VIA MEDICA

ORIGINAL ARTICLE

Cardiology Journal
2022, Vol. 29, No. 6, 954–965
DOI: 10.5603/CJ.a2020.0185

ISSN 1897–5593
eISSN 1898–018X

Sex difference after acute myocardial infarction patients with a history of current smoking and long-term clinical outcomes: Results of KAMIR Registry

Yong Hoon Kim[1,*], Ae-Young Her[1,*], Myung Ho Jeong[2], Byeong-Keuk Kim[3], Sung-Jin Hong[3], Seunghwan Kim[4], Chul-Min Ahn[3], Jung-Sun Kim[3], Young-Guk Ko[3], Donghoon Choi[3], Myeong-Ki Hong[3], Yangsoo Jang[3]

[1]Division of Cardiology, Department of Internal Medicine, Kangwon National University School of Medicine, Chuncheon, Republic of Korea
[2]Department of Cardiology, Cardiovascular Center, Chonnam National University Hospital, Gwangju, Republic of Korea
[3]Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
[4]Division of Cardiology, Inje University College of Medicine, Haeundae Paik Hospital, Busan, Republic of Korea

Abstract

Background: *The contribution of sex as an independent risk factor for cardiovascular disease still remains controversial. The present study investigated the impact of sex on long-term clinical outcomes in Korean acute myocardial infarction (AMI) patients with a history of current smoking on admission after drug-eluting stents (DESs).*

Methods: *A total of 12,565 AMI patients (male: n = 11,767 vs. female: n = 798) were enrolled. Major adverse cardiac events (MACEs) comprising all-cause death, recurrent myocardial infarction (Re-MI), and any repeat revascularization were the primary outcomes that were compared between the two groups. Probable or definite stent thrombosis (ST) was the secondary outcome.*

Results: *After adjustment, the early (30 days) cumulative incidences of MACEs (adjusted hazard ratio [aHR]: 1.457; 95% confidence interval [CI]: 1.021–2.216; p = 0.035) and all-cause death (aHR: 1.699; 95% CI: 1.074–2.687; p = 0.023) were significantly higher in the female group than in the male group. At 2 years, the cumulative incidences of all-cause death (aHR: 1.561; 95% CI: 1.103–2.210; p = 0.012) and Re-MI (aHR: 1.800; 95% CI: 1.089–2.974; p = 0.022) were significantly higher in the female group than in the male group. However, the cumulative incidences of ST were similar between the two groups (aHR: 1.207; 95% CI: 0.583–2.497; p = 0.613).*

Conclusions: *The female group showed worse short-term and long-term clinical outcomes compared with the male group comprised of Korean AMI patients with a history of current smoking after successful DES implantation. However, further studies are required to confirm these results.* (Cardiol J 2022; 29, 6: 954–965)

Key words: myocardial infarction, sex, smoking

Address for correspondence: Yong Hoon Kim, MD, PhD, Division of Cardiology, Department of Internal Medicine, Kangwon National University School of Medicine, 24289, 156 Baengnyeong Road, Chuncheon City, Gangwon Province, Republic of Korea, tel: +82-33-258-9455, fax: +82-33-258-2455, e-mail: yhkim02@kangwon.ac.kr

Received: 25.03.2020 Accepted: 6.12.2020 Early publication date: 31.12.2020

**The first two authors (Yong Hoon Kim and Ae-Young Her) are equally contributed to this work.*

Introduction

As age increases, the incidence and mortality rates of cardiovascular disease (CVD) also increases. Moreover, other factors affecting the long-term prognosis of CVD are of utmost importance for public heath investigators and cardiologists. Previously, based on sex difference, a higher mortality rate of myocardial infarction (MI) was observed in women than in men [1, 2]. However, the contribution of sex as an independent risk factor for CVD still remains controversial. Proposed explanations for higher mortality rate among women are advanced age and increased incidence of diabetes mellitus (DM), chronic heart failure (HF), and hypertension prior to MI [3]. Cigarette smoking is an important correctable risk factor and a major causative factor of recurrent MI and death after percutaneous coronary intervention (PCI) [4]. According to a recent report, the estimated prevalence of cigarette smoking was not strongly associated with sex difference [5]. In 2012, the estimated prevalence rates of smokers were greater than 40% among men and lower than 5% in women [5]. Additionally, controversy exists whether sex difference is associated with smoking and adverse cardiovascular clinical outcomes [6]. To date, the cumulative incidences of acute myocardial infarction (AMI) are increasing in South Korea [7]. In real-world practice, the use of bare-metal stent (BMS) is limited. Therefore, we investigated the impact of sex difference on the 2-year clinical outcomes in Korean AMI patients with a history of current smoking on admission who underwent successful PCI with drug-eluting stents (DESs).

Methods

Study design and population

This study was a nonrandomized, multicenter, observational retrospective cohort study, and the study population was obtained from the Korea AMI Registry (KAMIR). Detailed information about the KAMIR has already been published [7, 8]. A total of 20,174 AMI patients who were active smokers on admission between November 2005 and June 2015 were evaluated. Patients with the following characteristics were excluded from the study: (1) patients who underwent fibrinolysis (n = 609, 3.0%), (2) patients who did not undergo PCI (n = 616, 3.1%), (3) patients with failed PCI (n = 415, 2.1%), (4) patients who underwent coronary artery bypass graft (n = 55, 0.3%), (5) patients with BMS (n = 942, 4.7%), (6) patients with incomplete laboratory results (n = 3562, 17.6%), and (7) patients who were lost to follow-up (n = 1410, 7.0%). Finally, a total of 12,565 AMI patients who were active smokers at the time of admission who underwent successful PCI with DESs were enrolled. They were grouped based on their sex; male (n = 11,767, 93.6%) and female groups (n = 798, 6.4%) (Fig. 1, Table 1). This study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki. This study protocol was approved by the ethics committee of each participating center, and informed consent was obtained from all individual participants prior to their enrollment. All 12,565 AMI patients completed a 2-year clinical follow-up, and were tracked the enrolled patients via direct interviews, telephone contact, and chart reviews [9]. All clinical events were evaluated by an independent event adjudication committee. The event adjudication processes were described in a previous publication established by the KAMIR investigators [8].

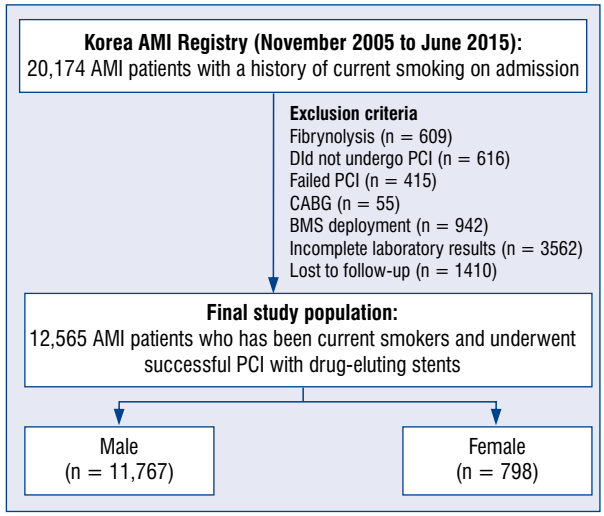

Figure 1. Flow chart; AMI — acute myocardial infarction; BMS — bare-metal stent; CABG — coronary artery bypass grafting; PCI — percutaneous coronary intervention.

