation in Acute Myocardial Infarction

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BACKGROUND: It remains controversial whether long-term clinical impact of newly diagnosed atrial fibrillation (AF) in the acute phase of acute myocardial infarction (AMI) is different from that of prior AF diagnosed before the onset of AMI.

METHODS AND RESULTS: The current study population from the CREDO-Kyoto AMI (Coronary Revascularization Demonstrating Outcome Study in Kyoto Acute Myocardial Infarction) Registry Wave-2 consisted of 6228 patients with AMI who underwent percutaneous coronary intervention. The baseline characteristics and long-term clinical outcomes were compared according to AF status (newly diagnosed AF: N=489 [7.9%], prior AF: N=589 [9.5%], and no AF: N=5150 [82.7%]). Median follow-up duration was 5.5 years. Patients with newly diagnosed AF and prior AF had similar baseline characteristics with higher risk profile than those with no AF including older age and more comorbidities. The cumulative 5-year incidence of all-cause death was higher in newly diagnosed AF and prior AF than no AF (38.8%, 40.7%, and 18.7%, P<0.001). The adjusted hazard ratios (HRs) for mortality of newly diagnosed AF and prior AF relative to no AF remained significant with similar magnitude (HR, 1.31; 95% CI, 1.12–1.54; P<0.001, and HR, 1.32; 95% CI, 1.14–1.52; P<0.001, respectively). The cumulative 5-year incidence of stroke decreased in the order of newly diagnosed AF, prior AF and no AF (15.5%, 12.9%, and 6.3%, respectively, P<0.001). The higher adjusted HRs of both newly diagnosed AF and prior AF relative to no AF were significant for stroke, with a greater risk of newly diagnosed AF than that of prior AF (HR, 2.05; 95% CI, 1.56–2.69; P<0.001, and HR, 1.33; 95% CI, 1.00–1.78; P=0.048, respectively). The higher stroke risk of newly diagnosed AF compared with prior AF was largely driven by the greater risk within 30 days. The higher adjusted HRs of newly diagnosed AF and prior AF relative to no AF were significant for heart failure hospitalization (HR, 1.73; 95% CI, 1.35–2.22; P<0.001, and HR, 2.23; 95% CI, 1.82–2.74; P<0.001, respectively) and major bleeding (HR, 1.46; 95% CI, 1.23–1.73; P<0.001, and HR, 1.36; 95% CI, 1.15–1.60; P<0.001, respectively).

CONCLUSIONS: Newly diagnosed AF in AMI had risks for mortality, heart failure hospitalization, and major bleeding higher than no AF, and comparable to prior AF. The risk of newly diagnosed AF for stroke might be higher than that of prior AF.

Key Words: acute myocardial infarction ■ anticoagulation ■ atrial fibrillation ■ percutaneous coronary intervention ■ stroke

Atrial fibrillation (AF) often coexists in patients with acute myocardial infarction (AMI), and its incidence in the setting of AMI was reported in 6% to 21% of patients.[1] AMI can induce AF through inflammation and atrial diastolic overload, whereas rapid heart rate of AF leads to increase in oxygen demand and worsen ischemia.[2] Several studies reported that AF in the setting of AMI was associated with poor in-hospital or midterm clinical outcomes including mortality and stroke.[1,3–6] There are 2 types of AF in the

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CLINICAL PERSPECTIVE

What Is New?

- Atrial fibrillation (AF) newly provoked by acute myocardial infarction is associated with poor clinical outcomes, however, the different impact on clinical outcome between newly diagnosed AF and prior AF in acute myocardial infarction has not been adequately evaluated yet.
- This study showed that newly diagnosed AF had comparable risk for mortality, heart failure, and major bleeding with prior AF, and higher risk for stroke than prior AF.

What Are the Clinical Implications?

- Once AF is newly detected in the acute phase of acute myocardial infarction, consideration of anticoagulation therapy is mandatory in patients with high risk for stroke (CHA_2DS_2-VASc score ≥2), although it should be noted that the risk of major bleeding is also high.

setting of AMI; prior AF diagnosed before the onset of AMI, and newly diagnosed AF emerging after the onset of AMI. The newly diagnosed AF is often self-limited and transient. It remains controversial whether long-term clinical impact of newly diagnosed AF during the acute phase of AMI is different from that of prior AF.[7–12] Patients with coronary artery disease and AF are known to be at high risk for both ischemic and bleeding events, and careful consideration would be needed for the decision to implement anticoagulation therapy concomitant with antiplatelet therapy.[13] In the current American Heart Association/American College of Cardiology/Heart Rhythm Society and European Society of Cardiology clinical guidelines, anticoagulation is recommended for patients with AMI and co-existing AF if CHA_2DS_2-Vasc score ≥2.[14,15] Regarding antithrombotic management for newly diagnosed AF, however, the American Heart Association/American College of Cardiology/Heart Rhythm Society clinical guidelines did not make a specific recommendation, while the European Society of Cardiology guidelines recommend the same management with prior AF, but without firm scientific evidences. Comprehensive data on thrombotic and bleeding risk is still sparse in patients with newly diagnosed AF relative to those without AF or relative to those with prior AF in the current primary percutaneous coronary intervention (PCI) era.

Therefore, the purpose of this study is to clarify the baseline characteristics and prognostic impact of newly diagnosed AF compared with those with prior AF and without AF in patients with AMI undergoing PCI in a large Japanese registry in real clinical practice.

METHODS

Study Population

The data that support the findings of this study are available from the corresponding author upon reasonable request. The CREDO-Kyoto AMI (Coronary Revascularization Demonstrating Outcome Study in Kyoto Acute Myocardial Infarction) registry Wave-2 is a physician-initiated, non-company-sponsored, multicenter registry that enrolled consecutive 6470 AMI patients who underwent coronary revascularization within 7 days of the onset of symptoms between January 2011 and December 2013 among 22 participating centers in Japan (Data S1). The relevant institutional review boards at all participating centers approved the study protocol, and written informed consent for this study was waived because of the retrospective nature of the study; however, we excluded those patients who refused participation in this study when contacted at follow-up. This strategy is concordant with the guidelines of the Japanese Ministry of Health, Labor and Welfare.

After excluding 21 patients who refused the study participation and 221 patients who received coronary artery bypass grafting, the current study population consisted of 6228 AMI patients who underwent PCI, and was divided into 3 groups according to the presence or absence of AF, and types of AF; newly diagnosed AF, prior AF, and no AF (Figure 1).

Definitions for Baseline Characteristics and Outcome Measures

We defined newly diagnosed AF as presumably newly developed AF documented during index hospitalization for AMI. Prior AF included all types of AF (paroxysmal, persistent, or permanent) diagnosed before admission for AMI. Prior AF was regarded as present when the diagnosis was indicated in the hospital charts in the participating centers. Other baseline clinical characteristics, such as hypertension, current smoking, heart failure, prior myocardial infarction, and chronic obstructive pulmonary disease were regarded as present when these diagnoses were documented in the hospital charts. Diabetes was defined as treatment with oral hypoglycemic agents or insulin, prior clinical diagnosis of diabetes, glycated hemoglobin level ≥6.5%, or non-fasting blood glucose level ≥200 mg/dL. Peripheral vascular disease was regarded as present when carotid, aortic, or other peripheral vascular diseases were being treated or scheduled for surgical or endovascular interventions. Renal function was evaluated by the estimated glomerular filtration rate calculated by the Modification of Diet in Renal Disease formula modified for Japanese patients.[16]

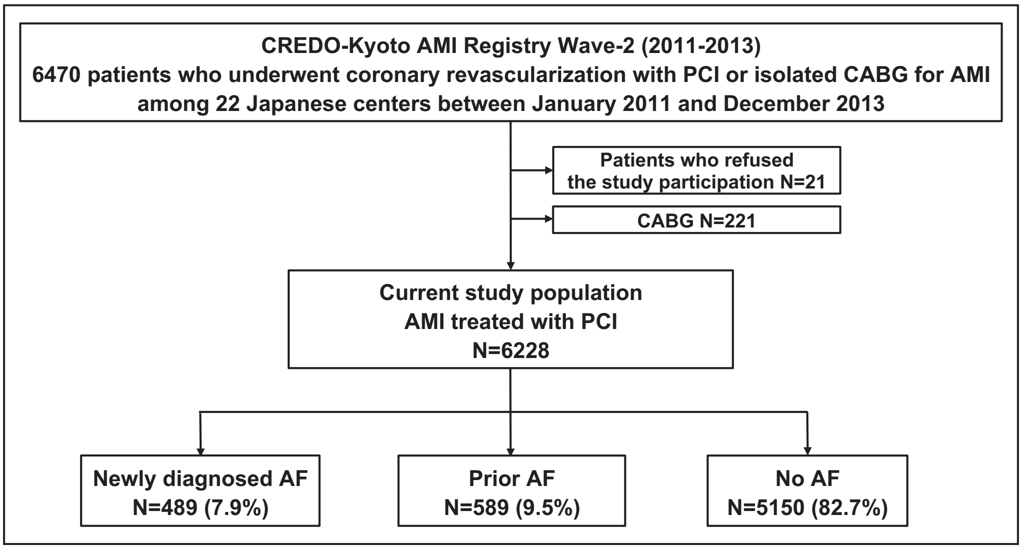


Figure 1. Study flow chart.
AF indicates atrial fibrillation; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CREDO-Kyoto AMI Registry Wave-2, Coronary Revascularization Demonstrating Outcome study in Kyoto AMI Registry Wave-2; and PCI, percutaneous coronary intervention.

The outcome measures in this study were all-cause death, cardiovascular death, myocardial infarction, stroke, hospitalization for heart failure, major bleeding, and any coronary revascularization. Death was regarded as cardiac in origin unless obvious non-cardiac causes could be identified. Any death during the index hospitalization for AMI was regarded as cardiac death. Cardiovascular death included cardiac death and other vascular death related to stroke, renal disease, and vascular disease. Myocardial infarction was defined according to the Academic Research Consortium definition.[17] Stroke was defined as ischemic or hemorrhagic stroke with neurological symptoms lasting >24 hours. Hospitalization for heart failure was defined as de novo hospitalization or prolongation of hospitalization due to heart failure requiring intravenous treatment. Major bleeding was defined according to the Bleeding Academic Research Consortium classification of type 3 or 5.[18] Any coronary revascularization included either PCI or coronary artery bypass grafting for any reasons. The clinical event committee adjudicated all the events for the outcome measures (Data S2).

