

# Influence of Sex on Long-Term Outcomes After Percutaneous Coronary Intervention With the Paclitaxel-Eluting Coronary Stent

## Results of the “TAXUS Woman” Analysis

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**Objectives** We conducted the “TAXUS Woman” analysis to assess the influence of sex on long-term outcomes after percutaneous coronary intervention using paclitaxel-eluting stents (PES) in a broad spectrum of patients.

**Background** Previous studies indicate that the sex gap suggesting worse outcomes in women has narrowed. However, limited data are available on long-term sex-based outcomes with drug-eluting stents despite their extensive use in current practice.

**Methods** We analyzed 2,271 PES-treated patients (women = 665), from 5 randomized trials and 7,492 PES-treated patients (women = 2,449) from 2 “real-world” registries. The trial and registry datasets were stratified by sex to compare long-term outcomes. Additionally, the outcomes in PES-treated women were compared with bare-metal stent-treated women (n = 395) in the randomized trials.

**Results** In the randomized trials, PES-treated women had a lower target lesion revascularization (TLR) rate (11.5% vs. 22.6%,  $p < 0.001$ ) than bare-metal stent-treated women, with no significant sex-based differences in death, myocardial infarction, stent thrombosis, or TLR through 5 years. In both the trials and the registries, although women had more adverse baseline characteristics including advanced age, hypertension, and diabetes, they had similar outcomes to men. In expanded-use patients, however, women showed significantly higher rates of death and TLR, although only the higher TLR rate was confirmed by multivariate analysis.

**Conclusions** This study of nearly 10,000 patients including more than 3,000 women demonstrates that despite their higher-risk profile, women have comparable benefits to men from percutaneous coronary intervention with PES except for a slightly higher revascularization rate in the high-risk cohort. (J Am Coll Cardiol Intv 2010;3:1250–9) © 2010 by the American College of Cardiology Foundation

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Coronary artery disease is the leading cause of death for both men and women in the U.S. and other developed countries. For more than 2 decades, more women than men have died of this disease (1). However, women continue to be under-represented in prospective clinical trials evaluating coronary revascularization strategies. Furthermore, compared with men, women tend to have more comorbid conditions at baseline and potentially complex coronary anatomy, challenging the validity of making treatment decisions for women based on data derived from predominantly male populations. A better understanding of sex-specific outcomes would potentially allow individualized revascularization strategies to be developed for the large and growing population of women with coronary artery disease.

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Previous sex-based studies in patients undergoing percutaneous coronary intervention (PCI) and coronary artery bypass graft have reported higher in-hospital mortality and increased risk for adverse outcomes in women than in men (2-4). A recent report indicates that, compared with men, women continue to be at an increased risk of operative mortality after isolated coronary artery bypass graft, although subsequent studies in patients undergoing PCI with bare-metal stents (BMS) indicate that the sex gap in outcomes has narrowed (5-7). In patients undergoing PCI, the sex gap has narrowed further with the introduction of drug-eluting stents (DES), where the angiographic and clinical benefits were found to be independent of sex in randomized trial cohorts with simple de novo lesions (8,9). However, the influence of sex on long-term DES outcomes has not been fully elucidated, and it is not clear if the pattern of equality holds true outside the realm of low-risk patient populations. Therefore, we compared sex-based outcomes in patients receiving paclitaxel-eluting stents (PES) in both the randomized trials and the "real-world" registries.

## Methods

**Study description.** Data from the TAXUS pivotal trials and the ATLAS trial were pooled. The TAXUS I, II SR, IV, and V trials (10-13) were prospective, multicenter, randomized, double-blind, controlled trials where increasingly complex patients with a single de novo lesion in a native coronary artery were randomized to receive either a

paclitaxel-eluting Taxus slow-release (commercialized) stent or an otherwise identical BMS (Boston Scientific Corporation, Natick, Massachusetts). The TAXUS III trial evaluating the feasibility and safety of PES for the treatment of in-stent restenosis and the TAXUS VI trial using the investigational moderate-release PES were not included in this analysis (14,15). Follow-up was available through 5 years for the TAXUS I, II, IV, and V trials. The ATLAS trial (16) is a prospective single-arm trial of the next generation Taxus Liberté stent (Boston Scientific Corporation) with follow-up available through 4 years.