Percutaneous coronary intervention procedure and medical treatment

Coronary angiography and PCI were performed as described before [10]. Before PCI, 200 to 300 mg of acetylsalicylic acid (ASA) and 300 to 600 mg of clopidogrel was administered. If possible, 180 mg of ticagrelor or 60 mg of prasugrel was administered. After discharge, 100 to 200 mg/ /day of ASA was continued indefinitely, and 75 mg/ /day of clopidogrel was maintained for at least

Table 1. Baseline clinical, laboratory, and procedural characteristics.

Variables	Male (n = 11,767)	Female (n = 798)	P	SD
Age [years]	56.7 ± 11.2	68.3 ± 11.5	< 0.001	1.21
LVEF [%]	52.6 ± 11.0	52.5 ± 11.8	0.724	–0.09
LVEF < 40%	1256 (10.7%)	96 (12.6%)	0.232	0.70
BMI [kg/m^2]	24.3 ± 3.1	23.3 ±3.6	<0.001	–2.98
SBP [mmHg]	130.0 ± 27.2	128.4 ± 28.9	0.103	–0.57
DBP [mmHg]	80.2 ± 16.6	77.5 ± 17.2	< 0.001	–1.60
STEMI	7480 (63.6%)	468 (58.6%)	0.005	–1.33
Primary PCI	6919 (92.5%)	429 (91.7%)	0.508	–0.33
NSTEMI	4287 (36.4%)	330 (41.4%)	0.005	1.34
PCI within 24 h	3342 (78.0%)	250 (75.8%)	0.354	–0.66
Hypertension	4237 (36.3%)	410 (51.4%)	< 0.001	3.99
Diabetes mellitus	2510 (21.3%)	216 (27.1%)	< 0.001	1.70
Dyslipidemia	1273 (10.8%)	80 (10.0%)	0.484	–0.31
Previous MI	338 (2.9%)	15 (1.9%)	0.101	–0.60
Previous PCI	476 (4.0%)	29 (3.6%)	0.567	–0.22
Previous CABG	27 (0.2%)	2 (0.3%)	0.904	0.07
Previous CVA	431 (3.7%)	51 (6.4%)	< 0.001	1.23
Previous HF	59 (0.5%)	11 (1.4%)	0.001	0.58
Cardiogenic shock	454 (3.9%)	48 (6.0%)	0.003	0.97
CPR on admission	364 (3.1%)	27 (3.4%)	0.648	0.16
CK-MB [mg/dL]	152.9 ± 149.4	140.4 ± 173.1	0.177	–0.77
Troponin-I [ng/mL]	52.1 ± 91.4	44.0 ± 41.5	0.473	–1.14
NT-ProBNP [pg/mL]	1042.6 ± 1119.8	3008.0 ± 3822.9	< 0.001	6.98
hs-CRP [mg/dL]	9.4 ± 51.0	8.6 ± 39.9	0.716	–0.17
Serum creatinine [mg/L]	1.1 ± 1.3	0.9 ± 0.6	0.001	–1.85
Total cholesterol [mg/dL]	187.4 ± 43.6	195.9 ± 48.2	< 0.001	1.98
Triglyceride [mg/L]	151.2 ± 129.5	137.2 ± 106.7	0.003	–1.18
HDL cholesterol [mg/L]	42.7 ± 18.5	45.0 ± 11.8	0.001	1.48
LDL cholesterol [mg/L]	119.5 ± 41.1	125.0 ± 42.7	< 0.001	1.31
Discharge medications:				
Acetylsalicylic acid	11410 (97.0%)	757 (94.9%)	0.001	–1.02
Clopidogrel	10473 (89.0%)	744 (93.2%)	< 0.001	1.88
Ticagrelor	648 (5.5%)	24 (3.0%)	0.002	–1.38
Prasugrel	485 (4.1%)	16 (2.0%)	0.003	–1.25
Cilostazole	2798 (23.8%)	194 (24.3%)	0.733	0.15
BBs	9563 (81.3%)	594 (74.4%)	< 0.001	–2.05
ACEIs	7207 (61.2%)	464 (58.1%)	0.082	–0.82
ARBs	2465 (20.9%)	160 (20.1%)	0.546	-0.25
CCBs	674 (5.7%)	56 (7.0%)	0.132	0.58
Lipid lowering agents	9669 (82.2%)	624 (78.2%)	0.005	-1.24
Angiographic and procedural characteristics				
Infarct-related artery				
Left main	174 (1.5%)	10 (1.3%)	0.608	–0.13
Left anterior descending	5765 (48.9%)	324 (40.6%)	< 0.001	–2.23
Left circumflex	2033 (17.3%)	133 (16.6%)	0.659	–0.24
Right coronary artery	3795 (32.3%)	331 (41.5%)	< 0.001	2.46

→

Table 1 (cont.). Baseline clinical, laboratory, and procedural characteristics.

Variables	Male (n = 11,767)	Female (n = 798)	P	SD
Treated vessel:				
Left main	249 (2.1%)	18 (2.3%)	0.791	0.12
Left anterior descending	6655 (56.6%)	403 (50.5%)	0.001	–1.61
Left circumflex	2956 (25.1%)	190 (23.8%)	0.408	–0.40
Right coronary artery	4530 (38.5%)	377 (47.2%)	< 0.001	2.30
ACC/AHA lesion type:				
Type B1	1801 (15.3%)	126 (15.8%)	0.714	0.17
Type B2	3554 (30.2%)	215 (26.9%)	0.052	–0.96
Type C	5148 (43.7%)	379 (47.5%)	0.039	1.00
Extent of coronary artery disease:				
1-vessel	5962 (50.7%)	369 (46.2%)	0.016	–1.19
2-vessel	3695 (31.4%)	233 (29.2%)	0.293	-0.63
≥ 3-vessel	2110 (17.9%)	196 (24.6%)	< 0.001	2.01
Drug-eluting stents:				
SES	2155 (18.3%)	168 (21.1%)	0.054	0.88
PES	1866 (15.9%)	141 (17.6%)	0.177	0.56
ZES	2866 (24.4%)	204 (25.6%)	0.332	0.36
EES	3640 (30.9%)	217 (27.2%)	0.027	–1.08
BES	1085 (9.2%)	56 (7.0%)	0.036	–0.98
Others	155 (1.3%)	12 (1.5%)	0.656	0.12
Stent diameter [mm]	3.2 ± 0.4	3.1 ± 0.4	< 0.001	–2.50
Stent length [mm]	26.1 ± 9.5	25.7 ± 8.9	0.327	–0.43
Number of stents	1.4 ± 0.8	1.5 ± 0.8	0.011	1.25

