ORIGINAL RESEARCH

Prognosis and Predictors of Mortality in Patients Suffering Myocardial Infarction With Non-Obstructive Coronary Arteries

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Background—Myocardial infarction with nonobstructive coronary arteries (MINOCA) is a heterogeneous disease entity. Its prognosis and predictor of mortality remain unclear. This study aimed to compare the prognosis between MINOCA and myocardial infarction with obstructive coronary artery disease and identify factors related to all-cause death in MINOCA using a nation-wide, multicenter, and prospective registry.

Methods and Results—Among 13 104 consecutive patients enrolled, patients without previous history of significant coronary artery disease who underwent coronary angiography were selected. The primary outcome was 2-year all-cause death. Secondary outcomes were cardiac death, noncardiac death, reinfarction, and repeat revascularization. Patients with MINOCA (n=396) and myocardial infarction with obstructive coronary artery disease (n=10 871) showed similar incidence of all-cause death (9.1% versus 8.8%; hazard ratio [HR], 1.04; 95% CI, 0.74–1.45; *P*=0.83). Risks of cardiac death, noncardiac death, and reinfarction were not significantly different between the 2 groups (HR, 0.82; 95% CI, 0.53–1.28; *P*=0.38; HR, 1.55; 95% CI, 0.93–2.56; *P*=0.09; HR, 1.23; 95% CI, 0.65–2.31; *P*=0.38, respectively). MINOCA patients had lower incidence of repeat revascularization (1.3% versus 7.2%; HR, 0.17; 95% CI, 0.07–0.41; *P*<0.001). Results were consistent after multivariable regression and propensity-score matching. In a multivariate model, several significant predictors of all-cause death of MINOCA were found, including the nonuse of renin-angiotensin system blockers (HR, 2.63; 95% CI, 1.08–6.25; *P*=0.033) and statins (HR, 2.17; 95% CI, 1.04–4.54; *P*=0.039).

Conclusions—Patients with MINOCA and those with myocardial infarction with obstructive coronary artery disease had comparable clinical outcomes. Use of renin-angiotensin system blockers and statins was associated with lower mortality in patients with MINOCA. **(*J Am Heart Assoc*. 2019;8:e011990. DOI: 10.1161/JAHA.119.011990.)**

Key Words: coronary vasospasm • myocardial infarction • prognosis • renin angiotensin system • statin

Myocardial infarction with nonobstructive coronary arteries (MINOCA) is characterized by a positive cardiac biomarker and appropriate clinical scenario consistent with acute myocardial infarction (AMI). MINOCA is an infrequent (5–10% of AMI) syndrome with heterogeneous etiologies, including plaque disruption, coronary spasm, and coronary thromboembolism. Sometimes it is difficult to differentiate it from stress-induced cardiomyopathy, myocarditis, and type 2 myocardial infarction (MI).[1]

Accordingly, data regarding the long-term prognosis and its predictors of MINOCA are limited and controversial. Previous studies have demonstrated that MINOCA has a low risk of adverse clinical outcomes.[2–4] Other studies have reported a considerable rate of mortality in MINOCA compared with MI

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Accompanying Appendix S1 and Tables S1 through S7 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.011990

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Clinical Perspective

What Is New?

- Patients with Myocardial infarction with nonobstructive coronary arteries (MINOCA) had similar risks of all-cause death and myocardial infarction compared with those with myocardial infarction with obstructive coronary artery disease.
- Risk of all-cause death of MINOCA with vasospasm did not differ from that of MINOCA without vasospasm.
- Use of renin-angiotensin system blockers and statins was independently associated with decreased risk of all-cause mortality in patients with MINOCA.

What Are the Clinical Implications?

- MINOCA is not a benign disease, but a disease which might require clinical attention and intensive medical treatment with renin-angiotensin system blockers and statins to reduce mortality.

with obstructive coronary artery disease (MI-CAD).[5–7] This uncertainty has led to variations in its treatment. Calcium-channel blockers and vasodilators can be used for patients with a positive coronary spasm test.[8] Conventional guideline-recommended therapies, such as dual antiplatelet therapy, renin-angiotensin system blockers, beta-blockers, and statins, can also be prescribed for patients with MINOCA.[9,10]

Therefore, the objective of this study was to evaluate the long-term risk of clinical outcomes in patients with MINOCA compared with MI-CAD. Independent predictors of mortality, including medications after discharge, were also determined using a large-scale, nation-wide, multicenter, dedicated registry for AMI.

Methods

Anonymized patient-level data will be made available by the corresponding author upon reasonable request.

Study Protocols and Population Selection

Patients were derived from the nation-wide, multicenter, prospective KAMIR-NIH (Korean Acute Myocardial Infarction-National Institutes of Health) registry. The KAMIR-NIH was a dedicated prospective registry that consecutively enrolled AMI-diagnosed patients at 20 tertiary university hospitals who were eligible for primary percutaneous coronary intervention from November 2011 to December 2015 without any exclusion criteria. The detailed study protocols have been previously published.[11] The protocol of the KAMIR-NIH registry was approved by the ethics committee at each participating center. This study was conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent upon enrollment.

To include the incident AMI patients only, we excluded patients who did not undergo coronary angiography (n=201) and those who had a previous history of MI, coronary intervention, or bypass surgery (n=1636) from 13 104 patients. We enrolled 396 patients with MINOCA (<50% stenosis in all vessels) and 10 871 patients with MI-CAD (≥50% stenosis in any of their coronary arteries). If MINOCA was suspected, a vasospasm test was recommended as a standard of care. Of patients with MINOCA, 95 (24% of MINOCA) demonstrated vasospasm defined by spontaneous coronary spasm with ST-segment elevation (≥0.1 mV) on the coronary angiogram and/or documented coronary spasm during an ergonovine provocation test (Figure 1). The test was considered positive for epicardial coronary spasm in the presence of focal or diffuse epicardial coronary diameter reduction ≥90% in comparison with the relaxed state following intracoronary nitroglycerine administration, associated with the reproduction of the patient's symptoms and ischemic electrocardiographic shifts.[12] Data from coronary intravascular imaging or magnetic resonance imaging were limited; we did not include them in this analysis.

Patient Management, Data Collection, and Follow-up

Patient management was performed according to current standard guidelines. Patients with MI-CAD underwent percutaneous coronary intervention by a standard technique if the patient was clinically indicated. Patients were also recommended to take aspirin indefinitely plus P2Y12 inhibitors, renin-angiotensin system blockers, beta-blockers, and statins that were prescribed according to the practice guidelines. Patients with MINOCA were treated with medications under the physician's discretion.

Demographic features and cardiovascular risk factors were collected by detailed patient interview. Patient chest pain was categorized according to the presence of substernal chest pain or discomfort that was provoked by exertion or emotional stress and was relieved by rest and/or nitroglycerin. Chest pain was classified as "typical" angina if all 3 descriptors were present and as "atypical" if <3 descriptors were present. During hospitalization, the findings of coronary angiography and detailed procedural characteristics of percutaneous coronary intervention as well as information on the discharge medications were collected. A successful percutaneous coronary intervention was defined as a decrease in minimum stenosis diameter to <30% with Thrombolysis in Myocardial Infarction flow grade ≥2 on coronary angiogram. Recurrent ischemia was defined as presence of angina and changes in

