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Comparison of Clinical Outcomes Following Acute Myocardial Infarctions in Hypertensive Patients With or Without Diabetes

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ABSTRACT

Background and Objectives: It is thought that patients with diabetes mellitus (DM) have a poor prognosis after an acute myocardial infarction (AMI), but the effect of diabetes on the outcomes of hypertensive patients with AMIs has not been elucidated in the Korean population. The aim of this study was to investigate the effects of diabetes on long-term clinical outcomes following AMIs in patients with hypertension. **Subjects and Methods**: Using data from the Korea Acute Myocardial Infarction Registry (November 2005 to December 2006), 2,233 hypertensive patients with AMIs were grouped as follows based on the presence of DM: group I, diabetic hypertension (n=892, 544 men, mean age=66.2±10.9 years); and group II, non-diabetic hypertension (n=1341, 938 men, mean age=63.9±12.8 years). The primary study outcomes included in-hospital death and major adverse cardiac events (MACE; cardiac death, myocardial infarction (MI), repeat percutaneous coronary intervention, and coronary artery bypass surgery) at the 1 year follow-up. **Results**: Hypertensive patients with DM were older and more likely to be women. The diabetic group had lower blood pressure ($p<0.001$), a lower left ventricular ejection fraction ($p<0.001$), a more severe degree of heart failure ($p<0.001$), a longer duration of coronary care unit admission ($p<0.001$), and a higher incidence of hyperlipidemia ($p=0.007$). The N-terminal pro-brain natriuretic peptide level (4602.5±8710.6 pg/mL vs. 2320.8 ±5837.9 pg/mL, $p<0.001$) was higher and the creatinine clearance (62.4±29.9 mL/min vs. 73.0±40.8 mL/min, $p<0.001$) was lower in the diabetic group than the non-diabetic group. Coronary angiographic findings revealed more frequent involvement of the left main stem ($p=0.002$) and multiple vessels ($p<0.001$) in the diabetic group. The rate of in-hospital death was higher in the diabetic group ($p<0.001$). During follow-up, the rates of composite MACE at 1 month, 6 months, and 12 months were higher in the diabetic group ($p<0.001$). **Conclusion**: In hypertensive patients with AMI, DM was associated with worse clinical and angiographic features, with a higher risk of development of severe heart failure, and an increased risk of MACE on long-term clinical follow-up. **(Korean Circ J 2009; 39:243-250)**

KEY WORDS: Diabetes mellitus; Hypertension; Myocardial infarction.

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Introduction

Diabetes mellitus (DM) is a common disease with substantial morbidity and mortality.[1)2)] Hypertension is a well-known risk factor for coronary artery disease and there is considerable evidence for an increased prevalence of hypertension in diabetics, affecting up to 60%.[2-5)] Moreover, each pathophysiologic disease entity serves to exacerbate the other.[3)6)] The presence of hypertension in diabetic patients significantly increases the risk of cardiovascular disease (CVD), including acute coronary syndrome.[5)7)] Generally, hypertension in type 2 diabetics clusters with other CVD risk factors, such as microalbuminuria, central obesity, insulin resistance, dyslipidemia, hypercoagulation, increased inflammation, and left ventricular hypertrophy.[5)] This clustering of risk factors in diabetics ultimately results in the development of CVD, which is the major cause of premature mortality in patients with type 2 DM. Previous studies are in agreement that DM is an independent risk for mortality after an acute myocardial infarction (AMI).[8-10)] Also, other several studies have shown that hypertension is associated with a worse prognosis after an AMI.[11-13)] Despite this consensus, the effect of DM on the outcomes of hypertensive patients following an AMI has not been clearly demonstrated within the Oriental population.

Therefore, we conducted the present study to analyze the clinical impact of DM on patients with hypertension following an AMI who were registered in the Korea Acute Myocardial Infarction Registry (KAMIR).