Values are mean ± standard deviation or number (%). The p values for continuous data were obtained from the analysis of the unpaired t-test. The p values for categorical data were obtained from the chi-square test. SD — standardized difference; LVEF — left ventricular ejection fraction; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-STEMI; PCI — percutaneous coronary intervention; MI — myocardial infarction; CABG — coronary artery bypass grafting; CVA — cerebrovascular accidents; HF — heart failure; CPR — cardiopulmonary resuscitation; CK-MB — creatine kinase myocardial band; NT-proBNP — N-terminal pro-B-type natriuretic peptide; HDL — high-density lipoprotein; LDL — low-density lipoprotein; BBs — beta-blockers; ACEIs — angiotensin converting enzyme inhibitors; ARBs — angiotensin receptor blockers; CCBs — calcium channel blockers; ACC/AHA — American College of Cardiology/American Heart Association; SES — sirolimus-eluting stents; PES — paclitaxel-eluting stents; ZES — zotarolimus-eluting stents; EES — everolimus-eluting stents; BES — biolimus-eluting stents

12 months. Triple antiplatelet therapy (TAPT) (100 mg of cilostazol [Pletaal®, Otsuka Pharmaceutical Co., Tokyo, Japan] twice a day added on a dual antiplatelet therapy) was left to the discretion of the individual operators [9].

Study definitions and clinical outcomes

Acute myocardial infarction was defined according to the current guidelines [11, 12]. Current smoking was defined as cigarette smoking within 1 year before the index PCI [9, 13]. Smoking history was assessed based on patient medical records. In this study, the occurrence of major adverse cardiac events (MACEs) was the primary endpoint. MACEs comprised all-cause death, recurrent myocardial infarction (Re-MI), and any repeat revascularization during a 2-year follow-up period. All-cause death was classified as a cardiac death (CD) or a non-CD. Re-MI was defined as the reoccurrence of AMI [14]. Any repeat revascularization comprised target lesion revascularization (TLR), target vessel revascularization (TVR), and non-TVR. Previously, the definitions of TLR, TVR, and non-TVR were published [14]. The secondary endpoint, the cumulative incidences of definite or probable stent thrombosis (ST), was defined according to the onset of this event as follows: acute (0–24 h), subacute (24 h–30 days), late (30 days–1 year), and very late (> 1 year) [14, 15].

Statistical analyses

The Statistical Package for the Social Sciences software version 20 (International Business Machines Corporation, Armonk, NY, USA) was used during the statistical analyses of this study. In case of continuous variables, differences between the

groups were evaluated using the unpaired t-test, and the data are expressed as the mean ± standard deviations. In case of categorical variables, the differences between two groups were analyzed with the χ^2 test, or, if not applicable, the Fisher exact test, and data are expressed as counts and percentages. Various clinical outcomes of this study were evaluated using the Kaplan-Meier method, and differences between two groups were compared using the log-rank test. Among the total covariates, only significant confounding covariates ($p < 0.001$ or those having predictive values) were included when performing multivariate Cox regression analysis, as shown in Table 2. For all analyses, two-sided p values < 0.05 were considered statistically significant [13].

Results

Baseline clinical, laboratory, angiographic, and procedural characteristics

The baseline, laboratory, angiographic, and procedural characteristics of the present study population are summarized in Table 1. The mean age of the patients in the female group was higher than that of the male group (68.3 ± 11.5 years vs. 56.7 ± 11.2 years, $p < 0.001$). The average level of left ventricular ejection fraction (LVEF) was similar and well preserved between the two groups (52.6 ± ± 11.0% vs. 52.5 ± 11.8, $p = 0.724$). The proportion of patients who had decreased LVEF (< 40%) was also similar between the two groups. The following values were higher in the male group than in the female group: number of ST-segment elevation myocardial infarction (STEMI); mean value of body mass index, diastolic blood pressure; serum creatinine level; triglyceride level; prescription rates of ASA, ticagrelor, prasugrel, beta-blockers, and lipid-lowering agents; and numbers of left anterior descending (LAD) artery as the infarct-related artery (IRA) or treated vessel; single-vessel disease; and the deployment of everolimus-eluting stents and biolimus-eluting stents. By contrast, the female group showed higher values than the male group for the following: number of non-STEMI; proportion of hypertension, DM, previous cerebrovascular accident (CVA), and HF; mean values of serum N-terminal pro-B-type natriuretic peptide, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol; prescription rates of clopidogrel; numbers of right coronary artery (RCA) as the IRA and treated vessel; ACC/ /AHA type C lesion; ≥ three-vessel disease; and number of deployed stent.

Clinical outcomes

Table 2 and Figure 2 show the clinical outcomes at 30 days, 1 year, and 2 years. During 1 month, the cumulative incidences of MACEs and all-cause death were significantly higher in the female group than in the male group. At 1 year after the index PCI, the cumulative incidences of MACEs, all-cause death, and Re-MI were also higher in the female group in the male group. Moreover, at 2 years, the cumulative incidences of all-cause death (adjusted hazard ratio [aHR]: 1.561; 95% confidence interval [CI]: 1.103–2.210; $p = 0.012$) and Re-MI (aHR: 1.800; 95% CI: 1.089–2.974; $p = 0.022$) were significantly higher in the female group than those in the male group. However, the cumulative incidences of ST, any repeat revascularization, TLR, TVR, and non-TVR were similar between the two groups.

Table 3 shows independent predictors for all-cause death and Re-MI at 2 years. Figure 3 shows the subgroup analyses for MACEs. In cases of over 40% of LVEF, non-hypertensive patients, ACC/ /AHA non-type C lesion, and patients who had non--RCA as IRA, who received lipid-lowering agents, and who currently smoke on admission showed worse outcomes for the female group compared with the male group in terms of MACEs.

Discussion

The main findings of the current study are as follows: 1) During 1 month, the cumulative incidences of MACEs and all-cause death were significantly higher in the female group than those in the male group; 2) At 1 year, the cumulative incidences of MACEs, all-cause death, and Re-MI were also higher in the female group than those in the male group; 3) At 2 years, the cumulative incidences of all-cause death and Re-MI were significantly higher in the female group than those in the male group; 4) However, the cumulative incidences of ST, any repeat revascularization, TLR, TVR, and non-TVR were similar between the two groups after adjustment.

