Atrial Fibrillation on Admission Is Related With Higher Mortality in ST-Segment Elevation Myocardial Infarction Patients

Lessons From the Korea Acute Myocardial Infarction Registry (KAMIR)

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Summary

The prognostic significance of atrial fibrillation (AF) on mortality in ST-segment elevation myocardial infarction (STEMI) patients is not clearly understood. To elucidate the clinical significance of AF on mortality for 1 year in STEMI patients, we retrospectively analyzed the Korea Acute Myocardial Infarction Registry (KAMIR) database, which spans January 2008 to September 2010 and includes 14,329 patients with acute myocardial infarction. We selected 5,556 patients with marked ECG rhythm (NSR, normal sinus rhythm or AF) on emergency room arrival, < 12 hours of symptom onset, and who underwent primary percutaneous coronary intervention (PCI) within 90 minutes of arriving at the hospital. Patients who had been followed-up for at least for 1 year were analyzed (2,636 of NSR, 119 of AF). At enrollment, AF patients were older (70.7 versus 65.5 years, $P < 0.001$) and had lower systolic blood pressure (120.6 versus 125.9 mmHg, $P = 0.050$), a higher heart rate (80.4 versus 75.6/minute, $P = 0.009$), and a higher rate of Killip III, IV (25.0 versus 14.2%, $P = 0.002$). Patients with AF showed clearly higher all-cause mortality (22.7 versus 9.5%, HR 2.51, 95%CI 1.68~3.76, $P < 0.001$) and cardiac death rate (17.7 versus 7.5%, HR 2.49, 95%CI 1.59~3.90, $P < 0.001$) at 1 year after admission compared patients with NSR. AF induced significantly higher all-cause mortality and cardiac mortality rate in STEMI patients who were appropriately revascularized with primary PCI compared to NSR at 1 year. (Int Heart J 2017; 58: 486-494)

Key words: Major adverse cardiac event, Target lesion revascularization, Normal sinus rhythm

The general prevalence of atrial fibrillation (AF) in developed countries is approximately 1.5~2%, and the average age of AF patients is continuously rising and is now between 75 and 85 years old.[1,2)] This arrhythmia is directly associated with a 5-fold risk of stroke, a 3-fold incidence of congestive heart failure (CHF), and higher mortality.[3)] The prevalence of AF is higher in diverse medical comorbid conditions such as hypertension, thyrotoxicosis, CHF, ischemic heart disease, left ventricular hypertrophy, and valvular heart diseases. In HF particularly, the prevalence of AF has been reported to range from 15 to 50% depending on age and the duration of underlying medical or cardiologic abnormalities.[4-6)] Lifelong or temporal oral anticoagulation was needed by 5~7% of patients who underwent percutaneous coronary intervention (PCI) with a stent, and most of them were patients with AF.[7)] AF patients undergoing PCI usually have more major adverse cardiac events compared to patients with normal sinus rhythm (NSR).[8)] The ARIAM registry showed higher in-hospital mortality in new onset AF compared to NSR or previously existing AF in acute coronary syndrome (ACS),[9)] and new onset AF was one of the important predictors of mortality, and non-coronary artery bypass graft (CABG) related major bleeding in ST-segment elevation myocardial infarction (STEMI) underwent primary PCI in HORIZON-AMI study.[10)] The Denmark Nationwide Study that included 89,703 patients with a first time acute myocardial infarction (AMI) proved new onset AF was an important risk factor related to higher all-cause mortality, cardiovascular (CV) mortality, and stroke in the future.[11)] In this study, we have attempted to determine the clinical impact of AF on emergency room (ER) arrival in STEMI patients who underwent primary PCI within 90 minutes of presentation at the ER.

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This work was supported by a research grant from Chungbuk National University in 2014.

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Received for publication June 17, 2016. Revised and accepted October 2, 2016.

Released in advance online on J-STAGE July 10, 2017.

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METHODS

Korea Acute Myocardial Infarction Registry (KAMIR): The KAMIR is a prospective, multicenter, observational registry, and was initiated in 2005 as a memorial academic project to celebrate the 50th anniversary of the Korean Society of Cardiology to determine the incidence, characteristics of presentation, mode of clinical treatment, and 1 year prognosis of AMI in the Republic of Korea (South Korea).[12] Registration started in 2005 with 41 general and educational hospitals that had catheterization laboratories and were performing primary PCI, but is now being carried out by 18 carefully selected educational hospitals.[12,13] A total of 46,591 patients with AMI were registered between 2006 and 2013, and the study is currently being continued through collaboration by the Korean Society of Cardiology and the Korean National Institute of Health.

