Clinical Characteristics and Outcomes of Japanese Women Undergoing Coronary Revascularization Therapy

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**Background:** Limited data are available for gender-based differences in patients undergoing coronary revascularization. This study aimed to identify gender-based differences in risk factor profiles and outcomes among Japanese patients undergoing coronary revascularization.

**Methods and Results:** The subjects consisted of 2,845 women and 6,843 men who underwent first percutaneous coronary intervention or coronary artery bypass grafting in 2000–2002. The outcome measures were all-cause death, major adverse cardiovascular events (MACE) as the composite of cardiovascular death, myocardial infarction and stroke, and any coronary revascularization. The females were older than the males and more frequently had histories of heart failure, diabetes, hypertension, chronic kidney disease, anemia, and dyslipidemia. Unadjusted survival analysis revealed a significantly lower incidence of any revascularization in women (at 3 years: 28.2% vs. 31.2%, P=0.0037), although no significant gender-based differences were shown in the incidence of all-cause death (at 3 years: 8.8% vs. 8.5%, P=0.37) or MACE (at 3 years: 12.0% vs. 11.5%, P=0.61). Multivariate analysis revealed that female gender was associated with significantly lower risks of any revascularization (relative risk = 0.93, 95% confidence interval [CI] = 0.88–0.99, P=0.014) and all-cause death (relative risk = 0.86, 95%CI = 0.77–0.96, P=0.005).

**Conclusions:** In Japanese patients undergoing first coronary revascularization, the coronary risk factor burden appeared greater in women than in men. Despite the greater modifiable risk factor accumulation, female gender was associated with a lower incidence of repeated revascularization relative to male gender. (Circ J 2011; 75: 1358–1367)

**Key Words:** Coronary artery disease; Outcomes; Revascularization; Risk factors; Women

Many studies have attempted to clarify gender-based differences in the outcomes of patients with coronary artery disease (CAD). Some studies have reported that female patients undergoing coronary revascularization have higher rates of mortality and major complications than men.1–6 While others have shown that the outcomes of female patients have improved and the gender-based differences of patients undergoing percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) have recently decreased.7–11 Moreover, there are also a few studies suggesting that the female gender is an independent predictor of better long-term survival after coronary revascularization.12–14 Gender-based differences in the outcomes of patients with CAD might be attributed, in part, to differences in the clinical backgrounds between female and male patients such as age, risk factor profiles, and comorbid diseases. Other factors that could cause gender-based differences in the outcomes might include unawareness of the importance of secondary prevention for CAD among women.

Most studies regarding gender-based differences in CAD patients have been performed in Caucasian patients. Despite...
significant differences in the prevalence of CAD between Caucasian and Asian patients, there are limited large-scale data for gender differences in the risk factor profiles and cardiovascular outcomes for Asian patients with CAD.

The purpose of the present study was to identify gender-based differences in risk factors and outcomes in Japanese patients undergoing coronary revascularization.

Methods

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in the a priori approval by the Human Research Committees of all participating institutions. Because the study subjects were retrospectively enrolled, written informed consent was not obtained in concordance with the guidelines for epidemiological studies issued by the Ministry of Health, Labour and Welfare of Japan. However, 73 patients were subsequently excluded because of their refusal to participate in the study when contacted for follow-up.

Study Subjects

Participants of the Coronary REvascularization Demonstrating Outcome study in Kyoto (CREDO – Kyoto) registry have been previously described.15,16 A total of 9,877 consecutive patients who underwent their first PCI or CABG between 2000 and 2002 from 30 institutions (Appendix) were registered.16 The subjects evaluated in the present study were 9,688 patients comprising 2,845 women and 6,843 men after excluding patients with malignant diseases. The baseline characteristics, treatments, in-hospital outcomes, and cardiovascular events during follow-up, including death, myocardial infarction, stroke, and any repeated revascularization procedures, were compared between women and men.