Data from the ARRIVE (TAXUS Peri-Approved Registry: A Multicenter Safety Surveillance) 1 and 2 registries (17) were pooled and analyzed separately from the trial data. The ARRIVE registries are 2-phase post-market registries undertaken to study Taxus Express<sup>2</sup> stent system usage in routine clinical practice through 2 years.

The pooled analysis design for the randomized trials and registries is illustrated in Figure 1.

**End points and definitions.** The following end points were examined to assess the influence of sex on long-term safety and effectiveness of PES: death, myocardial infarction (MI), stent thrombosis, and target lesion revascularization (TLR). Death was defined as all-cause mortality. Myocardial infarction was defined as either the development of pathological Q waves lasting at least 0.04 s in at least 2 contiguous leads with an elevated creatine kinase-myocardial band fraction level or, in the absence of Q waves, an elevation of creatine phosphokinase levels to greater than twice the upper limit of normal with an elevated creatine kinase-myocardial band level. Stent thrombosis data, adjudicated by the Academic Research Consortium "definite or probable" definition, were used in the present analysis (18). Target lesion revascularization was defined as repeat revascularization by either PCI or coronary artery bypass graft for ischemia with angiographic restenosis of at least 50% of the luminal diameter anywhere within the stent or the 5-mm borders proximal or distal to the stent. Data from the original databases as

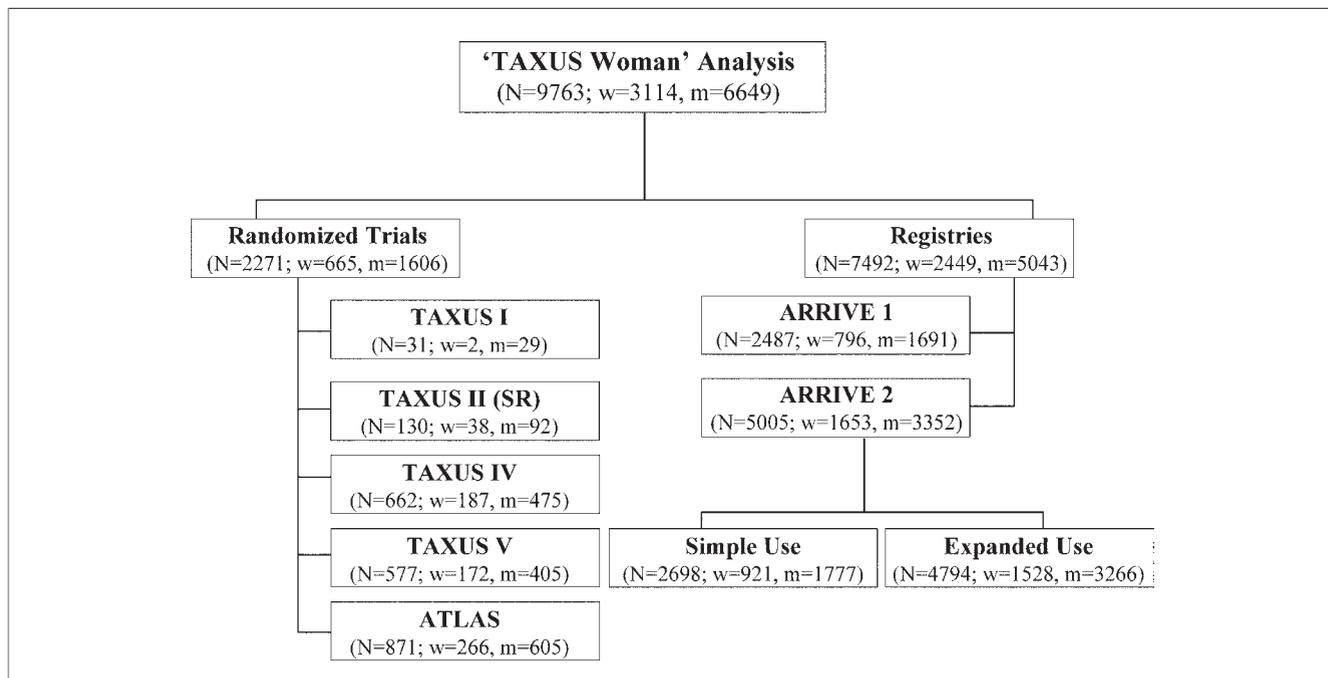
### Abbreviations and Acronyms

<b>BMS</b>	= bare-metal stent(s)
<b>DES</b>	= drug-eluting stent(s)
<b>MI</b>	= myocardial infarction
<b>PCI</b>	= percutaneous coronary intervention
<b>PES</b>	= paclitaxel-eluting stent(s)
<b>RVD</b>	= reference vessel diameter
<b>TLR</b>	= target lesion revascularization

