Gender-Specific Outcome After Paclitaxel-Eluting Stent Implantation in Japanese Patients With Coronary Artery Disease
– Sub-Analysis of the Japan TAXUS Express2 Post-Marketing Survey –
Hiroyuki Okura, MD; Masato Nakamura, MD; Jun-ichi Kotani, MD; Ken Kozuma, MD
for the TAXUS Japan Postmarket Surveillance Study (TAXUS-PMS) Investigators

Background: Although previous randomized and non-randomized studies have demonstrated the safety and efficacy of paclitaxel-eluting stents (PES), a higher revascularization rate has been reported in women than in men. A sub-analysis of the TAXUS Japan Post-market Surveillance Study (TAXUS-PMS) was done to assess the influence of gender on clinical outcome.

Methods and Results: A total of 2,132 PES-treated Japanese patients (women, n=551) from this registry were analyzed. Subjects were stratified by gender to compare 1-year clinical outcome. PES-treated women were older and more likely to have insulin-treated diabetes and hypertension. In contrast, PES-treated men were more likely to be smokers, have a previous history of myocardial infarction, and lower ejection fraction. While cardiac death, myocardial infarction and stent thrombosis were similar between men and women, major cardiac events tended to be lower in women than in men (6.4% vs. 8.8%, P=0.08). Although women had significantly smaller reference vessel size (2.46±0.53 mm vs. 2.59±0.60 mm, P<0.0001), the restenosis rate tended to be lower in women than in men (11.5% vs. 14.8%, P=0.11). Subsequently, the target lesion revascularization rate was significantly lower in women than in men (4.2% vs. 6.5%, P<0.05).

Conclusions: Despite a higher risk profile, Japanese women treated with PES did not have a higher rate of repeat revascularization or major adverse clinical outcome than PES-treated men at 1 year. (Circ J 2013; 77: 1430–1435)

Key Words: Drug-eluting stent; Sex; Stent

Previous data from randomized trials and registries have demonstrated that the paclitaxel-eluting stent (PES) is safe and effective in both men and women, except for a slightly higher revascularization rate in women among the highest risk population. Because of the differences in genetic background, clinical characteristics as well as body size between Western countries and Japan, it is unknown if the gender-specific difference can be generalized to the Japanese population.

The Japan Post-market Surveillance study of the TAXUS Express 2™ stent (TAXUS-PMS) is a nationwide real-world registry. We performed a sub-analysis of the TAXUS-PMS to assess the influence of gender on clinical outcome after implantation of PES in Japanese patients with coronary artery disease.

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Division of Cardiology, Kawasaki Medical School, Kurashiki (H.O.); Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, Tokyo (M.N.); Department of Cardiology, Teikyo University Hospital, Tokyo (K.K.); and Cardiovascular Division, National Cerebral and Cardiovascular Center, Suita (J.K.), Japan
Mailing address: Hiroyuki Okura, MD, Division of Cardiology, Kawasaki Medical School, 577 Matsushima, Kurashiki 701-0192, Japan.
E-mail: hokura@fides.dti.ne.jp
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Gender and TAXUS Stent

References vessel diameter (RVD), minimum lumen diameter (MLD), and % diameter stenosis (%DS) were measured at baseline.

Statistical Analysis
Continuous variables are expressed as mean±SD and categorical data are given as frequencies. For comparisons between men and women, a Fisher exact or ANOVA test was used, as appropriate. Quantitative coronary angiography (QCA) data were analyzed based on binary data. Cardiac events were analyzed using the Kaplan-Meier method and compared on log-rank test. A univariate and multivariate Cox proportional hazards regression model was used to identify predictors of MACE and TLR. $P<0.05$ was considered statistically significant.