Data Collection for Baseline Characteristics and Follow-Up Events

Baseline clinical, angiographic and procedural data were collected from medical charts or hospital databases according to the pre-specified definitions by the experienced clinical research coordinators from an independent clinical research organization (Research Institute for Production Development, Kyoto, Japan) (Data S3). Follow-up data were collected from the hospital charts and/or by contacting with patients, their relatives or family physicians between January 2018 and December 2019. Median follow-up duration was 5.5 years (interquartile range: 3.6–6.6 years). Complete 1-, 3-, and 5-year follow-up information was obtained in 96.5%, 93.6%, and 83.1% of patients, respectively.

Statistical Analysis

Categorical variables were presented as values and percentages, and were compared using the chi-square test. Continuous variables were presented as mean±SD or median and interquartile range and were compared using the analysis of variance or Kruskal-Wallis test according to their distributions. Cumulative incidences of the outcome measures were estimated with the Kaplan-Meier method, and the differences were assessed with the log-rank test. We also performed a landmark analysis at 30 days to estimate the cumulative incidence of the outcome measures within or beyond 30 days after index PCI for AMI. The cumulative incidence of a given event beyond 30 days was estimated by the Kaplan-Meier method among patients who were free from the event at 30 days. The effects of the newly diagnosed AF group and the prior AF group relative to the no AF group for the outcome measures were estimated by the Cox proportional hazard models and were expressed as hazard ratios (HRs) and their 95% CIs. In the multivariable Cox proportional hazard models in the entire follow-up period, we incorporated dummy-coded AF status together with the 28 clinically relevant risk-adjusting

Table 1. Baseline Characteristics

	Newly diagnosed AF (N=489)	Prior AF (N=589)	No AF (N=5150)	*P* value
Baseline characteristics				
Age, y	74.4±11.2	74.8±10.5	68.1±12.3	<0.001
Age ≥75 y*	264 (54%)	339 (58%)	1706 (33%)	<0.001
Men*	343 (70%)	403 (68%)	3927 (76%)	<0.001
Body mass index, kg/m^2	23.2±3.4	23.1±3.8	23.8±3.6	<0.001
Body mass index <25.0 kg/m^2*	360 (74%)	441 (75%)	3483 (68%)	<0.001
Hypertension*	379 (78%)	478 (81%)	4184 (81%)	0.13
Diabetes*	201 (41%)	209 (36%)	1840 (36%)	0.06
Treated with insulin	35 (7.2%)	49 (8.3%)	303 (5.9%)	0.045
Current smoking*	126 (26%)	135 (23%)	1865 (36%)	<0.001
Heart failure (prior and/or current)*	255 (52%)	303 (51%)	1459 (28%)	<0.001
Left ventricular ejection fraction (%)	47.9±13.7	51.3±13.8	55.4±12.2	<0.001
Left ventricular ejection fraction ≤40%	120 (27%)	113 (22%)	517 (11%)	<0.001
Mitral regurgitation grade 3/4	75 (17%)	110 (21%)	360 (7.6%)	<0.001
Prior myocardial infarction*	45 (11%)	92 (16%)	522 (10%)	<0.001
Prior stroke*	77 (16%)	151 (26%)	512 (9.9%)	<0.001
Prior ischemic stroke	67 (14%)	131 (22%)	406 (7.9%)	<0.001
Prior hemorrhagic stroke	12 (2.5%)	22 (3.7%)	112 (2.2%)	0.059
Peripheral vascular disease*	25 (5.1%)	45 (7.6%)	237 (4.6%)	0.005
eGFR <30 mL/min per 1.73 m^2 not on dialysis*	58 (12%)	64 (11%)	279 (5.4%)	<0.001
Dialysis*	14 (2.9%)	34 (5.8%)	175 (3.4%)	0.009
Prior gastrointestinal bleeding	13 (2.7%)	39 (6.6%)	144 (2.8%)	<0.001
Chronic obstructive pulmonary disease*	22 (4.5%)	39 (6.6%)	176 (3.4%)	<0.001
Malignancy*	54 (11%)	80 (14%)	556 (11%)	0.12
Liver cirrhosis*	9 (1.8%)	18 (3.1%)	107 (1.8%)	0.27
Anemia* (hemoglobin <11 g/dL)	85 (17%)	101 (17%)	580 (11%)	<0.001
Thrombocytopenia* (platelet <10^6/μL)	15 (3.1%)	20 (3.4%)	101 (2.0%)	0.03
White blood cell counts, /μL	10 859±4212	9405±3594	9827±3592	<0.001
$CHADS_2$ score	2.6±1.3	2.8±1.4	2.0±1.2	<0.001
$CHADS_2$ score ≥1	476 (97%)	569 (97%)	4786 (93%)	<0.001
CHA_2DS_2-Vasc score	3.9±1.7	4.2±1.8	3.0±1.7	<0.001
CHA_2DS_2-Vasc score ≥2	455 (93%)	542 (92%)	4103 (80%)	<0.001
ARC-HBR	349 (71%)	487 (83%)	2161 (42%)	<0.001
Presentation, angiographic, and procedural characteristics				
STEMI†	400 (82%)	410 (70%)	3815 (74%)	<0.001
Cardiogenic shock (Killip IV)*	145 (30%)	144 (25%)	632 (12%)	<0.001
Cardiopulmonary arrest on arrival	34 (7.0%)	33 (5.6%)	183 (3.6%)	<0.001
Intra-aortic balloon pump use	175 (36%)	127 (22%)	821 (16%)	<0.001
Percutaneous cardiopulmonary support use	34 (7.0%)	28 (4.8%)	130 (2.5%)	<0.001
Peak creatine kinase, U/L	2580 (1106–4785)	1240 (437–2871)	1336 (439–3037)	<0.001
Infarct related artery location				<0.001
Left anterior descending artery	205 (42%)	232 (39%)	2324 (45%)	
Left circumflex artery	76 (16%)	94 (16%)	731 (14%)	
Right coronary artery	167 (34%)	232 (39%)	1919 (37%)	
Left main coronary artery	38 (7.8%)	23 (3.9%)	152 (3.0%)	
Coronary artery bypass graft	3 (0.6%)	8 (1.4%)	24 (0.5%)	
Anterior wall infarction*	243 (50%)	257 (44%)	2484 (48%)	0.35

(*Continued*)

Table 1. Continued

	Newly diagnosed AF (N=489)	Prior AF (N=589)	No AF (N=5150)	*P* value
Multivessel disease*	320 (65%)	322 (55%)	2909 (57%)	<0.001
Target of proximal left anterior descending artery*	277 (57%)	272 (46%)	2847 (55%)	<0.001
Target of unprotected left main coronary artery*	51 (10%)	29 (4.9%)	244 (4.7%)	<0.001
Medication at discharge				
Aspirin	482 (99%)	565 (96%)	5074 (99%)	<0.001
Thienopyridine	469 (96%)	546 (93%)	5032 (98%)	<0.001
Oral anticoagulation	139 (28%)	322 (55%)	326 (6.3%)	<0.001
Warfarin	115 (24%)	275 (47%)	317 (6.2%)	<0.001
DOAC	25 (5.1%)	47 (8.0%)	9 (0.2%)	<0.001
Statins*	361 (74%)	420 (71%)	4346 (84%)	<0.001
β-blocker*	260 (53%)	329 (56%)	2650 (52%)	0.11
ACEI or ARB*	313 (64%)	370 (63%)	3959 (77%)	<0.001
ACEI	177 (36%)	167 (28%)	2065 (40%)	<0.001
ARB	138 (28%)	209 (35%)	1939 (38%)	<0.001
Nitrate	81 (17%)	108 (18%)	986 (19%)	0.36
Calcium channel blocker*	101 (21%)	168 (29%)	1259 (25%)	0.01
Proton pump inhibitor or Histamine 2 blocker*	419 (86%)	496 (84%)	4350 (85%)	0.76

Continuous variables were expressed as mean±SD, or median (interquartile range). Categorical variables were expressed as number (percentage). Values are missing for body mass index in 146 patients, for left ventricular ejection fraction in 649 patients, for mitral regurgitation in 505 patients, eGFR in 15 patients, for hemoglobin level in 13 patients, for platelet count in 19 patients, for white blood cell counts in 20 patients, and for peak creatine kinase in 83 patients. ACEI indicates angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; ARC-HBR, The Academic Research Consortium for High Bleeding Risk; CABG, coronary artery bypass grafting; DOAC, direct oral anticoagulants; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; and STEMI, ST-segment elevation myocardial infarction.

*Risk-adjusting variables selected for the Cox proportional hazard models.

†Risk-adjusting variable as the stratification variable for the Cox proportional hazard models.

variables listed in Table 1 without model selection procedures in consistent with our previous report.[19] Continuous risk-adjusting variables were dichotomized by clinically meaningful reference values to make proportional hazard assumptions robust and to be consistent with our previous reports.[20,21] The missing values for the risk-adjusting variables were imputed as "normal" in the binary classification, because data should have been available if abnormalities were suspected. Proportional hazard assumptions for the primary variable (newly diagnosed AF, prior AF, and no AF) and the risk-adjusting variables were assessed on the plots of log (time) versus log [–log (survival)] stratified by the variable. The assumptions were verified to be acceptable for all the variables except for ST-segment–elevation myocardial infarction, which was included as the stratification variable in the Cox proportional hazard models. We did not construct the multivariable models for the landmark analyses, because the number of patients with events was too small to construct the models within 30 days, and the multivariable models beyond 30 days were similar to those in the entire follow-up period.

Statistical analyses were conducted with JMP 14.0 software (SAS Institute, Inc., Cary, North California) and R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria). All statistical analyses were 2-tailed, and the threshold of *P* values for significance was *P*<0.05.

RESULTS

Baseline Characteristics

Among 6228 AMI patients who received PCI, there were 489 patients (7.9%) with newly diagnosed AF, 589 patients (9.5%) with prior AF, and 5150 patients (82.7%) with no AF (Figure 1).