To date, sex difference for MACEs and mortality showed debatable results [16, 17]. Other studies have reported that women have smaller arterial diameter and lower sensitivity to cardiac function tests and receive a more suboptimal medical treatment compared with men [18–20]. In the present cohort, before risk adjustment, the female group had less favorable baseline characteristics for CVD risk factor profiles such as old age, higher proportions of hypertension, DM, previous history

Table 2. Clinical outcomes by the Kaplan-Meier analysis and the Cox-proportional hazard ratio analysis up to 2 years.

Outcomes	Cumulative events (%)			Unadjusted		Adjusted*	
	Male (n = 11,767)	Female (n = 798)	Log--rank	HR (95% CI)	P	HR (95% CI)	P
30 days							
MACE	221 (1.9)	32 (4.0)	< 0.001	2.155 (1.487–3.122)	< 0.001	1.457 (1.021–2.216)	0.035
All-cause death	155 (1.3)	22 (2.8)	0.001	2.105 (1.347–3.289)	0.001	1.699 (1.074–2.687)	0.023
Cardiac death	145 (1.2)	19 (2.4)	0.006	1.942 (1.204–3.134)	0.007	1.505 (0.921–2.457)	0.102
Re-MI	47 (0.4)	6 (0.8)	0.133	1.896 (0.810–4.434)	0.140	1.806 (0.757–4.310)	0.183
Any revascularization	31 (0.3)	5 (0.6)	0.060	2.409 (0.937–6.196)	0.068	2.045 (0.865–3.374)	0.345
TLR	9 (0.1)	2 (0.3)	0.104	3.314 (0.716–15.34)	0.125	2.702 (0.539–13.56)	0.227
TVR	16 (0.1)	4 (0.5)	0.011	3.737 (1.249–11.18)	0.018	2.433 (0.990–8.502)	0.076
Non-TVR	14 (0.1)	1 (0.1)	0.951	1.066 (0.140–8.103)	0.951	1.131 (0.144–8.910)	0.907
ST (definite or probable)							
Acute	10 (0.1)	0 (0.0)	0.410	—	—	—	—
Subacute	29 (0.2)	3 (0.4)	0.483	1.342 (0.409–4.410)	0.627	1.031 (0.266–3.991)	0.965
Total	39 (0.3)	3 (0.4)	0.833	1.004 (0.310–3.249)	0.995	1.173 (0.322–4.264)	0.809
1 year							
MACEs	660 (5.7)	70 (8.9)	< 0.001	1.585 (1.239–2.028)	< 0.001	1.402 (1.090–1.803)	0.009
All-cause death	245 (2.1)	35 (4.4)	< 0.001	2.121 (1.489–3.023)	< 0.001	1.660 (1.153–2.390)	0.006
Cardiac death	204 (1.7)	24 (3.0)	0.009	1.747 (1.144–2.666)	0.010	1.238 (0.831–1.980)	0.261
Re-MI	107 (0.9)	16 (2.1)	0.002	2.229 (1.318–3.770)	0.003	2.040 (1.189–3.501)	0.010
Any revascularization	340 (3.0)	23 (3.0)	0.980	1.005 (0.659–1.534)	0.980	0.974 (0.635–1.495)	0.905
TLR	97 (0.9)	7 (0.9)	0.857	1.073 (0.498–2.311)	0.857	1.011 (0.464–2.204)	0.978
TVR	166 (1.5)	12 (1.6)	0.812	1.072 (0.598–1.929)	0.812	1.048 (0.578–1.900)	0.877
Non-TVR	177 (1.6)	11 (1.5)	0.794	1.084 (0.590–1.994)	0.794	1.174 (0.636–2.176)	0.608
ST (definite or probable)							
Late	35 (0.3)	4 (0.5)	0.316	1.885 (0.667–5.329)	0.232	1.343 (0.403–4.479)	0.631
Total (0–365 days)	74 (0.6)	7 (0.9)	0.397	1.372 (0.631–2.984)	0.424	1.116 (0.481–2.591)	0.799
2 years							
MACEs	819 (7.2)	78 (10.0)	0.003	1.419 (1.125–1.790)	0.003	1.264 (1.001–1.598)	0.052
All-cause death	283 (2.5)	38 (4.8)	< 0.001	1.988 (1.417–2.789)	< 0.001	1.561 (1.103–2.210)	0.012
Cardiac death	224 (1.9)	25 (3.2)	0.016	1.654 (1.094–2.500)	0.017	1.216 (0.797–1.857)	0.364
Re-MI	142 (1.3)	18 (2.4)	0.010	1.885 (1.154–3.078)	0.011	1.800 (1.089–2.974)	0.022
Any revascularization	444 (4.0)	27 (3.6)	0.594	1.111 (0.754–1.639)	0.594	1.161 (0.785–1.717)	0.453
TLR	121 (1.1)	8 (1.1)	0.956	1.021 (0.499–2.087)	0.956	1.008 (0.471–1.982)	0.982
TVR	228 (2.1)	14 (1.9)	0.726	1.101 (0.642–1.889)	0.726	1.094 (0.626–1.864)	0.745
Non-TVR	223 (2.0)	13 (1.7)	0.602	1.160 (0.663–2.030)	0.602	1.273 (0.725–2.235)	0.400
ST (definite or probable)							
Very late	15 (0.1)	1 (0.1)	0.988	1.021 (0.131–9.274)	0.684	1.042 (0.967–11.23)	0.280
Total (0–730 days)	89 (0.8)	8 (1.0)	0.445	1.104 (0.533–2.285)	0.790	1.207 (0.583–2.497)	0.613

*Adjusted by age, BMI, SBP, DBP, hypertension, diabetes, previous CVA, cardiogenic shock, NT-proBNP, total cholesterol, LDL cholesterol, clopidogrel, beta-blockers, lipid lowering agents, infarct-related artery (LAD and RCA), treated vessel (RCA), ≥ 3-vessel, stent diameter. HR — hazard ratio; CI — confidence interval; MACEs — major adverse cardiac events; Re-MI — re-myocardial infarction; TLR — target lesion revascularization; TVR — target vessel revascularization; ST — stent thrombosis

of CVA, HF, cardiogenic shock, and smaller mean diameter of deployed stents and showed significantly higher cumulative incidences of MACEs compared with the male group. These study results are consistent with the results of Bell's and Nappi's study [3]. The unfavorable effects of smoking on