Data Collection, Definitions and Follow-up

Clinical and analytical data for the study subjects were collected from hospital charts or databases in each center by independent clinical research coordinators (Appendix).15 The baseline data for the patients included: age; gender; smoking habit; body mass index (BMI); mode of revascularization; and comorbidities such as hypertension, diabetes mellitus (DM), dyslipidemia (low-density lipoprotein cholesterol [LDL-C] ≥130mg/dl, triglyceride ≥150mg/dl, high-density lipoprotein cholesterol [HDL-C] <40mg/dl), chronic kidney disease (CKD), anemia, peripheral vascular disease; history of heart failure, prior myocardial infarction, and prior cerebrovascular accident. DM was diagnosed by each physician based on the diagnosis and classification of DM of the expert committee.17 CKD was defined as a glomerular filtration rate estimated by the Cockcroft–Gault formula of <60ml·min⁻¹·1.73-m². Peripheral vascular disease was defined as being present when the patients were being treated for carotid, aortic, and/or other peripheral vascular diseases or scheduled for interventions. Anemia was defined as a blood hemoglobin level of <12g/dl. The patients were followed up with respect to mortality for a median of 3.6 years. All deaths were confirmed by medical records or telephone interviews with the patients’ families, and death was regarded as being cardiovascular in origin unless obvious non-cardiovascular causes were identified. Myocardial infarction was defined according to the Arterial Revascularization Therapy Study.18 In the present study, major adverse cardiovascular events (MACE) were defined as the composite of cardiovascular death, myocardial infarction, and stroke. Any revascularization procedures during follow-up included any PCI or CABG. Follow-up coronary angiography (CAG) was not performed routinely, but left to the discretion of the attending physician.

Statistical Analysis

All continuous variables were expressed as mean±SD. Differences in the baseline clinical characteristics and treatments between women and men were evaluated by the Pearson χ² test for categorical data and the Student’s t-test for continuous

Table 1. Comparisons of the Baseline Characteristics by Gender

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women (%)</th>
<th>Men (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years; mean±SD)</td>
<td>70.6±0.2</td>
<td>65.8±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age &gt;75 (%)</td>
<td>37.0</td>
<td>19.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI ≥25 (%)</td>
<td>30.0</td>
<td>31.0</td>
<td>0.33</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>20.9</td>
<td>27.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of heart failure (%)</td>
<td>20.5</td>
<td>15.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior stroke (%)</td>
<td>15.6</td>
<td>17.1</td>
<td>0.068</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>4.0</td>
<td>8.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>6.1</td>
<td>7.1</td>
<td>0.078</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>42.0</td>
<td>37.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>75.3</td>
<td>66.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BMI: body mass index; MI: myocardial infarction; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.
data. To identify significant and independent prognostic factors for clinical outcomes, we listed the following potential baseline variables: age; gender; BMI ≥ 25 kg/m²; DM; prior myocardial infarction; history of heart failure; prior stroke; peripheral vascular disease; atrial fibrillation; hypertension; CKD; anemia; LDL-C ≥ 130 mg/dl; triglyceride ≥ 150 mg/dl; HDL-C < 40 mg/dl; current smoking; multivessel coronary disease; and unstable angina. The following cardiovascular pharmacotherapies at hospital discharge were also listed: statins; angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers (ARB); β-adrenergic blockers; anti-platelet drugs; calcium channel blockers; and nitrates. Survival analyses were performed using the Kaplan–Meier method and differences in survival between women and men were examined using a log-rank test. The Cox proportional hazards model was used to adjust the results for baseline differences between women and men. The model included baseline variables, medications at discharge and revascularization strategy (PCI/CABG). In the analysis for predictors of any coronary revascularization, a variable indicating whether follow-up CAG was performed was included in the model, because several previous studies reported that angiographic follow-up after stent implantations influenced the rates of repeat revascularization procedures. Analysis for the predictors of repeat revascularization was also performed in the PCI-treated patients, because the incidence of repeat revascularization was distinctively higher in PCI-treated than CABG-treated patients and routine follow-up CAG is generally scheduled after PCI but rarely after CABG.

All analyses were conducted using the software JMP version 5 (SAS Institute Inc, Cary, NC, USA). All reported P-values were 2-sided. Values of \( P < 0.05 \) were considered to indicate statistical significance.

### Results

#### Baseline Characteristics

The baseline clinical characteristics of the women and men are listed in Table 1. The women were approximately 5 years older than the men, and 37% of the female patients were ≥75 years. Compared with men, women more frequently had many of the known cardiovascular risk factors such as history of heart failure, DM, hypertension, hyper-LDL-cholesterolemia, CKD, and anemia, while there were higher prevalences of prior myocardial infarction, peripheral vascular disease, hypo-HDL-cholesterolemia, and current smokers among the men. There were no significant differences in the rates of multivessel disease and unstable angina between the women and men.