Results

Patient Demographics and Lesion Characteristics
Patient demographics are listed in Table 1. PES-treated women were older and more likely to have insulin-treated diabetes and hypertension. In contrast, PES-treated men were more likely to be smokers, have a previous history of MI, higher BMI, and lower ejection fraction. Angiographic lesion char-

Table 1. Baseline Patient Characteristics

|                          | Men (n=1,581) | Women (n=551) | P-value |
|--------------------------|--------------|---------------|---------|
| Age (years)              | 67.0±9.6     | 71.9±8.4      | <0.0001 |
| BMI (kg/m²)              | 24.2±3.3     | 23.3±3.6      | <0.0001 |
| History of PCI           | 57.8         | 47.1          | <0.0001 |
| History of MI            | 36.3         | 27.1          | <0.0001 |
| History of CABG          | 7.8          | 5.6           | 0.09    |
| Unstable angina          | 16.6         | 20.1          | 0.07    |
| Silent ischemia          | 16.5         | 14.6          | 0.33    |
| Acute MI                 | 5.1          | 7.1           | 0.09    |
| Acute coronary syndrome  | 20.9         | 25.8          | 0.02    |
| Smoking                  | 67.5         | 16.6          | <0.0001 |
| Diabetes mellitus        | 43.2         | 47.9          | 0.06    |
| Insulin-treated          | 7.5          | 14.6          | <0.0001 |
| Insulin- or oral-treated | 33.2         | 38.1          | 0.04    |
| Hyperlipidemia           | 68.6         | 71.5          | 0.20    |
| Hypertension             | 82.0         | 86.9          | 0.008   |
| Family history of CAD    | 14.2         | 18.6          | 0.02    |
| Hemodialysis             | 5.3          | 6.2           | 0.43    |
| Peripheral vascular disease | 9.2         | 7.5           | 0.23    |
| LVEF (%)                 | 58.7±12.9    | 62.2±11.9     | <0.0001 |

Data given as mean±SD or as %. BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2. Baseline Lesion and Procedural Characteristics

|                          | Men (n=1,581) | Women (n=551) | P-value |
|--------------------------|--------------|---------------|---------|
| Type B2/C lesion         | 82.0         | 81.3          | 0.69    |
| Pre-procedure RVD (mm)   | 2.55±0.60    | 2.42±0.53     | <0.0001 |
| Pre-procedure MLD (mm)   | 0.81±0.45    | 0.79±0.43     | 0.40    |
| Pre-procedure lesion length (mm) | 18.9±12.4 | 19.1±13.5     | 0.80    |
| Max. stent deployment pressure (atm) | 14.5±3.5 | 14.0±3.5      | 0.009   |
| Max. post-dilatation pressure (atm) | 17.5±4.4 | 17.5±4.5      | 0.75    |

Data given as mean±SD or as %. MLD, minimum lumen diameter; RVD, reference vessel diameter.

at 1 year were determined at outpatient clinic visits or by telephone interview. This study was approved by the Institutional Review Boards of all participating institutions.

Clinical Follow-up
The primary endpoint of this study was the composite outcome of major adverse cardiac events (MACE) at 1 year. MACE was defined as cardiac death, non-fatal myocardial infarction (MI), and target vessel revascularization (TVR). TVR was defined as any ischemia-driven repeat percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) of the target vessel. Target lesion revascularization (TLR) was defined as CABG or repeat PCI at the original target lesion site including the area inside the stent and the adjacent 5-mm vessel segments. Stent thrombosis was classified according to the Academic Research Consortium (ARC) definitions of definite and probable. Target lesion failure was defined as the composite of cardiac death, target lesion MI, and TLR in the same lesion segment. Clinical outcome was compared between men (n=1,581) and women (n=551).

Angiography
A total of 2,019 lesions/1,729 patients were analyzed angiographically at 9 months by an independent core laboratory (Cardiocore, Tokyo, Japan) blinded to clinical outcome. Reference vessel diameter (RVD), minimum lumen diameter (MLD), and % diameter stenosis (%DS) were measured at baseline.

Cardiocore, Tokyo, Japan, blan...
characteristics are listed in Table 2. Women treated with PES had significantly smaller reference vessel size as compared with men treated with PES.

Angiographic and Clinical Follow-up

QCA data at 9 months are summarized in Table 3. In-stent late loss as well as restenosis rate were not significantly different between men and women (both P=NS). In contrast, in-lesion late loss was significantly smaller in women than in men (0.25±0.71 mm vs. 0.34±0.68 mm, P=0.03). As a result, %DS (30.19±17.49% vs. 31.88±19.77%, P=0.12) as well as restenosis rate (11.5% vs. 14.8%, P=0.11) tended to be lower in women than in men. Clinical outcomes are listed in Table 4. At 1-year follow-up, cardiac death, non-fatal MI and stent thrombosis (ARC definite or probable) were similar between men and women. TLR rate (4.2% vs. 6.5%, P<0.05) as well as TVR (4.9% vs. 7.6%, P<0.05) were significantly lower in women than in men. As a result, MACE tended to be lower in women than in men (6.4% vs. 8.8%, P=0.08).