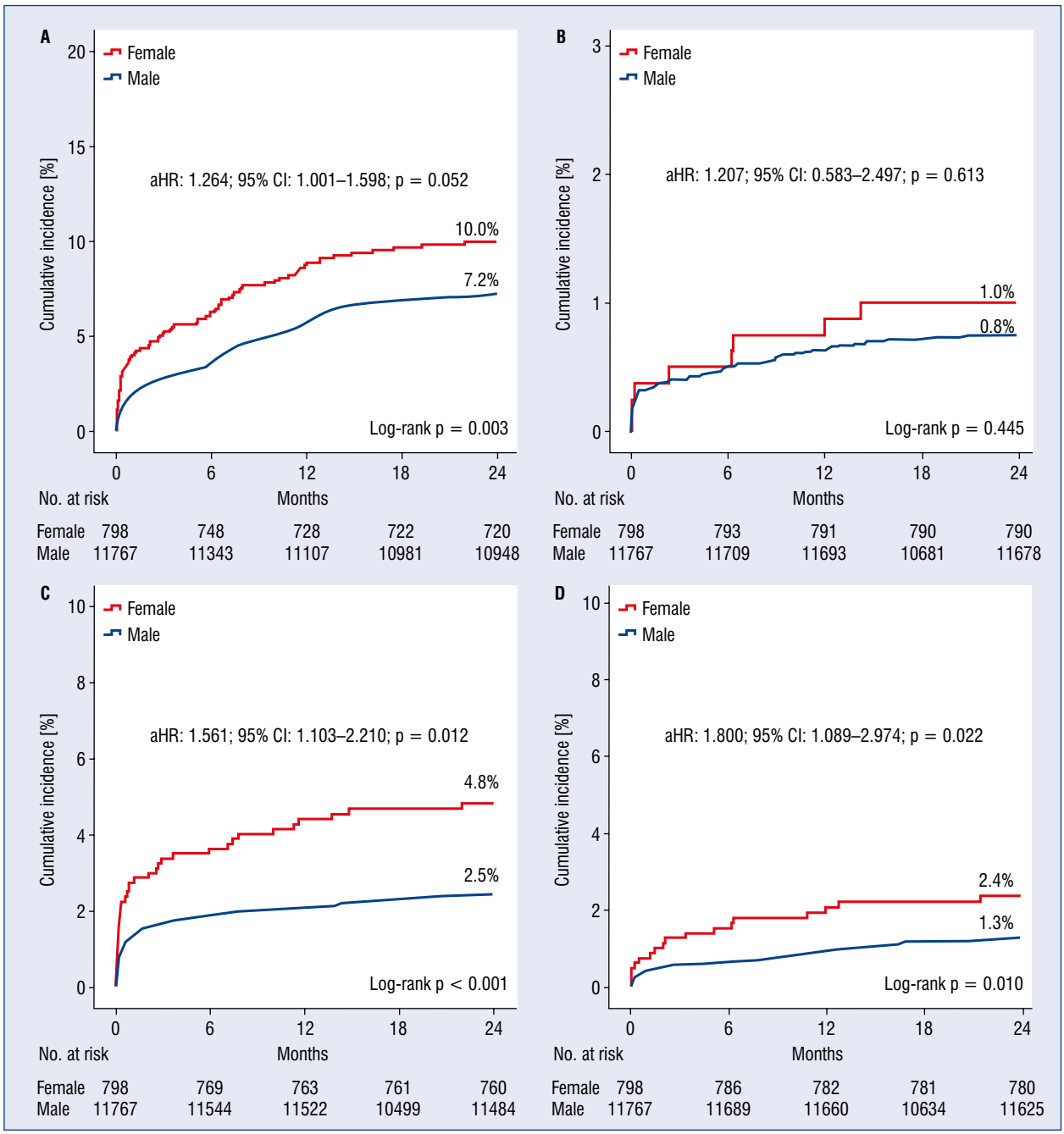

Figure 2. Kaplan-Meier Analysis for major adverse cardiac events (MACEs) (**A**), stent thrombosis (**B**), all-cause (**C**) and recurrent myocardial infarction (**D**); CI — confidence interval; aHR — adjusted hazard ratio.

CAD include increasing plasma fibrinogen level, reducing high-density lipoprotein cholesterol level, increasing carboxyhemoglobin level, and increasing platelet stickiness and aggregation under the milieu of AMI [21, 22]. Furthermore, endothelial dysfunctions, including reduced nitric oxide release [23] and inflammations [24], are involved in this process.

In this study, the cumulative incidence of all-cause death, both early (30 days) and late (1 year and 2 year), and the cumulative incidence of Re-MI after 1 month of the index PCI, were higher in the female group than that in the male group after adjustment (Fig. 2). The possible explanation for these worse clinical outcomes in the female smokers' group is related with the decreased estrogen activity or production [25]. Additionally, a Danish report suggested that women may be more sensitive compared with men to the

Table 3. Multivariable Cox-proportional regression analysis for predictors of all-cause death and recurrent myocardial infarction (Re-MI) at 2 years.

Variables	All-cause death				Re-MI			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Male vs. female	1.988 (1.417–2.789)	< 0.001	2.642 (1.984–3.327)	< 0.001	1.885 (1.154–3.078)	0.011	1.733 (1.035–2.902)	0.037
Age ≥ 65 years	3.656 (2.931–4.560)	< 0.001	2.507 (1.974–3.183)	< 0.001	1.335 (0.959–1.858)	0.087	1.128 (0.788–1.616)	0.510
LVEF < 40%	5.173 (4.127–6.483)	< 0.001	3.596 (2.831–4.568)	< 0.001	1.752 (1.159–2.650)	0.008	1.422 (0.927–2.180)	0.106
Diastolic blood pressure	0.989 (0.982–0.995)	0.001	1.005 (0.997–1.012)	0.242	1.001 (0.991–1.010)	0.863	1.002 (0.991–1.012)	0.756
STEMI	1.020 (0.813–1.279)	0.864	1.114 (0.945–1.281)	0.711	1.195 (0.859–1.664)	0.291	1.217 (0.862–1.720)	0.265
Hypertension	1.372 (1.101–1.710)	0.005	1.025 (0.813–1.291)	0.837	1.054 (0.766–1.450)	0.748	1.121 (0.801–1.568)	0.507
Diabetes mellitus	1.743 (1.380–2.202)	< 0.001	1.386 (1.085–1.771)	0.009	1.520 (1.082–2.136)	0.016	1.412 (0.991–2.010)	0.056
Previous CVA	2.896 (2.020–4.152)	< 0.001	1.772 (1.225–2.564)	0.002	2.441 (1.411–4.225)	0.001	2.178 (1.238–3.831)	0.007
Cardiogenic shock	3.103 (2.194–4.389)	< 0.001	2.829 (1.863–4.296)	< 0.001	1.132 (1.531–2.415)	0.748	1.226 (0.534–2.817)	0.631
Primary PCI	1.030 (0.825–1.286)	0.793	1.239 (0.706–2.174)	0.455	1.173 (0.852–1.615)	0.329	1.034 (0.480–2.226)	0.933
PCI within 24 h	1.069 (0.841–1.357)	0.586	1.423 (0.873–2.322)	0.157	1.288 (0.830–1.699)	0.346	1.190 (0.576–2.456)	0.639
Clopidogrel	1.344 (0.886–2.038)	0.165	1.075 (0.706–1.639)	0.735	1.199 (0.724–1.986)	0.480	1.322 (0.793–2.203)	0.284
Beta-blockers	3.796 (3.049–4.727)	< 0.001	3.153 (2.521–3.944)	< 0.001	1.007 (0.695–1.555)	0.849	1.061 (0.706–1.592)	0.777
LAD (IRA)	1.147 (0.921–1.428)	0.220	1.054 (0.779–1.406)	0.735	1.657 (1.207–2.275)	0.002	1.639 (1.203–2.626)	0.040
RCA (IRA)	1.221 (0.958–1.555)	0.106	1.657 (1.042–2.635)	0.033	1.478 (0.784–2.114)	0.032	1.237 (0.608–2.014)	0.284
RCA (treated)	1.108 (0.813–1.274)	0.879	1.248 (0.858–1.817)	0.247	1.260 (0.908–1.749)	0.166	1.141 (0.654–1.991)	0.642
ACC/AHA type B2/C lesion	1.266 (0.973–1.648)	0.079	1.256 (0.963–1.639)	0.093	1.059 (0.743–1.510)	0.751	1.019 (0.712–1.457)	0.919
≥ 3-vessel	2.013 (1.590–2.550)	< 0.001	1.329 (1.034–1.708)	0.027	1.429 (0.996–2.049)	0.053	1.291 (0.883–1.887)	0.188