honoraria from Boston Scientific and Cordis/Johnson & Johnson. Dr. Ormiston has received research grants and support from Boston Scientific, Johnson & Johnson, Abbott Vascular, and Elixir Medical as well as honoraria from Boston Scientific and Abbott Vascular and is an advisory board member for Boston Scientific, Abbott Vascular, and Devax. Dr. Stone has received research grants from Boston Scientific and Abbott Vascular. Dr. Turco has received research support and consulting fees

from and is a Speakers' Bureau member for Abbott, Boston Scientific, and Medtronic. Dr. Joshi is a full-time employee of Boston Scientific. Dr. Baim was a full-time employee and a stockholder of Boston Scientific. Drs. Gerber and Colombo have reported that they have no relationships to disclose. Dr. Baim is deceased.

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**Figure 1. TAXUS Woman Analysis Design**

Patients from 5 randomized trials and 2 “real-world” registries were pooled separately to compare sex-based outcomes.

adjudicated by an independent clinical events committee for each individual study were used in the present analysis.

**Statistical methods.** All statistical analyses were performed by biostatisticians at Boston Scientific Corporation. Potential bias was minimized by performing the analysis according to the intent-to-treat principle by including all patients randomized in the pooled trials and all patients receiving the Taxus stent in the pooled registries.

For continuous variables, comparison between the groups was performed with Student *t* test. Categorical variables were compared by the chi-square test. Time-to-event data were calculated and displayed as Kaplan-Meier estimates with comparison between groups by the log-rank test. Statistical significance was set at  $p < 0.05$ . Annualized *s* were calculated for every year after the index procedure using the person-year method. The approximate Poisson method (19) was used to calculate the 95% confidence intervals (CIs). Hazard rate differences between groups were calculated using the log-rank test.

Predictors of clinical outcomes were assessed with stepwise Cox proportional hazards regression with significance set at 0.05, with the exception of sex, which was forced into the model. Variables included in the model for the randomized trials were age, congestive heart failure, diabetes requiring medication, previous coronary artery bypass graft, percentage diameter stenosis, in-stent acute gain, hyperlipidemia, calcification, reference vessel

diameter (RVD), previous MI, minimum lumen diameter, unstable angina, left anterior descending artery versus non-left anterior descending location, lesion location, hypertension, smoking, treatment group (Taxus Express vs. Taxus Liberté), total occlusion, sex, and lesion length. For the registries, the variables included age, congestive heart failure, diabetes requiring medication, left main stenting, prior MI, diabetes requiring insulin, cardiogenic shock, graft stenting, hypertension, lesion length >28 mm, sex, hyperlipidemia, multiple planned stents, in-stent restenosis, lesion length, total occlusion, left anterior descending location, RVD, smoking, bifurcation, multiple lesions treated, RVD  $\leq 2.5$  mm, percentage diameter stenosis, and baseline acute MI.

## Results

**Randomized trials.** A total of 2,797 patients were enrolled in the TAXUS trials; 1,400 were randomized to PES and 1,397 to BMS. The 1,400 PES-treated patients were pooled with 871 PES-treated patients from the ATLAS trial (Fig. 1). Of the 2,271 pooled patients, 665 (29.3%) were women and 1,606 were men.

**BASELINE CHARACTERISTICS.** As shown in Table 1, women were significantly older than men, with lower body weight, more unstable angina, congestive heart failure, medically treated diabetes, hypertension, prior history of coronary artery disease, and peripheral vascular disease. They also had slightly smaller RVD than men did ( $2.63 \pm 0.46$  mm vs.  $2.79 \pm 0.52$