Patients with newly diagnosed AF and prior AF had similar baseline characteristics, who had significantly higher risk profile than those with no AF including older age and higher prevalence of comorbidities (Table 1). The mean CHA_2DS_2-Vasc score was significantly higher in newly diagnosed AF and prior AF than in no AF (3.9±1.7, 4.2±1.8, and 3.0±1.7), although majority of patients in all the 3 groups had high thrombotic risk score (CHA_2DS_2-Vasc score ≥2: 93% in newly diagnosed AF, 92% in prior AF, and 80% in no AF). Patients with newly diagnosed and prior AF also had higher prevalence of high bleeding risk than patients with no AF (Academic Research Consortium for High Bleeding Risk: 71% in newly diagnosed AF, 83% in prior AF, and 42% in no AF) (Table 1).

Regarding the clinical presentation, angiographic characteristics, and procedural characteristics, patients with newly diagnosed AF had larger infarct size as indicated by the lower left ventricular ejection fraction, and higher peak creatine kinase level, and had higher risk features with greater prevalence of ST-segment–elevation myocardial infarction, cardiogenic shock, and use of hemodynamic support devise than those with prior AF and no AF.

Despite their high thrombotic risk, only 28% of patients in newly diagnosed AF and 55% of those in prior AF had received anticoagulation therapy at hospital discharge from the index hospitalization. Dual antiplatelet therapy had been implemented in the vast majority of patients. The prescription rate of β-blocker was not different regardless of AF, while other evidence based medications such as statins and angiotensin converting enzyme inhibitors/angiotensin II receptor blockers were less often prescribed in patients with newly diagnosed AF and prior AF than in those with no AF (Table 1).

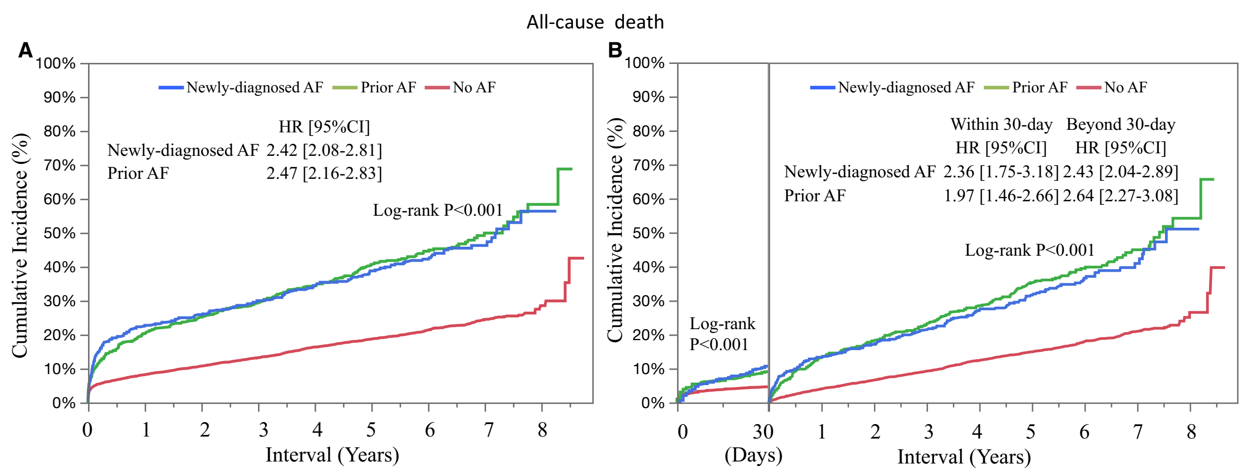
Clinical Outcomes

During median follow-up of 5.5 (3.6–6.6) years, the cumulative 5-year incidence of all-cause death was 38.8% in newly diagnosed AF, 40.7% in prior AF, and 18.7% in no AF (Log-rank *P*<0.001) (Figure 2). The cumulative incidence of all-cause death was consistently higher in newly diagnosed AF and prior AF than in no AF both within and beyond 30 days after index AMI (Figure 2 and Tables S1, S2). Even after adjusting for confounders, the higher HRs of newly diagnosed AF and prior AF relative to no AF remained significant for all-cause death with similar magnitude of HRs in newly diagnosed AF and prior AF (HR: 1.31, 95% CI: 1.12–1.54, *P*<0.001, and HR: 1.32, 95% CI: 1.14–1.52, *P*<0.001, respectively) (Table 2). Findings were consistent for cardiovascular death (Table 2, Figure 3, Figure S1, and Tables S1, S2).

Regarding hospitalization for heart failure, the cumulative 5-year incidence was 19.9% in newly diagnosed AF, 28.0% in prior AF, and 8.0% in no AF (Log-rank *P*<0.001) (Figure 3). After adjusting for confounders, the higher HRs of newly diagnosed AF and prior AF relative to no AF for hospitalization for heart failure remained significant (HR: 1.73, 95% CI: 1.35–2.22, *P*<0.001, and HR: 2.23, 95% CI: 1.82–2.74, *P*<0.001, respectively) (Table 2, Figure 3).

For myocardial infarction, there was no significantly higher adjusted HRs of newly diagnosed AF and prior AF relative to no AF (Table 2, Figure 3). For any coronary revascularization, the lower adjusted HR of prior AF relative to no AF was significant, while the lower adjusted HR of newly diagnosed AF relative to no AF was not significant (Table 2, Figure 3).

The cumulative 5-year incidence of stroke decreased in the order of newly diagnosed AF, prior AF



Interval	0 day	30 days	1 year	3 years	5 years
Newly-diagnosed AF group					
N of patients with event		53	108	141	177
N of patients at risk	489	434	352	303	227
Cumulative incidence		10.9%	22.5%	30.0%	38.8%
Prior AF group					
N of patients with event		53	117	167	224
N of patients at risk	589	526	444	376	273
Cumulative incidence		9.0%	20.3%	29.4%	40.7%
No AF group					
N of patients with event		239	417	663	916
N of patients at risk	5150	4860	4573	4179	3359
Cumulative incidence		4.7%	8.2%	13.2%	18.7%

Interval	0 day	30 days	1 year	3 years	5 years
Newly-diagnosed AF group					
N of patients with event		53	56	88	124
N of patients at risk	489	434	352	303	227
Cumulative incidence		10.9%	13.3%	21.5%	31.3%
Prior AF group					
N of patients with event		53	64	114	171
N of patients at risk	589	526	444	376	273
Cumulative incidence		9.0%	12.4%	22.4%	34.8%
No AF group					
N of patients with event		239	178	424	677
N of patients at risk	5150	4860	4573	4179	3359
Cumulative incidence		4.7%	3.7%	9.0%	14.7%

Figure 2. Kaplan-Meier event curves for all-cause death.
A, During the entire follow-up period, and (**B**) Landmark analysis at 30-day. Crude HRs and 95% CIs were indicated with reference to no AF. AF indicates atrial fibrillation; and HR, hazard ratio.

and no AF (15.5%, 12.9%, and 6.3%, respectively, Log-rank *P*<0.001) (Figure 4 and Figures S2, S3). Relative to no AF, long-term risk of stroke in newly diagnosed AF (HR: 2.05, 95% CI: 1.56–2.69, *P*<0.001) was numerically greater than that in prior AF (HR: 1.33, 95% CI: 1.00–1.78, *P*=0.048) (Table 2). The cumulative incidence of stroke at 30 days was much higher in newly diagnosed AF than in prior AF and no AF (4.5%, 1.8%, and 1.5% respectively, Log-rank *P*<0.001) (Figure 4 and Table S1). Beyond 30 days, the cumulative incidences of stroke in newly diagnosed AF and prior AF were comparable, and much higher than that in no AF (Figure 4 and Table S2).

The cumulative 5-year incidences of major bleeding were significantly higher in newly diagnosed AF and prior AF than in no AF (35.9%, 34.0%, and 19.4%, respectively, Log-rank *P*<0.001) (Figure 4). The higher adjusted HRs of newly diagnosed AF and prior AF relative to no AF remained significant for major bleeding (HR: 1.46, 95% CI: 1.23–1.73, *P*<0.001, and HR: 1.36, 95% CI: 1.15–1.60, *P*<0.001, respectively) (Table 2). Within 30 days, the cumulative incidence of major bleeding was higher in newly diagnosed AF than in prior AF, while beyond 30 days, it was higher in prior AF than in newly diagnosed AF (Figure 4 and Tables S1, S2).

