Original Article

Impact of sex difference on clinical outcomes in acute myocardial infarction patients with single-vessel and multi-vessel disease: based on Korea Acute Myocardial Infarction Registry-National Institute of Health

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Background: Several studies have compared clinical outcomes according to sex in patients with acute myocardial infarction (AMI). However, studies evaluating sex differences in clinical outcomes of single-vessel disease (SVD) and multi-vessel disease (MVD) in Korean patients with AMI are lacking. Therefore, this study aimed to analyze sex differences in the clinical characteristics of patients with AMI with SVD and MVD and to evaluate the impact of sex differences on the clinical outcomes in patients with AMI with SVD and MVD.

Methods: A total of 11,002 AMI patients from November 2011 to June 2015 in the Korea AMI Registry, National Institute of Health, were enrolled. The current study was retrospective observational study. Patients were divided into SVD (n=5,644) and MVD (n=5,358) groups, and clinical impact of sex difference were analyzed by propensity score matching analysis and Cox proportional hazard regression model.

Results: Women were older and had poor baseline clinical characteristics than men. Propensity score-matched analysis of men and women with SVD and MVD revealed that the adjusted 3-year risk of major adverse cardiac event (MACE) (15.0% *vs.* 9.4%; hazard ratio, 1.86; 95% confidence interval, 1.10–3.13; P=0.020) was higher in women with SVD aged <65 years. However, the incidence and risk of MACE were similar for men and women with MVD, and those with SVD aged ≥65 years.

Conclusions: In the present study of Korean patients with AMI, women were older and exhibited a higher prevalence of comorbidities than men. Women with SVD aged <65 years had a significantly higher risk of MACE.

Keywords: Sex difference; myocardial infarction; single-vessel disease (SVD); multi-vessel disease (MVD); prognosis

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Introduction

Despite remarkable advances in interventional cardiology and pharmacologic therapeutics, coronary artery disease (CAD) remains a leading cause of death in both men and women (1). Several studies have investigated sex-related differences in CAD (2-4). Generally, the incidence of CAD is relatively low in women, and CAD develops nearly 10 years later in women than in men (3,4). In addition, awareness regarding sex differences in the clinical characteristics, management, and mortality of acute myocardial infarction (AMI) has increased over the last several decades. Although there are conflicting results, several previous studies have reported that women with AMI have a poorer baseline risk profile, are less intensively treated, and have worse clinical outcomes (5,6).

Coronary angiographic studies have shown that nearly 50–60% of patients with AMI have multi-vessel disease (MVD). The clinical outcomes of MVD are unfavorable compared to those of single-vessel coronary artery disease (SVD) because patients with MVD tend to have more extensive atherosclerosis and a relatively high ischemic burden (7,8). The clinical impact of sex differences in patients with AMI with MVD has been evaluated in the Western population (9). Although there have been studies evaluating sex differences among Korean patients with AMI, studies evaluating sex differences in SVD and MVD in Korean patients with AMI are lacking (10-12).

Therefore, the main purpose of the present study was to analyze sex differences in the clinical characteristics of AMI patients with SVD and MVD. In addition, we aimed to evaluate the impact of sex differences on the clinical outcomes in patients with AMI with SVD and MVD. We present the following article in accordance with the STROBE reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-22-536/rc).

Highlight box

Key findings

- In Korean acute myocardial infarction (AMI) patients, women were older and had poor baseline clinical characteristics.
- Sex-related differences were noted in young AMI patients with AMI with single-vessel disease (SVD).
- There were no sex-related differences in clinical outcomes in patients with AMI with Multi-vessel disease (MVD).

What is known and what is new?

- There have been studies evaluating sex differences among Korean patients with AMI.
- This is the first study to evaluate the impact of sex differences on the clinical outcomes in Korean AMI patients with SVD and MVD.

What is the implication, and what should change now?

- Further specific and detailed prospective studies investigating sex differences in AMI are warranted.

Methods

Study population

A total of 13,903 patients with AMI enrolled in the Korea AMI-National Institute of Health (KAMIR-NIH) between November 2011 and June 2015 were selected. From these, the following patients were excluded: 1,988 patients with failure to achieve successful percutaneous coronary intervention (PCI), 570 patients with left main CAD, and 343 patients with follow-up loss or poor data quality. Finally, 11,002 patients were enrolled in the present study, of which 5,644 and 5,358 were diagnosed with SVD and MVD, respectively. Patients' data were analyzed to identify sex differences in outcomes according to age (<65 and ≥65 years) (Figure S1).

All patients received a 300 mg loading dose of aspirin and 180 mg of ticagrelor, 600 mg of clopidogrel, or 60 mg prasugrel before diagnostic coronary angiography (CAG). CAG was performed through the radial or femoral artery. PCI was performed using standard techniques. Postoperatively, other medications including β-blockers, renin-angiotensin system inhibitors, and statins were prescribed, and two-dimensional echocardiography was performed to evaluate left ventricular ejection fraction.

Study definition and clinical outcomes

MVD was defined as >50% diameter stenosis in at least two major epicardial coronary arteries on quantitative CAG. The primary end point of this study was the cumulative incidence of major adverse cardiac events (MACEs) during 3 years. MACE was a composite of all-cause death, non-fatal myocardial infarction (MI), repeated PCI, and stroke. Non-fatal MI was defined as recurrent symptoms with new ST-segment elevation on electrocardiography or re-elevation of cardiac markers to at least twice the upper limit of the normal range. Repeated PCI was defined as PCI for a target lesion, target vessel, or non-target vessel (13).

Statistical analysis

The clinical characteristics of the treatment groups were analyzed. Continuous variables are presented as means ± standard deviations and compared using unpaired Student's *t*-tests or Mann–Whitney *U* tests. Discrete variables are expressed as percentages and frequencies and were compared using chi-square or Fisher's exact tests. Logistic regression analysis with propensity score matching was performed to minimize selection bias in the direct comparison between the groups. The variables included were age, previous chest pain, atypical chest pain, Killip class, ST-segment elevation MI (STEMI), risk factors including hypertension, diabetes mellitus, previous MI, previous PCI, atrial fibrillation, stroke and smoking, left ventricular ejection fraction, infarct-related artery (IRA), preprocedural thrombolysis in myocardial infarction (TIMI) flow grade in IRA, lesion classification, vascular access, three-vessel disease, PCI modalities, and medications. Men and women were matched 1:1 using the nearest neighbor matching method (14), and the clinical characteristics of the matched population were compared. The risk of each clinical endpoint in both matched groups was compared using the Cox proportional hazard regression model with the covariables that showed statistical significance (P<0.1) in the univariate analysis or were considered clinically important in the multivariable model. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated.