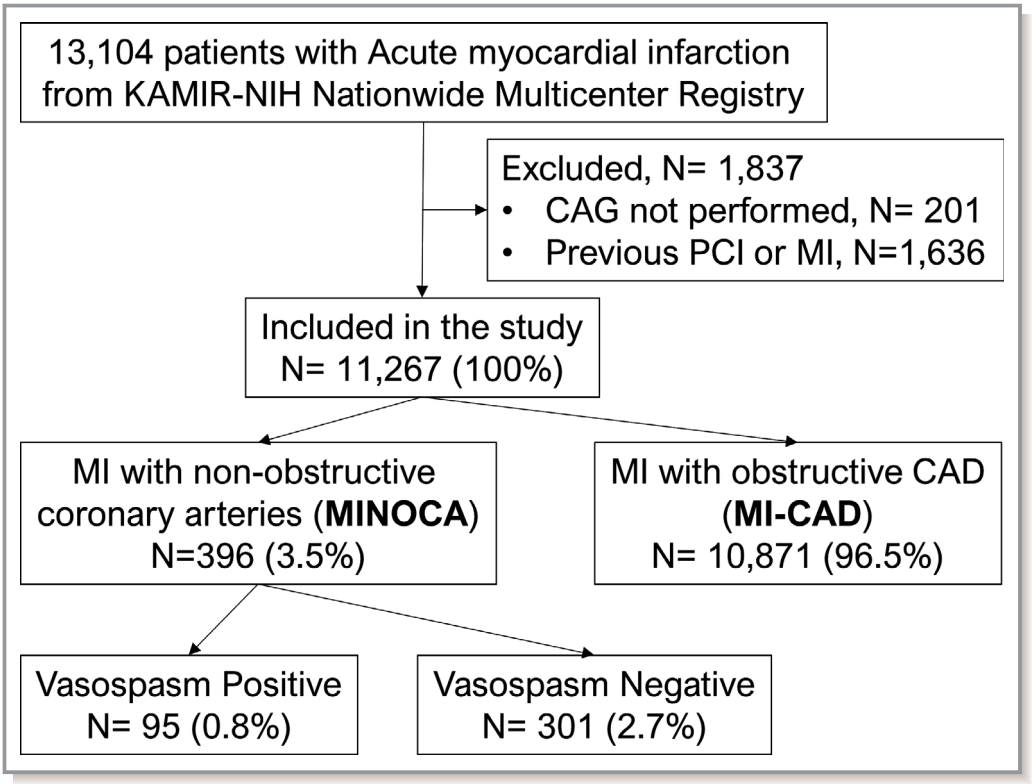

Figure 1. Study flow. The study population was derived from a nation-wide, multicenter, prospective KAMIR-NIH (Korea Acute Myocardial Infarction Registry-National Institute of Health) registry. CAG indicates coronary angiography; MI, myocardial infarction; MI-CAD, myocardial infarction with obstructive coronary artery disease; MINOCA, myocardial infarction with nonobstructive coronary arteries; PCI, percutaneous coronary intervention.

hemodynamics or ECG. After discharge, patients were followed at 6, 12, and 24 months by the attending physician. If patients did not visit on the day of the scheduled follow-up, the outcome data were assessed by a telephone interview. All data were collected by independent clinical research coordinators using a web-based case report form in the Internet-based Clinical Research and Trial management system (iCReaT), which is a data management system established by the Centers for Disease Control and Prevention, Ministry of Health and Welfare, Republic of Korea (iCReaT Study No. C110016). Clinical events that occurred within 2 years of follow-up were analyzed.

Primary and Secondary End Points

The primary end point was all-cause death. Secondary end points were cardiac death, noncardiac death, recurrent MI, and repeat revascularization. All deaths were considered cardiac unless an undisputed noncardiac cause was present. Recurrent MI was defined as recurrence of symptoms or presence of electrocardiographic changes in association with a rise in cardiac biomarker level above the upper limit of normal. Periprocedural MI was not included as a clinical outcome. Clinically driven revascularization that occurred after discharge from the index hospitalization was coded as a repeat revascularization event according to the Academic Research Consortium definitions.

Statistical Analysis

Categorical variables were presented as numbers and relative frequencies (percentages). They were compared using the chi-squared test. Continuous variables are expressed as mean±SD. They were compared using an independent-sample *t* test. Cumulative event rates were calculated based on Kaplan–Meier censoring estimates. Comparison of clinical outcomes between patients with MINOCA and patients with MI-CAD was performed with a log-rank test. Given that differences in baseline characteristics could significantly affect outcomes, a multivariable Cox regression model was performed, adjusting for confounders as much as possible. Covariates in the multivariable model were selected if they were significantly different between the 2 groups, including the following: age, sex, Killip class at initial presentation, diabetes mellitus, current smoking, ST changes in the initial ECG, lipid profile, and left ventricular ejection fraction. A

Table 1. Baseline Demographic, Laboratory, and Angiographic Characteristics

	Overall Population (N=13 104)	MINOCA (N=396)	MI-CAD (N=10 871)	*P* Value
Demographic characteristics				
Age, y	64.0±12.6	62.3±12.6	63.4±12.7	0.097
Male	9686 (73.9%)	227 (57.3%)	8144 (74.9%)	<0.001
BMI, kg/m^2	24.0±3.4	23.8±3.4	24.0±3.3	0.149
Symptom at presentation				
Typical chest pain	11 294 (86.2%)	315 (79.5%)	9475 (87.2%)	<0.001
Dyspnea	3105 (23.7%)	85 (21.5%)	2482 (22.8%)	0.540
Killip				0.008
1	10 220 (78.0%)	325 (82.1%)	8602 (79.1%)	
2	1133 (8.6%)	42 (10.6%)	893 (8.2%)	
3	977 (7.5%)	14 (3.5%)	741 (6.8%)	
4	773 (5.9%)	15 (3.8%)	634 (5.8%)	
Cardiac arrest on arrival	96 (0.7%)	2 (0.5%)	77 (0.7%)	1.0
Previous history of angina	1279 (9.8%)	48 (12.1%)	394 (3.6%)	<0.001
Previous history of heart failure	213 (1.6%)	12 (3.0%)	92 (0.8%)	<0.001
Hypertension	6690 (51.1%)	201 (50.8%)	5320 (48.9%)	0.506
Diabetes mellitus	3752 (28.6%)	87 (22.0%)	2882 (26.5%)	0.050
Dyslipidemia	1388 (10.6%)	35 (8.8%)	1116 (10.3%)	0.397
Family history of CAD	830 (6.3%)	19 (4.8%)	715 (6.6%)	0.182
Current smoking	5113 (39.0%)	126 (31.8%)	4492 (41.3%)	<0.001
Previous CVA	888 (6.8%)	23 (5.8%)	671 (6.2%)	0.904
Initial vital sign				
Systolic BP	130.1±30.0	132.8±30.7	130.5±29.9	0.136
Diastolic BP	78.6±18.3	78.9±17.9	79.0±18.3	0.920
Heart rate	78.7±19.6	80.2±18.6	78.3±19.3	0.046
Initial ECG				
ST elevation	6194 (46.9%)	59 (14.9%)	5684 (52.3%)	<0.001
ST depression	1567 (12.0%)	36 (9.1%)	1285 (11.8%)	0.115
Wide QRS tachycardia	112 (0.8%)	6 (1.5%)	83 (0.8%)	0.134
Atrial fibrillation	712 (5.4%)	30 (7.6%)	610 (5.6%)	0.093
Complete atrioventricular block	62 (0.5%)	0 (0.0%)	58 (0.5%)	0.271
Laboratory characteristics				
Creatinine, mg/dL	1.1±1.2	1.0±1.0	1.1±1.1	0.085
Peak CK-MB, ng/mL	110.6±164.4	31.1±67.3	118.5±170.1	<0.001
Troponin, ng/mL				
Troponin I	46.8±105.6 (n=11 182)	9.6±26.7 (n=368)	50.2±111.7 (n=9197)	<0.001
Troponin T	14.2±459.6 (n=1922)	0.6±0.9 (n=28)	15.9±492.4 (n=1674)	<0.001
Total cholesterol	177.9±46.3	169.1±55.3	182.4±45.2	<0.001
Triglyceride, mg/dL	134.5±120.1	128.5±207.9	136.8±120.1	0.231
HDL-C, mg/dL	42.8±12.5	47.2±14.2	42.8±12.0	<0.001
LDL-C, mg/dL	112.0±39.6	100.6±36.0	116.0±39.1	<0.001
LVEF, %	51.9±11.2	58.5±11.0	52.2±10.6	<0.001

Continued

Table 1. Continued

	Overall Population (N=13 104)	MINOCA (N=396)	MI-CAD (N=10 871)	*P* Value
Regional wall motion index	1.42±0.39	1.19±0.33	1.41±0.37	<0.001
Angiographic characteristics				
Multivessel disease	5761 (44.0%)		5024 (46.2%)	
Left main disease	658 (5.0%)		526 (4.8%)	
Culprit lesion				
Left main	274 (2.1%)		217 (2.0%)	
LAD	5476 (41.8%)		4910 (45.2%)	
LCX	2053 (15.7%)		1790 (16.5%)	
RCA	3951 (30.2%)		3462 (31.8%)	
Pre-TIMI flow of culprit				
0	5518 (42.1%)		4956 (47.8%)	
1	1286 (9.8%)		1113 (10.7%)	
2	1813 (13.8%)		1566 (15.1%)	
3	3137 (23.9%)		2744 (26.4%)	
Culprit treatment				
Plain balloon angioplasty	802 (6.1%)		458 (4.4%)	
Bare-metal stent	325 (2.5%)		312 (3.0%)	
First-generation DES	170 (1.3%)		148 (1.4%)	
Second-generation DES	10 381 (79.2%)		9400 (91.1%)	
Successful PCI	11 580 (88.4%)		10 236 (94.2%)	
Total revascularization	8063 (61.5%)		7442 (68.5%)	
Total number of stent	1.3±0.9		1.4±0.8	
CABG	258 (2.0%)		199 (1.8%)	