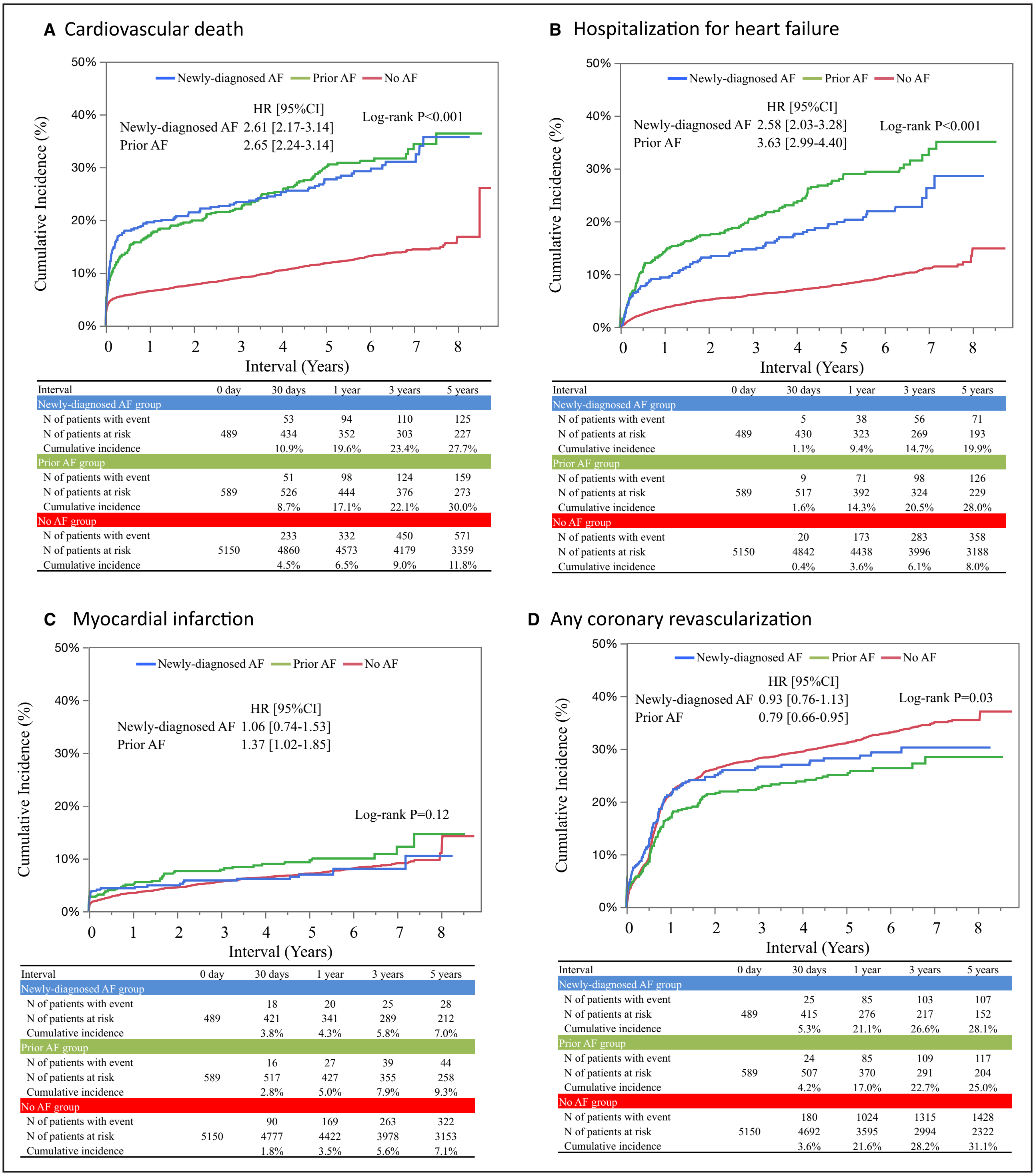
DISCUSSION

The main findings of the present study were as follows; (1) Newly diagnosed AF was found in 7.9% of patients during index hospitalization in AMI patients who underwent PCI; (2) Newly diagnosed AF had risks for mortality, heart failure hospitalization, and major bleeding higher than no AF, and comparable to prior AF; (3) The risk of newly diagnosed AF for stroke might be higher than that of prior AF; (4) Only less than one-third of patients with newly diagnosed AF had received anticoagulation therapy at discharge from index hospitalization, although most of the patients had CHA_2DS_2-Vasc score ≥2.

Table 2. Clinical Outcomes

End points	Rhythm	N of patients with event (cumulative 5-y incidence)		Unadjusted HR [95% CI]	*P* value	Adjusted HR [95% CI]	*P* value
All-cause death	Newly diagnosed AF	202	(38.8%)	2.42 [2.08–2.81]	<0.001	1.31 [1.12–1.54]	<0.001
	Prior AF	255	(40.7%)	2.47 [2.16–2.83]	<0.001	1.32 [1.14–1.52]	<0.001
	No AF	1080	(18.7%)	Reference		Reference	
Cardiovascular death	Newly diagnosed AF	135	(27.7%)	2.61 [2.17–3.14]	<0.001	1.29 [1.06–1.57]	0.01
	Prior AF	168	(30.0%)	2.65 [2.24–3.14]	<0.001	1.34 [1.12–1.60]	0.001
	No AF	640	(11.8%)	Reference		Reference	
Myocardial infarction	Newly diagnosed AF	31	(7.0%)	1.06 [0.74–1.53]	0.74	1.01 [0.70–1.48]	0.94
	Prior AF	49	(9.3%)	1.37 [1.02–1.85]	0.04	1.16 [0.85–1.58]	0.36
	No AF	369	(7.1%)	Reference		Reference	
Stroke	Newly diagnosed AF	60	(15.5%)	2.64 [2.02–3.44]	<0.001	2.05 [1.56–2.69]	<0.001
	Prior AF	56	(12.9%)	1.93 [1.47–2.54]	<0.001	1.33 [1.00–1.78]	0.048
	No AF	284	(6.3%)	Reference		Reference	
Ischemic stroke	Newly diagnosed AF	50	(12.7%)	2.61 [1.93–3.54]	<0.001	1.95 [1.42–2.68]	<0.001
	Prior AF	51	(10.8%)	2.13 [1.58–2.89]	<0.001	1.45 [1.06–1.99]	0.02
	No AF	251	(4.7%)	Reference		Reference	
Hemorrhagic stroke	Newly diagnosed AF	17	(3.2%)	2.37 [1.42–3.97]	0.001	2.08 [1.22–3.54]	0.007
	Prior AF	11	(2.5%)	1.23 [0.66–2.29]	0.52	0.90 [0.47–1.71]	0.74
	No AF	97	(1.9%)	Reference		Reference	
Hospitalization for heart failure	Newly diagnosed AF	79	(19.9%)	2.58 [2.03–3.28]	<0.001	1.73 [1.35–2.22]	<0.001
	Prior AF	136	(28.0%)	3.63 [2.99–4.40]	<0.001	2.23 [1.82–2.74]	<0.001
	No AF	431	(8.0%)	Reference		Reference	
Major bleeding	Newly diagnosed AF	323	(35.9%)	2.14 [1.81–2.52]	<0.001	1.46 [1.23–1.73]	<0.001
	Prior AF	189	(34.0%)	1.93 [1.65–2.26]	<0.001	1.36 [1.15–1.60]	<0.001
	No AF	1010	(19.4%)	Reference		Reference	
Any coronary revascularization	Newly diagnosed AF	110	(28.1%)	0.93 [0.76–1.13]	0.44	0.89 [0.73–1.09]	0.27
	Prior AF	122	(25.0%)	0.79 [0.66–0.95]	0.01	0.77 [0.63–0.93]	0.01
	No AF	1514	(31.1%)	Reference		Reference	

Cumulative incidence was estimated by Kaplan-Meier method, and was represented with that at 5-year. Number of patients with event and HRs with 95% CIs were estimated throughout the entire follow-up period by the Cox proportional hazard models. AF indicates atrial fibrillation; and HR, hazard ratio.



A Cardiovascular death

Interval	0 day	30 days	1 year	3 years	5 years
Newly-diagnosed AF group					
N of patients with event		53	94	110	125
N of patients at risk	489	434	352	303	227
Cumulative incidence		10.9%	19.6%	23.4%	27.7%
Prior AF group					
N of patients with event		51	98	124	159
N of patients at risk	589	526	444	376	273
Cumulative incidence		8.7%	17.1%	22.1%	30.0%
No AF group					
N of patients with event		233	332	450	571
N of patients at risk	5150	4860	4573	4179	3359
Cumulative incidence		4.5%	6.5%	9.0%	11.8%

B Hospitalization for heart failure

Interval	0 day	30 days	1 year	3 years	5 years
Newly-diagnosed AF group					
N of patients with event		5	38	56	71
N of patients at risk	489	430	323	269	193
Cumulative incidence		1.1%	9.4%	14.7%	19.9%
Prior AF group					
N of patients with event		9	71	98	126
N of patients at risk	589	517	392	324	229
Cumulative incidence		1.6%	14.3%	20.5%	28.0%
No AF group					
N of patients with event		20	173	283	358
N of patients at risk	5150	4842	4438	3996	3188
Cumulative incidence		0.4%	3.6%	6.1%	8.0%

C Myocardial infarction

Interval	0 day	30 days	1 year	3 years	5 years
Newly-diagnosed AF group					
N of patients with event		18	20	25	28
N of patients at risk	489	421	341	289	212
Cumulative incidence		3.8%	4.3%	5.8%	7.0%
Prior AF group					
N of patients with event		16	27	39	44
N of patients at risk	589	517	427	355	258
Cumulative incidence		2.8%	5.0%	7.9%	9.3%
No AF group					
N of patients with event		90	169	263	322
N of patients at risk	5150	4777	4422	3978	3153
Cumulative incidence		1.8%	3.5%	5.6%	7.1%

