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

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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
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 health 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].

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
| 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/m²]                          | 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 CAGB                        | 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 [mL]                    | 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|
| Cilostazol                           | 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

|                        | Male (n = 11,767) | Female (n = 798) | P      | SD  |
|------------------------|-------------------|------------------|--------|-----|
| 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|
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 χ² 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 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-TV-R 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-TV-R 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...
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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
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

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.
### 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 |
|------------------------------------|-----------------|-------|------------|--------------|------------|--------------|
|                                    | P               | HR (95% CI) P | HR (95% CI) P | HR (95% CI) P | HR (95% CI) P | HR (95% CI) P |
| Male vs. female                    | 0.011           | 1.988 (1.54–3.078) | 0.011 | 1.885 (1.54–3.078) | 0.011 | 1.733 (1.035–2.902) |
| Age ≥ 65 years                     | 0.001           | 3.686 (1.931–6.960) | < 0.001 | 5.173 (2.127–12.483) | < 0.001 | 5.173 (2.127–12.483) |
| LVEF < 40%                         | 0.001           | 0.989 (0.982–0.995) | 0.001 | 1.055 (1.017–1.102) | 0.001 | 1.055 (1.017–1.102) |
| STEMI                              | 0.001           | 1.920 (1.014–3.621) | < 0.001 | 2.172 (1.325–3.564) | < 0.001 | 2.172 (1.325–3.564) |
| Hypertension                       | 0.001           | 1.698 (1.101–2.577) | 0.001 | 1.529 (1.028–2.294) | 0.001 | 1.529 (1.028–2.294) |
| Diabetes mellitus                  | 0.001           | 1.439 (1.076–1.950) | < 0.001 | 1.439 (1.076–1.950) | < 0.001 | 1.439 (1.076–1.950) |
| Previous CVA                       | 0.001           | 1.069 (0.874–1.307) | 0.001 | 1.069 (0.874–1.307) | 0.001 | 1.069 (0.874–1.307) |
| Cardiacogenic shock                | 0.001           | 3.103 (2.194–4.388) | < 0.001 | 3.103 (2.194–4.388) | < 0.001 | 3.103 (2.194–4.388) |
| Primary PCI                        | 0.001           | 1.372 (1.101–1.710) | < 0.001 | 1.372 (1.101–1.710) | < 0.001 | 1.372 (1.101–1.710) |
| Primary PCI within 24 h            | 0.001           | 1.743 (1.380–2.202) | < 0.001 | 1.743 (1.380–2.202) | < 0.001 | 1.743 (1.380–2.202) |
| Clopidogrel                         | 0.001           | 1.221 (1.057–1.404) | < 0.001 | 1.221 (1.057–1.404) | < 0.001 | 1.221 (1.057–1.404) |
| Beta-blockers                      | 0.001           | 3.796 (3.049–4.727) | < 0.001 | 3.796 (3.049–4.727) | < 0.001 | 3.796 (3.049–4.727) |
| LAD (IRA)                          | 0.001           | 1.167 (0.921–1.498) | < 0.001 | 1.167 (0.921–1.498) | < 0.001 | 1.167 (0.921–1.498) |
| RCA (IRA)                          | 0.001           | 1.221 (1.057–1.404) | < 0.001 | 1.221 (1.057–1.404) | < 0.001 | 1.221 (1.057–1.404) |
| RIVA (IRA)                         | 0.001           | 1.108 (0.915–1.353) | < 0.001 | 1.108 (0.915–1.353) | < 0.001 | 1.108 (0.915–1.353) |
| RCA (treated)                      | 0.001           | 1.148 (0.957–1.375) | < 0.001 | 1.148 (0.957–1.375) | < 0.001 | 1.148 (0.957–1.375) |
| ≥ 3-vessel                         | 0.001           | 2.073 (1.589–2.650) | < 0.001 | 2.073 (1.589–2.650) | < 0.001 | 2.073 (1.589–2.650) |

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.
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, single-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.

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