All analyses were performed using SPSS for Windows, version 25.0 (Armonk, NY). All statistical tests were 2-tailed, and statistical significance was defined as P≤0.05.

Ethical statement

The KAMIR-NIH is a prospective, open, observational, on-line registry, multicenter cohort study that investigates real-world outcomes of Korean patients with AMI. Cases of AMI diagnosed at community and teaching hospitals with facilities for primary PCI and on-site cardiac surgery are registered online on www.kamir.or.kr since November 2005. Trained study coordinators at each participating institution collect data through face-to-face interviews, phone calls, or chart review. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The present study retrospectively evaluated data from the KAMIR-NIH database and the current study was approved by the ethics committee of Chonnam National University Hospital (No. CNUH-2022-341). Written informed consent was obtained from all participants.

Results

Clinical characteristics in SVD patients

Among patients with SVD aged <65 years, women were older than men (56.0±6.8 *vs.* 52.2±7.6 years, P<0.001). Women frequently complained of previous chest pain and presented with atypical angina symptoms. The proportion of patients classified as Killip class III–IV was higher and that of patients with STEMI was lower in women than in men. Moreover, risk factors such as hypertension, diabetes, and history of stroke were more frequently observed in women. The left anterior descending artery was the most common IRA, and the frequency of pre-TIMI flow grades of 0 or 1 was lower in women. Moreover, women were frequently treated with plain balloon angioplasty and thrombus aspiration (*Table 1*).

Among patients with SVD aged ≥65 years, women were older than men (75.7±6.1 *vs.* 72.9±5.8 years, P<0.001). The proportion of patients with STEMI was lower in women than in men. Among cardiovascular risk factors, hypertension was more frequently observed in women than in men. The left anterior descending artery was the most common IRA, and patients were frequently treated with plain balloon angioplasty alone (*Table 2*). After propensity score matching, the clinical characteristics were comparable between women and men and between both age groups.

Clinical characteristics in MVD patients

Among patients with MVD aged <65 years, women were older than men (57.9±5.7 *vs.* 53.8±6.9 years, P<0.001). The proportion of patients classified as Killip III–IV was higher, and that of patients with STEMI was lower in women than in men. Among the cardiovascular risk factors, hypertension and diabetes were more frequently observed in women. Comparison of IRA treatment modalities showed that thrombus aspiration was less frequently performed in women (*Table 3*).

Among patients with MVD aged ≥65 years, women were older than men (76.7±6.3 *vs.* 73.3±5.9 years, P<0.001). Women frequently reported previous chest pain and complained of atypical angina symptoms. The proportion of patients classified as Killip III–IV was higher and that of patients with STEMI was lower in women than that in men. Risk factors such as hypertension and diabetes were more

Table 1 Clinical characteristics in SVD patients with <65 years old among total and matched population

Characteristics	Total			Matched		
	Female (n=340)	Male (n=2,897)	P value	Female (n=339)	Male (n=339)	P value
Age, years	56.0±6.8	52.2±7.6	<0.001	55.9±6.8	54.8±6.9	0.074
Symptom						
Previous chest pain	100 (29.4)	707 (24.4)	0.043	100 (29.5)	104 (30.7)	0.738
Atypical angina	40 (11.8)	204 (7.1)	0.002	39 (11.5)	47 (13.9)	0.356
Killip class III, IV	35 (10.3)	187 (6.5)	0.008	34 (10.0)	31 (9.1)	0.696
STEMI	172 (50.6)	1,700 (58.7)	0.004	172 (50.7)	188 (55.5)	0.218
Risk factors						
Hypertension	154 (45.3)	976 (33.7)	<0.001	153 (45.1)	146 (43.1)	0.588
Diabetes mellitus	79 (23.2)	505 (17.4)	0.008	78 (23.0)	74 (21.8)	0.713
Previous MI	15 (4.4)	139 (4.8)	0.752	15 (4.4)	15 (4.4)	1.000
Previous PCI	26 (7.6)	190 (6.6)	0.447	26 (7.7)	27 (8.0)	0.886
Atrial fibrillation	8 (2.4)	87 (3.0)	0.502	8 (2.4)	9 (2.7)	0.806
Stroke	16 (4.7)	76 (2.6)	0.029	16 (4.7)	16 (4.7)	1.000
Smoking	46 (13.5)	1,893 (65.3)	<0.001	46 (13.6)	50 (14.8)	0.659
LVEF, %	54.2±10.1	53.7±9.3	0.398	54.2±10.1	53.2±9.6	0.285
Infarct related artery						
Left anterior descending	202 (59.4)	1,554 (53.6)	0.043	201 (59.3)	190 (56.0)	0.393
Right coronary	85 (25.0)	862 (29.8)	0.068	85 (25.1)	95 (28.0)	0.487
Left circumflex	53 (15.6)	481 (16.6)	0.633	53 (15.6)	54 (15.9)	0.924
Pre-TIMI flow grade 0 or 1	192 (56.5)	1,833 (63.3)	0.014	191 (56.3)	201 (59.3)	0.418
B2/C lesion	280 (82.4)	2,472 (85.3)	0.146	279 (82.3)	285 (84.1)	0.538
Trans-radial approach	136 (40.0)	1,167 (40.3)	0.920	136 (40.1)	133 (39.2)	0.814
IRA PCI modality						
Balloon angioplasty	33 (9.7)	190 (6.6)	0.030	33 (9.7)	27 (8.0)	0.417
BMS	4 (1.2)	79 (2.7)	0.087	4 (1.2)	3 (0.9)	0.704
1st generation DES	13 (3.8)	94 (3.2)	0.572	13 (3.8)	11 (3.2)	0.678
2nd generation DES	290 (85.3)	2,534 (87.5)	0.255	289 (85.3)	298 (87.9)	0.311
Thrombus aspiration	78 (22.9)	931 (32.1)	0.001	78 (23.0)	90 (26.5)	0.278
Medications						
Aspirin	338 (99.4)	2,869 (99.0)	0.491	337 (99.4)	337 (99.4)	1.000
Clopidogrel	226 (66.5)	1,761 (60.8)	0.042	225 (66.4)	215 (63.4)	0.421
Prasugrel	44 (12.9)	490 (16.9)	0.062	44 (13.0)	56 (16.5)	0.194
Ticagrelor	64 (18.8)	600 (20.7)	0.415	64 (18.9)	61 (18.0)	0.766
β-blocker	297 (87.4)	2,544 (87.8)	0.806	296 (87.3)	296 (87.6)	1.000
RAS inhibitors	280 (82.4)	2,417 (83.4)	0.614	279 (82.3)	282 (83.2)	0.760
Statin	318 (93.5)	2,751 (95.0)	0.260	317 (93.5)	319 (94.1)	0.750