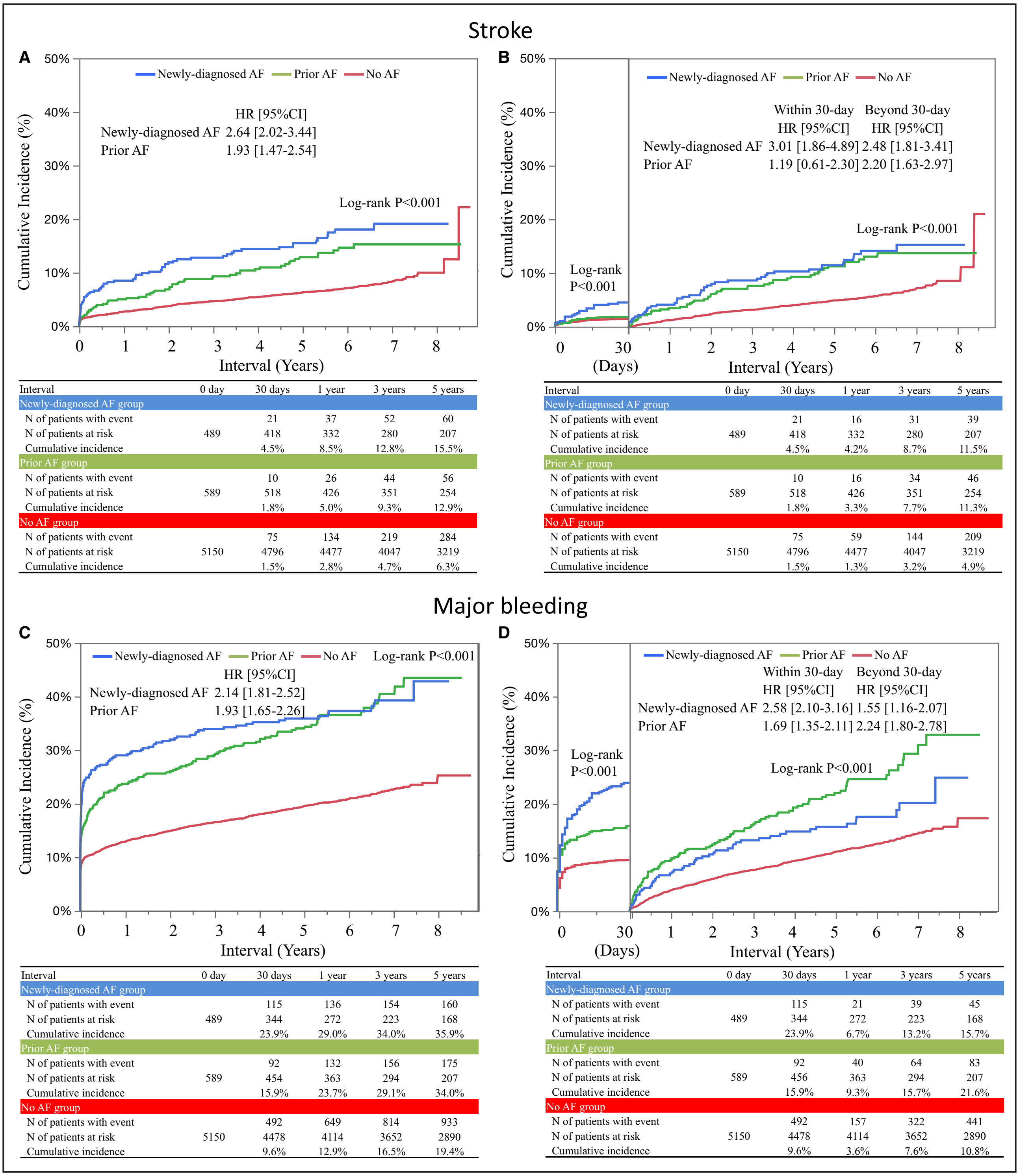
D Any coronary revascularization

Interval	0 day	30 days	1 year	3 years	5 years
Newly-diagnosed AF group					
N of patients with event		25	85	103	107
N of patients at risk	489	415	276	217	152
Cumulative incidence		5.3%	21.1%	26.6%	28.1%
Prior AF group					
N of patients with event		24	85	109	117
N of patients at risk	589	507	370	291	204
Cumulative incidence		4.2%	17.0%	22.7%	25.0%
No AF group					
N of patients with event		180	1024	1315	1428
N of patients at risk	5150	4692	3595	2994	2322
Cumulative incidence		3.6%	21.6%	28.2%	31.1%

Figure 3. Kaplan-Meier event curves for cardiovascular death, hospitalization for heart failure, myocardial infarction, and any coronary revascularization.

A, Cardiovascular death, (**B**) Hospitalization for heart failure, (**C**) Myocardial infarction, and (**D**) Any coronary revascularization. Crude HRs and 95% CIs were indicated with reference to no AF. AF indicates atrial fibrillation; and HR, hazard ratio.

The prevalence of newly diagnosed AF in the acute phase of AMI in the present study (7.9%) was consistent with those reported in previous studies (3.7–10.3%), indicating that newly diagnosed AF during the acute phase of AMI is not rare in daily clinical practice.[8,9,11,12] AF, newly diagnosed AF in particular, had adverse effects on hemodynamics through tachycardia, atrioventricular dyssynchrony, and reduced



A

Interval	0 day	30 days	1 year	3 years	5 years
Newly-diagnosed AF group					
N of patients with event		21	37	52	60
N of patients at risk	489	418	332	280	207
Cumulative incidence		4.5%	8.5%	12.8%	15.5%
Prior AF group					
N of patients with event		10	26	44	56
N of patients at risk	589	518	426	351	254
Cumulative incidence		1.8%	5.0%	9.3%	12.9%
No AF group					
N of patients with event		75	134	219	284
N of patients at risk	5150	4796	4477	4047	3219
Cumulative incidence		1.5%	2.8%	4.7%	6.3%

B

Interval	0 day	30 days	1 year	3 years	5 years
Newly-diagnosed AF group					
N of patients with event		21	16	31	39
N of patients at risk	489	418	332	280	207
Cumulative incidence		4.5%	4.2%	8.7%	11.5%
Prior AF group					
N of patients with event		10	16	34	46
N of patients at risk	589	518	426	351	254
Cumulative incidence		1.8%	3.3%	7.7%	11.3%
No AF group					
N of patients with event		75	59	144	209
N of patients at risk	5150	4796	4477	4047	3219
Cumulative incidence		1.5%	1.3%	3.2%	4.9%

C

Interval	0 day	30 days	1 year	3 years	5 years
Newly-diagnosed AF group					
N of patients with event		115	136	154	160
N of patients at risk	489	344	272	223	168
Cumulative incidence		23.9%	29.0%	34.0%	35.9%
Prior AF group					
N of patients with event		92	132	156	175
N of patients at risk	589	454	363	294	207
Cumulative incidence		15.9%	23.7%	29.1%	34.0%
No AF group					
N of patients with event		492	649	814	933
N of patients at risk	5150	4478	4114	3652	2890
Cumulative incidence		9.6%	12.9%	16.5%	19.4%

D

Interval	0 day	30 days	1 year	3 years	5 years
Newly-diagnosed AF group					
N of patients with event		115	21	39	45
N of patients at risk	489	344	272	223	168
Cumulative incidence		23.9%	6.7%	13.2%	15.7%
Prior AF group					
N of patients with event		92	40	64	83
N of patients at risk	589	456	363	294	207
Cumulative incidence		15.9%	9.3%	15.7%	21.6%
No AF group					
N of patients with event		492	157	322	441
N of patients at risk	5150	4478	4114	3652	2890
Cumulative incidence		9.6%	3.6%	7.6%	10.8%

Figure 4. Kaplan-Meier event curves for stroke and major bleeding.
A, Stroke during the entire follow-up period, (**B**) Landmark analysis at 30-day for stroke, (**C**) Major bleeding during the entire follow-up period, and (**D**) Landmark analysis at 30-day for major bleeding. Crude HRs and 95% CIs were indicated with reference to no AF. AF indicates atrial fibrillation; and HR, hazard ratio.

cardiac output.[1,4,22] Indeed, the prevalence of cardiogenic shock, and use of hemodynamic support devises was higher in patients with AF, newly diagnosed AF in particular, than in patients without AF. Thus, AF would trigger hemodynamic compromise, while hemodynamic compromise might beget AF.[2] The previous reports indicated that AMI induces AF through inflammation, catecholamine drive, and necrosis, and therefore, hemodynamic compromise in AMI might be important for the development of AF.[12,22]

Patients with AF were older and more often had comorbidities than patients without AF. Therefore, it has been well known that AF coexisting with AMI was associated with higher risk of acute and long-term mortality than no AF.[4,5] However, it remains controversial whether long-term clinical impact of newly diagnosed AF during acute phase of AMI, which is often self-limited and transient, is different from prior AF diagnosed before the onset of AMI.[7–12] In this study including a large number of AMI patients who received coronary revascularization, patients with newly diagnosed AF had long-term risks of mortality, heart failure hospitalization, and major bleeding comparable to those with prior AF, which were much higher than that in those without AF. One of the reasons for this poor prognosis of newly diagnosed AF might be partly explained by the relatively large infarct size, and hemodynamic instability in those patients. Another reason might be that patients with newly diagnosed AF and prior AF had similar baseline characteristics with high thrombotic and bleeding risk features. On the other hand, the risk for any coronary revascularization was not higher in patients with newly diagnosed AF and significantly lower in those with prior AF as compared with that in those without AF. The reason for this unexpected finding was unclear. However, one of the possible explanations might be related to the higher prevalence of elderly patients in both AF groups than in the no AF group. It would be likely that attending physicians tended to avoid coronary revascularization in older patients with many comorbidities due to high procedural risk.

In this study, both newly diagnosed AF and prior AF were associated with significantly higher risk for stroke than no AF. In the recent American Heart Association/American College of Cardiology/Heart Rhythm Society clinical guidelines for AF, anticoagulation is recommended as class I indication for patient with acute coronary syndrome and AF with CHA_2DS_2-Vasc score ≥2.[14] It is based on 3 randomized controlled trials that demonstrated a lower risk of bleeding events with a comparable risk of cardiovascular events with dual therapy with $P2Y_{12}$ receptor blocker and anticoagulant as compared with triple antithrombotic therapy.[23–25] However, these trials included only patients with prior AF. For patients with newly diagnosed AF during the acute phase of AMI, European Society of Cardiology clinical guidelines for ST-segment–elevation myocardial infarction also recommend anticoagulation as class IIa indication, if CHA_2DS_2-Vasc score ≥2,[15] although the recommendation was based on relatively old studies in which primary PCI was not prevalent.[1,3] Despite the guideline recommendation, anticoagulation was not widely implemented in real-world clinical practice.[7,12,26] Indeed, in the present study, only less than one-third of patients with newly diagnosed AF had received anticoagulation therapy, although most of the patients had CHA_2DS_2-Vasc score ≥2. A previous study from the SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies) registry reported that patients with newly diagnosed AF who resumed sinus rhythm at discharge still had substantially higher risk of stroke than patients without AF, although they had lower risk of stroke than those with newly diagnosed AF who had AF at discharge.[11] In the present study, patient characteristics and long-term risk of stroke were similar in patients with newly diagnosed and prior AF. Therefore, it would be reasonable to implement anticoagulation therapy in patients with newly diagnosed AF if CHA_2DS_2-Vasc score ≥2 as recommended in the European Society of Cardiology guidelines.[15] In the present study, long-term risk of stroke in newly diagnosed AF was numerically greater than that in prior AF. The higher stroke risk of newly diagnosed AF compared with prior AF was largely driven by the greater risk within 30 days of AMI. We might have to consider implementing anticoagulation therapy as soon as AF is newly detected. However, in the acute phase of AMI, the risk of major bleeding was also very high in newly diagnosed AF patients. Dual therapy with $P2Y_{12}$ receptor blocker and reduced dose of direct oral anticoagulant might be a reasonable option, but further investigations are obviously needed to define optimal antithrombotic therapy in this setting.