**Table 1. Baseline Clinical and Lesion Characteristics for Patients Receiving PES in the Randomized Trials**

Variable	Women (n = 665)	Men (n = 1,606)	p Value
Age, yrs	64.9 ± 11.1 (665)	61.4 ± 10.7 (1,606)	<0.001
Weight, lbs	171.3 ± 37.1 (397)	200.8 ± 38.4 (970)	<0.001
<b>Cardiac history</b>			
Stable angina	55.1% (365/663)	57.8% (929/1,606)	0.22
Unstable angina	37.4% (248/663)	31.5% (496/1,577)	0.006
Silent ischemia	10.1% (67/665)	12.5% (201/1,602)	0.10
Congestive heart failure	7.7% (51/664)	3.9% (63/1,605)	<0.001
Previous myocardial infarction	25.8% (171/663)	31.8% (501/1,577)	0.005
Previous percutaneous coronary intervention	28.0% (174/622)	33.8% (500/1,481)	0.01
Previous coronary artery bypass graft	5.9% (39/663)	9.3% (146/1,577)	0.008
<b>Cardiac risk factors</b>			
Current smoking	20.8% (138/665)	23.5% (378/1,606)	0.15
Diabetes, medically treated	33.5% (223/665)	21.9% (352/1,606)	<0.001
Hypertension	78.0% (519/665)	69.5% (1,116/1,606)	<0.001
Hyperlipidemia	71.7% (477/665)	72.8% (1,166/1,602)	0.61
History of coronary artery disease	62.0% (372/600)	52.6% (762/1,450)	<0.001
<b>Comorbid conditions</b>			
Peripheral vascular disease	10.2% (63/615)	7.6% (112/1,475)	0.046
Previous transient ischemic attack	3.7% (7/187)	2.9% (14/475)	0.60
Previous cerebrovascular accident	6.0% (27/453)	3.8% (41/1,080)	0.06
Renal disease	5.1% (23/453)	3.9% (42/1,080)	0.29
<b>Lesion characteristics (by QCA)</b>			
Reference vessel diameter, mm	2.63 ± 0.46 (659)	2.79 ± 0.52 (1,597)	<0.001
Minimum lumen diameter, mm	0.87 ± 0.35 (658)	0.89 ± 0.35 (1,569)	0.24
Diameter stenosis, %	67.09 ± 11.54 (658)	67.98 ± 11.14 (1,569)	0.09
Lesion length, mm	14.65 ± 7.31 (659)	14.72 ± 7.31 (1,592)	0.84
Left anterior descending vessel location	39.0% (259/664)	41.2% (661/1,603)	0.33
Bend >45°	23.8% (148/622)	22.2% (328/1,476)	0.43
Tortuosity	11.9% (74/622)	10.5% (155/1,475)	0.35
<b>Modified ACC/AHA lesion type</b>			
A	8.0% (50/622)	7.1% (105/1,478)	0.45
B1	22.5% (140/622)	24.4% (361/1,478)	0.35
B2	41.6% (259/622)	38.6% (571/1,478)	0.20
C	27.8% (173/622)	29.8% (441/1,478)	0.35
B2/C	69.5% (432/622)	68.5% (1,012/1,478)	0.66

Values are mean ± SD (n) or % (count/sample size). The p values for continuous variables were calculated by Student *t* test and for categorical variables were calculated by the chi-square test.

ACC = American College of Cardiology; AHA = American Heart Association; PES = paclitaxel-eluting stent(s); QCA = quantitative coronary angiography.