Values are presented as the n (%) or mean ± SD. SVD, single-vessel disease; STEMI, ST segment elevation myocardial infarction; MI, myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; IRA, infarct related artery; TIMI, thrombolysis in myocardial infarction; BMS, bare metal stent; DES, drug eluting stent; RAS, renin angiotensin system.

Table 2 Clinical characteristics in SVD patients with ≥65 years old among total and matched population

Characteristics	Total			Matched		
	Female (n=978)	Male (n=1,429)	P value	Female (n=844)	Male (n=844)	P value
Age, year	75.7±6.1	72.9±5.8	<0.001	74.8±5.9	74.3±6.0	0.095
Symptom						
Previous chest pain	257 (26.3)	344 (24.1)	0.220	218 (25.8)	201 (23.8)	0.338
Atypical angina	147 (15.0)	211 (14.8)	0.858	128 (15.2)	126 (14.9)	0.892
Killip class III, IV	141 (14.4)	183 (12.8)	0.255	122 (14.5)	114 (13.5)	0.574
STEMI	480 (49.1)	796 (55.7)	0.001	429 (50.8)	444 (52.6)	0.465
Risk factors						
Hypertension	654 (66.9)	758 (53.0)	<0.001	554 (65.6)	525 (62.2)	0.149
Diabetes mellitus	301 (30.8)	389 (27.2)	0.058	260 (30.8)	243 (28.8)	0.366
Previous MI	71 (7.3)	124 (8.7)	0.211	60 (7.1)	69 (8.2)	0.410
Previous PCI	110 (11.2)	194 (13.6)	0.091	100 (11.8)	110 (13.0)	0.461
Atrial fibrillation	58 (5.9)	115 (8.0)	0.048	55 (6.5)	63 (7.5)	0.445
Stroke	75 (7.7)	118 (8.3)	0.601	70 (8.3)	78 (9.2)	0.491
Smoking	51 (5.2)	448 (31.4)	<0.001	51 (6.0)	61 (7.2)	0.328
LVEF, %	51.3±10.7	51.9±10.9	0.241	51.4±10.4	51.5±10.8	0.511
Infarct related artery						
Left anterior descending	550 (56.2)	722 (50.5)	0.006	472 (55.9)	458 (54.3)	0.493
Right coronary	266 (27.2)	503 (35.2)	<0.001	242 (28.7)	265 (31.4)	0.222
Left circumflex	162 (16.6)	204 (14.3)	0.125	130 (15.4)	121 (14.3)	0.538
Pre-TIMI flow grade 0 or 1	578 (59.1)	817 (57.2)	0.347	487 (57.7)	492 (58.3)	0.805
B2/C lesion	834 (85.3)	1,231 (86.1)	0.549	710 (84.1)	725 (85.9)	0.306
Trans-radial approach	324 (35.1)	532 (37.2)	0.039	287 (34.0)	293 (34.7)	0.758
IRA PCI modality						
Balloon angioplasty	99 (10.1)	98 (6.9)	0.004	74 (8.8)	69 (8.2)	0.662
BMS	52 (5.3)	73 (5.1)	0.821	45 (5.3)	39 (4.6)	0.502
1st generation DES	16 (1.6)	39 (2.7)	0.078	16 (1.9)	22 (2.6)	0.325
2nd generation DES	811 (82.9)	1,219 (85.3)	0.115	709 (84.0)	714 (84.6)	0.738
Thrombus aspiration	217 (22.2)	367 (25.7)	0.051	194 (23.0)	201 (23.8)	0.687
Discharge medications						
Aspirin	951 (97.2)	1,396 (97.7)	0.485	823 (97.5)	819 (97.0)	0.550
Clopidogrel	757 (77.4)	1,004 (70.3)	<0.001	641 (75.9)	625 (74.1)	0.368
Prasugrel	33 (3.4)	116 (8.1)	<0.001	33 (3.9)	36 (4.3)	0.712
Ticagrelor	157 (16.1)	270 (18.9)	0.073	145 (17.2)	157 (18.6)	0.446
β-blocker	827 (84.6)	1,108 (77.5)	<0.001	706 (83.6)	697 (82.5)	0.586
RAS inhibitors	767 (78.4)	1,097 (76.8)	0.339	662 (78.4)	649 (76.9)	0.447
Statin	884 (90.4)	1,305 (91.3)	0.433	766 (90.8)	760 (90.0)	0.620

Values are presented as the n (%) or mean ± SD. SVD, single-vessel disease; STEMI, ST segment elevation myocardial infarction; MI, myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; IRA, infarct related artery; TIMI, thrombolysis in myocardial infarction; BMS, bare metal stent; DES, drug eluting stent; RAS, renin angiotensin system.