#### Treatments

Comparisons of the treatments between women and men are shown in Table 2. Among the 9,688 patients, PCI was performed in 6,740 (69.7%) patients while CABG was performed in 2,948 (30.3%) patients. There were no significant differences in the selection of revascularization strategy (PCI or CABG) between the women and men. In the PCI-treated patients, the use of stents was comparable between women and men (81.4% vs. 82.1%), and the numbers of implanted stents per patient were also comparable between women and men (1.23±0.02 vs. 1.23±0.01). All stents used in the patients registered in the CREDO–Kyoto registry in 2000–2002 were bare metal stents. In the CABG-treated patients, the total numbers of grafts were similar between the women and men (2.40±0.02 vs. 2.41±0.01). However, use of the left internal thoracic artery (ITA) was less frequent in women than in men (85.7% vs. 90.4%, \( P < 0.001 \)).

With regard to medications at discharge, there were no significant differences between the women and men in the...
proportions of patients treated with β-adrenergic blockers (16.6% vs. 16.6%), anti-platelet drugs (94.9% vs. 95.5%), and nitrates (63.0% vs. 61.8%). However, ACEI/ARB (35.0% vs. 31.8%, P=0.002), statins (35.5% vs. 25.0%, P<0.001), and calcium channel blockers (61.3% vs. 57.9%, P=0.002) were more frequently prescribed in women than in men. The rate of follow-up CAG was comparable between women and men (60.4% vs. 61.2%) in all subjects. However, when the PCI-treated patients were analyzed, the rate of follow-up CAG was significantly lower in women than in men (79.5% vs. 81.8%, P=0.027).

In-Hospital Outcomes
There were no significant differences in the incidences of inhospital death, Q-wave myocardial infarction, and stroke between women and men. However, the incidence of non-Q-wave MI (2.9% vs. 1.7%, P<0.001) was significantly higher in women than in men (Table 3).

Mortality and MACE During Follow-up
Figure 1 indicates the unadjusted incidences of all-cause death and MACE during follow-up. No significant differences were shown between women and men in the incidences of all-cause death (at 3 years, 8.8% vs. 8.5%) and MACE (at 3 years, 12.0% vs. 11.5%). When the patients were divided into PCI-treated and CABG-treated patients according to the revascularization procedures, there were also no significant differences in the unadjusted incidence of all-cause death or MACE between women and men (Figure 2). Table 4 shows the 3-year unadjusted outcomes in detail in the female vs. male patients. Female gender was associated with fewer unadjusted incidences of sudden death, although the numbers of cumulative events at 3 years were small in both groups (25 events, 1.0% in women; 98 events, 1.6% in men).

The results of a multivariate Cox proportional hazards model (Table S1) indicated that female gender was associated with a significantly lower adjusted risk of all-cause death (relative risk, 0.86; 95%CI, 0.77–0.96; P=0.005). BMI >25 and uses of anti-platelet drugs and statins at discharge were also included in the significant predictors of better survival. The independent predictors of all-cause mortality in our analyses were age ≥75 years, DM, history of heart failure, history of peripheral vascular disease, CKD, anemia, current smoker, and multivessel disease.

Coronary Revascularization During Follow-up
The incidence of any revascularization was significantly lower in women than in men (at 3 years, 28.2% vs. 31.2%, log-rank P=0.0037; Table 4, Figure 3A). The difference was mostly derived from the significantly lower incidence of

### Table 3. Crude In-Hospital Event Rates in Women vs. Men

<table>
<thead>
<tr>
<th>Event</th>
<th>Women (%)</th>
<th>Men (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital death (%)</td>
<td>1.4</td>
<td>1.2</td>
<td>0.45</td>
</tr>
<tr>
<td>MI (%)</td>
<td>3.8</td>
<td>2.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Q-wave MI (%)</td>
<td>0.95</td>
<td>0.94</td>
<td>0.95</td>
</tr>
<tr>
<td>Non-Q-wave MI (%)</td>
<td>2.9</td>
<td>1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>0.70</td>
<td>0.75</td>
<td>0.82</td>
</tr>
<tr>
<td>Emergent PCI (%)</td>
<td>1.1</td>
<td>0.94</td>
<td>0.40</td>
</tr>
<tr>
<td>Emergent CABG (%)</td>
<td>0.21</td>
<td>0.19</td>
<td>0.45</td>
</tr>
<tr>
<td>Acute/subacute coronary occlusion (PCI group) (%)</td>
<td>1.0</td>
<td>0.68</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Abbreviations see in Tables 1, 2.
Figure 2. Incidence of all-cause death and major adverse cardiovascular events (MACE) in the percutaneous coronary intervention (PCI)-treated or coronary artery bypass graft (CABG)-treated patients. There were no significant differences between women (red lines) and men (green lines) in the unadjusted long-term incidence of all-cause death or MACE both in the PCI-treated and the CABG-treated subgroups. (A) Incidence of all-cause death in the PCI-treated patients. (B) Incidence of MACE in the PCI-treated patients. (C) Incidence of all-cause death in the CABG-treated patients. (D) Incidence of MACE in the CABG-treated patients.