Limitations

Several limitations of this study should be considered. First, due to the retrospective and observational study design, there might be unmeasured confounders for estimating the long-term risk of cardiovascular events, although we attempted an extensive multivariable adjustment. Second, the diagnosis of AF was based on the physicians' diagnosis and records in the hospital charts. Therefore, very short duration of AF could have been overlooked, or newly diagnosed AF could actually have been undiagnosed paroxysmal AF before the onset of AMI. Third, ECGs were not evaluated at discharge or during follow-up. We did not know how many patients with newly diagnosed AF resumed sinus rhythm, which was reported to be associated with lower risk,[27,28] and how many patients with no AF or newly diagnosed AF with sinus rhythm at discharge developed AF after discharge. Fourth, the definition of stroke included not only cardiogenic cerebral infarction derived from AF, but also other types of stroke such as atherosclerotic ischemic stroke, lacunar stroke, and cardiogenic stroke due to thrombus in the left ventricle. Additionally, in some patients with stroke that developed during hospitalization, AF could occur after the onset of stroke because of sympathetic nerve activation or hypovolemia induced by stroke. Finally, the low prevalence of anticoagulation might be attributed to the study period of 2011 to 2013, when the use of direct oral anticoagulant and dual therapy with $P2Y_{12}$ receptor blocker and direct oral anticoagulant were not common for patients with AF undergoing PCI.

CONCLUSIONS

Newly diagnosed AF in AMI had risks for mortality, heart failure hospitalization, and major bleeding higher than no AF, and comparable to prior AF. The risk of newly diagnosed AF for stroke might be higher than that of prior AF.

ARTICLE INFORMATION

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Dr Shiomi reports personal fees from Boston Scientific, personal fees from Abbot Vascular, and personal fees from Daiichi Sankyo. Dr Morimoto reports modest honoraria from Bayer and Kowa, and modest expert witness from Boston Scientific and Sanofi. Dr Tamura reports personal fees from Daiichi Sankyo and personal fees from Bayer. Dr Furukawa reports personal fees from Daiichi Sankyo, personal fees from Bayer, personal fees from Bristol Myers Squibb, personal fees from Pfizer, and personal fees from Boehringer Ingelheim. Dr Nakagawa reports modest research grant from Abbott Vascular and Boston Scientific, and modest honoraria from Abbott Vascular, Bayer, and Boston Scientific. Dr Kimura reports significant honoraria from Abbott Vascular, and modest honoraria from Astellas, AstraZeneca, Bayer, Boston Scientific, Kowa, and Sanofi. The remaining authors have no disclosures to report.

Supplementary Material

Datas S1–S3
Tables S1–S2
Figures S1–S3

REFERENCES

1. 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. doi: 10.1093/eurheartj/ehn579
2. Vermond RA, Van Gelder IC, Crijns HJ, Rienstra M. Does myocardial infarction beget atrial fibrillation and atrial fibrillation beget myocardial infarction? *Circulation*. 2015;131:1824–1826. doi: 10.1161/CIRCULATIONAHA.115.016595
3. Siu CW, Jim MH, Ho HH, Miu R, Lee SWL, Lau CP, Tse HF. Transient atrial fibrillation complicating acute inferior myocardial infarction: implications for future risk of ischemic stroke. *Chest*. 2007;132:44–49. doi: 10.1378/chest.06-2733
4. Jabre P, Roger VL, Murad MH, Chamberlain AM, Prokop L, Adnet F, Jouven X. Mortality associated with atrial fibrillation in patients with myocardial infarction: a systematic review and meta-analysis. *Circulation*. 2011;123:1587–1593. doi: 10.1161/CIRCULATIONAHA.110.986661
5. Garg L, Agrawal S, Agarwal M, Shah M, Garg A, Patel B, Agarwal N, Nanda S, Sharma A, Cox D. Influence of atrial fibrillation on outcomes in patients who underwent primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *Am J Cardiol*. 2018;121:684–689. doi: 10.1016/j.amjcard.2017.12.003
6. Luo J, Xu S, Li H, Li Z, Liu B, Qin X, Gong M, Shi B, Wei Y. Long-term impact of new-onset atrial fibrillation complicating acute myocardial infarction on heart failure. *ESC Heart Fail*. 2020;7:2762–2772. doi: 10.1002/ehf2.12872
7. Zeymer U, Annemans L, Danchin N, Pocock S, Newsome S, Van de Werf F, Medina J, Bueno H. Impact of known or new-onset atrial fibrillation on 2-year cardiovascular event rate in patients with acute coronary syndromes: results from the prospective EPICOR Registry. *Eur Heart J Acute Cardiovasc Care*. 2019;8:121–129. doi: 10.1177/2048872618769057
8. Jabre P, Jouven X, Adnet F, Thabut G, Bielinski SJ, Weston SA, Roger VL. Atrial fibrillation and death after myocardial infarction: a community study. *Circulation*. 2011;123:2094–2100. doi: 10.1161/CIRCULATIONAHA.110.990192
9. Wang C-L, Chen P-C, Juang H-T, Chang C-J. Adverse outcomes associated with pre-existing and new-onset atrial fibrillation in patients with acute coronary syndrome: a retrospective cohort study. *Cardiol Ther*. 2019;8:117–127. doi: 10.1007/s40119-019-0136-3
10. Biasco L, Radovanovic D, Moccetti M, Rickli H, Roffi M, Eberli F, Jeger R, Moccetti T, Erne P, Pedrazzini G. New-onset or pre-existing atrial fibrillation in acute coronary syndromes: two distinct phenomena with a similar prognosis. *Rev Esp Cardiol*. 2019;72:383–391. doi: 10.1016/j.rec.2018.03.002
11. Batra G, Svennblad B, Held C, Jernberg T, Johanson P, Wallentin L, Oldgren J. All types of atrial fibrillation in the setting of myocardial infarction are associated with impaired outcome. *Heart*. 2016;102:926–933. doi: 10.1136/heartjnl-2015-308678
12. Braga CG, Ramos V, Martins J, Arantes C, Abreu G, Vieira C, Salgado A, Gaspar A, Azevedo P, Álvares Pereira M, et al. Impact of atrial fibrillation type during acute coronary syndromes: clinical features and prognosis. *Rev Port Cardiol*. 2015;34:403–410. doi: 10.1016/j.repc.2015.01.010
13. Dewilde WJM, Janssen PWA, Verheugt FWA, Storey RF, Adriaenssens T, Hansen ML, Lamberts M, Ten Berg JM. Triple therapy for atrial fibrillation and percutaneous coronary intervention: a contemporary review. *J Am Coll Cardiol*. 2014;64:1270–1280. doi: 10.1016/j.jacc.2014.06.1193
14. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*. 2019;140:e125–e151. doi: 10.1016/j.jacc.2019.01.011
15. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2018;39:119–177. doi: 10.1093/eurheartj/ehx393
16. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009;53:982–992. doi: 10.1053/j.ajkd.2008.12.034

17. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, Van Es G-A, Gabriel Steg P, Morel M-angèle, Mauri L, Vranckx P, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115:2344–2351. doi: 10.1161/CIRCULATIONAHA.106.685313
18. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2736–2747. doi: 10.1161/CIRCULATIONAHA.110.009449
19. Goto K, Nakai K, Shizuta S, Morimoto T, Shiomi H, Natsuaki M, Yahata M, Ota C, Ono K, Makiyama T, et al. Anticoagulant and antiplatelet therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention. *Am J Cardiol*. 2014;114:70–78. doi: 10.1016/j.amjcard.2014.03.060
20. Kimura T, Morimoto T, Furukawa Y, Nakagawa Y, Kadota K, Iwabuchi M, Shizuta S, Shiomi H, Tada T, Tazaki J, et al. Long-term safety and efficacy of sirolimus-eluting stents versus bare-metal stents in real world clinical practice in Japan. *Cardiovasc Interv Ther*. 2011;26:234–245. doi: 10.1007/s12928-011-0065-0
21. Kimura T, Morimoto T, Furukawa Y, Nakagawa Y, Shizuta S, Ehara N, Taniguchi R, Doi T, Nishiyama K, Ozasa N, et al. Long-term outcomes of coronary-artery bypass graft surgery versus percutaneous coronary intervention for multivessel coronary artery disease in the bare-metal stent era. *Circulation*. 2008;118:S199–S209. doi: 10.1161/CIRCULATIONAHA.107.735902
22. Fukunami M. Transient atrial fibrillation during acute myocardial infarction is a predictor of poor outcomes. *Circ J*. 2016;80:1534–1536. doi: 10.1253/circj.CJ-16-0529
23. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, Maeng M, Merkely B, Zeymer U, Gropper S, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med*. 2017;377:1513–1524. doi: 10.1056/NEJMoa1708454
24. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Birmingham M, Ianus J, Burton P, Van Eickels M, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med*. 2016;375:2423–2434. doi: 10.1056/NEJMoa1611594
25. Dewilde WJM, Oirbans T, Verheugt FWA, Kelder JC, De Smet BJGL, Herrman J-P, Adriaenssens T, Vrolix M, Heestermans AACM, Vis MM, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet*. 2013;381:1107–1115. doi: 10.1016/S0140-6736(12)62177-1
26. Lopes RD, Li L, Granger CB, Wang TY, Foody JM, Funk M, Peterson ED, Alexander KP. Atrial fibrillation and acute myocardial infarction: antithrombotic therapy and outcomes. *Am J Med*. 2012;125:897–905. doi: 10.1016/j.amjmed.2012.04.006
27. Axelrod M, Gilutz H, Plakht Y, Greenberg D, Novack L. Early atrial fibrillation during acute myocardial infarction may not be an indication for long-term anticoagulation. *Angiology*. 2020;71:559–566. doi: 10.1177/0003319720908760
28. Su KJ, Lin WY, Lin WS, Lin CS, Cheng CC, Liou JT, Ho CH, Yang SP, Cheng SM, Hung Y. Prognostic effect of restoring sinus rhythm in patients with new-onset atrial fibrillation during acute coronary syndrome. *Acta Cardiol Sin*. 2021;37:155–165. doi: 10.6515/ACS.202103_37(2).20200915A

SUPPLEMENTAL MATERIAL

Data S1.

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Data S2.

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Data S3.

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Table S1. Clinical outcomes within 30 days.