Table 3 Clinical characteristics in MVD patients with <65 years old among total and matched population

Characteristics	Total			Matched		
	Female (n=247)	Male (n=2,221)	P value	Female (n=243)	Male (n=243)	P value
Age, year	57.9±5.7	53.8±6.9	<0.001	57.8±5.7	56.5±7.2	0.061
Symptom						
Previous chest pain	68 (27.5)	570 (25.7)	0.525	66 (27.2)	67 (27.6)	0.919
Atypical angina	28 (11.3)	210 (9.5)	0.342	28 (11.5)	29 (11.9)	0.888
Killip class III, IV	34 (13.8)	214 (9.6)	0.041	32 (13.2)	34 (14.0)	0.791
STEMI	103 (41.7)	1,199 (54.0)	<0.001	103 (42.4)	109 (44.9)	0.583
Risk factors						
Hypertension	138 (55.9)	936 (42.1)	<0.001	134 (55.1)	119 (49.0)	0.173
Diabetes mellitus	113 (45.7)	597 (26.9)	<0.001	110 (45.3)	102 (42.0)	0.464
Previous MI	15 (6.1)	158 (7.1)	0.543	15 (6.2)	16 (6.6)	0.853
Previous PCI	25 (10.1)	200 (9.0)	0.563	24 (9.9)	23 (9.5)	0.878
Atrial fibrillation	3 (1.2)	57 (2.6)	0.191	3 (1.2)	3 (1.2)	1.000
Stroke	16 (6.5)	86 (3.9)	0.051	16 (6.6)	14 (5.8)	0.706
Smoking	32 (13.0)	1,403 (63.2)	<0.001	32 (13.2)	42 (17.3)	0.207
LVEF, %	51.4±11.9	52.5±10.4	0.113	51.7±11.5	51.9±10.3	0.854
Infarct related artery						
Left anterior descending	119 (48.2)	927 (41.7)	0.052	116 (47.7)	107 (44.0)	0.413
Right coronary	90 (36.4)	840 (37.8)	0.670	89 (36.6)	89 (36.6)	1.000
Left circumflex	38 (15.4)	454 (20.4)	0.059	38 (15.6)	47 (19.3)	0.283
Pre-TIMI flow grade 0 or 1	141 (57.1)	1,345 (60.6)	0.290	138 (56.8)	142 (58.4)	0.713
B2/C lesion	220 (89.1)	1,945 (87.6)	0.497	216 (88.9)	209 (86.0)	0.338
Trans-radial approach	91 (36.8)	908 (40.9)	0.220	90 (37.0)	95 (39.1)	0.640
Three-vessel disease	78 (31.6)	755 (34.0)	0.446	77 (31.7)	81 (33.3)	0.698
Culprit only PCI	110 (44.5)	1,102 (49.6)	0.130	110 (45.3)	120 (49.4)	0.364
IRA PCI modality						
Balloon angioplasty	18 (7.3)	129 (5.8)	0.351	16 (6.6)	13 (5.3)	0.566
BMS	1 (0.4)	23 (1.0)	0.338	1 (0.4)	3 (1.2)	0.315
1st generation DES	10 (4.0)	111 (5.0)	0.512	10 (4.1)	8 (3.3)	0.631
2nd generation DES	218 (88.3)	1,958 (88.2)	0.963	216 (88.9)	219 (90.1)	0.657
Thrombus aspiration	44 (17.8)	573 (25.8)	0.006	44 (18.1)	56 (23.0)	0.178
Medications						
Aspirin	242 (98.0)	2,188 (98.5)	0.514	238 (97.9)	241 (99.2)	0.253
Clopidogrel	177 (71.7)	1,337 (60.2)	<0.001	173 (71.2)	161 (66.3)	0.240
Prasugrel	17 (6.9)	335 (15.1)	<0.001	17 (7.0)	29 (11.9)	0.063
Ticagrelor	48 (19.4)	513 (23.1)	0.192	48 (19.8)	49 (20.2)	0.910
β-blocker	211 (85.4)	1,963 (88.4)	0.173	209 (86.0)	204 (84.0)	0.526
RAS inhibitors	198 (80.2)	1,799 (81.0)	0.751	195 (80.2)	196 (80.7)	0.909
Statin	229 (92.7)	2,112 (95.1)	0.108	226 (93.0)	228 (93.8)	0.715

Values are presented as the n (%) or mean ± SD. MVD, multi-vessel disease; STEMI, ST segment elevation myocardial infarction; MI, myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; IRA, infarct related artery; TIMI, thrombolysis in myocardial infarction; BMS, bare metal stent; DES, drug eluting stent; RAS, renin angiotensin system.

frequent in women than in men. Three-vessel disease was more frequently observed in women than in men (*Table 4*). After propensity score matching, the clinical characteristics were comparable between women and men and between both age groups.

Clinical outcomes

Among patients with SVD aged <65 years, the cumulative incidence and 3-year risk of MACE in the crude population was higher in women than in men (15.0% *vs.* 8.4%; HR, 1.46; 95% CI, 1.07–1.99; P=0.017). Moreover, the incidence of stroke was higher in women than in men (2.1% *vs.* 0.6%; HR, 3.09; 95% CI, 1.23–7.76; P=0.016). The incidence and 3-year risk of MACE (15.0% *vs.* 9.4%; HR, 1.86; 95% CI, 1.10–3.13; P=0.020) and stroke (2.1% *vs.* 0.6%; HR, 6.85; 95% CI, 1.16–12.3; P=0.034) in the matched population were also significantly higher in women than in men.

The 3-year risk of MACE in patients with SVD aged ≥65 years was similar for men and women (21.6% *vs.* 20.9%; HR, 0.90; 95% CI, 0.75–1.08; P=0.258). However, the incidence of stroke events was significantly higher in women than in men (3.2% *vs.* 1.4%; HR, 2.49; 95% CI, 1.38–4.53; P=0.003). In the matched population, the 3-year risk and incidence of MACE and other individual clinical events were comparable between men and women (*Table 5*) (*Figure 1*).

In patients with MVD aged <65 years, the cumulative 3-year incidence of MACE in the crude population was 21.1% and 17.6% for women and men, respectively (HR, 1.09; 95% CI, 0.80–1.47; P=0.596). The incidence of individual clinical events was also similar between the groups. Multivariable analysis after propensity score matching showed that the 3-year risk of MACE was similar in both groups (21.0% *vs.* 18.5%; HR, 1.12; 95% CI, 0.75–1.69; P=0.575).