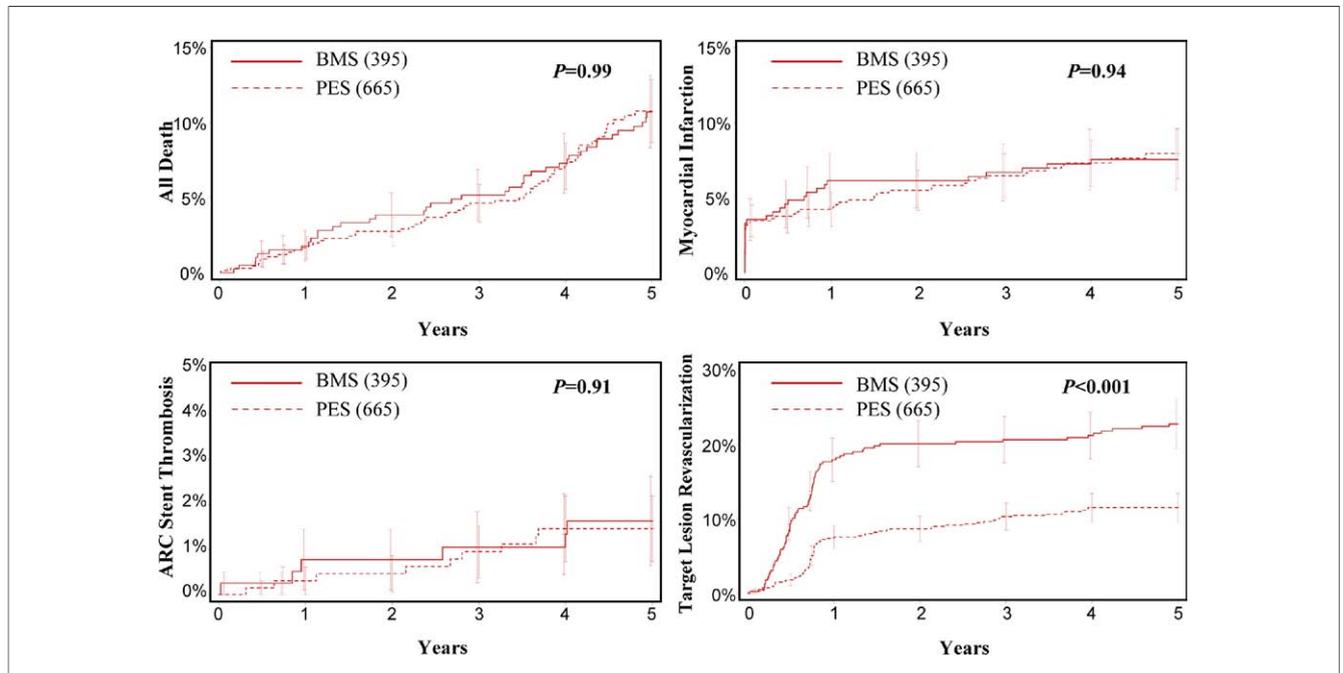
mm,  $p < 0.001$ ). In contrast, men were more likely to have had a previous MI, PCI, and coronary artery bypass graft.

**SAFETY AND EFFICACY END POINTS.** In the randomized trials, PES-treated women had significantly lower TLR rate than BMS-treated women did, with no significant differences in the rates of death, MI, and stent thrombosis between PES and BMS through 5-year follow-up (Fig. 2). Comparison of PES-treated women with PES-treated men (Table 2) showed no significant sex differences in all-cause death, MI, and TLR either at 1-year or between 1 and 5 years. However, women appeared to suffer less definite/probable stent thrombosis in 0 to 1

year than men did (0.31% vs. 1.27%,  $p = 0.04$ ), although this finding was not sustained during the subsequent years.

The Kaplan-Meier curves in Figure 3 demonstrate the lack of differences between genders in death, MI, stent thrombosis, and TLR rates over 5 years. At hospital discharge, 100% of women and 99.9% of men were receiving dual antiplatelet therapy ( $p = 0.52$ ). The antiplatelet compliance remained similar through follow-up, having fallen to 36.1% for women and 37.4% for men at 5 years.

**MULTIVARIATE PREDICTORS OF 5-YEAR CLINICAL OUTCOMES.** Adjusted for other covariates, sex was not a significant predictor of any of the adverse outcomes; death (hazard



**Figure 2. Clinical Outcomes for Women in Randomized Trials**

Kaplan-Meier estimates of 5-year cumulative rates of death (A), myocardial infarction (B), Academic Research Consortium–defined definite/probable stent thrombosis (C), and target lesion revascularization (D) for women receiving paclitaxel-eluting stent(s) versus bare-metal stent(s) in the randomized trials. Error bars are  $\pm 1.5$  SE. ARC = Academic Research Consortium; BMS = bare-metal stent(s); PES = paclitaxel-eluting stent(s).

ratio [HR]: 0.83, 95% CI: 0.60 to 1.14), MI (HR: 1.12, 95% CI: 0.80 to 1.58), stent thrombosis (HR: 0.56, 95% CI: 0.27 to 1.16), and TLR (HR: 0.96, 95% CI: 0.72 to 1.26). **Registries.** A total of 2,487 and 5,005 patients were enrolled in the ARRIVE 1 and ARRIVE 2 registries,

respectively. Of these 7,492 pooled PES-treated patients, 4,794 (64%) were classified as expanded-use based on patient and/or lesion characteristics considered outside the 2,698 simple-use population. The expanded-use cohort included patients with acute MI, lesion length >28 mm, RVD <2.5 mm, multivessel stenting, bifurcation lesions, in-stent restenosis, vein graft, renal disease, and chronic total occlusion. Of the 2,698 simple-use patients, 921 (34%) were women and of the 4,794 expanded-use patients, 1,528 (32%) were women.