HR — hazard ratio; CI — confidence interval; LVEF — left ventricular ejection fraction; STEMI — ST-segment elevation myocardial infarction; CVA — cerebrovascular accidents; PCI — percutaneous coronary intervention; LAD — left anterior descending coronary artery; IRA — infarct-related artery; RCA — right coronary artery; ACC/AHA — American College of Cardiology/American Heart Association

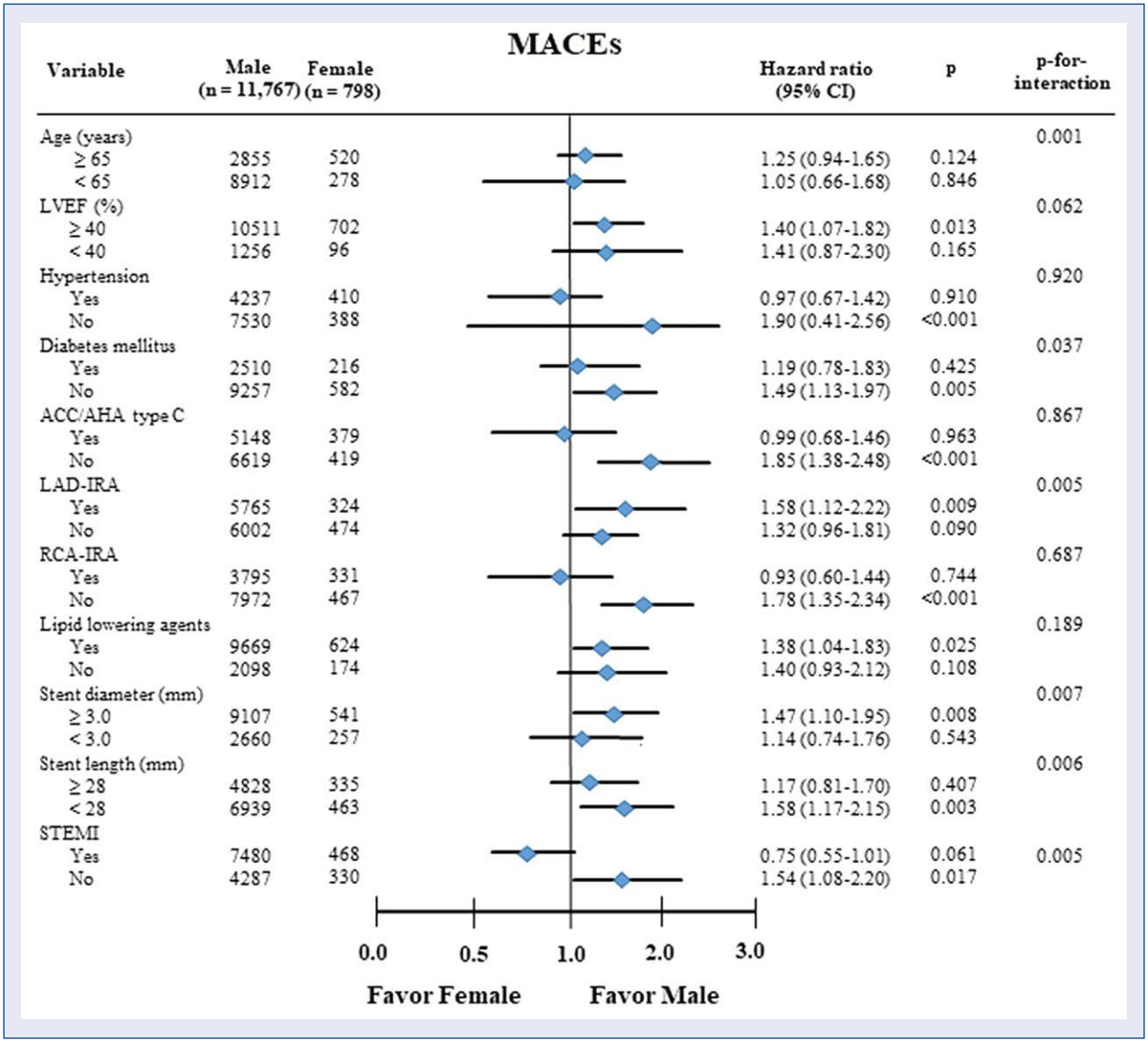

Figure 3. Subgroup analyses for major adverse cardiac events (MACEs). CI — confidence interval; LVEF — left ventricular ejection fraction; ACC/AHA — American College of Cardiology/American Heart Association; LAD — left anterior descending coronary artery; RCA — right coronary artery; IRA — infarct-related artery; STEMI — ST-segment elevation myocardial infarction.

deleterious effects of smoking [6]. According to other studies [21, 26], women are more susceptible to the effects of nicotine consumption, which causes vasoconstriction, compared with men. Although previous studies [20, 27] have reported that less aggressive treatment of acute coronary syndrome may be a causative factor to poorer outcomes in women than in men, in this study, the proportions of primary PCI (92.5% vs. 91.7%, p = 0.508) and PCI within 24 h (78.0% vs. 75.8%, p = 0.354) were similar at baseline (Table 1). Moreover, both primary PCI and PCI within 24 h were not predictors of all-cause death and Re-MI in our study (Table 3).

In the GUSTO-1 trial, single-vessel disease was more frequently observed in smokers compared with nonsmokers (63% vs. 55%) [28]. In the current study, singe-vessel disease was also more frequently observed compared with multivessel disease in both sexes (Table 1). It is highly likely that the mortality rate for RCA as an IRA is lower than for LAD [29]. Despite the number of RCA as an IRA was higher in the female group than that in the male group (47.2% vs. 43.7%, p = 0.039), all-cause death was significantly higher in the female group than that in the male group after adjustment. Hence, sex difference for the major clinical outcomes was strongly suggested in this cohort study.