Regarding clinical outcomes of patients with MVD aged ≥65 years, the cumulative 3-year incidence of MACE in the crude population was 28.1% and 28.2% in women and men, respectively (HR, 0.95; 95% CI, 0.82–1.10; P=0.452), and the incidence of individual clinical events was also comparable. Multivariable analysis after propensity score matching showed that the 3-year incidence and risk of MACE were similar in both groups (26.3% *vs.* 29.5%; HR, 0.93; 95% CI, 0.79–1.10; P=0.404) (*Table 6*, *Figure 2*).

Independent predictors for MACE

Table S1 lists the independent predictors for MACE in patients with AMI with SVD and MVD. Patients with AMI aged ≥65 years had more statistically significant clinical predictors for MACE compared patients with AMI aged <65 years. For instance, medical treatment with statins, β-blockers, and renin-angiotensin system inhibitors and use of second-generation drug-eluting stents in the IRA and in patients with Killip class III and IV were independent predictors for MACE in patients with SVD or MVD aged ≥65 years. Female sex was an independent clinical predictor for 3-year MACE in patients with SVD aged <65 years (HR, 1.86; 95% CI, 1.10–3.13; P=0.020).

Discussion

The principal findings from this study based on the KAMIR-NIH registry are as follows: (I) baseline clinical characteristics were different between men and women. Compared with men, women were older, commonly presented with Killip class III or IV, and showed a lower incidence of STEMI. Generally, women had more cardiovascular risk factors, including hypertension and diabetes, but their past history of cigarette smoking was significantly lower than that of men. (II) Among young (<65 years) patients with SVD, women had a higher incidence and 3-year risk of MACE and stroke. (III) However, there were no sex-related differences in clinical outcomes in patients with AMI with MVD or SVD aged ≥65 years.

Many studies have compared the clinical characteristics and outcomes of patients with AMI based on sex differences over the last several decades (5-12). Although there is a paucity of data, numerous studies have reported sex differences in clinical, angiographic, and procedural factors, and clinical outcomes among patients with AMI (15-17). Women tend to be under-treated with both revascularization strategies and medical treatment compared with men (18,19). In a global case–control study, Anand *et al.* (20) demonstrated that women experience their first AMI event on average nine years later than men, and older age led to a higher proportion of women suffering from comorbidities such as hypertension. Among the 27,098 study participants, the median age at the first AMI event was 65 years in women and 56 years in men and women were significantly more likely to have hypertension than men (28.3% *vs.* 19.7%). The delay in the occurrence of AMI could be explained by the protective effect of estrogen until menopause (21,22). Matthews *et al.* (22) evaluated the high-density lipoprotein cholesterol and low-

Table 4 Clinical characteristics in MVD patients with ≥65 years old among total and matched population

Characteristics	Total			Matched		
	Female (n=1,200)	Male (n=1,690)	P value	Female (n=741)	Male (n=741)	P value
Age, year	76.7±6.3	73.3±5.9	<0.001	75.7±5.8	74.8±6.1	0.062
Symptom						
Previous chest pain	342 (28.5)	421 (24.9)	0.031	293 (27.6)	281 (26.5)	0.558
Atypical angina	244 (20.3)	281 (16.6)	0.011	194 (18.3)	188 (17.7)	0.735
Killip class III, IV	236 (19.7)	288 (17.0)	0.071	201 (19.0)	190 (17.9)	0.538
STEMI	521 (43.4)	785 (46.4)	0.106	465 (43.9)	466 (44.0)	0.965
Risk factors						
Hypertension	899 (74.9)	997 (59.0)	<0.001	765 (72.2)	724 (68.3)	0.052
Diabetes mellitus	472 (39.3)	581 (34.3)	0.006	410 (38.7)	401 (37.8)	0.688
Previous MI	72 (6.0)	158 (9.3)	0.001	67 (6.3)	77 (7.3)	0.388
Previous PCI	119 (9.9)	233 (13.8)	0.002	118 (11.1)	128 (12.1)	0.498
Atrial fibrillation	81 (6.8)	122 (7.2)	0.627	72 (6.8)	74 (7.0)	0.864
Stroke	131 (10.9)	155 (9.2)	0.122	115 (10.8)	120 (11.3)	0.729
Smoking	77 (6.4)	514 (30.4)	<0.001	77 (7.3)	92 (8.7)	0.229
LVEF, %	50.6±11.4	49.8±11.1	0.085	50.6±11.3	50.1±11.1	0.455
Infarct related artery						
Left anterior descending	498 (41.5)	697 (41.2)	0.890	438 (41.3)	438 (41.3)	1.000
Right coronary	456 (38.0)	658 (38.9)	0.611	401 (37.8)	412 (38.9)	0.623
Left circumflex	246 (20.5)	335 (19.8)	0.654	221 (20.8)	210 (19.8)	0.553
Pre-TIMI flow grade 0 or 1	648 (54.0)	912 (54.0)	0.985	572 (54.0)	572 (54.0)	1.000
B2/C lesion	1,050 (87.5)	1,497 (88.6)	0.376	927 (87.5)	935 (88.2)	0.595
Trans-radial approach	421 (35.1)	645 (38.2)	0.091	384 (36.2)	412 (38.9)	0.209
Three-vessel disease	500 (41.7)	638 (37.8)	0.034	432 (40.8)	411 (38.8)	0.351
Culprit only PCI	640 (53.3)	926 (54.8)	0.438	564 (53.2)	555 (52.4)	0.695
IRA PCI modality						
Balloon angioplasty	84 (7.0)	112 (6.6)	0.695	73 (6.9)	80 (7.5)	0.557
BMS	50 (4.2)	52 (3.1)	0.118	39 (3.7)	34 (3.2)	0.551
1st generation DES	35 (2.9)	50 (3.0)	0.948	34 (3.2)	28 (2.6)	0.438
2nd generation DES	1,031 (85.9)	1,476 (87.3)	0.267	914 (86.2)	918 (86.6)	0.800
Thrombus aspiration	232 (19.3)	348 (20.6)	0.405	210 (19.8)	215 (20.3)	0.786
Discharge medications						
Aspirin	1,162 (96.8)	1,640 (97.0)	0.748	1,025 (96.7)	1,024 (96.6)	0.904
Clopidogrel	934 (77.8)	1,245 (73.7)	0.010	813 (76.7)	804 (75.8)	0.646
Prasugrel	29 (2.4)	84 (5.0)	<0.001	29 (2.7)	35 (3.3)	0.446
Ticagrelor	196 (16.3)	308 (18.2)	0.187	180 (17.0)	181 (17.1)	0.954
β-blocker	964 (80.3)	1,364 (80.7)	0.801	851 (80.3)	846 (79.8)	0.786
RAS inhibitors	943 (78.6)	1,323 (78.3)	0.847	837 (79.0)	823 (77.6)	0.461
Statin	1,070 (89.2)	1,521 (90.0)	0.469	954 (90.0)	950 (89.6)	0.774