**BASELINE CHARACTERISTICS.** The registry data demonstrated a similar pattern of increased adverse baseline characteristics for women compared with men (Table 3). Women were older, more likely to be hypertensive, have diabetes, previous stroke, and smaller RVD. Men, by contrast, were more likely to have had a previous MI, PCI, and coronary artery bypass graft. They were also more likely to have left main and multivessel disease.

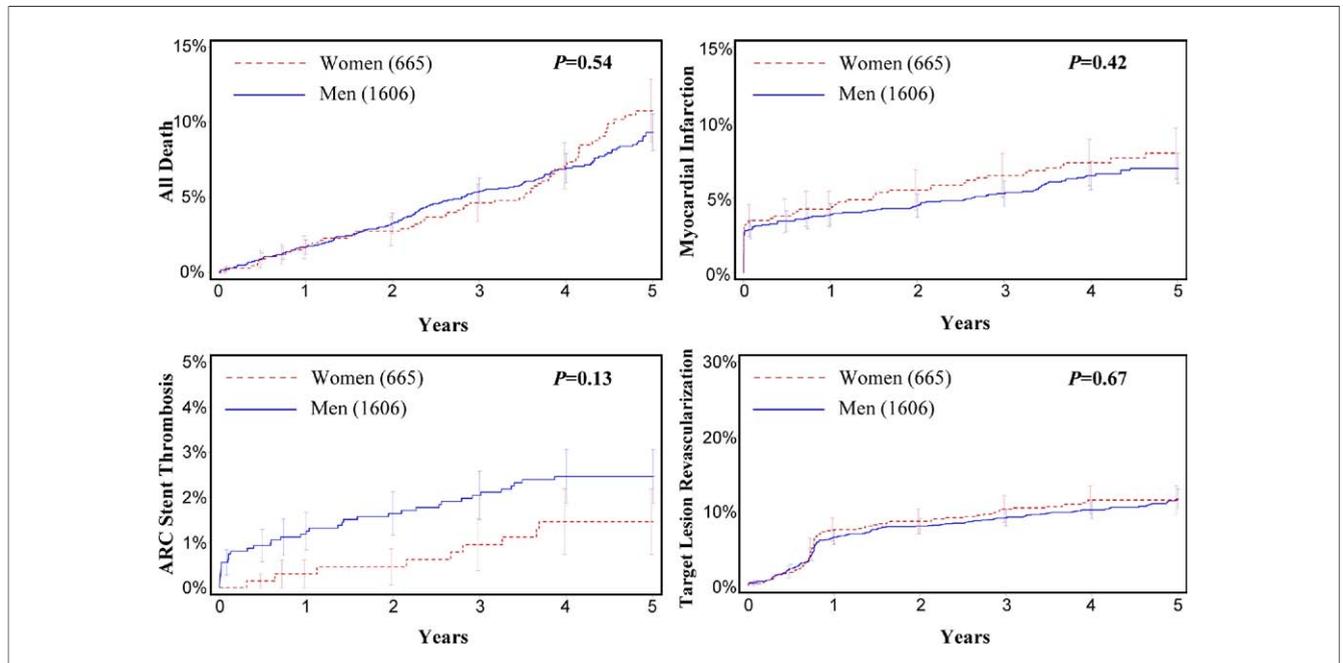
**SAFETY AND EFFICACY END POINTS.** Simple-use registry patients showed no significant sex differences in death, MI, stent thrombosis, and TLR through 2 years (Table 4). Also, as in the randomized trial patients, women tended to have lower stent thrombosis rates (albeit not statistically significant) than men.

The Kaplan-Meier curves in Figure 4 demonstrate the absence of sex-based differences in the simple-use patients. In the expanded-use patients, however, women had significantly higher death and TLR rates than men (Fig. 5).