Approximately 23% of patients who quit smoking at 30 days had relapsed at 12 months [30]. One Asian study showed that a total of 34.1% of smokers continued to smoke or relapsed after a period of time of quitting smoking [31]. Therefore, it can be assumed that greater than 30% of the enrolled patients continued to smoke after the index PCI during the follow-up period.

In the present cohort study, the proportion of women was relatively smaller compared to the total number of men (93.6% vs. 6.4%). This proportional difference of enrolled patients between the two groups is consistent with the previous studies [32, 33]. In the previous studies, the number of smokers is relatively lower in women than in men with some regional variations, specifically in Asian regions where the prevalence of women smoking is less than 10% [32, 33]. Moreover, the KAMIR is a nationwide, prospective, observational multicenter registry in South Korea, and more than 50 high-volume university or community hospitals participated in this study [7, 8]. Therefore, we believe that in this study, the study population is not small for providing reasonably accurate results.

Limitations of the study

This study has the following limitations. First, due to the characteristics of the nonrandomized retrospective nature of the study, there may be some incomplete variables. Second, the smoking status of the study population was assessed on admission, and the registry data did not include full detailed data concerning the status of smoking including before admission and during the follow-up period [9, 13]. Therefore, these factors may contribute bias. Third, this study assessed the discharge medications. Fourth, it was not possible to compare the initial laboratory results with the serial follow-up results because of the limited registry data, subsequently introducing bias. Fifth, although multivariate Cox proportional regression analysis was performed, the results of the present study are relatively different according to the variables included or excluded when performing this analysis. Sixth, the strategy of antiplatelet therapy (e.g., dual antiplatelet therapy or TAPT) was left to the physician's discretion, which may have influenced the major clinical outcomes [9]. Finally, AMI was defined according to the current guidelines including the 3rd universal definition of MI [11, 12] in this study. However, the fourth universal definition of MI [34] contains more updated and accurate diagnostic criteria than those of the third universal definition of MI.

Conclusions

In conclusion, the female group showed worse short-term and long-term clinical outcomes compared with the male group comprising Korean AMI patients with history of current smoking who underwent successful DES implantation. However, additional studies are required to determine the clinical implications of these results.

Acknowledgments

This research was supported by a fund (2016-ER6304-02) by Research of Korea Centers for Disease Control and Prevention.

Korea Acute Myocardial Infarction (KAMIR) Investigators

Myung Ho Jeong, MD, Young Keun Ahn, MD, Sung Chul Chae, MD, Jong Hyun Kim, MD, Seung-Ho Hur, MD, Young Jo Kim, MD, In Whan Seong, MD, Donghoon Choi, MD, Jei Keon Chae, MD, Taek Jong Hong, MD, Jae Young Rhew, MD, Doo-Il Kim, MD, In-Ho Chae, MD, Junghan Yoon, MD, Bon-Kwon Koo, MD, Byung-Ok Kim, MD, Myoung Yong Lee, MD, Kee-Sik Kim, MD, Jin-Yong Hwang, MD, Myeong Chan Cho, MD, Seok Kyu Oh, MD, Nae-Hee Lee, MD, Kyoung Tae Jeong, MD, Seung-Jea Tahk, MD, Jang-Ho Bae, MD, Seung-Woon Rha, MD, Keum-Soo Park, MD, Chong Jin Kim, MD, Kyoo-Rok Han, MD, Tae Hoon Ahn, MD, Moo-Hyun Kim, MD, Ki Bae Seung, MD, Wook Sung Chung, MD, Ju-Young Yang, MD, Chong Yun Rhim, MD, Hyeon-Cheol Gwon, MD, Seong-Wook Park, MD, Young-Youp Koh, MD, Seung Jae Joo, MD, Soo-Joong Kim, MD, Dong Kyu Jin, MD, Jin Man Cho, MD, Byung Ok Kim, MD, Sang-Wook Kim, MD, Jeong Kyung Kim, MD, Tae Ik Kim, MD, Deug Young Nah, MD, Si Hoon Park, MD, Sang Hyun Lee, MD, Seung Uk Lee, MD, Hang-Jae Chung, MD, Jang-Hyun Cho, MD, Seung Won Jin, MD, Myeong-Ki Hong, MD, Yangsoo Jang, MD, Jeong Gwan Cho, MD, Hyo-Soo Kim, MD, and Seung-Jung Park, MD.

Conflict of interest: None declared

References

1. Kannel W, Sorlie P, Mcnamara P. Prognosis after initial myocardial infarction: the Framingham study. Am J Cardiol. 1979; 44(1): 53–59, doi: 10.1016/0002-9149(79)90250-9.