Subjects and Methods

Patient population and study design

The KAMIR is a prospective, multi-center, observational registry designed to examine current epidemiology, in-hospital management, and outcome of patients with AMIs in Korea for the commemoration of the 50th anniversary of the Korean Circulation Society.[14)15)] Among the patients with AMIs, 2,233 hypertensive patients who were followed-up at 1 year were included in the present study. These patients were grouped as follows based on the presence of DM: group I, patients who were assigned to the diabetic hypertensive group (total 892, 544 males, mean age=66.2±10.9 years); and group II, patients who were assigned to the non-diabetic hypertensive group (total 1,341, 938 males, mean age=63.9±12.8 years). Hypertension was defined as a blood pressure ≥140/90 mmHg, or when the patient was taking antihypertensive medication based on a history of diagnosed hypertension. DM was defined as a fasting plasma glucose level ≥126 mg/dL, a random plasma glucose level ≥200 mg/dL, or when the patient was taking oral hypoglycemic agents or using subcutaneous insulin based on a history of diagnosed DM. Eligible patients for this study were required to have all three of the following: 1) symptoms of ischemia increasing or occurring at rest, 2) an elevated cardiac troponin-I level (≥2.0 ng/mL) or creatine kinase-myocardial infarction (CK-MB) (19 U/L, exceeding twice the upper limit of normal), and 3) ischemic changes assessed by electrocardiography (ST-segment elevation, depression, or T wave inversion of ≥0.2 mV in two contiguous leads). Our study included patients in cardiogenic shock state (Killip class IV).

We analyzed baseline demographic and clinical characteristics, relevant laboratory results and pharmacotherapy. Echocardiography was performed in all patients before discharge. Major adverse cardiac events (MACE) at the 1 month, 6 months, and 1 year clinical follow-up were evaluated and were defined as the composite of 1) cardiac death, 2) non-cardiac death, 3) non-fatal myocardial infarction (MI), and 4) re-percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). Re-infarction was defined as the recurrence of symptoms or electrocardiographic changes in association with a rise in cardiac enzymes above the upper limit of normal. All data were recorded on a standardized, electronic, web-based registry at http://www.kamir.or.kr.

Statistical analysis

We compared the in-hospital mortality, the duration of admission to the coronary care unit, and the incidence of MACE during 1 month, 6 months, and 1 year of clinical follow-up between the 2 groups. The predictive factors for MACE at the 1 year clinical follow-up were calculated by multiple logistic regression analysis.

The Statistical Package for Social Sciences (SPSS) for Windows, version 15.0 (SPSS, Inc., Chicago, IL, USA) was used for all analysis. Continuous variables with normal distributions were expressed as the mean±standard deviation (SD) and they were compared with the use of an unpaired Student's t-test. Categorical variables were compared with the use of the chi-square test, where appropriate. A $p<0.05$ was deemed to be statistically significant.

Results

Baseline clinical characteristics of the study population

Among the 2,233 hypertensive patients with AMI who were followed-up for 1 year, there were 892 diabetic patients and 1,342 non-diabetic patients. The baseline clinical characteristics and laboratory findings of the study population are described in Table 1 and 2. Hypertensive patients with DM were older ($p<0.001$) and more likely to be women ($p<0.001$). Also, patients with DM had a higher proportion of smokers ($p<0.001$) and hyperlipidemia ($p=0.007$). The diabetic group had lower blood pressure ($p<0.001$), a lower left ventricular ejection frac-

Table 1. Baseline characteristics according to the presence of diabetes

	Group I (n=892)	Group II (n=1,342)	p
Mean age (years)	66.2±10.9	63.9±12.8	<0.001
Male (%)	544 (61.0)	938 (70.0)	<0.001
Obesity (%)	522 (58.5)	733 (54.7)	0.068
Past history (%)			
Smoking	427 (47.9)	775 (57.8)	<0.001
Hyperlipidemia	341 (38.2)	487 (36.2)	0.007
Familial history of coronary artery disesse	68 (7.6)	103 (7.7)	0.669
Prior angina	87 (9.8)	88 (6.6)	0.847
Prior myocardial infarction	45 (5.1)	50 (3.7)	0.522
Prior percutaneous coronary intervention	64 (7.2)	57 (4.3)	0.486
Prior coronary artery bypass graft	10 (1.1)	9 (0.7)	0.829
Symptoms and hemodynamics on admission			
Chest pain (%)	707 (79.3)	1,115 (83.1)	<0.001
Dyspnea (%)	259 (29.1)	312 (23.3)	<0.001
Systolic blood pressure (mmHg)	134.6±31.9	139.7±27.6	<0.001
Heart rate (beats/min)	81.5±21.2	76.2±17.8	<0.001
Killip class (%)			<0.001
I	587 (65.8)	1,050 (78.2)	
II	130 (14.6)	171 (12.7)	
III	106 (11.9)	64 (4.8)	
IV	56 (6.3)	37 (2.8)	
ST-segment elevation myocardial infarction	464 (67.1)	775 (57.8)	0.005
Echocardiogram findings			
Left ventricular ejection fraction (%)	49.9±13.2	53.5±12.1	<0.001
Total wall motion score	17.8±11.0	17.6±10.1	0.722