Study design: We analyzed the KAMIR database entries that were registered from January 2008 to September 2009 and identified 14,329 patients with AMI. We then selected data for 5,356 patients based on the following criteria. First, we identified 8,196 patients who had remarkable ECG rhythms (NSR or AF) with STEMI by discarding the data of 6,133 patients with non-STEMI and/or ambiguous ECG rhythms (for example; ventricular fibrillation/tachycardia, junctional rhythm, asystole, ectopic atrial rhythm, supraventricular tachycardia, complete atrioventricular block). Other data were discarded for the following reasons; chest pain lasting more than 12 hours upon ER arrival (n = 2,188), a door-to-balloon time for primary PCI exceeding 90 minutes (n = 652), and loss or incomplete 1 year follow-up (n = 2,601). The final data set consisted of 2,755 patients with STEMI and AF/NSR on arrival, chest pain onset < 12 hours, door-to-balloon time for primary PCI < 90 minutes, and successful follow-up for 1 year (Figure 1). Major adverse cardiac events (MACE) consisted of cardiac death, MI, and PCI or CABG. The baseline clinical, laboratory, and angiographic characteristics between NSR patients and AF patients were compared. The 1 year all-cause mortality and MACE rate including the cardiac death rate were compared between the NSR and AF groups. The statistical impact of AF on mortality was examined by univariate and multivariate analyses.

Statistical analysis: All continuous variables are reported as the median or mean ± SD, and all categorical variables are expressed as the frequency and percentage. Categorical variables were compared with the chi-square or Fischer's exact test, and continuous variables were analyzed with the Student t-test. Kaplan-Meier analysis and the log-rank test were used to prepare 1-year survival curves of patients with AF or NSR upon ER arrival. The Cox proportional hazards model was used to confirm the independent prediction power of AF for mortality. The clinical variables selected in the univariate analysis, for example, age, Killip classification, and systolic and diastolic blood pressure upon ER arrival were entered into the multivariate Cox proportional hazard model to determine the importance of AF on mortality in the population. All statistical analyses were performed using SPSS version 21 (IBM Corporation, Armonk, NY, USA), and $P < 0.05$ was considered to be statistically significant.

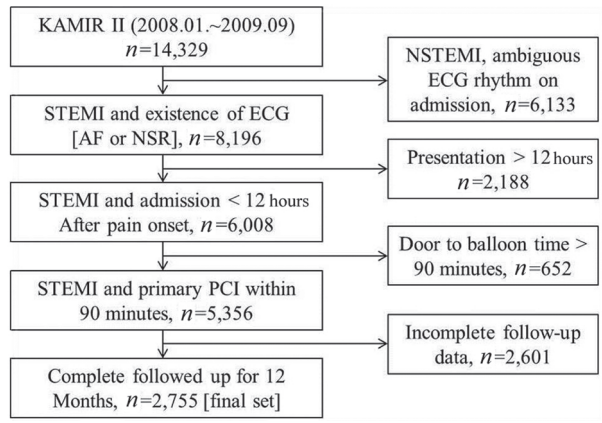

Figure 1. Study design. From the KAMIR database, patients with STEMI who arrived at the emergency room < 12 hours after symptom onset and had obvious ECG rhythm, a door-to- balloon time of < 90 minutes before primary PCI was performed, and complete follow-up for 1 year were selected. KAMIR indicates Koran Acute Myocardial Infarction Registry; NSTEMI, non ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; ECG, electrocardiogram; AF, atrial fibrillation; NSR, normal sinus rhythm; and PCI, percutaneous coronary intervention.

RESULTS

Baseline characteristics: Baseline variables are presented in Table I. Patients with AF on admission (n = 119, 4.3%), as compared to patients with NSR (n = 2,636, 95.7%) on admission, were older (70.7 ± 13.6 versus 65.5 ± 12.7 years old, $P <$ 0.001), had lower systolic blood pressure (120.6 ± 30.2 versus 125.9 ± 28.0 mmHg, P = 0.050), a faster heart rate (80.4 ± 29.0 versus 75.6 ± 18.3/minute, P = 0.009), higher Killip classification (I to IV, 58.0/17.0/9.8/15.2 versus 71.8/14.0/6.7/7.5%, P = 0.004), and lower rate of dyslipidemia (5.9 versus 11.9%, P = 0.049). Gender composition, height, weight, body mass index, abdominal circumference, hip circumference, diastolic blood pressure on ER arrival, and history of hypertension or diabetes mellitus were comparable between the AF and NSR patients. The AF group had a higher prevalence of ischemic heart disease, but the difference was not statistically significant (16.0 versus 11.0%, P = 0.092). The proportions of current smokers and patients with familial CV disease were comparable in the 2 groups. Thus, patients with AF in the ER were significantly more frail than the NSR patients. AF patients were prescribed significantly less clopidogrel (75.6 versus 88.1%, $P <$ 0.001), angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) (67.2 versus 79.0%, P = 0.002), beta blockers (60.5 versus 76.8%, $P <$ 0.001), and statins (58.8 versus 69.3%, P = 0.016) (Table I). However, the use of a statin or a statin plus ezetimibe was similar in the two groups (79.8 versus 82.0%, P = 0.600). The prescription rate for aspirin was comparable (96.8 versus 98.4%, P = 0.230), while warfarin was prescribed more frequently in AF patients (7.6 versus 2.1%, $P <$ 0.001), but warfarin was rarely prescribed for them. The proportions of triple antiplatelet users who were prescribed aspirin, clopidogrel, and warfarin were similar in the two groups (2.5 versus 1.7%, P = 0.483). Spironolactone (15.7 versus 9.3%, P = 0.042) and loop diuretics (26.7 versus 16.6%, P = 0.013) were more frequently used in