Values are n (%) or mean±SD. *P* value is from a comparison of MINOCA and MI-CAD. BMI indicates body mass index; BP, blood pressure; CABG, coronary artery bypass surgery; CAD, coronary artery disease; CK-MB, creatine kinase-myocardial band; CVA, cerebrovascular accident; DES, drug-eluting stent; HDL-C, high-density lipoprotein cholesterol; LAD, left anterior descending artery; LCX, left circumflex artery; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI-CAD, myocardial infarction with obstructive coronary artery disease; MINOCA, myocardial infarction with nonobstructive coronary arteries; PCI, percutaneous coronary intervention; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.

propensity score analysis was also performed to adjust for potential confounders with a logistic regression model. The variables listed above were used. Prediction accuracy of the logistic model was assessed with an area under the receiver-operating characteristic curve (C statistic), which was 0.802 (95% CI, 0.780–0.825). According to the propensity score, patients were selected by 1:1 matching without replacement using the nearest neighbor method. A caliper width of 0.2 standardized differences (SD) was used for matching. This value has been shown to eliminate almost 99% of the bias in observed confounders.[13] Furthermore, to identify independent predictors of all-cause death in patients with MINOCA, we used a multivariable Cox proportional hazard model. The C-statistics with 95% CI were calculated to validate the discriminant function of the model. Echocardiogram data of 486 patients (4.3%) was missing: 25 in MINOCA (6.3%) and 461 in MI-CAD (4.2%). We performed the multiple imputation for missing data of the echocardiogram. As a sensitivity analysis, we analyzed data of patients without missing data of echocardiogram (Tables S1 through S3). In all analyses, participating centers were included as the stratification factor. All probability values were 2-sided, and $P<0.05$ was considered statistically significant. Statistical packages of SPSS software (version 22.0; SPSS, Inc., Chicago, IL) were used for all statistical analyses.

Results

Baseline Characteristics Between the Groups

Baseline characteristics of the patient groups are listed in Table 1. Compared with patients with MI-CAD, those with MINOCA were more likely to be women, but less likely to be diabetic. They had a lower Killip class, lower creatine kinase-myocardial band level, lower low-density lipoprotein cholesterol, higher high-density lipoprotein cholesterol, higher

ejection fraction, and lower regional wall motion score in the echocardiogram. However, rates of previous angina and previous heart failure were higher in MINOCA than in MI-CAD.

In-Hospital Events and Medications After Discharge

In-hospital clinical events in patients and medications at discharge and 1 year are summarized in Table 2. Frequencies of cardiogenic shock and ventricular arrhythmias were lower in patients with MINOCA than in those with MI-CAD during hospitalization. Rate of in-hospital death, recurrent MI, stroke, acute kidney injury, sepsis, or multiorgan failure did not significantly differ between the 2 groups of patients. However, the discharge therapies, including dual antiplatelet therapy, renin-angiotensin system blockers, beta-blockers, and statin, were less frequently used in patients with MINOCA. Use of calcium-channel blockers was higher in patients with MINOCA than that in those with significant stenosis. This trend of the medications was maintained at 12 months after the index hospitalization.

Mid-Term Clinical Outcomes

Results of the comparison of clinical outcomes at 2 years between MINOCA and MI-CAD are shown in Table 3 and Figure 2. The median follow-up duration of patients with MINOCA was similar to that of those with MI-CAD (median [interquartile range]; 733 [697–759] versus 732 days [694–760]; P=0.68). The unadjusted rate of all-cause death at 2 years (ie, the primary outcome) did not significantly differ between patients with MINOCA and those with MI-CAD. For the secondary outcomes, the rate of cardiac death, noncardiac death, and recurrent MI was not significantly different between the 2 groups either. However, the rate of repeat revascularization was higher in patients with MI-CAD.

Risk of all-cause death in patients with MINOCA did not significantly differ from that of those with MI-CAD after multivariate adjustment (hazard ratio [HR], 1.18; 95% CI, 0.74–1.87; P=0.49) and propensity matching (HR, 1.25; 95% CI, 0.77–2.05; P=0.36; Tables S4 and S5). Risk of cardiac death, noncardiac death, or recurrent MI was not significantly different either between the 2 groups. However, risk of repeat revascularization was higher in patients with MI-CAD after multivariate adjustment and propensity matching.

Characteristics and Clinical Results According to Coronary Spasm Test in Patients With MINOCA

Patients with positive vasospasm were younger, more male, and more likely to have typical symptoms, ST elevation on the ECG, low serum creatinine, high ejection fraction, and low regional wall motion index compared with those with MINOCA and negative vasospasm (Table S6). The rate of in-hospital events was not different between the 2 groups.

Table 2. In-Hospital Events and Medications After Discharge

	MINOCA (N=396)	MI-CAD (N=10 871)	P Value
In-hospital events			
Cardiogenic shock	20 (5.1%)	971 (8.9%)	0.008
New-onset heart failure	14 (3.5%)	452 (4.2%)	0.689
Recurrent ischemia	0 (0.0%)	96 (0.9%)	0.051
Recurrent MI	0 (0.0%)	43 (0.4%)	0.406
Cerebral infarction	4 (1.0%)	69 (0.6%)	0.327
Cerebral hemorrhage	1 (0.3%)	14 (0.1%)	0.416
Hemoglobin decrease >5 g/dL	3 (0.8%)	128 (1.2%)	0.632
Ventricular arrhythmia	8 (2.0%)	514 (4.7%)	0.014
Acute kidney injury	4 (1.0%)	99 (0.9%)	0.785
Sepsis	4 (1.0%)	60 (0.6%)	0.288
Multiorgan failure	2 (0.5%)	69 (0.6%)	1.000
Temporary pacemaker	0 (0.0%)	347 (3.2%)	<0.001
ICD	0 (0.0%)	6 (0.1%)	1.000
In-hospital death	11 (2.8%)	382 (3.5%)	0.575
Cardiac death	7 (1.8%)	323 (3.0%)	0.182
Noncardiac death	4 (1.0%)	59 (0.5%)	
Medication at discharge			
Aspirin	378 (95.5%)	10 840 (99.7%)	<0.001
P2Y12 inhibitor	146 (36.9%)	10 493 (96.5%)	<0.001
Calcium-channel blocker	208 (52.5%)	596 (5.5%)	<0.001
Beta-blocker	133 (33.6%)	9080 (83.5%)	<0.001
RAS blocker	192 (48.5%)	8517 (78.3%)	<0.001
Statin	289 (73.0%)	9988 (91.9%)	<0.001
Medication at 1 year			
Aspirin	293 (84.9%)	8783 (91.2%)	<0.001
P2Y12 inhibitor	57 (16.5%)	5306 (55.1%)	<0.001
Calcium-channel blocker	179 (51.9%)	647 (6.7%)	<0.001
Beta-blocker	90 (26.1%)	7176 (74.5%)	<0.001
RAS blocker	137 (39.7%)	6567 (68.2%)	<0.001
Statin	223 (64.6%)	8591 (89.2%)	<0.001

Values are n (%). ICD indicates implantable cardioverter-defibrillator; MI, myocardial infarction; MI-CAD, myocardial infarction with obstructive coronary artery disease; MINOCA, myocardial infarction with nonobstructive coronary arteries; RAS, renin-angiotensin system.

Table 3. Comparison of 2-Year Clinical Outcomes

	MINOCA (N=396)	MI-CAD (N=10 871)	Unadjusted		Multivariable-Adjusted		Propensity-Score Matched	
			HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All-cause death*	9.1 (36)	8.8 (954)	1.04 (0.74–1.45)	0.832	1.18 (0.74–1.87)	0.493	1.25 (0.77–2.05)	0.364
Noncardiac death	4.0 (16)	2.6 (285)	1.55 (0.93–2.56)	0.09	1.21 (0.59–2.48)	0.596	1.81 (0.80–4.10)	0.154
Cardiac death	5.1 (20)	6.2 (669)	0.82 (0.53–1.28)	0.384	1.13 (0.62–2.08)	0.689	1.01 (0.54–1.87)	0.986
Recurrent MI	2.8 (11)	2.2 (241)	1.23 (0.65–2.31)	0.528	1.12 (0.52–2.42)	0.764	0.92 (0.39–2.18)	0.856
Any repeat revascularization	1.3 (5)	7.2 (783)	0.17 (0.07–0.41)	<0.001	0.22 (0.09–0.53)	0.001	0.15 (0.06–0.38)	<0.001
Death or MI	11.6 (46)	10.7 (1158)	1.08 (0.81–1.46)	0.594	1.17 (0.78–1.75)	0.451	1.14 (0.74–1.74)	0.554

Values are % (n), unless otherwise indicated. Cumulative incidences of clinical outcomes at 2 years are presented. The number of patients with specific events is presented in parentheses. Multivariable Cox proportional hazard regression model and propensity-score–matched cohort were used to adjust for baseline differences between the comparative groups. HR indicates hazard ratio; MI, myocardial infarction; MI-CAD, myocardial infarction with obstructive coronary artery disease; MINOCA, myocardial infarction with nonobstructive coronary arteries.
*The primary outcome of the study.