Endpoints	Rhythm	N of patients with event (Cumulative 30-day incidence)		Crude HR [95% CI]	P value
All-cause death	Newly-diagnosed AF	53	(10.9%)	2.36 [1.75-3.18]	<0.001
	Prior AF	53	(9.0%)	1.97 [1.46-2.66]	<0.001
	No AF	239	(4.7%)	Reference	
Cardiovascular death	Newly-diagnosed AF	53	(10.9%)	2.42 [1.79-3.26]	<0.001
	Prior AF	51	(8.7%)	1.95 [1.44-2.63]	<0.001
	No AF	233	(4.5%)	Reference	
Myocardial infarction	Newly-diagnosed AF	18	(3.8%)	2.14 [1.29-3.54]	0.003
	Prior AF	16	(2.8%)	1.59 [0.93-2.71]	0.09
	No AF	90	(1.8%)	Reference	
Stroke	Newly-diagnosed AF	21	(4.5%)	3.01 [1.86-4.89]	<0.001
	Prior AF	10	(1.8%)	1.19 [0.61-2.30]	0.61
	No AF	75	(1.5%)	Reference	
Ischemic stroke	Newly-diagnosed AF	18	(3.8%)	3.07 [1.82-5.19]	<0.001
	Prior AF	10	(1.8%)	1.42 [0.73-2.76]	0.31
	No AF	63	(1.3%)	Reference	
Hemorrhagic stroke	Newly-diagnosed AF	3	(0.7%)	2.66 [0.75-9.44]	0.13
	Prior AF	0	(0.0%)	N/A	N/A
	No AF	12	(0.2%)	Reference	
Hospitalization for heart failure	Newly-diagnosed AF	5	(1.1%)	2.72 [1.02-7.25]	0.045

	Prior AF	9	(1.6%)	4.08 [1.86-8.97]	0.001
	No AF	20	(0.4%)	Reference	
Major bleeding	Newly-diagnosed AF	115	(23.9%)	2.58 [2.10-3.16]	<0.001
	Prior AF	92	(15.9%)	1.69 [1.35-2.11]	<0.001
	No AF	492	(9.6%)	Reference	
Any coronary revascularization	Newly-diagnosed AF	25	(5.3%)	1.49 [0.98-2.27]	0.06
	Prior AF	24	(4.2%)	1.20 [0.78-1.83]	0.41
	No AF	180	(3.6%)	Reference	

HR=hazard ratio; CI=confidence interval; AF=atrial fibrillation; N/A: not available

Table S2. Clinical outcomes beyond 30 days.

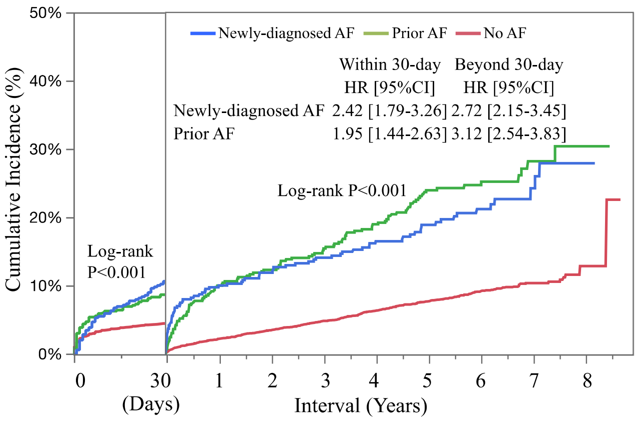
Endpoints	Rhythm	N of patients with event (Cumulative 5-year incidence)		Crude HR [95% CI]	P value
All-cause death	Newly-diagnosed AF	149	(31.3%)	2.43 [2.04-2.89]	<0.001
	Prior AF	202	(34.8%)	2.64 [2.27-3.08]	<0.001
	No AF	841	(14.7%)	Reference	
Cardiovascular death	Newly-diagnosed AF	82	(18.9%)	2.72 [2.15-3.45]	<0.001
	Prior AF	117	(23.4%)	3.12 [2.54-3.83]	<0.001
	No AF	407	(7.6%)	Reference	
Myocardial infarction	Newly-diagnosed AF	13	(3.2%)	0.63 [0.36-1.10]	0.11
	Prior AF	33	(6.7%)	1.29 [0.90-1.85]	0.16
	No AF	279	(5.4%)	Reference	
Stroke	Newly-diagnosed AF	42	(11.5%)	2.48 [1.81-3.41]	<0.001
	Prior AF	46	(11.3%)	2.20 [1.63-2.97]	<0.001
	No AF	221	(4.9%)	Reference	
Ischemic stroke	Newly-diagnosed AF	32	(9.2%)	2.40 [1.65-3.49]	<0.001
	Prior AF	41	(9.2%)	2.43 [1.73-3.41]	<0.001
	No AF	188	(3.5%)	Reference	
Hemorrhagic stroke	Newly-diagnosed AF	14	(2.6%)	2.31 [1.31-4.06]	0.004
	Prior AF	11	(2.5%)	1.44 [0.77-2.70]	0.26
	No AF	85	(1.6%)	Reference	
Hospitalization for heart failure	Newly-diagnosed AF	74	(19.0%)	2.57 [2.01-3.29]	<0.001

	Prior AF	127	(26.8%)	3.60 [2.95-4.39]	<0.001
	No AF	411	(7.6%)	Reference	
Major bleeding	Newly-diagnosed AF	208	(15.7%)	1.55 [1.16-2.07]	0.003
	Prior AF	97	(21.6%)	2.24 [1.80-2.78]	<0.001
	No AF	518	(10.8%)	Reference	
Any coronary revascularization	Newly-diagnosed AF	85	(24.1%)	0.84 [0.67-1.04]	0.11
	Prior AF	98	(21.8%)	0.73 [0.59-0.89]	0.003
	No AF	1334	(28.5%)	Reference	

HR=hazard ratio; CI=confidence interval; AF=atrial fibrillation.

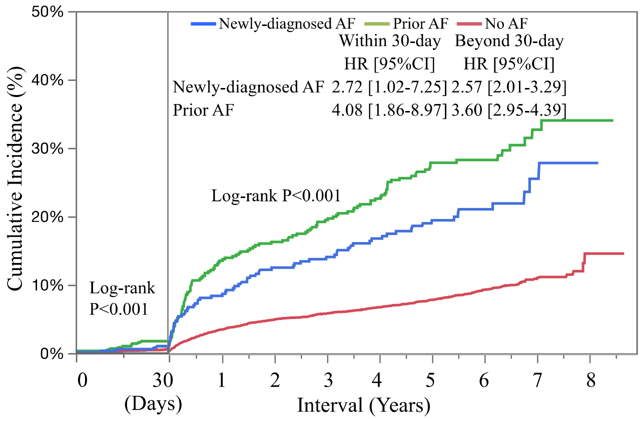
Figure S1. Kaplan-Meier event curves within/beyond 30 days for cardiovascular death, hospitalization for heart failure, myocardial infarction, and any coronary revascularization.

A. Cardiovascular death



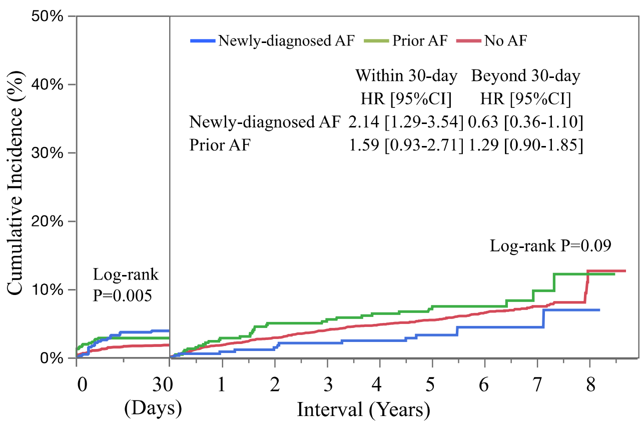
Interval	0 day	30 days	1 year	3 years	5 years
Newly-diagnosed AF group					
N of patients with event		53	41	57	72
N of patients at risk	489	434	352	303	227
Cumulative incidence		10.9%	9.8%	14.1%	18.9%
Prior AF group					
N of patients with event		51	47	73	108
N of patients at risk	589	526	444	376	273
Cumulative incidence		8.7%	9.2%	14.7%	23.4%
No AF group					
N of patients with event		233	99	217	338
N of patients at risk	5150	4860	4573	4179	3359
Cumulative incidence		4.5%	2.1%	4.7%	7.6%

B. Hospitalization for heart failure



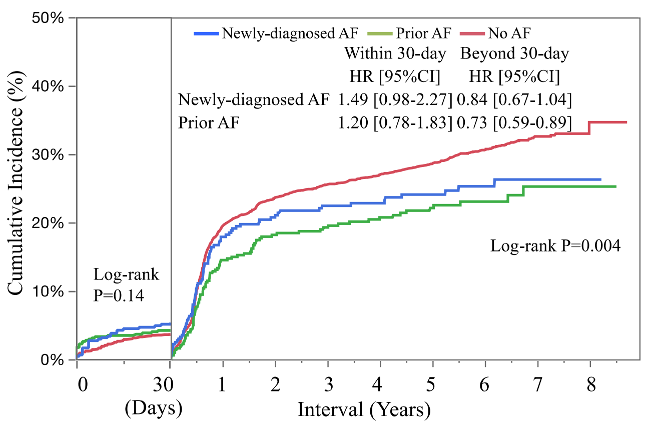
Interval	0 days	30 days	1 year	3 years	5 years
Newly-diagnosed AF group					
N of patients with event		5	33	51	66
N of patients at risk	489	430	323	269	193
Cumulative incidence		1.1%	8.4%	13.8%	19.0%
Prior AF group					
N of patients with event		9	62	89	117
N of patients at risk	589	517	392	324	229
Cumulative incidence		1.6%	12.9%	19.2%	26.8%
No AF group					
N of patients with event		20	153	263	338
N of patients at risk	5150	4842	4438	3996	3188
Cumulative incidence		0.4%	3.3%	5.7%	7.6%