Table I. Baseline Clinical and Laboratory Characteristics in STEMI Patients With NSR and AF

	NSR on admission (n = 2,636)	AF on admission (n = 119)	P
Clinical Characteristics			
Anthropometric values			
Age (years)	65.5 ± 12.7	70.7 ± 13.6	< 0.001
Female (%)	26.0	21.0	0.227
Height (cm)	164.2 ± 8.8	165.6 ± 8.7	0.108
Weight (kg)	65.4 ± 11.5	65.5 ± 12.5	0.897
BMI (kg/m^2)	24.2 ± 3.2	23.7 ± 3.3	0.210
AC (cm)	84.1 ± 15.3	85.0 ± 10.0	0.468
HC (cm)	91.4 ± 7.9	90.8 ± 9.6	0.645
Hemodynamics in ER			
Systolic BP (mmHg)	125.9 ± 28.0	120.6 ± 30.2	0.050
Diastolic BP (mmHg)	77.8 ± 16.8	75.3 ± 17.1	0.126
Heart rate (/minute)	75.6 ± 18.3	80.4 ± 29.0	0.009
Killip class (%, I/II/III/IV)	71.8/14.0/6.7/7.5	58.0/17.0/9.8/15.2	0.004
Past medical history			
Previous angina (%)	36.9	37.8	0.844
Hypertension (%)	44.9	47.9	0.516
Diabetes mellitus (%)	24.5	24.4	0.983
Ischemic heart disease (%)	11.0	16.0	0.092
Dyslipidemia (%)	11.9	5.9	0.049
Current smoker (%)	47.0	44.4	0.793
Family history of CVD (%)	7.20	6.00	0.606
Discharge medication (%)			
Aspirin	98.4	96.8	0.230
Clopidogrel	88.1	75.6	< 0.001
Cilostazol	26.9	20.0	0.145
ACEI or ARB	79.0	67.2	0.002
Beta blocker	76.8	60.5	< 0.001
Statin	69.3	58.8	0.016
Statin or Statin +Ezetimibe	82.0	79.8	0.600
Warfarin	2.1	7.6	< 0.001
TAPT	1.7	2.5	0.483
Loop diuretic	16.6	26.7	0.013
Spironolactone	9.3	15.7	0.042
Laboratory characteristics			
Laboratory in ER and ward			
Glucose on ER (mg/dL)	179.4 ± 80.8	197.8 ± 115.7	0.097
Creatinine (mg/dL)	1.10 ± 1.05	1.09 ± 0.33	0.892
Maximal CK (IU/L)	1753.9 ± 2453.8	1693.4 ± 3191.2	0.851
Maximal CK-MB (IU/L)	160.1 ± 242.3	142.9 ± 155.0	0.445
Maximal cTnI (pg/mL)	65.7 ± 111.9	58.5 ± 78.9	0.383
Initial NT-proBNP (mg/dL)	1579.8 ± 4301.3	2465.0 ± 5547.1	0.049
Initial BNP (pg/mL)	350.1 ± 1835.6	1642.9 ± 6078.8	0.006
Initial hs-CRP (mg/dL)	5.0 ± 18.0	4.3 ± 10.3	0.563
Metabolic laboratory values			
Total cholesterol (mg/dL)	182.0 ± 43.1	171.9 ± 46.3	0.009
Triglycerides (mg/dL)	131.8 ± 102.3	126.6 ± 94.5	0.604
HDL-C (mg/dL)	43.5 ± 15.0	44.6 ± 15.9	0.458
LDL-C (mg/dL)	116.8 ± 36.7	107.1 ± 39.4	0.009
HbA1C (%)	6.5 ± 2.0	6.6 ± 1.4	0.798
Echocardiographic values			
LV EF (%)	52.3 ± 14.2	49.6 ± 13.7	0.057
LVESD (mm)	34.6 ± 8.8	35.3 ± 9.6	0.409
LVEDD (mm)	48.5 ± 9.6	49.0 ± 8.9	0.562
LVESV (mL)	46.6 ± 22.8	49.8 ± 29.1	0.364
LVEDV (mL)	90.1 ± 28.6	93.1 ± 36.0	0.593

NSR indicates normal sinus rhythm; AF, atrial fibrillation; BMI, body mass index; AC, abdominal circumference; HC, hip circumference; ER, emergency room; BP, blood pressure; CVD, cardiovascular disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; TAPT, triple antiplatelet therapy, aspirin + clopidogrel + warfarin; CK, creatinine kinase; CK-MB, CK-MB isoform; NT-proBNP, n-terminal pro B-type natriuretic peptide; BNP, B-type natriuretic peptide; hs-CRP, high sensitive C-reactive protein; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; LVESV, left ventricular end-systolic volume; and LVEDV, left ventricular end-diastolic volume.

AF patients upon discharge from hospital. The older age, lower systolic blood pressure, and higher class of Killip of the AF patients might have limited the wider use of the above critical medications such as clopidogrel, beta-blockers, or ACE inhibitors/ARB for STEMI. The higher Killip classification might be the main cause of the frequent use of diuretics in AF patients.