On Kaplan-Meier analysis, cumulative event rate of cardiac death was similar between men and women (Figure 2). In contrast, the cumulative event rate of TVR at 1 year was significantly lower in women than in men (Figure 3). As a result, the cumulative event rate of MACE tended to be lower in women than in men (Figure 4).

Male gender was a borderline univariate predictor of TLR (P=0.059) and MACE (P=0.113). On multivariate Cox regression analysis, male gender was a borderline predictor of TLR (P=0.079), but not an independent predictor of MACE (P=0.207).

Discussion

The primary finding of this study is that Japanese women treated with PES tended to have marginally better overall clinical outcome than PES-treated men at 1 year. In particular, PES-treated women had a lower risk of repeat revascularization despite their higher risk profile.

Previous studies have suggested possible gender-specific differences in clinical outcome in patients with coronary artery disease. The mortality rate of women after MI may be higher than in men.4–7 Time course between symptom onset and hospital visit or revascularization tend to be longer in women than

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**Table 3. QCA Data at 9-Month Follow-up**

|                  | Men (n=1,518) | Women (n=501) | P-value |
|------------------|--------------|--------------|---------|
| **In-stent**     |              |              |         |
| RVD (mm)         | 2.78±0.54    | 2.68±0.48    | 0.0006  |
| MLD (mm)         | 2.09±0.63    | 2.03±0.56    | 0.10    |
| %DS (%)          | 25.03±17.83  | 24.21±17.34  | 0.43    |
| Late loss (mm)   | 0.53±0.60    | 0.50±0.54    | 0.34    |
| Restenosis       | 9.7          | 8.1          | 0.36    |
| **In-lesion**    |              |              |         |
| RVD (mm)         | 2.76±0.54    | 2.67±0.50    | 0.005   |
| MLD (mm)         | 1.89±0.67    | 1.89±0.67    | 0.97    |
| %DS (%)          | 31.88±19.77  | 30.19±17.49  | 0.12    |
| Late loss (mm)   | 0.34±0.68    | 0.25±0.71    | 0.03    |
| Restenosis       | 14.8         | 11.5         | 0.11    |

Data given as mean±SD or as %. %DS, percent diameter stenosis; MLD, minimum lumen diameter; QCA, quantitative coronary angiography; RVD, reference vessel diameter.

**Table 4. Clinical Outcome at 1 Year**

|                  | Men (n=1,581) | Women (n=551) | P-value |
|------------------|--------------|--------------|---------|
| MACE†            | 8.8 (35)     | 6.4 (34)     | 0.08    |
| Cardiac death or MI | 1.7 (26)   | 2.2 (12)     | 0.41    |
| Cardiac death    | 1.0 (15)     | 1.3 (7)      | 0.51    |
| MI               | 0.8 (13)     | 1.1 (6)      | 0.56    |
| Q-Wave MI        | 0.3 (4)      | 0.6 (3)      | 0.30    |
| Non-Q-wave MI    | 0.6 (9)      | 0.5 (3)      | 0.95    |
| TVR              | 7.6 (116)    | 4.9 (26)     | 0.04    |
| TLR              | 6.5 (99)     | 4.2 (22)     | 0.049   |
| Non-TLR          | 1.6 (24)     | 1.5 (8)      | 0.92    |
| All-cause death  | 1.9 (29)     | 2.4 (13)     | 0.44    |
| Non-cardiac death| 0.9 (14)    | 1.1 (6)      | 0.66    |
| ARC ST definite/probable | 0.5 (8) | 0.2 (1) | 0.31  |
| Protocol-defined ST | 0.6 (10)    | 0.2 (1)      | 0.21    |

Data given as % (n). †Cardiac death, non-fatal MI, and TVR. ARC, Academic Research Consortium; MACE, major adverse cardiac events; MI, myocardial infarction; ST, stent thrombosis; TLR, target lesion revascularization; TVR, target vessel revascularization.
Gender and TAXUS Stent

Sub-analysis of the TAXUS-IV trial compared clinical outcome between men and women enrolled in the pivotal trial. Although women treated with PES (n=187) had similar 1-year rates of MACE (13.5% vs. 9.9%, P=0.24), women compared with men had significantly higher 1-year rates of TLR (7.6% vs. 3.2%, P=0.03). More recently, results from the TAXUS Woman analysis have been reported. A total of 2,271 PES-treated patients (women, n=665), from 5 randomized trials and 7,492 PES-treated patients (women, n=2,449) from 2 real-world registries were analyzed. Although PES-treated women in both

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Figure 1. One-year cumulative event rate of cardiac death.