Most of the patients with positive vasospasm were prescribed calcium-channel blockers whereas dual antiplatelet therapy, renin-angiotensin system blockers, and beta-blockers were used less frequently in patients with positive vasospasm. This trend was also maintained at 12 months after the index hospitalization (Table S7). Incidence of all-cause death was lower in patients with positive vasospasm than in those with negative vasospasm (3.2% versus 11.0%; *P*=0.023). There is no difference in occurrence of recurrent MI (4.2% versus 2.3%; *P*=0.304) and repeat revascularization (3.2% versus 0.7%; *P*=0.092) between the 2 groups.

Independent Predictors of Mortality in Patients With MINOCA

Multivariable Cox proportional hazard models were used to identify the independent predictors of all-cause death at 2 years in patients with MINOCA (Table 4). At the patients' initial presentation, an old age, atypical symptoms, ST elevation on the ECG, Killip Class IV, and diabetes mellitus were independent predictors of all-cause death at 2 years. MI by vasospasm was not associated with risk of all-cause death at 2 years (HR, 0.54; 95% CI, 0.16–1.84; *P*=0.323). Patients with ST elevation had lower ejection fraction (54.1±12.1% versus 59.7±10.9%; *P*=0.003), but higher regional wall motion index (1.41±0.43 versus 1.16±0.31; *P*<0.001). Regarding medical treatment, the nonuse of renin-angiotensin system blockers (HR, 2.63; 95% CI, 1.08–6.25; *P*=0.033) and statins (HR, 2.17; 95% CI, 1.04–4.54; *P*=0.039) were independently associated with an increased risk of all-cause death at 2 years.

Discussion

In the present study, 2-year clinical outcomes were compared between MINOCA and MI-CAD using data from a nation-wide, multicenter, prospective MI registry. Although patients with MINOCA had lower risk profiles compared with those with MI-CAD, their frequencies of in-hospital events, such as MI, stroke, acute kidney injury, sepsis, and multiorgan failure and rates of mortality and recurrent MI at 2 years, were similar. For patients with MINOCA, use of renin-angiotensin system blockers and statins showed a significantly lower risk of all-cause death.

Previous meta-analyses have demonstrated that patients with MINOCA have a lower likelihood of death or cardiovascular events than those with MI-CAD.[14,15] Baseline characteristics were comparable with previous studies. MINOCA patients of our study also were less likely to be male, diabetic, current smoker, and to be treated with antiplatelet agents, beta-blockers, renin-angiotensin system blockers, and statins. Age and frequency of hypertension in MINOCA patients were higher compared with the previous studies. The results of each of the studies enrolled in the meta-analysis are heterogeneous. Several studies have reported that patients with MINOCA and those with MI-CAD show a similar long-term mortality.[6,7,16–18] The reason for such discrepancies among the studies is likely attributed to the different inclusion criteria because patients with MINOCA have heterogenous mechanistic profiles. In particular, Takostubo syndrome is 1 of the primary mechanisms of MINOCA.[1] Other medical conditions and neurological disorders are critical triggering factors and contribute to the mortality increase in Takostubo syndrome.[19] In the present study, frequency of those conditions in the index hospitalization did not significantly differ between the MINOCA group and the MI-CAD group. A previous study[16] reported that causes of death of MINOCA patients were significantly less often cardiovascular. Though the rate of noncardiac death was numerically higher in patients with MINOCA of previous studies those with MINOCA in this study, it was not statistically significant in every analysis. This

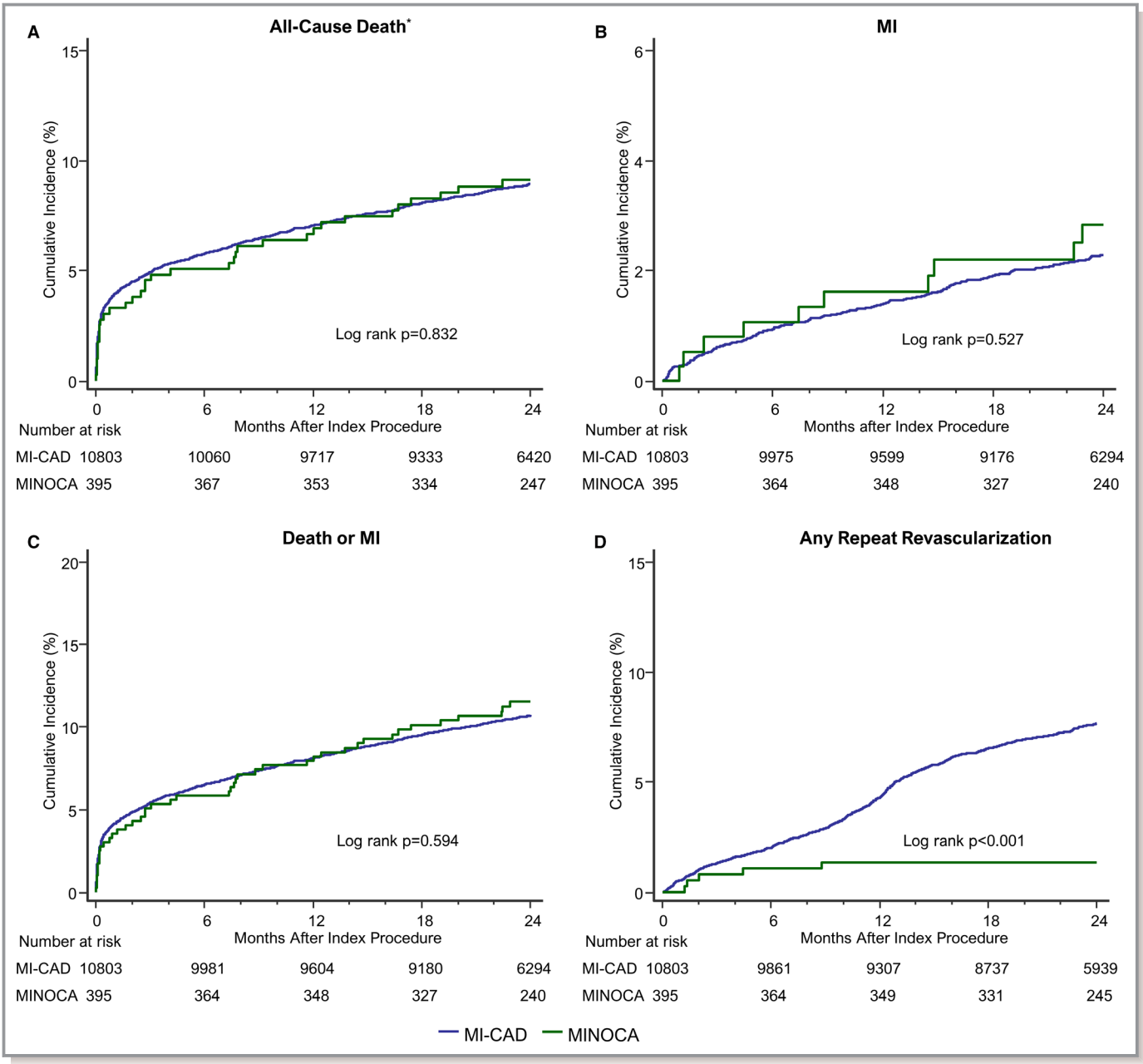

Figure 2. Cumulative incidence of primary and secondary outcomes. Kaplan–Meier curves with cumulative hazards of (A) all-cause death, (B) MI, (C) death or MI, and (D) any repeat revascularization. MI indicates myocardial infarction; MI-CAD, myocardial infarction with obstructive coronary artery disease; MINOCA, myocardial infarction with nonobstructive coronary arteries. *The primary outcome of the study.

suggests that MINOCA patients in this study were more homogenous than those of the other studies.

Elucidating the pathophysiological cause of MINOCA is challenging, but crucial to establish an appropriate management strategy. Coronary spasm and spontaneous coronary dissection (type 2 MI) as well as atherosclerotic plaque disruption and coronary thrombosis (type 1 MI) may be the cause of MINOCA.[20] A provocation test with intracoronary acetylcholine or ergonovine to rule out the vasospasm in MINOCA can be performed safely to identify high-risk patients.[8] In this study, 24% of patients with MINOCA had vasospasm. That rate was comparable with the rate reported in previous studies.[15] The prognosis of patients with MINOCA by vasospasm remains controversial.[8] However, the presence of vasospasm did not influence the risk of all-cause death in the present study.

The long-term medical treatment strategy in patients with MINOCA is also a challenging issue. Previous studies have suggested that use of renin-angiotensin system blockers[9,10] and statins[9] is associated with a lower risk of all-cause death.