Laboratory characteristics: The laboratory values and echocardiography results of the patients are described in Table I. Patients who presented with AF had significantly higher initial NT-proBNP (2465.0 ± 5547.1 versus 1579.8 ± 4301.3 mg/dL, $P = 0.049$) and initial BNP levels (1642.9 ± 6078.8 versus 350.1 ± 1835.6 pg/mL, $P = 0.006$), and lower total cholesterol (171.9 ± 46.3 versus 182.0 ± 43.1 mg/dL, $P = 0.009$) and LDL-C values (107.1 ± 39.4 versus 116.8 ± 36.7 mg/dL, $P = 0.009$). The random glucose level upon ER arrival was numerically higher in the AF group, although it did not reach statistical significance (197.8 ± 115.7 versus 179.4 ± 80.8 mg/dL, $P = 0.097$). The creatinine, maximal CK/CK-MB/cTnI, hs-CRP, triglyceride, and HbA1c values were similar in the AF and NSR groups. Left ventricular ejection fraction (LVEF) was slightly higher in the NSR group, but the difference was not statistically significant (52.3 ± 14.2 versus 49.6 ± 13.7%, $P = 0.057$). Left ventricular end diastolic (48.5 ± 9.6 versus 49.0 ± 8.9 mm, $P = 0.562$)/systolic (34.6 ± 8.8 versus 35.3 ± 9.6 mm, $P = 0.409$) dimension and left ventricular diastolic (90.1 ± 28.6 versus 93.1 ± 36.0 mL, $P = 0.593$)/systolic (46.6 ± 22.8 versus 49.8 ± 29.1 mL, $P = 0.364$) volume were comparable in the NSR and AF groups (Table I).

Survival analysis: The incidences of MACE after primary PCI in STEMI in the AF and NSR patients are presented in Table II. The incidence of all-cause mortality was significantly higher in the AF group (22.7 versus 9.5%, HR 2.51, 95%CI 1.68~3.76, $P < 0.001$) compared to the NSR group for 1 year. Composite MACE consisted of cardiac death, MI, and PCI or CABG for 1 year. AF patients had a significantly higher composite MACE rate (20.2 versus 13.8%, HR 1.58, 95%CI 1.05~2.39, $P = 0.030$). The cardiac death rate was higher in the AF group than in the NSR group (17.7 versus 7.5%, HR 2.49, 95%CI 1.59~3.90, $P < 0.001$), while the rate of MI (0.8 versus 1.2%, HR 0.77, 95%CI 0.11~5.67, $P = 0.801$) and rate of PCI or CABG (1.7 versus 5.1%, HR 0.37, 95%CI 0.09~1.49, $P = 0.162$) were comparable in the 2 groups. We performed univariate analysis to identify significant risk factors, including baseline clinical characteristics and laboratory variables, to predict all-cause mortality and to examine the significance of AF on mortality in the study population for 1 year after primary PCI (Table III). Age (HR 1.07, 95%CI 1.06~1.08, $P < 0.001$), female gender (HR 2.40, 95%CI 1.86~3.09, $P < 0.001$), systolic (HR 0.98, 95%CI 0.97~0.99, $P < 0.001$)/diastolic (HR 0.97, 95%CI 0.96~0.98, $P < 0.001$) blood pressure on ER arrival, heart rate (HR 1.02, 95%CI 1.01~1.03, $P < 0.001$), glucose (HR 1.01, 95%CI 1.01~1.02, $P < 0.001$), and creatinine

Table II. Incidence of Major Adverse Cardiac Events in STEMI With AF and NSR Patients for 1 Year

	NSR ($n = 2,636$)	AF ($n = 119$)	HR (95%CI)	*P*
All-cause mortality	251 (9.5%)	27 (22.7%)	2.51 (1.68~3.76)	< 0.001
MACE	363 (13.8%)	24 (20.2%)	1.58 (1.05~2.39)	0.030
Cardiac death	198 (7.5%)	21 (17.7%)	2.49 (1.59~3.90)	< 0.001
MI	31 (1.2%)	1 (0.8%)	0.77 (0.11~5.67)	0.801
PCI or CABG	134 (5.1%)	2 (1.7%)	0.37 (0.09~1.49)	0.162

NSR indicates normal sinus rhythm; AF, atrial fibrillation; HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiac event; MI, myocardial infarction; NA, not available; PCI, percutaneous coronary intervention; and CABG, coronary artery bypass graft.

Table III. Univariate Analysis for All-Cause Mortality

	Hazard Ratio	95%CI	*P*
Age (years)	1.07	1.06~1.08	< 0.001
Gender (female to male)	2.40	1.86~3.09	< 0.001
Systolic blood pressure	0.98	0.97~0.99	< 0.001
Diastolic blood pressure	0.97	0.96~0.98	< 0.001
Heart rate	1.02	1.01~1.03	< 0.001
Glucose	1.01	1.01~1.02	< 0.001
Creatinine	1.11	1.06~1.16	< 0.001
Hypertension	1.80	1.41~2.30	< 0.001
Diabetes mellitus	1.49	1.15~1.93	0.003
Ischemic heart disease	1.64	1.19~2.26	0.003
Dyslipidemia	0.51	0.31~0.83	0.007
Current smoker	0.48	0.36~0.62	< 0.001
Killip class II (compared to I)	2.82	1.92~4.14	< 0.001
Killip class III (compared to I)	8.70	6.16~12.31	< 0.001
Killip class IV (compared to I)	12.82	9.36~17.56	< 0.001
NT-proBNP Q2 (compared to Q1)	3.82	1.55~9.43	0.004
NT-proBNP Q3 (compared to Q1)	4.48	1.85~10.89	0.001
NT-proBNP Q4 (compared to Q1)	15.86	6.86~35.83	< 0.001
LV ejection fraction	0.94	0.93~0.96	< 0.001
Atrial fibrillation	2.51	1.68~3.76	< 0.001