Figure 2. One-year cumulative event rate of non-fatal myocardial infarction.

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in men, probably because of atypical or ambiguous symptoms as compared with men. As a result, women after MI tend to receive more conservative therapy than men. Recently, it has been reported that left ventricular diastolic function may be worse in elderly women than in elderly men in an apparently healthy population. These differences in baseline diastolic function may also explain the higher mortality rate in elderly women with MI.

Although women tend to have small vessel size and higher prevalence of diabetes mellitus, several observational registries have reported that TLR rates after balloon angioplasty were similar or even better in women than in men. The present results are concordant with these previous observations but discordant with previous studies on PES.

Sub-analysis of the TAXUS-IV trial compared clinical outcome between men and women enrolled in the pivotal trial. Although women treated with PES (n=187) had similar 1-year rates of MACE (13.5% vs. 9.9%, P=0.24), women compared with men had significantly higher 1-year rates of TLR (7.6% vs. 3.2%, P=0.03). More recently, results from the TAXUS Woman analysis have been reported. A total of 2,271 PES-treated patients (women, n=665), from 5 randomized trials and 7,492 PES-treated patients (women, n=2,449) from 2 real-world registries were analyzed. Although PES-treated women in both
Although the present results suggest that PES-treated women had a significantly lower TLR rate than men, multivariate analysis did not show that male sex was an independent predictor of TLR. Although PES-treated women had smaller vessel size and higher prevalence of insulin-treated diabetes, both of which are known strong predictors of restenosis and TLR or TVR, women had a paradoxically lower likelihood of TLR during the first year after PES implantation. It is possible that covariates such as history of CABG, history of PCI, and smoking might affect the results. Previous studies have suggested that restenosis (or TLR) is affected by diabetic status after sirolimus-eluting stent implantation but not after PES implantation. As noted, women treated with PES had a higher prev-

**Figure 3.** One-year cumulative event rate of target vessel revascularization.

**Figure 4.** One-year cumulative event rate of major adverse cardiac events.

the randomized trials and the registries had a higher prevalence of adverse baseline characteristics including advanced age, hypertension, and diabetes, they had similar TLR and MACE to men. In expanded-use patients (defined as patients with acute MI, lesion length >28 mm, RVD <2.5 mm, multi-vessel stenting, bifurcation lesions, in-stent restenosis, vein graft, renal disease, and chronic total occlusion), women had significantly higher rates of death and TLR. Even after adjustment of the covariates, female sex were still an independent predictor of TLR in the expanded-use group. Similarly, a pooled analysis comparing everolimus-eluting stent and PES found a higher TLR rate (7.3% vs. 4.2%, P=0.02) at 2 years after intervention.
alence of insulin-treated diabetes. PES might have reduced the risk of TLR and MACE in these high-risk patients in the Japanese population.

In addition, differences in clinical practice between Japan and Western countries may be responsible for the differences between the present results and previous reports. First, intravascular ultrasound and optical coherence tomography are more frequently used during PCI in Japan than in any other countries. This might affect the better results of the Japanese women treated with TAXUS stent. Second, as compared with Western countries, routine angiographic follow-up is commonly performed in Japan. This might possibly result in the relatively higher TVR rate in male subjects. Figures 3, 4 show that the cumulative event rate diverged over time after 6–9 months when follow-up angiography was generally performed. QCA analysis at 9 months indicated significantly lower in-lesion late loss and a trend towards lower restenosis rate in women. Therefore, vessel response to the PES in Japanese women may be different from that in Western countries. Plaque characteristics and its relationship with vessel response after PES implantation in Japanese women should be investigated further.

**Conclusion**

Despite a higher risk profile, Japanese women treated with PES did not have a higher rate of repeat revascularization or major adverse clinical outcome than PES-treated men at 1 year.

**Acknowledgment**

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