Values are presented as the n (%) or mean ± SD. MVD, multi-vessel disease; STEMI, ST segment elevation myocardial infarction; MI, myocardial infarction; PCI, percutaneous coronary intervention; LVEF, left ventricular ejection fraction; IRA, infarct related artery; TIMI, thrombolysis in myocardial infarction; BMS, bare metal stent; DES, drug eluting stent; RAS, renin angiotensin system.

Table 5 Clinical outcomes in SVD patients among total and matched population

Clinical outcomes	Total				Matched			
	Female	Male	Adjusted HR (95% CI)	P value	Female	Male	Adjusted HR (95% CI)	P value
<65 years old								
n	340	2,897			339	339		
MACE†	51 (15.0)	242 (8.4)	1.46 (1.07–1.99)	0.017	51 (15.0)	32 (9.4)	1.86 (1.10–3.13)	0.020
All-cause death	10 (2.9)	71 (2.5)	0.71 (0.35–1.45)	0.348	10 (2.9)	9 (2.7)	2.10 (0.66–6.64)	0.209
Cardiac death	6 (1.8)	49 (1.7)	0.57 (0.22–1.47)	0.243	6 (1.8)	5 (1.5)	4.71 (0.81–27.5)	0.085
Non-fatal MI	10 (2.9)	42 (1.4)	1.79 (0.88–3.63)	0.107	10 (2.9)	4 (1.2)	1.78 (0.44–7.18)	0.420
Any repeated PCI	29 (8.5)	152 (5.2)	1.48 (0.99–2.23)	0.058	29 (8.6)	19 (5.6)	1.56 (0.79–3.09)	0.201
Stroke	7 (2.1)	17 (0.6)	3.09 (1.23–7.76)	0.016	7 (2.1)	2 (0.6)	6.85 (1.16–12.3)	0.034
≥65 years old								
n	978	1,429			844	844		
MACE†	211 (21.6)	298 (20.9)	0.90 (0.75–1.08)	0.258	173 (20.5)	181 (21.4)	0.93 (0.76–1.15)	0.524
All-cause death	147 (15.0)	202 (14.1)	0.98 (0.71–1.13)	0.309	117 (13.9)	123 (14.6)	0.98 (0.76–1.26)	0.858
Cardiac death	113 (11.6)	139 (9.7)	0.99 (0.77–1.29)	0.955	84 (10.0)	86 (10.2)	1.01 (0.74–1.37)	0.973
Non-fatal MI	23 (2.4)	35 (2.4)	0.86 (0.47–1.43)	0.821	19 (2.3)	21 (2.5)	0.86 (0.46–1.61)	0.643
Any repeated PCI	40 (4.1)	85 (5.9)	0.68 (0.46–1.01)	0.052	36 (4.3)	48 (5.7)	0.73 (0.47–1.13)	0.155
Stroke	31 (3.2)	20 (1.4)	2.49 (1.38–4.53)	0.003	27 (3.2)	14 (1.7)	1.87 (0.97–3.57)	0.061

Values are presented as the n (%). †, composite of all-cause death, non-fatal MI, any repeated PCI, stroke. SVD, single-vessel disease; HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiac event; MI, myocardial infarction; PCI, percutaneous coronary intervention.

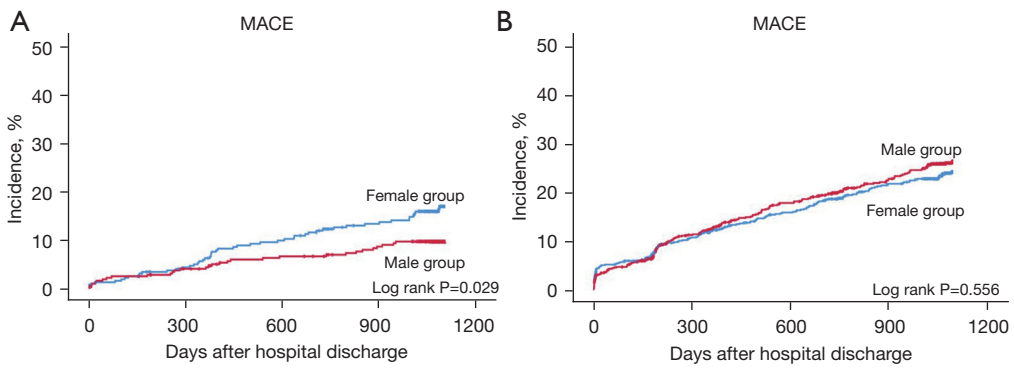

Figure 1 Kaplan-Meier curves for MACE in SVD <65 years (A) and ≥65 years (B). MACE, major adverse cardiac event; SVD, single-vessel disease.

density lipoprotein cholesterol levels in premenopausal women and women with menopause 2.5 years earlier. In women who had a natural menopause and did not receive hormone-replacement therapy, serum levels of high-density lipoprotein cholesterol were lower, and levels of low-density lipoprotein cholesterol were higher than those in premenopausal controls (–0.09 *vs.* 0.00 mmol/L, P=0.01; 0.31 *vs.* 0.14 mmol/L, P=0.04, respectively). Thus, loss of estrogen could lead to unfavorable lipid metabolism, which may contribute to an increased risk of AMI in later life in women (22). The findings in the present study were similar to those of previous studies (15-20). Moreover, women