Table 4. Independent Predictors of All-Cause Death in Patients With MINOCA

	Hazard Ratio	95% CI	*P* Value
Age	1.04	1.01 to 1.08	0.02
Atypical symptom	5.98	2.68 to 13.37	<0.001
ST elevation at presentation	3.57	1.61 to 7.90	0.002
Killip Class I	Reference		
Class II	0.81	0.27 to 2.40	0.705
Class III	1.81	0.64 to 5.17	0.265
Class IV	6.05	2.13 to 17.20	0.001
Diabetes mellitus	3.12	1.47 to 6.64	0.003
Nonuse of RAS blocker	2.63	1.08 to 6.25	0.033
Nonuse of statin	2.17	1.04 to 4.54	0.039

Multivariate Cox model analysis for all-cause death. MINOCA indicates myocardial infarction with nonobstructive coronary arteries; RAS, renin-angiotensin system.

Our study was in line with those studies. Although one-quarter of the patients had vasospasm, use of calcium-channel blockers was not related to mortality. Use of dual antiplatelet therapy or use of beta-blockers was not an independent predictor of all-cause death either. Because nonobstructive coronary artery lesions cause most MIs,[21] use of renin-angiotensin system blockers and statins might be able to suppress the progression of nonobstructive plaques and the occurrence of major cardiac events. Nevertheless, in patients with CAD and absence of heart failure or depressed left ventricular function, renin-angiotensin system blockers has shown beneficial effects on mortality and morbidity.[9] Properly designed and powered randomized clinical trials are needed to confirm this hypothesis.

Consistent with a previous study,[22] the present study revealed that nonobstructive coronary artery disease was more common in patients with non-ST elevation MI than that in patients with ST-elevation MI. The present study also showed that ST elevation in MINOCA was associated with an increased risk of all-cause death. This can be explained by more extensive myocardial damage on echocardiography. Female sex also was not the predictor of mortality of MINOCA. Excess risk of post-MI death in women is restricted to those with MI-CAD in previous studies.[14,23] Furthermore, atypical symptoms was also an independent predictor of all-cause death in MINOCA. Compared with typical symptoms, atypical symptoms in MI are related to higher risk profiles of patients and delayed initial management known to be associated with increased mortality.[24]

This study had an inherent limitation regarding its observational nature with registry data. However, the KAMIR-NIH registry used standardized definitions for all collected variables regulated and monitored by the National Institutes of Health. In addition, this study did not include information from coronary intravascular imaging or magnetic resonance imaging to reveal all specific causes of AMIs. Stratification by the cause through an in-depth investigation might provide the prognosis and appropriate management strategy according to causes of MINOCA.

Conclusion

Patients with MINOCA have similar risk of all-cause death and MI at 2 years compared with those with MI-CAD. Treatment with renin-angiotensin system blockers and statins might improve the prognosis of these high-risk patients.

Disclosures

None.

References

1. Agewall S, Beltrame JF, Reynolds HR, Niessner A, Rosano G, Caforio AL, De Caterina R, Zimarino M, Roffi M, Kjeldsen K, Atar D, Kaski JC, Sechtem U, Tornvall P. ESC working group position paper on myocardial infarction with non-obstructive coronary arteries. *Eur Heart J*. 2017;38:143–153.
2. Roe MT, Harrington RA, Prosper DM, Pieper KS, Bhatt DL, Lincoff AM, Simoons ML, Akkerhuis M, Ohman EM, Kitt MM, Vahanian A, Ruzyllo W, Karsch K, Califf RM, Topol EJ. Clinical and therapeutic profile of patients presenting with acute coronary syndromes who do not have significant coronary artery disease. The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial Investigators. *Circulation*. 2000;102:1101–1106.
3. Diver DJ, Bier JD, Ferreira PE, Sharaf BL, McCabe C, Thompson B, Chaitman B, Williams DO, Braunwald E. Clinical and arteriographic characterization of patients with unstable angina without critical coronary arterial narrowing (from the TIMI-IIIA Trial). *Am J Cardiol*. 1994;74:531–537.
4. Patel MR, Chen AY, Peterson ED, Newby LK, Pollack CV Jr, Brindis RG, Gibson CM, Kleiman NS, Saucedo JF, Bhatt DL, Gibler WB, Ohman EM, Harrington RA, Roe MT. Prevalence, predictors, and outcomes of patients with non-ST-segment elevation myocardial infarction and insignificant coronary artery disease: results from the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) initiative. *Am Heart J*. 2006;152:641–647.
5. Dokainish H, Pillai M, Murphy SA, DiBattiste PM, Schweiger MJ, Lotfi A, Morrow DA, Cannon CP, Braunwald E, Lakkis N. Prognostic implications of elevated troponin in patients with suspected acute coronary syndrome but no critical epicardial coronary disease: a TACTICS-TIMI-18 substudy. *J Am Coll Cardiol*. 2005;45:19–24.
6. Andersson HB, Pedersen F, Engstrom T, Helqvist S, Jensen MK, Jorgensen E, Kelbaek H, Rader S, Saunamaki K, Bates E, Grande P, Holmvang L, Clemmensen P. Long-term survival and causes of death in patients with ST-elevation acute coronary syndrome without obstructive coronary artery disease. *Eur Heart J*. 2018;39:102–110.
7. Planer D, Mehran R, Ohman EM, White HD, Newman JD, Xu K, Stone GW. Prognosis of patients with non-ST-segment-elevation myocardial infarction and nonobstructive coronary artery disease: propensity-matched analysis from the Acute Catheterization and Urgent Intervention Triage Strategy trial. *Circ Cardiovasc Interv*. 2014;7:285–293.
8. Montone RA, Niccoli G, Fracassi F, Russo M, Gurgoglione F, Camma G, Lanza GA, Crea F. Patients with acute myocardial infarction and non-obstructive coronary arteries: safety and prognostic relevance of invasive coronary provocative tests. *Eur Heart J*. 2018;39:91–98.
9. Lindahl B, Baron T, Erlinge D, Hadziosmanovic N, Nordenskjold A, Gard A, Jernberg T. Medical therapy for secondary prevention and long-term outcome in patients with myocardial infarction with nonobstructive coronary artery disease. *Circulation*. 2017;135:1481–1489.
10. Manfrini O, Morrell C, Das R, Barth JH, Hall AS, Gale CP, Cenko E, Bugiardini R. Effects of angiotensin-converting enzyme inhibitors and beta blockers on

clinical outcomes in patients with and without coronary artery obstructions at angiography (from a Register-Based Cohort Study on Acute Coronary Syndromes). *Am J Cardiol*. 2014;113:1628–1633.