CI indicates confidence interval; NT-proBNP, n-terminal pro B-type natriuretic peptide; and LV, left ventricle.

Table IV. Multivariate Analysis for All-Cause Mortality

	Hazard Ratio	95%CI	*P*
Age (year)	1.05	1.02~1.07	< 0.001
Systolic blood pressure	0.99	0.98~1.00	0.066
Heart rate	1.02	1.01~1.03	< 0.001
Creatinine	1.22	0.98~1.51	0.074
Killip class II (compared to I)	1.53	0.84~2.79	0.166
Killip class III (compared to I)	1.99	1.06~3.72	0.032
Killip class IV (compared to I)	2.34	1.14~4.79	0.020
NT-proBNP Q2 (compared to Q1)	9.54	1.24~73.64	0.031
NT-proBNP Q3 (compared to Q1)	8.11	1.04~63.38	0.046
NT-proBNP Q4 (compared to Q1)	20.07	2.68~150.07	0.005
LV ejection fraction	0.99	0.97~1.00	0.131
Atrial fibrillation	2.43	1.28~4.59	0.006

CI indicates confidence interval; NT-proBNP, n-terminal pro B-type natriuretic peptide; and LV, left ventricle.

level (HR 1.11, 95%CI 1.05~1.16, $P < 0.001$) all had significant correlations to all-cause mortality for 1 year. A history of hypertension (HR 1.80, 95%CI 1.41~2.30, $P < 0.001$), diabetes mellitus (HR 1.49, 95%CI 1.15~1.93, $P = 0.003$), and ischemic heart disease (HR 1.64, 95%CI 1.19~2.26, $P = 0.003$) showed positive correlations to mortality, and a history of dyslipidemia (HR 0.51, 95%CI 0.31~0.83, $P = 0.007$) and current smoking (HR 0.48, 95%CI 0.36~0.62, $P < 0.001$) had negative correlations to mortality. Killip classification and quartile classification of NT-proBNP level upon ER arrival showed clear direct correlations, while left ventricular systolic function showed an inverse correlation with 1 year mortality. LVEF was related with all-cause mortality (HR 0.94, 95%CI 0.93~0.96, $P < 0.001$) and AF was also a significant predictor for 1 year all-cause mortality (HR 2.51, 95%CI 1.68~3.76, $P < 0.001$) (Table III). With those clinical and laboratory variables that were critically related with 1 year all-cause mortality, we performed multivariate analysis in a stepwise manner (Table IV). After multivariate analysis for mortality, age (HR 1.05, 95%CI 1.02~1.07, $P < 0.001$), heart rate (HR 1.02, 95%CI 1.01~1.03, $P < 0.001$), Killip class III (HR 1.99, 95%CI 1.06~3.72, $P = 0.032$), Killip class IV (HR 2.34, 95%CI 1.14~4.79, $P = 0.020$) (compared to Killip class I), and the second (HR 9.54, 95%CI 1.23~73.64, $P = 0.031$), third (HR 8.11, 95%CI 1.04~63.38, $P = 0.046$) and fourth quartile values (HR 20.07, 95%CI 2.68~150.07, $P = 0.005$) of NT-proBNP (compared to the first quartile) were important predictors for all-cause mortality for 1 year. AF was also a very strong predictor for all-cause mortality for 1 year in multivariate analysis (HR 2.43, 95%CI 1.28~4.59, $P = 0.006$) (Table IV). Systolic blood pressure, creatinine, LVEF, and Killip class II (compared to I) lost significance for predicting death in 1 year after adjustment with multivariate analysis (Table IV). In the survival analysis with the Kaplan-Meier analysis, the AF group had significantly higher all-cause mortality for 1 year compared to the NSR group (log-rank $P < 0.001$) (Figure 2) and higher composite MACE (log-rank $P = 0.028$) (Figure 3A). Cardiac death for 1 year was significantly higher in the AF group (log-rank $P < 0.001$), but MI (log-rank $P = 0.800$) and PCI or CABG (log-rank $P = 0.144$) were comparable in the 2 groups (Figure 3B, C, D).