2. El-Menyar AA, Al Suwaidi J. Impact of gender in patients with acute coronary syndrome. Expert Rev Cardiovasc Ther. 2009; 7(4): 411–421, doi: 10.1586/erc.09.10, indexed in Pubmed: 19379065.
3. Bell DM, Nappi J. Myocardial infarction in women: a critical appraisal of gender differences in outcomes. Pharmacotherapy. 2000; 20(9): 1034–1044, doi: 10.1592/phco.20.13.1034.35034, indexed in Pubmed: 10999494.
4. Reitsma M, Fullman N, Ng M, et al. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: a systematic analysis from the Global Burden of Disease Study 2015. Lancet. 2017; 389(10082): 1885–1906, doi: 10.1016/s0140-6736(17)30819-x, indexed in Pubmed: 28390697.
5. Ng M, Freeman MK, Fleming TD, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980–2012. JAMA. 2014; 311(2): 183–192, doi: 10.1001/jama.2013.284692, indexed in Pubmed: 24399557.
6. Prescott E, Hippe M, Schnohr P, et al. Smoking and risk of myocardial infarction in women and men: longitudinal population study. BMJ. 1998; 316(7137): 1043–1047, doi: 10.1136/bmj.316.7137.1043, indexed in Pubmed: 9552903.
7. Sim DS, Jeong MHo. Differences in the Korea acute myocardial infarction registry compared with western registries. Korean Circ J. 2017; 47(6): 811–822, doi: 10.4070/kcj.2017.0027, indexed in Pubmed: 29035427.
8. Kim JuH, Chae SC, Oh DJ, et al. Korea Acute Myocardial Infarction-National Institutes of Health Registry Investigators. 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(6): 1427–1436, doi: 10.1253/circj.CJ-16-0061, indexed in Pubmed: 27118621.
9. Kim YH, Her AY, Jeong MHo, et al. A comparison of the impact of current smoking on 2-year major clinical outcomes of first- and second-generation drug-eluting stents in acute myocardial infarction: Data from the Korea Acute Myocardial Infarction Registry. Medicine (Baltimore). 2019; 98(10): e14797, doi: 10.1097/MD.0000000000014797, indexed in Pubmed: 30855497.
10. Grech ED. ABC of interventional cardiology: percutaneous coronary intervention. II: the procedure. BMJ. 2003; 326(7399): 1137–1140, doi: 10.1136/bmj.326.7399.1137, indexed in Pubmed: 12763994.
11. Thygesen K, Alpert JS, Jaffe AS, et al. Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. Circulation. 2012; 126(16): 2020–2035, doi: 10.1161/CIR.0b013e31826e1058, indexed in Pubmed: 22923432.
12. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014; 64(24): e139–e228, doi: 10.1016/j.jacc.2014.09.017, indexed in Pubmed: 25260718.
13. Kim YH, Her AY, Jeong MHo, et al. Impact of current smoking on 2-year clinical outcomes between durable-polymer-coated stents and biodegradable-polymer-coated stents in acute myocardial infarction after successful percutaneous coronary intervention: Data from the KAMIR. PLoS One. 2018; 13(10): e0205046, doi: 10.1371/journal.pone.0205046, indexed in Pubmed: 30289945.
14. Kim YH, Her AY, Rha SW, et al. Three-year major clinical outcomes of phosphorylcholine polymer- vs biolinx polymer-zotarolimus-eluting stents: A propensity score matching study. Medicine (Baltimore). 2019; 98(32): e16767, doi: 10.1097/MD.0000000000016767, indexed in Pubmed: 31393396.
15. Bundhun PK, Wu ZiJ, Chen MH. Is there any significant difference in stent thrombosis between sirolimus and paclitaxel eluting stents?: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2016; 95(5): e2651, doi: 10.1097/MD.0000000000002651, indexed in Pubmed: 26844487.
16. Kovacic JC, Mehran R, Karajgikar R, et al. Female gender and mortality after percutaneous coronary intervention: results from a large registry. Catheter Cardiovasc Interv. 2012; 80(4): 514–521, doi: 10.1002/ccd.23338, indexed in Pubmed: 22045678.
17. Jacobs A, Johnston J, Haviland A, et al. Improved outcomes for women undergoing contemporary percutaneous coronary intervention. J Am Coll Cardiol. 2002; 39(10): 1608–1614, doi: 10.1016/s0735-1097(02)01835-1.
18. Douglas PS, Ginsburg GS. The evaluation of chest pain in women. N Engl J Med. 1996; 334(20): 1311–1315, doi: 10.1056/NEJM199605163342007, indexed in Pubmed: 8609950.
19. Kwok Y, Kim C, Grady D, et al. Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol. 1999; 83(5): 660–666, doi: 10.1016/s0002-9149(98)00963-1.
20. Shaw LJ, Bairey Merz CN, Pepine CJ, et al. WISE Investigators. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. J Am Coll Cardiol. 2006; 47(3 Suppl): S4–SS20, doi: 10.1016/j.jacc.2005.01.072, indexed in Pubmed: 16458170.
21. Benowitz N. Cigarette smoking and cardiovascular disease: pathophysiology and implications for treatment. Prog Cardiovasc Dis. 2003; 46(1): 91–111, doi: 10.1016/s0033-0620(03)00087-2.
22. Law M, Wald N. Environmental tobacco smoke and ischemic heart disease. Prog Cardiovasc Dis. 2003; 46(1): 31–38, doi: 10.1016/s0033-0620(03)00078-1.
23. Messner B, Bernhard D. Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. Arterioscler Thromb Vasc Biol. 2014; 34(3): 509–515, doi: 10.1161/ATVBAHA.113.300156, indexed in Pubmed: 24554606.
24. Tibuakuu M, Kamimura D, Kianoush S, et al. The association between cigarette smoking and inflammation: The Genetic Epidemiology Network of Arteriopathy (GENOA) study. PLoS One. 2017; 12(9): e0184914, doi: 10.1371/journal.pone.0184914, indexed in Pubmed: 28922371.
25. Berta L, Frairia R, Fortunati N, et al. Smoking effects on the hormonal balance of fertile women. Horm Res. 1992; 37(1-2): 45–48, doi: 10.1159/000182280, indexed in Pubmed: 1398476.
26. Tamis-Holland JE. Sex and outcomes after percutaneous coronary intervention: a cause for concern for young women and those with ST-segment elevation myocardial infarction? J Am Heart Assoc. 2017; 6(3), doi: 10.1161/JAHA.117.005739, indexed in Pubmed: 28320751.
27. Ani C, Pan D, Martins D, et al. Age- and sex-specific in-hospital mortality after myocardial infarction in routine clinical practice. Cardiol Res Pract. 2010; 2010: 752765, doi: 10.4061/2010/752765, indexed in Pubmed: 21234360.
28. Barbash G, Reiner J, White H, et al. Evaluation of paradoxic beneficial effects of smoking in patients receiving thrombolytic therapy for acute myocardial infarction: Mechanism of the "smoker's paradox" from the GUSTO-I trial, with angiographic insights.

J Am Coll Cardiol. 1995; 26(5): 1222–1229, doi: 10.1016/0735-1097(95)00299-5.

29. Thanavaro S, Kleiger RE, Province MA, et al. Effect of infarct location on the in-hospital prognosis of patients with first transmural myocardial infarction. Circulation. 1982; 66(4): 742–747, doi: 10.1161/01.cir.66.4.742, indexed in Pubmed: 7116591.
30. Yudi MB, Farouque O, Andrianopoulos N, et al. Melbourne Interventional Group. The prognostic significance of smoking cessation after acute coronary syndromes: an observational, multicentre study from the Melbourne interventional group registry. BMJ Open. 2017; 7(10): e016874, doi: 10.1136/bmjopen-2017-016874, indexed in Pubmed: 28988174.
31. Liu J, Zhu Zy, Gao Cy, et al. Long-term effect of persistent smoking on the prognosis of Chinese male patients after percutaneous coronary intervention with drug-eluting stent implantation. J Cardiol. 2013; 62(5): 283–288, doi: 10.1016/j.jjcc.2013.05.010, indexed in Pubmed: 23834958.
32. Martiniuk ALC, Lee CMY, Lam TH, et al. Asia Pacific Cohort Studies Collaboration. The fraction of ischaemic heart disease and stroke attributable to smoking in the WHO Western Pacific and South-East Asian regions. Tob Control. 2006; 15(3): 181–188, doi: 10.1136/tc.2005.013284, indexed in Pubmed: 16728748.
33. Huxley R, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. Lancet. 2011; 378(9799): 1297–1305, doi: 10.1016/s0140-6736(11)60781-2, indexed in Pubmed: 21839503.
34. Thygesen K, Alpert JS, Jaffe AS, et al. Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018; 138(20): e618–e651, doi: 10.1161/CIR.0000000000000617, indexed in Pubmed: 30571511.