Table 4. Crude 3-Year Event Rates in Women vs. Men

<table>
<thead>
<tr>
<th>Follow-up outcomes (at 3 years)</th>
<th>Women</th>
<th>Men</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death (%)</td>
<td>8.8</td>
<td>8.5</td>
<td>0.37</td>
</tr>
<tr>
<td>Cardiovascular death (%)</td>
<td>6.4</td>
<td>5.5</td>
<td>0.064</td>
</tr>
<tr>
<td>Cardiac death (%)</td>
<td>4.9</td>
<td>4.5</td>
<td>0.30</td>
</tr>
<tr>
<td>Sudden death (%)</td>
<td>0.96</td>
<td>1.6</td>
<td>0.031</td>
</tr>
<tr>
<td>MI (%)</td>
<td>3.4</td>
<td>3.3</td>
<td>0.96</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>4.3</td>
<td>5.0</td>
<td>0.055</td>
</tr>
<tr>
<td>MACE (%)</td>
<td>12.0</td>
<td>11.5</td>
<td>0.61</td>
</tr>
<tr>
<td>PCI (%)</td>
<td>26.2</td>
<td>29.0</td>
<td>0.006</td>
</tr>
<tr>
<td>CABG (%)</td>
<td>3.5</td>
<td>4.0</td>
<td>0.09</td>
</tr>
<tr>
<td>Any revascularization (%)</td>
<td>28.2</td>
<td>31.2</td>
<td>0.0037</td>
</tr>
<tr>
<td>TLR PCI (PCI group) (%)</td>
<td>24.9</td>
<td>28.9</td>
<td>0.002</td>
</tr>
<tr>
<td>Non-TLR PCI (PCI group) (%)</td>
<td>17.2</td>
<td>19.2</td>
<td>0.043</td>
</tr>
</tbody>
</table>

MACE is defined as the composite of cardiovascular death, MI, and stroke. MACE, major adverse cardiovascular events; TLR, target lesion revascularization. Other abbreviations see in Tables 1, 2.
Outcomes of Women With CAD

revascularization in women in the PCI-treated patients, and the incidence of coronary revascularization was comparable between women and men in the CABG-treated patients (Figures 3B,C). In the PCI-treated patients, the significantly lower incidence in women was seen both in target lesion revascularization (TLR)-PCI and in non-TLR-PCI (Figure 4).

In a multivariate Cox proportional hazards model in all patients, DM, multivessel disease, use of nitrates at discharge, PCI as the revascularization procedure, and follow-up CAG were the independent predictors of any coronary revascularization during follow-up. Female gender was significantly associated with a lower incidence of any revascularization procedures, with a relative risk of 0.93 (95%CI, 0.88–0.99, \( P=0.014 \)). Use of anti-platelet drugs at discharge was also associated with a lower incidence of any revascularization procedures (Table S2). In a multivariate analysis in the PCI-treated patients, female gender was also significantly associ-
ated with a lower incidence of any revascularization, with a relative risk of 0.92 (95% CI, 0.87–0.98, P=0.010). In addition, follow-up CAG was the strongest predictor of any coronary revascularization (Table S3).

Discussion

The present study has revealed that the prevalence of major coronary risk factors such as older age, DM, hypertension, hyper-LDL-cholesterolemia, and CKD were significantly higher in female Japanese patients undergoing coronary revascularization than in male patients. Despite the greater risk factor accumulation, the female gender conferred better long-term outcomes with regard to repeated coronary revascularization.

Baseline Characteristic Differences Between Female and Male Patients

Considering that the clinical presentation of CAD in women lagged 10 to 20 years behind men, it is not surprising that the women were approximately 5 years older than the men when the patients underwent first coronary revascularization. In addition, as previously reported,2-7,10,12-14,21 women had higher incidences of coronary risk factors such as DM, hypertension, dyslipidemia, and CKD. Despite the greater risk factor accumulation including older age in women, the proportions of female and male patients with multivessel disease were similar in the present study. Female gender itself might play a protective role against the development of atherosclerotic diseases.