Table 2. Laboratory findings according to the presence of diabetes

	Group I (n=892)	Group II (n=1,342)	p
Creatinine clearance (mL/min)	62.4±29.9	73.0±40.8	<0.001
CK-MB (U/L)	118.5±169.8	144.7±216.6	0.001
Troponin-I (ng/mL)	46.4±76.0	50.2±92.9	0.368
Total cholesterol (mg/dL)	188.3±44.6	181.3±47.5	0.001
Triglyceride (mg/dL)	139.1±116.6	128.5±85.3	0.020
Low density lipoprotein-cholesterol (mg/dL)	116.5±45.2	121.2±42.3	0.017
High density lipoprotein-cholesterol (mg/dL)	43.9±13.9	46.3±16.5	<0.001
High sensitivity C-reactive protein (mg/dL)	30.3±130.7	25.6±119.2	0.423
N-terminal pro-brain natriuretic peptide (pg/mL)	4602.5±8710.6	2320.8±5837.9	<0.001

CK-MB: creatine kinase-myocardial band isoenzyme

tion (p<0.001), more severe heart failure (p<0.001), and a higher proportion of ST segment elevation myocardial infarction (STEMI; p=0.005). N-terminal pro-brain natriuretic peptide level (p<0.001) was higher and creatinine clearance (p<0.001) was lower in the diabetic group than the non-diabetic group.

Coronary angiographic findings

In the diabetic hypertension group, coronary angiography was performed in 92.9% of the patients during hospitalization, compared with 95.4% of the patients in the non-diabetic hypertension group. Also, PCI was done in 89.5% of patients in the diabetic group relative to 94.4% in the non-diabetic group, but the success rate of PCI showed no significant difference between the 2 groups. The baseline coronary angiographic characteristics are shown in Table 3. The most common infarct-related artery was the left anterior descending artery in both groups. The types of lesions according to the American College of Cardiology/American Heart Association (ACC/AHA) classification and the Thrombolysis In Myocardial Infarction (TIMI) flow grade before and after PCI showed no significant differences between the two groups. Left main stem and multivessel involvement were more pre

Table 3. Coronary angiographic findings according to the presence of diabetes

	Group I (n=892)	Group II (n=1,342)	p
Coronary angiogram, n (%)	829 (92.9)	1,280 (95.4)	0.009
Infarct-related artery, n (%)			
Left main stem	25 (3.0)	14 (1.1)	0.002
Left anterior descending artery	389 (47.0)	648 (50.6)	0.113
Left circumflex artery	138 (16.6)	240 (18.8)	0.229
Right coronary artery	277 (33.4)	378 (29.5)	0.070
ACC/AHA lesion type, n (%)			0.666
A	27 (4.5)	65 (5.1)	
B1	144 (17.2)	207 (16.2)	
B2	184 (22.2)	302 (23.6)	
C	364 (43.9)	546 (42.7)	
Diseased vessel number, n (%)			<0.001
Single vessel	281 (33.9)	562 (43.9)	
Two vessel	273 (32.9)	425 (33.2)	
Three vessel	275 (33.2)	293 (22.9)	
Percutaneous coronary intervention (PCI)	798 (89.5)	1,267 (94.4)	<0.001
Successful result of PCI	759 (95.1)	1,225 (96.7)	0.080
Pre-PCI TIMI flow grade, n (%)			0.281
0	303 (36.5)	524 (40.9)	
I	108 (13.0)	132 (10.3)	
II	149 (18.0)	213 (16.6)	
III	269 (32.5)	411 (32.2)	
Post-PCI TIMI flow grade, n (%)			0.090
0	19 (2.5)	22 (1.9)	
I	11 (1.5)	10 (0.9)	
II	35 (4.7)	44 (3.7)	
III	685 (91.3)	1,091 (93.5)	