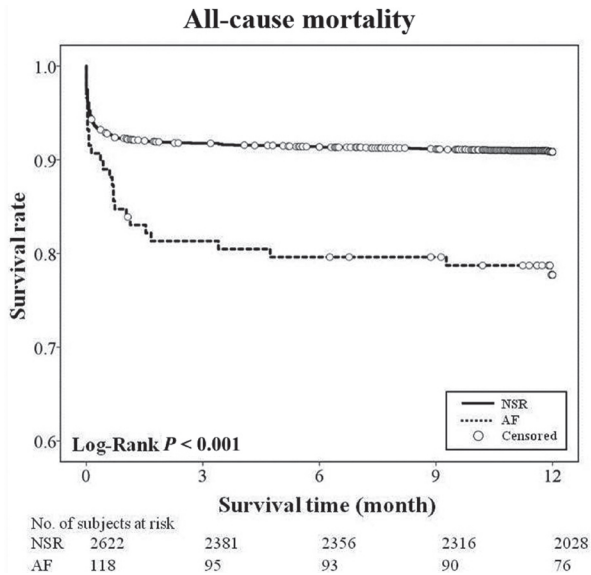

Figure 2. Kaplan-Meier analysis of all-cause mortality for 1 year. AF patients showed significantly higher morality compared to patients with NSR (HR 2.51, 95%CI 1.68~3.76, log-rank $P < 0.001$). NSR indicates normal sinus rhythm; and AF, atrial fibrillation.

Discussion

AMI is one of the most serious CV diseases and is directly related to higher mortality, a higher induction rate of HF, and higher medical costs in developed countries.[14-20] Furthermore, AF is an important disease entity which is directly related to recurrent systemic thromboembolic events, especially cerebral infarction, HF, and bleeding events provoked by long-term antiplatelet agent or anticoagulant prescription, especially in elderly populations.[19] About 30% of strokes in patients older than 70 years originate purely from AF.[21-24] AF is also known as an important clinical factor for MACE in AMI.[25] AMI induces an abrupt incremental increase in adrenal catecholamine discharge and increases left atrial pressure related to left ventricular dysfunction, and these changes are also capable of inducing new onset AF.[10,11] In previous studies, patients with permanent AF or new onset AF had higher rates of CV mortality as well as readmission for HF in AMI, irrespective of