11. Kim JH, Chae SC, Oh DJ, Kim HS, Kim YJ, Ahn Y, Cho MC, Kim CJ, Yoon JH, Park HY, Jeong MH. Multicenter cohort study of acute myocardial infarction in Korea—interim analysis of the Korea Acute Myocardial Infarction Registry-National Institutes of Health Registry. *Circ J*. 2016;80:1427–1436.
12. Shin DI, Baek SH, Her SH, Han SH, Ahn Y, Park KH, Kim DS, Yang TH, Choi DJ, Suh JW, Kwon HM, Lee BK, Gwon HC, Rha SW, Jo SH. The 24-month prognosis of patients with positive or intermediate results in the intracoronary ergonovine provocation test. *JACC Cardiovasc Interv*. 2015;8:914–923.
13. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat*. 2011;10:150–161.
14. Pizzi C, Xhyheri B, Costa GM, Faustino M, Flacco ME, Gualano MR, Fragassi G, Grigioni F, Manzoli L. Nonobstructive versus obstructive coronary artery disease in acute coronary syndrome: a meta-analysis. *J Am Heart Assoc*. 2016;5:e004185. DOI: 10.1161/JAHA.116.004185.
15. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic review of patients presenting with suspected myocardial infarction and nonobstructive coronary arteries. *Circulation*. 2015;131:861–870.
16. Redondo-Dieguez A, Gonzalez-Ferreiro R, Abu-Assi E, Raposeiras-Roubin S, Aidhodjayeva O, Lopez-Lopez A, Castineira-Busto M, Pena-Gil C, Garcia-Acuna JM, Gonzalez-Juanatey JR. Long-term prognosis of patients with non-ST-segment elevation acute myocardial infarction and coronary arteries without significant stenosis. *Rev Esp Cardiol (Engl Ed)*. 2015;68:777–784.
17. Safdar B, Spatz ES, Dreyer RP, Beltrame JF, Lichtman JH, Spertus JA, Reynolds HR, Geda M, Bueno H, Dziura JD, Krumholz HM, D'Onofrio G. Presentation clinical profile, and prognosis of young patients with myocardial infarction with nonobstructive coronary arteries (MINOCA): results from the VIRGO study. *J Am Heart Assoc*. 2018;7:e009174. DOI: 10.1161/JAHA.118.009174.
18. Da Costa A, Isaaz K, Faure E, Mourot S, Cerisier A, Lamaud M. Clinical characteristics, aetiological factors and long-term prognosis of myocardial infarction with an absolutely normal coronary angiogram; a 3-year follow-up study of 91 patients. *Eur Heart J*. 2001;22:1459–1465.
19. Ghadri JR, Kato K, Cammann VL, Gili S, Jurisic S, Di Vece D, Candreva A, Ding KJ, Micek J, Szawan KA, Bacchi B, Bianchi R, Levinson RA, Wischnewsky M, Seifert B, Schlossbauer SA, Citro R, Bossone E, Munzel T, Knorr M, Heiner S, D'Ascenzo F, Franke J, Sarcon A, Napp LC, Jaguszewski M, Noutsias M, Katus HA, Burgdorf C, Schunkert H, Thiele H, Bauersachs J, Tschope C, Pieske BM, Rajan L, Michels G, Pfister R, Cuneo A, Jacobshagen C, Hasenfuss G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Banning A, Cuculi F, Kobza R, Fischer TA, Vasankari T, Airaksinen KEJ, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Empen K, Felix SB, Delmas C, Lairez O, El-Battrawy I, Akin I, Borggrefe M, Horowitz J, Kozel M, Tousek P, Widimsky P, Gilyarova E, Shilova A, Gilyarov M, Winchester DE, Ukena C, Bax JJ, Prasad A, Bohm M, Luscher TF, Ruschitzka F, Templin C. Long-term prognosis of patients with Takotsubo syndrome. *J Am Coll Cardiol*. 2018;72:874–882.
20. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. 2019;40:237–269.
21. Chang HJ, Lin FY, Lee SE, Andreini D, Bax J, Cademartiri F, Chinnaiyan K, Chow BJW, Conte E, Cury RC, Feuchtner G, Hadamitzky M, Kim YJ, Leipsic J, Maffei E, Marques H, Plank F, Pontone G, Raff GL, van Rosendael AR, Villines TC, Weirich HG, Al'Aref SJ, Baskaran L, Cho I, Danad I, Han D, Heo R, Lee JH, Rivzi A, Stuijfzand WJ, Gransar H, Lu Y, Sung JM, Park HB, Berman DS, Budoff MJ, Samady H, Shaw LJ, Stone PH, Virmani R, Narula J, Min JK. Coronary atherosclerotic precursors of acute coronary syndromes. *J Am Coll Cardiol*. 2018;71:2511–2522.
22. Johnston N, Jonelid B, Christersson C, Kero T, Renlund H, Schenck-Gustafsson K, Lagerqvist B. Effect of gender on patients with ST-elevation and non-ST-elevation myocardial infarction without obstructive coronary artery disease. *Am J Cardiol*. 2015;115:1661–1666.
23. Smilowitz NR, Mahajan AM, Roe MT, Hellkamp AS, Chiswell K, Gulati M, Reynolds HR. Mortality of myocardial infarction by sex, age, and obstructive coronary artery disease status in the ACTION Registry-GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry-Get With the Guidelines). *Circ Cardiovasc Qual Outcomes*. 2017;10:e003443.
24. Fujino M, Ishihara M, Ogawa H, Nakao K, Yasuda S, Noguchi T, Ozaki Y, Kimura K, Suwa S, Fujimoto K, Nakama Y, Morita T, Shimizu W, Saito Y, Hirohata A, Morita Y, Inoue T, Okamura A, Uematsu M, Ako J, Nakai M, Nishimura K, Miyamoto Y. Impact of symptom presentation on in-hospital outcomes in patients with acute myocardial infarction. *J Cardiol*. 2017;70:29–34.

Supplemental Material

Appendix

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Principal Investigator	Myung Ho Jeong	Chonnam National University Hospital	Gwangju
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Sub-investigator	Chong Jin Kim	Kyunghee University Hospital at Gangdong	Seoul
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Co-investigator	Hyeon-Cheol Gwon	Samsung Medical Center	Seoul
Co-investigator	Ki Bae Seung	Seoul St. Mary's Hopital	Seoul
Co-investigator	Dong Joo Oh	Korea University Guro Hospital	Seoul
Co-investigator	Shung Chull Chae	Kyungpook National University hospital	Daegu
Co-investigator	Kwang Soo Cha	Pusan National University Hospital	Busan
Co-investigator	Junghan Yoon	WONJU SEVERANCE CHRISTIAN HOSPITAL	Wonju
Co-investigator	Jei-Keon Chae	Chonbuk National University Hospital	Jeongju(Jeollabuk-do)
Co-investigator	Seung Jae Joo	Jeju National University Hospital	Jeju
Co-investigator	Dong-Ju Choi	Seoul National University Bundang Hospital	Bundang(Gyeonggi)
Co-investigator	Seung-Ho Hur	KEIMYUNG UNIVERSITY DONGSAN MEDICAL CENTER	Daegu
Co-investigator	In Whan Seong	CHUNGNAM NATIONAL UNIVERSITY HOSPITAL	Daejeon
Co-investigator	Doo Il Kim	Inje University Haeundae Paik Hospital	Busan
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Co-investigator	Tae Hoon Ahn	Gachon University Gil Medical Center	Incheon
Co-investigator	Jin-Yong Hwang	Gyeongsang National University Hospital	Jinju(Gyeongsangnam-do)

Table S1. Baseline demographic, laboratory, and angiographic characteristics in patients without missing data of echocardiogram.

	MINOCA (N=371)	**MI-CAD (N=10,410)**	**p Value**
Demographic characteristics			
Age, years	62.0±12.7	63.2±12.6	0.070
Male	214(57.7%)	7810(75.0%)	<0.001
BMI, kg/m^2	23.8±3.3	24.0±3.3	0.188
Symptom at presentation			
Typical chest pain	296(79.8%)	91005(87.4%)	<0.001
Dyspnea	80(21.6%)	2354(22.6%)	0.665
Killip			0.007
1	306(82.5%)	8330(80.0%)	
2	41(11.1%)	862(8.3%)	
3	14(3.8%)	713(6.8%)	
4	10(2.7%)	505(4.9%)	
Cardiac arrest on arrival	1 (0.3%)	53 (0.5%)	1.0
Prior history of angina	44 (11.9%)	377 (3.6%)	<0.001
Prior history of heart failure	12 (3.2%)	102 (1.0%)	<0.001

Hypertension	187(50.4%)	5065(48.7%)	0.526
Diabetes	82(22.1%)	2734(26.3%)	0.083
Dyslipidemia	31(8.4%)	1075(10.3%)	0.259
Family history of CAD	17(4.6%)	692(6.6%)	0.140
Current Smoking	119(32.1%)	4340(41.7%)	<0.001
Previous CVA	22(5.9%)	643(6.2%)	0.988
Initial Vital Sign			
Systolic BP	133.8±28.5	131.1±29.0	0.077
Diastolic BP	79.9±16.3	79.5±17.9	0.603
Heart Rate	79.8±17.8	78.2±18.8	0.082
Initial ECG			
ST elevation	50(13.5%)	5413(52.0%)	<0.001
ST depression	34(9.2%)	1237(11.9%)	0.123
Wide QRS Tachycardia	6(1.6%)	80(0.8%)	0.076
Atrial fibrillation	26(7.0%)	570(5.5%)	0.201
Complete AV Block	0(0.0%)	48(0.5%)	0.414
Laboratory Characteristics			
Creatinine, mg/dl	1.0±1.0	1.1±1.1	0.085

Peak CK-MB, ng/ml	31.1±67.3	118.5±170.1	<0.001
Troponin, ng/ml			
Troponin I	9.3±25.3 (n=352)	49.4±111.2 (n=8,965)	<0.001
Troponin T	0.7±1.0 (n=19)	16.1±497.2 (n=1,445)	<0.001
Total cholesterol	170.0±53.2	182.7±44.2	<0.001
Triglyceride, mg/dl	130.0±194.7	136.4±115.2	0.532
HDL-C, mg/dl	46.6±13.2	42.8±11.6	<0.001
LDL-C, mg/dl	102.7±33.2	116.2±37.9	<0.001
LVEF (%)	59.0±11.3	52.2±10.8	<0.001
Regional wall motion index	1.19±0.34	1.41±0.38	<0.001
Angiographic characteristics			
Multivessel disease		4801(46.1%)	
Left main disease		477(4.6%)	
Culprit lesion			
Left main		191(1.8%)	
LAD		4699(45.1%)	
LCX		1728(16.6%)	

RCA		3334(32.0%)	
Pre-TIMI flow of Culprit			
0		4737(47.6%)	
1		1066(10.7%)	
2		1524(15.3%)	
3		2625(26.4%)	
Culprit Treatment			
Plain balloon angioplasty		421(4.3%)	
Bare-metal stent		279(2.8%)	
First-generation DES		144(1.5%)	
Second-generation DES		9051(91.5%)	
Successful PCI		9840(94.5%)	
Total Revascularization		7191(69.1%)	
Total Number of Stent		1.4±0.8	
CABG		188(1.8%)	

Values are n (%) or mean ±SD. MINOCA= myocardial infarction with non-obstructive coronary arteries; MI-CAD= myocardial infarction with obstructive coronary artery disease; BMI= body mass index; CAD= coronary artery disease; CVA= cerebrovascular accident; BP= blood pressure; ECG= electrocardiogram; CK-MB= creatine kinase-myocardial band; HDL-C= high density lipoprotein cholesterol; LDL-C= low density lipoprotein cholesterol; LVEF= left ventricular ejection fraction; ; LAD = left anterior descending artery; LCX= left circumflex artery; RCA= right coronary artery; TIMI =Thrombolysis In Myocardial Infarction; DES=drug-eluting stent; PCI= percutaneous coronary intervention; CABG= coronary artery bypass surgery.