ACC/AHA: American College of Cardiology/American Heart Association, TIMI: Thrombolysis In Myocardial Infarction

Table 4. Clinical outcomes and MACE during follow-up and 12 months after discharge

	Group I (n=892)	Group II (n=1,342)	p
Outcomes in-hospital period			
In-hospital death, n (%)	87 (9.8)	51 (3.8)	<0.001
Coronary care unit admission duration (days)	4.5±5.7	3.2±3.0	<0.001
The composite of MACE at 1 month, n (%)	63 (7.1)	48 (3.8)	<0.001
Cardiac death	24 (2.7)	12 (0.9)	0.002
Non-cardiac death	8 (0.9)	4 (0.3)	0.061
Myocardial infarction	12 (1.3)	14 (1.0)	0.514
Re-percutaneous coronary intervention	14 (1.6)	17 (1.1)	0.548
Coronary artery bypass graft	5 (0.6)	1 (0.1)	0.028
The composite of MACE at 6 months, n (%)	147 (16.5)	143 (10.7)	<0.001
Cardiac death	46 (5.2)	28 (2.1)	<0.001
Non-cardiac death	14 (1.6)	9 (0.7)	0.052
Myocardial infarction	19 (2.1)	19 (1.4)	0.204
Re-percutaneous coronary intervention	60 (6.7)	80 (6.0)	0.460
Coronary artery bypass graft	8 (0.9)	7 (0.5)	0.292
The composite of MACE at 12 months, n (%)	172 (19.3)	165 (12.3)	<0.001
Cardiac death	53 (5.9)	33 (2.5)	<0.001
Non-cardiac death	18 (2.0)	12 (0.9)	0.025
Myocardial infarction	20 (2.2)	23 (1.7)	0.374
Re-percutaneous coronary intervention	72 (8.1)	88 (6.6)	0.173
Coronary artery bypass graft	9 (1.0)	9 (0.7)	0.384

MACE: major adverse cardiac event

valent in the diabetic group than the non-diabetic group (p=0.002 and p<0.001 respectively).

In-hospital outcomes and major adverse cardiac events

The clinical outcomes during the 1 year follow-up are shown in Table 4. The estimated in-hospital mortality was 9.8% in the diabetic group and 3.8% in the non-diabetic group (p<0.001). The duration of admission to the coronary care unit was significantly longer in the diabetic group (4.5 vs. 3.2 days, p<0.001). The rates of cardiac death were higher in the diabetic group at the 1 month, 6 months, and 12 months clinical follow-ups (p=0.002, p<0.001, and p<0.001 respectively). The rates of CABG at 1 month and non-cardiac death at 12 months were higher in the diabetic group (p=0.028 and p=0.025 respectively). The incidence of composite MACE was higher in the diabetic group at the 1 month, 6 months, and 12 months clinical follow-ups (p<0.001, p<0.001, and p<0.001 respectively).

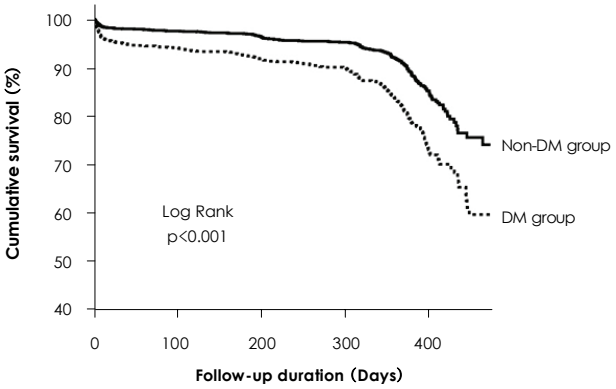

Fig. 1. Kaplan-Meier survival curves for the 2 groups. Survival curve analysis reveals significantly higher mortality rate in diabetic group than non-diabetic group.

Survival curve and multivariate analysis of predictors of 1 year major adverse cardiac events

The Kaplan-Meier survival curve for mortality showed a significantly higher mortality in diabetic hypertensive patients (Fig. 1). Multivariate analysis was conducted to identify the independent predictors of the 1 year MACE using the meaningful factors in univariate analysis (Table 5 and 6).

The independent predictors for 1 year MACE were 3-vessel involvement (p=0.001), presence of DM (p=0.017), and a lower ejection fraction (p=0.045) (Table 7).