Revascularization Procedures and In-Hospital Outcomes

In the present study, in-hospital mortality and MACE were consistently comparable between women and men among all patients and among the PCI-treated or CABG-treated patients. In the PCI-treated patients there were no significant differences between women and men in terms of the ratios of stent use and the numbers of implanted stents per patient. Contrary to the similarities in the procedures for the PCI-treated patients, use of an ITA graft among the CABG-treated patients was less frequent in women than in men. The less frequent use of an ITA graft was consistent with previous observations,10,14 and might be caused by smaller vessel sizes rather than the female gender itself.

It has been shown that in-hospital mortality is higher for women than men among patients undergoing CABG or PCI. In the 1985–1986 PTCA registry, in-hospital death was 10-fold higher in women than in men and female gender was an independent predictor of in-hospital death.2 Similarly, a retrospective study in a cohort from 1985 to 1993 found a higher rate of in-hospital death in women compared with men, and this difference remained statistically significant after adjustment for differences in baseline characteristics.22 In patients undergoing CABG, 2.5-fold higher in-hospital mortality was reported in women relative to men.23 The higher in-hospital mortality has been explained in part by advanced age, a higher prevalence of risk factors in women and difficulties associated with the procedures because of smaller physical and vessel sizes in women. In contrast to these studies, more recent studies have reported improved outcomes in women and described that greater experience as well as advances in technology and procedural techniques might contribute to more favorable outcomes in women.9,10,13,24 In accordance with these reports, the present study showed comparable incidences of in-hospital death among women and men.

Previous studies have suggested the existence of gender-based differences in the treatment practices of CAD, which led to less intensive treatments for women than men.24-26 Not only indication of invasive procedures but also the strategies of procedures such as PCI might differ by patients’ gender. However, in the present study, there were no significant procedural differences between the women and men in the PCI-treated patients, for example, comparable numbers of used stents. Thus, our male and female patients appeared to be similarly treated in the index PCI procedures, and it is unlikely that the differences in the strategies of index PCI affected the differences in the outcomes between women and men. Although the use of an ITA graft was slightly less frequent in the CABG-treated women relative to men, this might be caused by the smaller vessel size in women, and the use of an ITA graft might not significantly affect the short-term in-hospital outcomes. Other techniques such as off-pump CABG might contribute to the improvement of in-hospital outcomes of both female and male patients and attenuate the gender-based differences.27

In the patients in the current study, the unadjusted incidence of in-hospital non-Q-wave myocardial infarction was significantly higher in female than male patients. However, the difference did not appear to critically affect the in-hospital as well as the long-term mortality.

Long-Term Outcomes in Women Relative to Men

Unadjusted survival analyses revealed that there were no significant differences according to gender with regard to all-cause death and MACE during long-term follow-up. After adjustment for possible confounding factors, including a higher baseline risk status in women, female gender was independently associated with a lower adjusted risk for mortality after revascularization. Moreover, better unadjusted survival free from any coronary revascularization was observed in female patients relative to male patients, and survival remained better in women after the adjustments.

There are several potential explanations for the possible differences in the long-term outcomes between female and male patients after revascularization. In the patients in the present study, women were treated more intensively with evidence-based secondary preventative medical therapies such as statins and ACEI/ARB. The more intensive use of medical therapies in women than in men might be rational in our patients, because greater coronary risk factor accumulation was seen in the female patients. A discrepancy exists between our observations and a previous report showing lower use of these medications in female patients with CAD.28 As women have recently become more active in society, female CAD patients might become more intensively managed. Similar to the possible effects on in-hospital outcomes, improvements in technology and procedural techniques might contribute to improvement of the long-term outcomes of all CAD patients and attenuate the gender-based differences.

Although use of an ITA graft was a significant predictor of better long-term outcomes in patients undergoing CABG, the less frequent use of an ITA graft in female patients did not result in worse long-term outcomes in the present study. Better evidence-based medical treatment, especially therapy with statins, in female patients might have counteracted this disadvantage. It is also possible that the follow-up period was too short to reveal the effects of the difference in the use of an ITA graft between women and men.