Table S2. In-hospital events and medications after discharge in patients without missing data of echocardiogram.

	MINOCA (N=371)	**MI-CAD (N=10,410)**	**p Value**
In-hospital Events			
Cardiogenic shock	14(3.81%)	785(7.5%)	0.007
New onset heart failure	14(3.8%)	430(4.1%)	0.894
Recurrent ischemia	0(0.0%)	86(0.8%)	0.124
Recurrent MI	0(0.0%)	42(0.4%)	0.404
Cerebral infarction	4(1.1%)	67(0.6%)	0.310
Cerebral hemorrhage	1(0.3%)	12(0.1%)	0.366
Hemoglobin decrease > 5g/dL	3(0.8%)	107(1.0%)	1.000
Ventricular Arrhythmia	7(1.9%)	438(4.2%)	0.023
Acute Kidney Injury	1(0.3%)	89(0.9%)	0.377
Sepsis	4(1.1%)	52(0.5%)	0.126
Multiorgan failure	1(0.3%)	43(0.4%)	1.000
Temporary pacemaker	0(0.0%)	311(3.0%)	<0.001
ICD	0(0.0%)	6(0.1%)	1.000
In-hospital Death	8(2.2%)	192(1.8%)	0.560

Cardiac death	4(1.1%)	147(1.4%)	0.167
Non-cardiac Death	4(1.0%)	45(0.4%)	
Medication at Discharge			
Aspirin	356(96.0%)	10394(99.8%)	<0.001
P2Y12 inhibitor	137(36.9%)	10144(97.4%)	<0.001
Calcium channel blocker	195(52.6%)	574(5.5%)	<0.001
Beta blocker	128(34.5%)	8848(85.0%)	<0.001
RAS blocker	187(50.4%)	8307(79.8%)	<0.001
Statin	277(74.7%)	9717(93.3%)	<0.001
Medication at 1 year			
Aspirin	281(85.2%)	8584(91.3%)	<0.001
P2Y12 inhibitor	54(16.4%)	5192(55.2%)	<0.001
Calcium channel blocker	169(51.2%)	621(6.6%)	<0.001
Beta blocker	88(26.7%)	7026(74.7%)	<0.001
RAS blocker	134(40.6%)	6433(68.4%)	<0.001
Statin	218(66.1%)	8395(89.2%)	<0.001

Values are n (%). MINOCA= myocardial infarction with non-obstructive coronary arteries; MI-CAD= myocardial infarction with obstructive coronary artery disease; MI= myocardial infarction; ICD= implantable cardioverter-defibrillator; RAS= renin-angiotensin system.

Table S3. Comparison of 2-Year Clinical Outcomes in patients without missing data of echocardiogram.

	MINOCA (N=371)	**MI-CAD (N=10410)**	**Unadjusted**		**Multivariable-Adjusted**		**Propensity-Score Matched**	
			HR(95% CI)	p value	HR(95% CI)	p value	HR(95%CI)	p value
All-cause death*	7.5 (28)	7.1 (737)	1.07(0.74-1.57)	0.715	1.12(0.70-1.82)	0.618	1.07(0.73-1.57)	0.718
Non-cardiac death	3.8 (14)	2.5 (261)	1.51(0.87-2.59)	0.129	1.23(0.60-2.52)	0.596	1.52(0.87-2.60)	0.129
Cardiac death	3.8 (14)	4.6 (476)	0.83(0.49-1.41)	0.492	1.04(0.55-1.97)	0.689	0.83(0.49-1.41)	0.492
Recurrent MI	2.7 (10)	2.1 (220)	1.29(0.68-2.43)	0.434	1.15(0.53-2.48)	0.726	1,29(0.68-2.42)	0.434
Any repeat revascularization	1.3 (5)	7.3 (758)	0.18(0.07-0.44)	<0.001	0.22(0.09-0.54)	0.001	0.18(0.07-0.44)	<0.001
Death or MI	10.0 (37)	8.8 (921)	1.14(0.82-1.58)	0.444	1.16(0.77-1.75)	0.492	1.14(0.82-1.58)	0.444

Values are % (n) unless otherwise indicated. The cumulative incidences of clinical outcomes at 2 years are presented. The number of patients with specific events is presented in parentheses. Multivariable Cox proportional hazard regression model and propensity-score matched cohort

were used to adjust for baseline differences between the comparative groups. MINOCA= myocardial infarction with non-obstructive coronary arteries; MI-CAD= myocardial infarction with obstructive coronary artery disease; MI= myocardial infarction. * indicates the primary outcome of the study.

Table S4. Baseline demographic, laboratory and angiographic characteristics in a propensity score matched population.

	MINOCA(N=394)	MI-CAD (N=394)	p
Demographic characteristics			
Age, yrs	62.5±12.4	62.6±12.8	0.881
Male	227(57.6%)	214(54.3%)	0.389
BMI, kg/m^2	23.8±3.4	24.0±3.5	0.433
Symptom at presentation			
Typical chest pain	313(79.4%)	348(88.3%)	0.001
Dyspnea	84(21.3%)	77(19.5%)	0.596
Killip			0.173
1	323(82.0%)	325(82.5%)	
2	42(10.7%)	28(7.1%)	
3	14(3.6%)	18(4.6%)	
4	15(3.8%)	23(5.8%)	
Cardiac arrest on arrival	2 (0.5%)	2 (0.5%)	1.0
Prior history of angina	48 (12.2%)	24 (6.1%)	0.004
Prior history of heart failure	12 (3.0%)	8 (2.0%)	0.498
Hypertension	201(51.0%)	223(56.6%)	0.133
Diabetes	87(22.1%)	84(21.3%)	0.863
Dyslipidemia	35(8.9%)	47(11.9%)	0.199
Family history of CAD	18(4.6%)	30(7.6%)	0.100
Current Smoking	125(31.7%)	130(33.0%)	0.761
Previous CVA	23(5.8%)	34(8.6%)	0.169

Initial Vital Sign			
Systolic BP	132.9±30.8	134.6±31.6	0.422
Diastolic BP	79.0±17.9	80.6±18.6	0.198
Heart Rate	80.3±18.6	78.3±19.6	0.157
Initial ECG			
ST elevation	59(15.0%)	60(15.2%)	1.000
ST depression	36(9.1%)	86(21.8%)	<0.001
Wide QRS Tachycardia	6(1.5%)	4(1.0%)	0.752
Atrial fibrillation	30(7.6%)	28(7.1%)	0.892
Complete AV Block	0(0.0%)	3(0.8%)	0.249
Laboratory Characteristics			
Creatinine, mg/dl	1.0±1.0	1.0±1.0	0.652
Peak CK-MB, ng/ml	30.9±67.2	66.7±92.0	0.000
Troponin, ng/ml			
Troponin I	9.5±26.7 (n=366)	27.0±62.1 (n=341)	<0.001
Troponin T	0.6±0.9 (n=28)	2.3±4.0 (n=53)	<0.001
Total cholesterol	169.3±55.4	169.0±40.9	0.937
Triglyceride, mg/dl	128.9±208.5	133.4±132.2	0.735
HDL-C, mg/dl	47.3±14.2	45.8±14.3	0.164
LDL-C, mg/dl	100.8±36.0	103.6±34.2	0.282
LVEF (%)	59.0±11.3	58.5±9.6	0.535
Regional wall motion index	1.2±0.3	1.2±0.3	0.141

Angiographic characteristics			
Multivessel disease		157(39.8%)	
Left main disease		20(5.1%)	
Culprit lesion			
Left main		10(2.5%)	
LAD		163(41.4%)	
LCX		85(21.6%)	
RCA		110(27.9%)	
Pre-TIMI flow of Culprit			
0		84(22.8%)	
1		46(12.5%)	
2		85(23.1%)	
3		153(41.6%)	
Culprit Treatment			
Plain balloon angioplasty		21(5.7%)	
Bare-metal stent		10(2.7%)	
First-generation DES		3(0.8%)	
Second-generation DES		332(90.7%)	
Successful PCI		365(92.6%)	
Total Revascularization		289(73.4%)	
Total Number of Stent		1.4±0.8	
CABG		4(1.0%)	

Values are n (%) or mean ±SD. MINOCA= myocardial infarction with non-obstructive coronary arteries; MI-CAD= myocardial infarction with obstructive coronary artery disease;

BMI= body mass index; CAD= coronary artery disease; CVA= cerebrovascular accident; BP= blood pressure; ECG= electrocardiogram; CK-MB= creatine kinase-myocardial band; HDL-C= high density lipoprotein cholesterol; LDL-C= low density lipoprotein cholesterol; LVEF= left ventricular ejection fraction; ; LAD = left anterior descending artery; LCX= left circumflex artery; RCA= right coronary artery; TIMI =Thrombolysis In Myocardial Infarction; DES=drug-eluting stent; PCI= percutaneous coronary intervention; CABG= coronary artery bypass surgery.