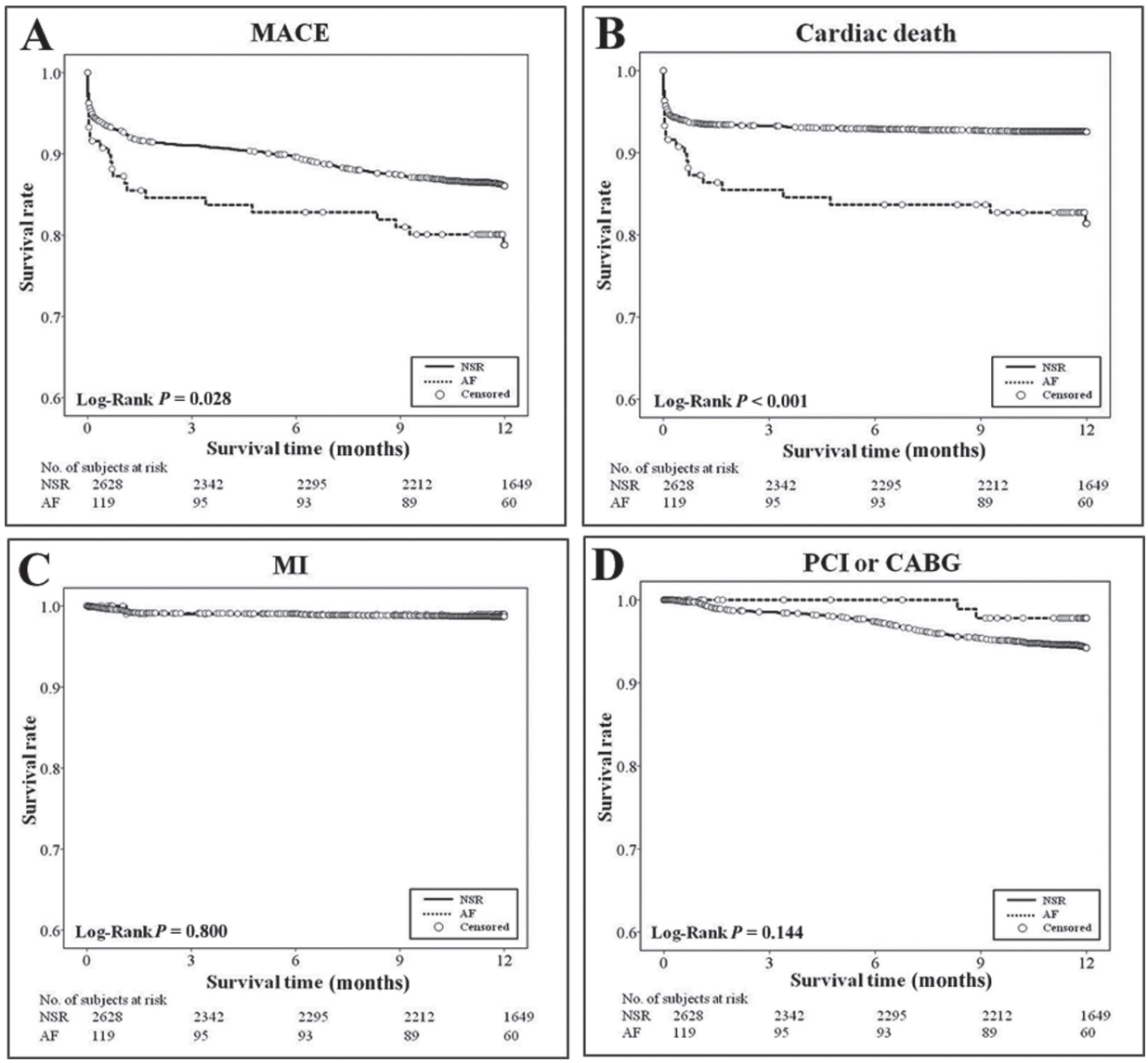

Figure 3. MACE-free survival in patients with NSR and AF. Cardiac death was higher in AF patients compared to NSR patients (HR 2.49, 95%CI 1.59~3.90, log-rank $P < 0.001$), but MI, and PCI or CABG rate were comparable in the 2 groups. The composite MACE rate was higher in the AF group than the NSR group (HR 1.58, 95%CI 1.05~2.39, log-rank $P = 0.028$). MACE indicates major adverse cardiac event; NSR, normal sinus rhythm; AF, atrial fibrillation; MI, myocardial infarction; PCI, percutaneous coronary intervention; and CABG, coronary artery bypass graft.

STEMI or NSTEMI.[9-11] Patients with AF often have multiple comorbidities, for example, older age, small body weight, hypertension, left ventricular hypertrophy, and/or ventricular systolic dysfunction.[26] With these clinical characteristics, AF patients are vulnerable to HF and cardiogenic shock in the initial phase of AMI, and suffer prevalent events of bleeding and major arterial embolism during the chronic phase of MI.[26-29] These concerns directly increase all-cause mortality or CV death after MI. Recent analyses of ethnic differences in clinical trials using novel oral anticoagulants have found Asian populations have a higher risk of arterial thromboembolic events in AF, and a higher bleeding rate compared to Caucasian populations.[30,31] In Korea, STEMI accounts for 50% of all AMI, and almost all STEMI patients will be treated with primary PCI based on drug eluting stents rather than with a thrombolytic agent. The primary PCI rate for STEMI in Korea was reported to be more than 95% in a recent analysis, and in this study we have attempted to determine the clinical impact of AF in STEMI patients who were treated appropriately with primary PCI in a Korean population.[13,20] We thought it would be very important to clarify the clinical importance and prognosis of any type of AF documented on ER arrival, irrespective of whether it was persistent or new onset AF, in STEMI patients who were treated with primary PCI in the modern era of cardiology practice. Based on this background clinical concept, we selected only STEMI patients in the KAMIR database who presented within 12 hours after chest pain onset and underwent primary PCI appropriately. We then compared the rates of all-cause mortality and MACE in patients with NSR and AF. After completing that statistical analysis, we attempted to identify clini-

cal and laboratory factors related to all-cause mortality. We found that AF on the admission ECG in the ER was significantly related with all-cause mortality and cardiac death for 1 year after discharge in STEMI compared to NSR. We selected 2,755 patients with STEMI who fulfilled the above inclusion criteria from the KAMIR database and were registered between January 2008 and September 2009 from among an initial total of 14,329 AMI patients. Compared with the NSR group, AF patients had poor baseline clinical and laboratory characteristics. Patients with AF on ER arrival were significantly older and had lower systolic blood pressure, a faster heart rate, and higher grade of Killip class. The proportions of Killip class III or IV were 14.2% in the NSR patients and 25.0% in the AF patients. The levels of NT-proBNP and BNP were significantly higher in the AF group. The total cholesterol and LDL-C levels were lower in the AF group, which led us to conclude this might be related to the older age and lower prevalence of dyslipidemia (5.9 versus 11.9%, $P = 0.049$) in the AF group compared to the NSR group. LVEF was slightly lower in the AF group than in the NSR group, but the difference was not statistically significant (49.6 ± 13.7 versus 52.3 ± 14.2%, $P = 0.057$). AF patients in this registration were generally older and more frail than the patients with NSR and thus were prescribed significantly less critical medication on discharge. Clopidogrel, ACE inhibitors or ARB, beta blockers, and statins were prescribed less often for AF patients, which could be one reason that explains the higher mortality in the AF group. AF patients were prescribed more warfarin compared to NSR patients on discharge (7.6 versus 2.1%, $P < 0.001$), but the prescription rate of warfarin was extremely low in AF patients. This could also be a reason for the higher rate of cardiac or all-cause mortality in the AF patients, and signifies that the clinical recommendation of anticoagulant usage for AF in STEMI patients was not realized in daily clinical practice. However, this data came from a relatively older registration, so we are performing a new analysis for this clinical fact with a newer version of the KAMIR database. AF patients had significantly higher all-cause mortality (22.7% versus 9.5%, HR 2.51, 95%CI 1.68~3.76, $P < 0.001$) and cardiac death (17.7% versus 7.5%, HR 2.49, 95%CI 1.59~3.90, $P < 0.001$) in the survival analysis using Kaplan-Meier curves. MI (log-rank $P = 0.800$) and PCI or CABG free survival (log-rank, $P = 0.144$) were comparable in the 2 groups, but composite MACE free survival was higher in the NSR group (log-rank, $P = 0.028$). The all-cause mortality rate in NSR patients who had been treated with primary PCI was 8.8%, and the death rate of all enrolled patients was 9.3% in this data set. This mortality data was very similar to the OPERA registry, Vienna STEMI registry, and SWEDEHEART registry which were established with modern treatment modalities including primary PCI, and the active use of antiplatelet agents, beta blockers, RAS blockers, and statins.[32-35] Thus, we believe that our registry and dataset are an accurate reflection of the real clinical situation for STEMI treatment. Several clinical reports, such as the HORIZONS-AMI study,[10] have reminded us of the importance of AF in AMI or STEMI populations. However, these data had some limitations, such as relatively advanced age,[8] mixed population of ACS,[9] and only including new onset AF that occurred after primary PCI.[10,11] To overcome these limitations, we selected STEMI patients who arrived at the ER within 12 hours after chest pain onset and underwent primary PCI within 90 minutes after ER arrival from the KAMIR database to reflect the real situation of modern treatment modalities for STEMI. With this patient data set, we found that AF was an important clinical factor related to 1 year cardiac death and all-cause mortality. In our study, the prescription rate for warfarin in AF patients with STEMI was exceptionally low. The proportion of patients who need oral anticoagulation in the PCI field is not negligible, and usually 5~7% of PCI patients have an indication for temporary or permanent oral anticoagulant.[36] They are patients with AF, mechanical valve implantation, deep vein thrombosis, or pulmonary thromboembolism, but most have AF.[36] New onset AF after PCI also occurs at a rate of 2~6% in daily practice.[37] AF occurs in 6 to 11% of STEMI patients, and has been associated with increased in-hospital and long-term morality.[38-41] Recently, Batra, *et al* published a paper on the importance of AF in AMI patients, including STEMI and NSTEMI.[42] They found that irrespective of AF type, for example, new onset, paroxysmal, or chronic AF, AF patients suffered a higher rate of MACE compared to NSR, and there was no difference in the MACE rate between the types of AF.[42]