C. Myocardial infarction



Interval	0 days	30 days	1 year	3 years	5 years
Newly-diagnosed AF group					
N of patients with event		18	2	7	10
N of patients at risk	489	421	341	289	212
Cumulative incidence		3.8%	0.5%	2.1%	3.2%
Prior AF group					
N of patients with event		16	11	23	28
N of patients at risk	589	517	427	355	258
Cumulative incidence		2.8%	2.3%	5.2%	6.7%
No AF group					
N of patients with event		90	79	173	232
N of patients at risk	5150	4777	4422	3978	3153
Cumulative incidence		1.8%	1.7%	3.9%	5.4%

D. Any coronary revascularization



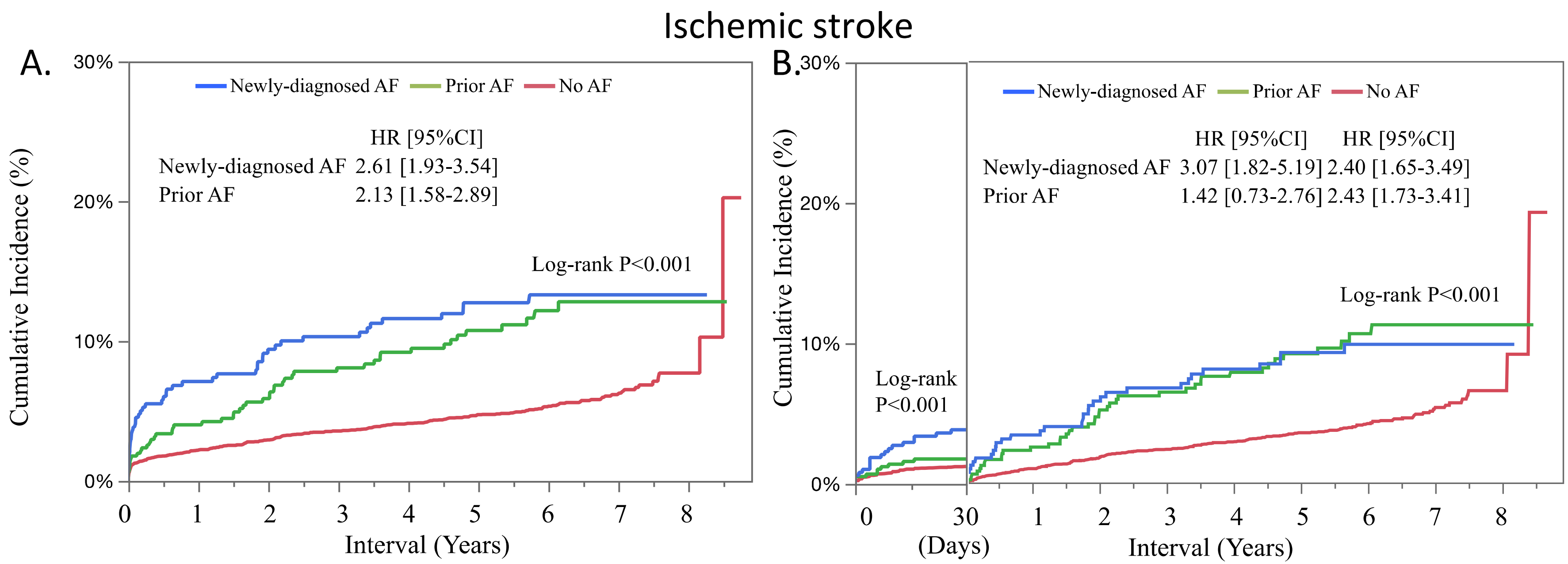
Interval	0 days	30 days	1 year	3 years	5 years
Newly-diagnosed AF group					
N of patients with event		25	60	78	82
N of patients at risk	489	415	276	217	152
Cumulative incidence		5.3%	16.7%	22.5%	24.1%
Prior AF group					
N of patients with event		24	61	85	93
N of patients at risk	589	507	370	291	204
Cumulative incidence		4.2%	13.3%	19.3%	21.8%
No AF group					
N of patients with event		180	844	1135	1248
N of patients at risk	5150	4692	3595	2994	2322
Cumulative incidence		3.6%	18.7%	25.5%	28.5%

(A) Cardiovascular death, (B) Hospitalization for heart failure, (C) Myocardial infarction, and (D) Any coronary revascularization

Crude HRs and 95%CIs were indicated with reference to no AF.

HR=hazard ratio; CI=confidence interval; AF=atrial fibrillation.

Figure S2. Kaplan-Meier event curves for ischemic stroke.



Interval	0 day	30 days	1 year	3 years	5 years
Newly-diagnosed AF group					
N of patients with event		18	31	42	49
N of patients at risk	489	420	336	286	211
Cumulative incidence		3.8%	7.1%	10.3%	12.7%
Prior AF group					
N of patients with event		10	21	38	47
N of patients at risk	589	520	428	352	254
Cumulative incidence		1.8%	4.0%	8.1%	10.8%
No AF group					
N of patients with event		63	108	168	213
N of patients at risk	5150	4804	4492	4071	3247
Cumulative incidence		1.3%	2.2%	3.6%	4.7%

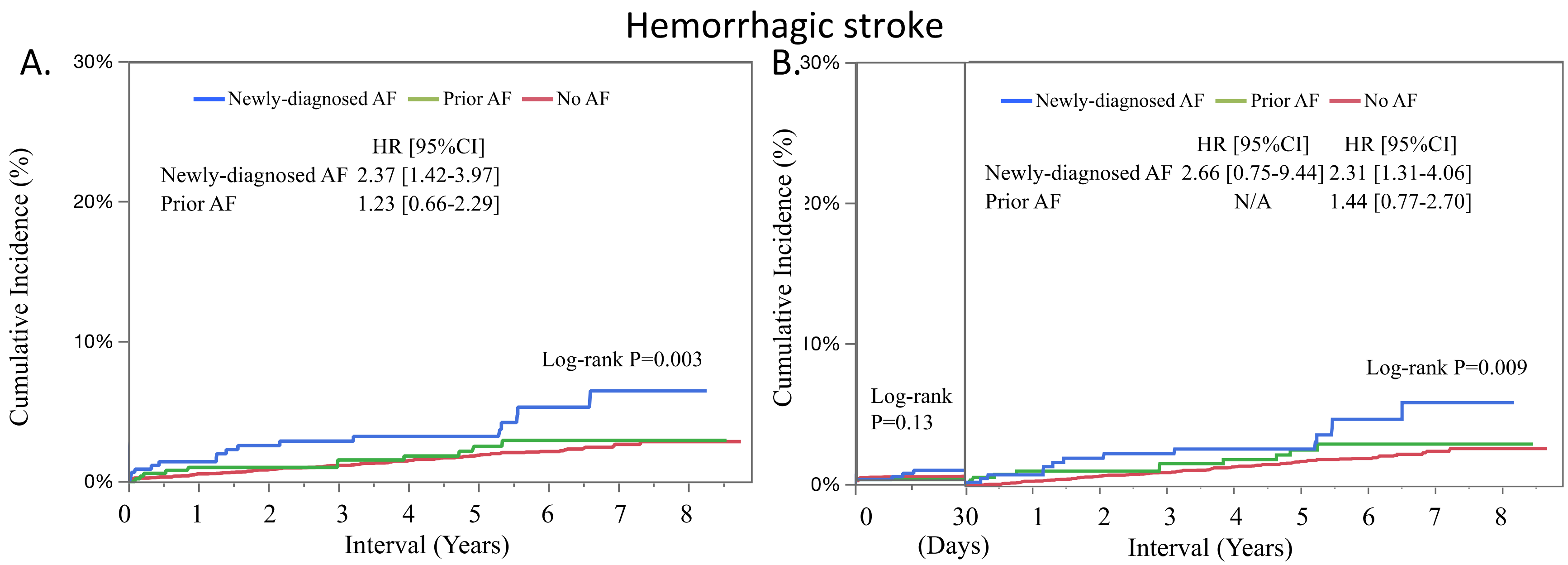
Interval	0 day	30 days	1 year	3 years	5 years
Newly-diagnosed AF group					
N of patients with event		18	13	24	31
N of patients at risk	489	420	336	286	211
Cumulative incidence		3.8%	3.4%	6.7%	9.2%
Prior AF group					
N of patients with event		10	11	28	37
N of patients at risk	589	520	428	352	254
Cumulative incidence		1.8%	2.3%	6.4%	9.2%
No AF group					
N of patients with event		63	45	105	150
N of patients at risk	5150	4804	4492	4071	3247
Cumulative incidence		1.3%	1.0%	2.3%	3.5%

(A) Ischemic stroke during the entire follow-up period, and (B) Landmark analysis at 30-day for ischemic stroke

Crude HRs and 95%CIs were indicated with reference to no AF.

HR=hazard ratio; CI=confidence interval; AF=atrial fibrillation.

Figure S3. Kaplan-Meier event curves for hemorrhagic stroke.



Interval	0 day	30 days	1 year	3 years	5 years
Newly-diagnosed AF group					
N of patients with event		3	6	11	12
N of patients at risk	489	432	347	296	222
Cumulative incidence		0.7%	1.4%	2.9%	3.2%
Prior AF group					
N of patients with event		0	5	7	10
N of patients at risk	589	526	442	374	273
Cumulative incidence		0.0%	1.0%	1.5%	2.5%
No AF group					
N of patients with event		12	26	53	81
N of patients at risk	5150	4854	4560	4155	3328
Cumulative incidence		0.2%	0.5%	1.2%	1.9%

Interval	0 day	30 days	1 year	3 years	5 years
Newly-diagnosed AF group					
N of patients with event		3	3	8	9
N of patients at risk	489	432	347	296	222
Cumulative incidence		0.7%	0.8%	2.2%	2.6%
Prior AF group					
N of patients with event		0	5	7	10
N of patients at risk	589	526	442	374	273
Cumulative incidence		0.0%	1.0%	1.5%	2.5%
No AF group					
N of patients with event		12	14	41	69
N of patients at risk	5150	4854	4560	4155	3228
Cumulative incidence		0.2%	0.3%	0.9%	1.6%

(A) Hemorrhagic stroke during the entire follow-up period, and (B) Landmark analysis at 30-day for hemorrhagic stroke

HR=hazard ratio; CI=confidence interval; AF=atrial fibrillation; N/A= not available

Crude HRs and 95%CIs were indicated with reference to no AF.