Table 6 Clinical outcomes in MVD patients among total and matched population

Clinical outcomes	Total				Matched			
	Female	Male	Adjusted HR (95% CI)	P value	Female	Male	Adjusted HR (95% CI)	P value
<65 years old								
n	247	2,221			243	243		
MACE†	52 (21.1)	391 (17.6)	1.09 (0.80–1.47)	0.596	51 (21.0)	45 (18.5)	1.12 (0.75–1.69)	0.575
All-cause death	18 (7.3)	81 (3.6)	1.17 (0.67–2.04)	0.578	17 (7.0)	10 (4.1)	1.37 (0.58–3.22)	0.472
Cardiac death	13 (5.3)	68 (3.1)	1.01 (0.53–1.92)	0.971	12 (4.9)	9 (3.7)	1.04 (0.34–2.57)	0.900
Non-fatal MI	7 (2.8)	59 (2.7)	0.93 (0.41–2.07)	0.850	7 (2.9)	7 (2.9)	0.96 (0.32–2.94)	0.948
Any repeated PCI	34 (13.8)	278 (12.5)	1.15 (0.79–1.66)	0.457	34 (14.0)	32 (13.2)	1.08 (0.67–1.77)	0.747
Stroke	2 (0.8)	29 (1.3)	0.35 (0.08–1.52)	0.162	2 (0.8)	6 (2.5)	0.19 (0.04–1.10)	0.064
≥65 years old								
n	1,200	1,690			1,060	1,060		
MACE†	338 (28.1)	477 (28.2)	0.95 (0.82–1.10)	0.452	279 (26.3)	313 (29.5)	0.93 (0.79–1.10)	0.404
All-cause death	205 (17.1)	273 (16.2)	0.92 (0.76–1.11)	0.387	162 (15.3)	185 (17.5)	0.94 (0.76–1.16)	0.543
Cardiac death	154 (12.8)	191 (11.3)	0.96 (0.76–1.20)	0.701	118 (11.1)	128 (12.1)	1.01 (0.78–1.29)	0.964
Non-fatal MI	38 (4.2)	54 (3.2)	0.87 (0.56–1.34)	0.523	32 (3.0)	35 (3.3)	0.90 (0.55–1.46)	0.662
Any repeated PCI	112 (9.3)	184 (10.9)	0.97 (0.76–1.24)	0.807	104 (9.8)	119 (11.2)	0.91 (0.69–1.18)	0.468
Stroke	33 (2.8)	41 (2.4)	1.12 (0.69–1.82)	0.643	26 (2.5)	21 (2.0)	1.25 (0.70–2.23)	0.452

Values are presented as n (%). †, composite of all-cause death, non-fatal MI, any repeated PCI, stroke. MVD, multi-vessel disease; HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiac event; MI, myocardial infarction; PCI, percutaneous coronary intervention.

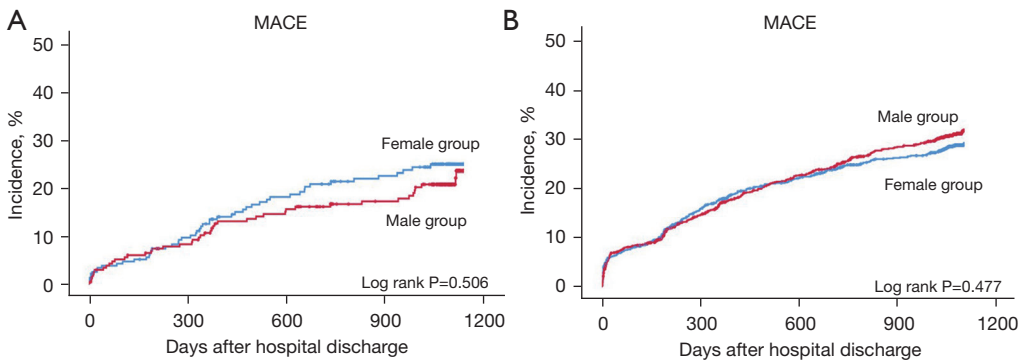

Figure 2 Kaplan-Meier curves for MACE in MVD <65 years (A) and ≥65 years (B). MACE, major adverse cardiac event; MVD, multi-vessel disease.

were older and had a more frequent history of hypertension compared with men in the SVD and MVD groups and in both age groups.

In this study, women with SVD had a significantly higher incidence and risk of MACE in the <65 years group; however, clinical characteristics were similar in women with SVD aged ≥65 years. Vaccarino *et al.* (23) first reported that in younger patients with AMI, early mortality was higher in women than in men. Based on a nationwide prospective multicenter registry in the United States, the overall mortality during hospitalization was 16.7% among women and 11.5% among men. The mortality for women was

more than twice that for men in patients aged <50 years; the difference in mortality decreased with increasing age and was not significant after the age of 74 years. Khera *et al.* (24) reported that among patients with STEMI aged <60 years in the US, the risk of risk-adjusted in-hospital mortality and longer hospital stay was greater in women than in men. In addition, a multicenter prospective cohort study by Vaccarino *et al.* (25) demonstrated that the overall 2-year mortality was higher in women (28.9%) than in men (19.6%), and after adjusting demographic confounders, women aged <60 years had a higher mortality than men of a similar age.

Although many questions remain unanswered, the potential reasons for poor clinical outcomes in young women with AMI could be explained by several pathophysiological and psychosocial factors (26-28). According to the Variation in Recovery: Role of Gender on Outcomes of Young Acute Myocardial Infarction Patients (VIRGO) study (27), women were more likely to exceed symptom to medical contact time and door-to-needle time than men. Furthermore, some experts have assumed that younger women have a lower burden of CAD than men, which gives a lower chance of myocardial ischemic preconditioning, leading to a vulnerable condition in AMI (29). Concurrently, the VIRGO study (28) showed that women exhibited higher levels of depression and stress, poorer physical and mental health status, and lower quality of life, leading to poor clinical outcomes. For instance, young women in the VIRGO study were significantly more likely to be divorced or separated than men. In addition, they were significantly more likely to be unemployed and have lower household incomes. Socioeconomic strain can lead to psychological risks such as depression, and a previous study have demonstrated that depression could increase a woman's risk of cardiovascular disease and atherosclerosis due to low-grade inflammation (30).