Our data definitely has some limitations. First, the data came from a retrospective analysis of a pre-existing registry and not a prospective trial. Caution should be exercised from a clinical standpoint when generalizing these results. However, KAMIR is an unrestricted clinical registration, and the 1 year morality rate was 9.3% in our selected dataset in STEMI. This mortality is very similar to other major STEMI registries and national mortality statistics in Korea.[20] Therefore, we believe that our results can reflect the real situation of clinical results in daily practice of STEMI with AF patients. Second, the prescription rate of warfarin for AF with STEMI patients was markedly lower than expected. This may be a critical cause of the higher levels of all-cause mortality and cardiac death in AF patients. This means that we need to promote a more stringent use of optimal anticoagulants, including novel oral anticoagulants for this high risk population. The AF patients were more frail in the analysis of clinical characteristics, and the prescription rates of critical drugs including antiplatelet agents, beta blockers, and statins were lower than STEMI with NSR patients. Third, the prescription rates for a statin or statin plus ezetimibe were also lower than expected. The period of this KAMIR database enrollment was from 2008 to 2009. The usual LDL-C target at that time was generally less than 100 mg/dL, and less than 70 mg/dL was adopted for high risk ACS patients.[43,44] According to our dataset, 48.1% of AF patients and 32.2% of NSR patients had LDL-C of less than 100 mg/dL, while 16.4% of AF patients and 9.1% of NSR patients had LDL-C of less than 70 mg/dL at entry. Thus, at least 30% of the enrollees had LDL-C of less than 100 mg/dL and 10% had less than 70 mg/dL at baseline in this study. This is one possible explanation for the lower use of a statin or a statin plus ezetimibe in this study. Fourth, Batra, *et al* showed that the type of AF (new onset, paroxysmal, or chronic AF) did not make a difference in MACE in AMI patients, and new onset AF was still a more important risk factor for death in AMI patients compared to NSR or chronic AF in major clinical data.[10,11,42] The KAMIR database did not provide exact information with respect to the types of AF so we were unable to determine if there was any difference in the clinical impact on AF type. This may be one more limitation of our data. Fifth, the KAMIR data did not collect data on bleeding complica-

tions or stroke in patients with AMI. Therefore, we could not show the incidences or importance of bleeding and stroke in these higher risk patients for bleeding and arterial embolism. We are working to overcome these limitations of the KAMIR database in the current KAMIR-V and KAMIR-NIH databases. We hope that we will be able to demonstrate the importance of AF type and bleeding or atrial embolism including stroke in AMI patients with AF within the next few years. Even with the above limitations, our results strongly suggest that Asian AF patients with STEMI showed very high rates of all-cause mortality and cardiac death even after appropriate treatment with primary PCI. This serious clinical outcome might result from the fundamental frailty of AF patients, and the lower use of prognosis-improving drugs for ACS, including anticoagulants. More detailed evaluations of baseline characteristics, optimal medications after appropriate revascularization, and careful medical surveillance to detect bleeding and MACE should be performed for this high risk subset of patients in order to improve their prognosis.

Disclosure

Conflict of interest statement: The authors have no conflicts of interest to report regarding the design or conduct of this study.

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