Discussion

The aim of this study was to examine the relationship between DM and clinical outcomes in 2,233 hypertensive patients with AMIs in the KAMIR during 12 months of follow-up. Our results demonstrated that diabetic hypertensive patients with AMIs have a poorer outcome in clinical and angiographic features, and a higher risk of death on short- and long-term follow-up relative to non-diabetic hypertensive patients.

DM is associated with a high risk of CVD and is the leading cause of end-stage renal disease, blindness, and non-traumatic amputations. Hypertension by itself is a powerful risk factor for cardiovascular morbidity and mortality. Although the effects of DM and hypertension on the cardiovascular system are often distinct, we can easily presume that their combined presence in the same patient is devastating to the cardiovascular system. Epi-

Table 5. Univariate analysis for the predictors of 1 year major adverse cardiac events

	Odd ratio	95% confidence interval	p
Low ejection fraction (≤40%)	1.848	1.382−2.471	<0.001
Three vessel involvement	1.697	1.282−2.247	<0.001
Old age (≥65 years)	1.557	1.204−2.014	0.001
Diabetes mellitus	1.555	1.213−1.993	0.001
High killip class (≥class III)	1.607	1.142−2.261	0.009
Percutaneous coronary intervention	0.631	0.439−0.907	0.016
Gender	0.784	0.608−1.013	0.064
Treatment of HMG Co-A reductase inhibitor	0.779	0.587−1.035	0.096
Treatment of angiotensin converting enzyme inhibitor	0.845	0.654−1.179	0.154
Treatment of low molecular weighted heparin	0.834	0.657−1.082	0.184
Left main stem disease	1.641	0.713−3.777	0.217
Hyperlipidemia	1.271	0.840−1.924	0.258
Treatment of platelet glycoprotein IIb/IIIa inhibitor	1.259	0.845−1.876	0.276
Treatment of beta blocker	1.191	0.887−1.598	0.276
Successful result of percutaneous coronary intervention	0.809	0.545−1.202	0.286
Smoking	0.877	0.684−1.125	0.309
ST segment elevation myocardial infarction	0.909	0.708−1.167	0.456
Treatment of angiotensin receptor blocker	0.873	0.628−1.215	0.463

HMG Co-A: 3-hydroxy-3-methylglutaryl coenzyme A

Table 6. Laboratory findings according to the MACE

	MACE group	No MACE group	p
N-terminal pro-brain natriuretic peptide (pg/mL)	5480.8±9034.9	2902.3±6848.1	<0.001
Creatinine clearance (mL/min)	61.7±29.8	69.1±28.8	<0.001
CK-MB (U/L)	124.2±187.0	135.3±201.2	0.354

MACE: major adverse cardiac event, CK-MB: creatine kindase-myocardial band isoenzyme

Table 7. Multivariate analysis for the predictors of one year major adverse cardiac events

	Odd ratio	95% confidence interval	p
Multivessel involvement			<0.001
2 vessel	1.929	1.330−2.799	0.001
3 vessel	2.462	1.681−3.605	<0.001
Diabetes mellitus	1.439	1.068−1.938	0.017
Ejection fraction (%)			0.045
≤29	1.910	1.218−1.986	0.011
30-39	1.696	1.034−2.782	0.036
40-49	1.225	0.804−1.868	0.345
50-59	1.460	0.777−2.741	0.239
60-69	1.039	0.532−2.029	0.912
Percutaneous coronary intervention	1.432	0.873−2.351	0.155
N-terminal pro-brain natriuretic peptide (pg/mL)	1.110	0.874−1.473	0.222
Killip class			0.614
II	1.117	0.733−1.703	0.607
III	1.416	0.815−2.460	0.217
IV	1.270	0.591−2.726	0.540
Age			0.668
40-49	0.734	0.255−2.113	0.567
50-59	0.539	0.194−1.492	0.234
60-69	0.612	0.225−1.666	0.336
70-79	0.639	0.234−1.741	0.381
≥80	0.739	0.254−2.152	0.579
Creatinine clearance (mL/min)	1.001	0.993−1.009	0.792