Table S5. In-hospital events and medications after discharge in a propensity score matched population.

	MINOCA(N=394)	MI-CAD (N=394)	p
In-hospital Events			
Cardiogenic shock	20(5.1%)	31(7.9%)	0.147
New onset heart failure	14(3.6%)	10(2.5%)	0.535
Recurrent ischemia	0(0.0%)	6(1.5%)	0.031
Reinfarction	0(0.0%)	0(0.0%)	1
Cerebral infarction	4(1.0%)	3(0.8%)	1
Cerebral hemorrhage	1(0.3%)	0(0.0%)	1
Hemoglobin decrease > 5g/dL	3(0.8%)	6(1.5%)	0.505
Ventricular Arrhythmia	8(2.0%)	12(3.0%)	0.498
Acute Kidney Injury	4(1.0%)	5(1.3%)	1
Sepsis	4(1.0%)	1(0.3%)	0.373
Multiorgan failure	2(0.5%)	2(0.5%)	1.000
Temporary pacemaker	0(0.0%)	18(4.6%)	<0.001
ICD	0(0.0%)	0(0.0%)	1
In-hospital Death	11(2.8%)	13(3.3%)	0.836
Cardiac death	7(1.8%)	11(2.8%)	0.458
Non-cardiac Death	4(1.0%)	2(0.5%)	
Medication at Discharge			
Aspirin	376(95.4%)	390(99.0%)	0.004
P2Y12 inhibitor	145(36.8%)	376(95.4%)	<0.001
Calcium channel blocker	207(52.5%)	40(10.2%)	<0.001

Beta blocker	133(33.8%)	317(80.5%)	<0.001
RAS blocker	192(48.7%)	316(80.2%)	<0.001
Statin	288(73.1%)	362(91.9%)	<0.001
Medication at 1 year			
Aspirin	291(84.8%)	319(90.6%)	0.021
P2Y12 inhibitor	56(16.3%)	174(49.4%)	<0.001
Calcium channel blocker	178(51.9%)	45(12.8%)	<0.001
Beta blocker	90(26.2%)	241(68.5%)	<0.001
RAS blocker	137(39.9%)	228(64.8%)	<0.001
Statin	222(64.7%)	307(87.2%)	<0.001

Values are n (%). MINOCA= myocardial infarction with non-obstructive coronary arteries; MI-CAD= myocardial infarction with obstructive coronary artery disease; MI= myocardial infarction; ICD= implantable cardioverter-defibrillator; RAS= renin-angiotensin system.

Table S6. Baseline demographic, laboratory and angiographic characteristics according to the presence of vasospasm.

	Positive vasospasm (N=95)	**insignificant stenosis(N=301)**	**p Value**
Demographic characteristics			
Age, yrs	57.5±11.8	63.8±12.5	<0.001
Male	69(72.6%)	158(52.5%)	0.001
BMI, kg/m^2	24.3±3.7	23.6±3.3	0.086
Symptom at presentation			
Typical chest pain	88(92.6%)	227(75.4%)	<0.001
Dyspnea	16(16.8%)	69(22.9%)	0.252
Killip			0.092
1	85(89.5%)	240(79.7%)	
2	4(4.2%)	38(12.6%)	
3	2(2.1%)	12(4.0%)	
4	4(4.2%)	11(3.7%)	
Cardiac arrest on arrival	1 (1.1%)	1 (0.3%)	0.423
Prior history of angina	19 (20.0%)	29 (9.6%)	<0.001
Prior history of heart failure	0 (0%)	12 (4.0%)	0.078
Hypertension	46(48.4%)	155(51.5%)	0.639
Diabetes	14(14.7%)	73(24.3%)	0.064
Dyslipidemia	7(7.4%)	28(9.3%)	0.681
Family history of CAD	6(6.3%)	13(4.3%)	0.416

Current Smoking	35(36.8%)	91(30.2%)	0.256
Previous CVA	4(4.2%)	19(6.3%)	0.616
Initial Vital Sign			
Systolic BP	128.1±28.3	134.2±31.4	0.090
Diastolic BP	78.2±16.5	79.2±18.3	0.651
Heart Rate	80.5±19.6	80.2±18.3	0.872
Initial ECG			
ST elevation	21(22.1%)	38(12.6%)	0.031
ST depression	5(5.3%)	31(10.3%)	0.156
Wide QRS Tachycardia	1(1.1%)	5(1.7%)	1.000
Atrial fibrillation	5(5.3%)	25(8.3%)	0.383
Complete AV Block	0	0	
Laboratory Characteristics			
Creatinine, mg/dl	0.8±0.2	1.1±1.2	0.022
Peak CK-MB, ng/ml	45.6±95.6	26.6±54.8	0.016
Troponin, ng/ml			
Troponin I	11.3±28.3 (n=81)	9.2±26.2 (n=287)	0.337
Troponin T	0.8±1.3 (n=14)	0.5±0.4 (n=14)	0.548
Total cholesterol	173.2±81.7	167.7±43.2	0.417
Triglyceride, mg/dl	160.5±383.1	118.1±98.5	0.113
HDL-C, mg/dl	47.3±13.2	47.2±14.5	0.952
LDL-C, mg/dl	100.0±35.8	100.8±36.1	0.865

LVEF (%)	62.5±9.5	57.8±11.6	0.001
Regional wall motion index	1.13±0.27	1.21±0.35	0.016

Values are n (%) or mean ±SD. The abbreviations are as in Table S1.

Table S7. In-hospital events and medication after discharge according to the presence of vasospasm.

	Positive vasospasm (N=95)	insignificant stenosis(N=301)	p Value
In-hospital Events			
Cardiogenic shock	5(5.3%)	15(5.0%)	1.000
New onset heart failure	2(2.1%)	12(4.0%)	0.533
Recurrent ischemia	0	0	
Reinfarction	0	0	
Cerebral infarction	0(0.0%)	4(1.3%)	0.576
Cerebral hemorrhage	0(0.0%)	1(0.3%)	1.000
Hemoglobin decrease > 5g/dL	0(0.0%)	3(1.0%)	1.000
Ventricular Arrhythmia	3(3.2%)	5(1.7%)	0.404
Acute Kidney Injury	1(1.1%)	3(1.0%)	1.000
Sepsis	2(2.1%)	2(0.7%)	0.244
Multiorgan failure	0(0.0%)	2(0.7%)	1.000
Temporary pacemaker	0	0	
ICD	0	0	
In-hospital Death	2(2.1%)	9(3.0%)	1.000
Cardiac death	1(1.1%)	6(2.0%)	0.831
Non-cardiac Death	1(1.1%)	3(1.0%)	
Medication at Discharge			
Aspirin	90(94.7%)	288(95.7%)	0.778
P2Y12 inhibitor	24(25.3%)	122(40.5%)	0.007

Calcium channel blocker	88(92.6%)	120(39.9%)	<0.001
Beta blocker	4(4.2%)	129(42.9%)	<0.001
RAS blocker	29(30.5%)	163(54.2%)	<0.001
Statin	70(73.7%)	219(72.8%)	0.895
Medication at 1 year			
Aspirin	78(89.7%)	215(83.3%)	0.170
P2Y12 inhibitor	6(6.9%)	51(19.8%)	0.004
Calcium channel blocker	77(88.5%)	102(39.5%)	<0.001
Beta blocker	3(3.4%)	87(33.7%)	<0.001
RAS blocker	30(34.5%)	107(41.5%)	0.258
Statin	61(70.1%)	162(62.8%)	0.244

Values are n (%). The abbreviations are as in Table S2.