In the current study, the 3-year incidence of MACE was comparable between men and women with MVD. These findings are consistent with those of several previous studies (31-33). A meta-analysis by Berger *et al.* (31) revealed that 30-day mortality among women and men was largely explained by baseline angiographic severity, and MVD could be regarded as a severe angiographic disease compared with SVD. The 30-day mortality was significantly higher in women with STEMI; however, no significant interaction was detected between STEMI and angiographic severity in the adjusted model. The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) trial (34) showed that women had fewer and more focal non-culprit lesions and necrotic cores and significantly less plaque rupture compared with men. However, despite the fact that women had less extensive coronary atherosclerosis, cardiovascular events including cardiac death and MI during 3 years of follow-up were similar in both groups. The PROSPECT sub-study (34) concluded that women had other high-risk plaque characteristics, including less calcium concentration and a smaller minimal lumen area, compared with men.

Limitations

This study had some limitations. First, this was a retrospective analysis and not a randomized clinical trial. The study was based on registry data; consequently, there could have been a selection bias. Although propensity score matching was performed, and most potential confounders were adjusted prior to analysis, other variables that could influence the clinical outcomes might have not been included. Second, the current study population lacked laboratory data, including cardiac biomarker levels or renal function test findings, due to a significant amount of missing data. Such laboratory data could have a significant impact on the results of the current study. Third, we did not evaluate socioeconomic factors or medical compliance data, which might show great disparities between the groups. Fourth, the interpretation of the current study results has potential for errors due to multiple testing based on sex and age differences. Although there have been previous studies on sex differences in different age groups, further analysis for multiple testing correction was not performed in this study. Also, external validation was not done. Therefore, to clarify the generalizability of the current data result, external validation is needed based on other large scale clinical patient data.

Conclusions

Women were older and had a higher prevalence of comorbidities than men in Korean AMI patients. Further, women with SVD aged <65 years had a significantly higher risk of MACE after adjusting for other clinical confounders. However, the risk of MACE was comparable in older patients with SVD and in patients with MVD. Further specific and detailed prospective studies investigating sex

differences in AMI are warranted.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-22-536/rc

Data Sharing Statement: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-22-536/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-22-536/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of Chonnam National University Hospital (No. CNUH-2022-341). Written informed consent was obtained from all participants.

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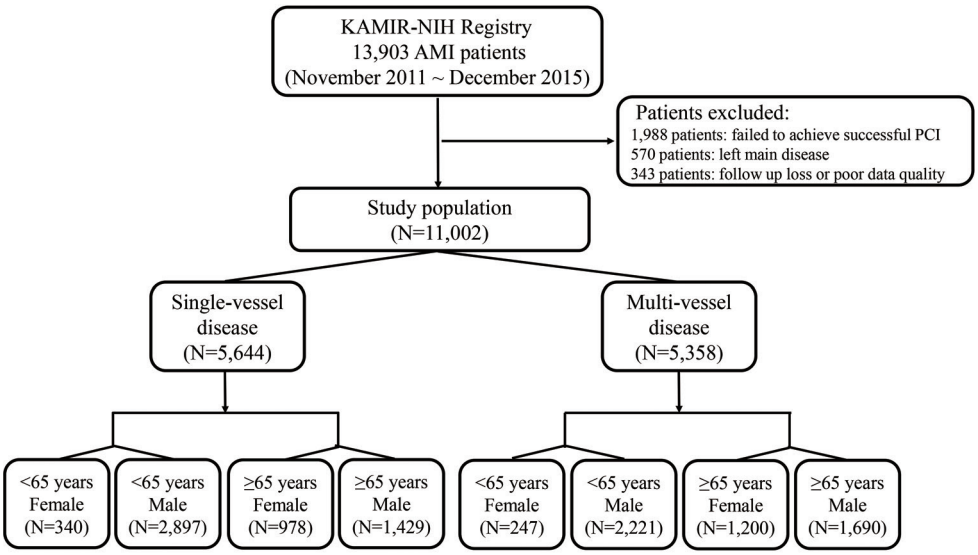

Figure S1 Study flow chart. AMI, acute myocardial infarction; PCI, percutaneous coronary intervention.

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Table S1 Multivariate analysis showing independent parameters for MACE

Variables	Adjusted HR (95% CI)	P value
MVD <65 years		
DM	1.88 (1.18–2.98)	0.008
IRA LAD	1.69 (1.10–2.62)	0.018
MVD ≥65 years		
Killip class III, IV	1.44 (1.18–1.74)	<0.001
Culprit only PCI	1.39 (1.17–1.64)	<0.001
Statin	0.31 (0.25–0.38)	<0.001
ß-blocker	0.57 (0.47 0.74)	<0.001
RAS inhibitors	0.59 (0.49–0.71)	<0.001
IRA 2nd generation DES	0.61 (0.49–0.74)	<0.001
SVD <65 years		
IRA 2nd generation DES	0.50 (0.30–0.84)	0.009
Statin	0.49 (0.25–0.97)	0.042
Female	1.86 (1.10–3.13)	0.020
Killip class III, IV	1.93 (1.05–3.55)	0.033
SVD ≥65 years		
DM	1.49 (1.19–1.85)	<0.001
Killip class III, IV	1.46 (1.12–1.92)	0.006
Statin	0.33 (0.25–0.43)	<0.001
ß-blocker	0.49 (0.39–0.62)	<0.001
RAS inhibitors	0.53 (0.42–0.68)	<0.001
IRA 2nd generation DES	0.54 (0.42–0.69)	<0.001

MACE, major adverse cardiac event; HR, hazard ratio; CI, confidence interval; MVD, multi-vessel disease; DM, diabetes mellitus; IRA, infarct related artery; LAD, left anterior descending artery; RAS, renin angiotensin system; DES, drug eluting stent.

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