The long-term survival rate free from any coronary revascularizations was significantly higher in women than in men.
in the present study, which was supported by the results of multivariate analyses indicating a significant association between female gender and lower incidence of revascularization. Because this difference by gender was mostly attributed to the difference in the PCI-treated patients and the survival curves began to separate at 6 months, the lower incidence of revascularization due to restenosis in women might cause this difference. There are several possible explanations for the lower incidence of restenosis-driven revascularization. If the female gender itself is an inhibitory factor for restenosis, the lower incidence of revascularization in women could be rational. It has been reported that sex hormones, especially estrogen, might prevent restenosis by attenuating the responses of vessel walls to injury. \(^{29-31}\) However, the impact of sex hormones might be negligible in the present study because of the older age of the study patients. Thus, it is unlikely that the female gender conferred preventive effects for restenosis by the effects of sex hormones and overwhelmed the considerably increased restenosis risk by the smaller coronary artery diameters in women. Routine follow-up CAG might increase revascularization in patients with restenosis but without symptom and evidenced ischemia ("oculo-stenotic" reflex). Because follow-up CAG was less frequently performed in women, it might be possible that reduced non-clinically driven PCI resulted in the lower incidence of revascularization. In the present study, the rate of follow-up CAG after PCI was lower in women than in men. Women might be less willing to undergo invasive investigations than men, \(^{32}\) and there might be more asymptomatic female patients who had restenosis but did not undergo revascularization. In addition, physician-based prejudices and gender-specific perception of angina symptoms might also be possible reasons. \(^{33,34}\) As expected from previous studies, \(^{19,20}\) follow-up CAG was a strong predictor of any revascularization procedure in the present study. However, after adjustment by the multivariate analysis, which included follow-up CAG as a variable, female gender still remained an independent predictor of freedom from any revascularization.

**Study Limitations**

Several limitations must be noted in addition to the limitations that are common to all observational studies caused by differences in patients’ background characteristics among groups. Although angiographic findings such as vessel size, lesion length, stent length, and stent diameter might be associated with the occurrence of restenosis after PCI, such angiographic data were not available in this study cohort.

Data regarding blood tests, smoking habits, and medical therapies were only obtained at one time point, namely at hospitalization or discharge of the index hospitalization. Therefore, lifestyle modifications after revascularization such as discontinuation of smoking and improvement or deterioration of hypertension, DM and dyslipidemia, and adherence to medical therapies were not considered in the analyses.

Our database does not distinguish clinically driven PCI from non-clinically driven PCI. It is also impossible to distinguish scheduled routine follow-up CAG and follow-up CAG for symptomatic patients. Thus, the effects of follow-up CAG on the incidence of revascularization should be carefully interpreted, although the difference between men and women in the rate of follow-up CAG might be accounted for by scheduled routine follow-up CAG.

It could cause a critical bias to include follow-up CAG as a variable in the multivariate analysis for predictors of all-cause death. Because all patients who died before scheduled follow-up CAG were included in the patient group who did not undergo follow-up CAG and the total number of all-cause death might not be enough to dilute such a bias, the association of follow-up CAG or each of the other variables with the outcome might not be correctly assessed. Thus, follow-up CAG was not assessed in the multivariate analysis for possible predictors of all-cause death and MACE in the present study. Further studies designed to determine the long-term clinical benefits of follow-up CAG are needed.

Finally, in this observational study, indications for revascularization therapies were not defined but depended on the decision of each participating physician. Therefore, a gender-related selection bias could exist in the indications of treatment strategies between women and men. In addition, there are gender-related differences in angina symptoms and in the incidences of coronary spastic angina and microvascular angina that do not require revascularization. \(^{35,36}\) Such differences can also affect the indications for CAG and coronary revascularization.

**Conclusion**

Because more modifiable coronary risk factors were accumulated in women who undergo coronary revascularization compared with men, more intensive management including evidence-based medications is required in female patients. However, the incidence of cardiovascular events was not higher in women than men and female gender was associated with a lower incidence of repeated revascularization relative to male gender in the era of bare metal stent use.

**Acknowledgments**

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**Disclosure**

The authors declare no conflict of interest.

**References**


Appendix

Participating Centers and Investigators

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Outcomes of Women With CAD

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Clinical Research Coordinators

Supplemental Files

Supplemental File 1
Table S1. Multivariate Analyses for Predictors of All-Cause Death
Table S2. Multivariate Analyses for Predictors of Any Coronary Revascularization in All Patients
Table S3. Multivariate Analyses for Predictors of Any Coronary Revascularization in the PCI-Treated Patients

Please find supplemental file(s):