demiologic studies have provided evidence for the coexistence of hypertension and DM and possibly point toward a common genetic and environmental factor promoting both DM and hypertension. Similarly, clustering of hypertension, insulin resistance, frank type 2 DM, hyperlipidemia, and central obesity has been documented in several populations.[16] Insulin resistance, increased tissue inflammation, and reactive oxygen species production, resulting in endothelial dysfunction, increased tissue renin-angiotensin-aldosterone activity, and increased sympathetic nervous system activity have all been implicated in this complex pathophysiology of DM and hypertension. It is estimated that about 25% to 47% of persons with hypertension have insulin resistance or impaired glucose tolerance.[17] With insulin resistance there is impaired biologic and physiologic tissue responses to insulin. The relationship between insulin resistance, DM, and hypertension is complex and interrelated. Untreated patients with essential hypertension have higher fasting and postprandial insulin levels than age- and gender-matched normotensive persons, regardless of body mass; a direct correlation between plasma insulin levels and blood pressure exists.[5][18] Interestingly, the relationship between hyperinsulinemia and hypertension is not observed in secondary hypertension.[18] This indicates that insulin resistance and hyperinsulinemia are not consequences of hypertension, but rather a genetic predisposition that exists for both diseases. This notion is supported by the observation that there is abnormal glucose metabolism in the offspring of hypertensive patients.[19] Thus, there is a strong association between hypertension, DM, and insulin resistance.

Both hypertension and DM are well-identified risk factors for atherogenesis. Coronary artery disease is much more common in patients with both DM and hypertension than in patients with hypertension alone, and the development of atherosclerosis was found to be accelerated, with more plaque fissure and a lower coronary perfusion reserve index when DM and hypertension coexist.[20][21] Our study revealed that diabetic hypertensive

patients have a higher prevalence of multivessel involvement than the non-diabetic population following an AMI and multivessel disease is related to worse long-term clinical outcome. Patients with combined DM and hypertension also tend to have impaired systolic and diastolic ventricular function with more severe left ventricular hypertrophy and congestive heart failure than counterparts with hypertension alone.[20)22)] The extensive degenerative changes in the diabetic hypertensive heart may be related to abnormalities in the microcirculation. The most striking microscopic findings of the hypertensive diabetic heart seem to be the distribution of dense interstitial connective tissue throughout the myocardium. As expected, we found that in diabetic hypertensive patients left ventricular ejection fraction was significantly lower. In our analysis of patients, the combination of DM and hypertension was more common in females, but after univariate analysis, the risk of death was not significantly different among male and female patients as in a previous study.[23)]

The most important result of this study was that DM is a strong risk factor for cardiovascular events; hypertensive patients with DM were more likely to have a cardiovascular event than non-diabetic hypertensive patients. Our study showed that the in-hospital mortality rate for diabetic hypertensive patients with an AMI was higher than for non-diabetic hypertensive patients. In many previous studies, hospital case-fatality rates for diabetic patients with acute coronary syndrome were almost twice as high as those for non-diabetic patients.[24-27)] Also, these results agree with a previous study which reported DM to be one of the most important risk factors for new cardiovascular events following an AMI.[28)] Factors, such as diabetic cardiomyopathy, small vessel disease, increased platelet activity, decreased fibrinolysis, and autonomic neuropathy leading to ventricular arrhythmia may account for the poor prognostic outlook of diabetic hypertensive patients.[29)30)] In our analysis, long-term clinical outcomes of diabetic hypertensive patients following an AMI showed worse progression relative to the non-diabetic hypertensive population.

This study had several limitations. First, our study was a multi-center prospective registry, and it was not a randomized, controlled study. Thus, there was probably a selection bias when enrolling patients into both study groups.

The proportion of STEMI patients was higher in the group I patients than in the group II patients. Second, a value of blood glucose at follow-up was not recorded in the registry, therefore the relationship between adequate control of blood glucose and the prognosis of the patients was not estimated exactly. Third, whether long-term and more aggressive treatment of high blood glucose in patients with AMI can reduce adverse outcomes remains unknown. Finally, the period of our study was relatively short because our study was a comparison of the MACE at the 1 year clinical follow-up.

In conclusion, in hypertensive Korean patients with AMIs, DM was associated with worse clinical and angiographic features, with a higher risk of development of severe heart failure and increased risk of MACE on long-term clinical follow-up.

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Korea Acute Myocardial Infarction Registry (KAMIR) Study Group of Korean Society of Cardiology

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