**Table 2. Annualized Hazard Rates for Patients Receiving PES in the Randomized Trials**

	Women (n = 665)	Men (n = 1,606)	p Value
<b>All-cause death</b>			
0-1 yr	1.69%	1.71%	0.97
1-5 yrs	2.20%	1.96%	0.48
0-5 yrs	2.08%	1.90%	0.54
<b>Myocardial infarction</b>			
0-1 yr	4.47%	4.06%	0.69
1-5 yrs	1.00%	0.87%	0.62
0-5 yrs	1.86%	1.60%	0.42
<b>ARC stent thrombosis (definite/probable)</b>			
0-1 yr	0.31%	1.27%	0.04
1-5 yrs	0.33%	0.35%	0.88
0-5 yrs	0.33%	0.57%	0.13
<b>Target lesion revascularization</b>			
0-1 yr	7.75%	6.69%	0.39
1-5 yrs	1.60%	1.58%	0.95
0-5 yrs	2.85%	2.67%	0.67

ARC = Academic Research Consortium; PES = paclitaxel-eluting stent(s).



**Figure 3. Sex-Based Clinical Outcomes in the Randomized Trials**

Kaplan-Meier estimates of 5-year cumulative rates of death (A), myocardial infarction (B), Academic Research Consortium (ARC)-defined definite/probable stent thrombosis (C), and target lesion revascularization (D) for women versus men for patients receiving paclitaxel-eluting stent(s) in the randomized trials. Error bars are  $\pm 1.5$  SE.

**Multivariate predictors of 2-year clinical outcomes.** The higher rates of death and TLR in women in the expanded-use patients could be confounded by the higher baseline risk factors in women than in men. This is supported by multivariate analysis, wherein sex was not found to be a significant independent predictor of any adverse outcomes among simple-use patients; death (HR: 0.90, 95% CI: 0.60 to 1.34), MI (HR: 0.94, 95% CI: 0.54 to 1.64), stent thrombosis (HR: 0.62, 95% CI: 0.29 to 1.34), and TLR (HR: 1.39, 95% CI: 0.98 to 1.98). In the expanded-use patients, sex was not a significant predictor of death (HR: 1.05, 95% CI: 0.85 to 1.31), MI (HR: 1.18, 95% CI: 0.85 to 1.63), and stent thrombosis (HR: 1.13, 95% CI: 0.80 to 1.61) but remained a significant predictor of TLR (HR: 1.36, 95% CI: 1.11 to 1.67).

Further, subgroup analysis in the expanded-use patients indicated that the increase in the TLR rate in women was generalized across high-risk subgroups, although no individual subgroup reached statistical significance. The subgroup hazard ratios for TLR (women vs. men) were as follows: acute MI (HR: 1.48, 95% CI: 0.86 to 2.57), in-stent restenosis (HR: 1.00, 95% CI: 0.59 to 1.72), lesion length  $>28$  mm (HR: 0.94, 95% CI: 0.61 to 1.44), RVD  $<2.5$  mm (HR: 1.26, 95% CI: 0.56 to 2.86), multivessel stenting (HR: 1.20, 95% CI: 0.85 to 1.69), bifurcation lesion (HR: 1.09, 95% CI: 0.66 to 1.79), chronic total occlusion (HR: 1.38, 95% CI: 0.53 to 3.59).

## Discussion

Due to the relative under-representation of women in PCI trials, and the prior suggestions that women have worse outcomes than men, more detailed investigations of the influence of sex on PCI outcomes in current practice are needed. To our knowledge, the “TAXUS Woman” analysis, which included more than 3,000 women, is the largest evaluation to date that examines the influence of sex on long-term performance of a single DES across low- to high-risk patient/lesion characteristics. This analysis demonstrated that women had significantly more adverse baseline risk factors, yet had comparable safety and efficacy outcomes to men.

The data on 665 women in the randomized trials showed that PES provided a significant reduction in TLR compared with BMS through 5 years without an associated increase in other adverse events. The study extends upon the previous studies (20,21). It is important to note that because of the blinded nature of these studies, the use of dual antiplatelet therapy over time was the same in both the PES and BMS arms.

In the randomized trials and in the simple-use registry patients, there were no significant sex-based differences in long-term safety or efficacy outcomes. In the expanded-use registry patients, however, univariate analysis showed that women had significantly higher 1- and 2-year death rates, which was also observed as a trend in a recent study (21).

**Table 3. Baseline Clinical and Lesion Characteristics for Patients Receiving PES in the Registries**

Variable	Simple-Use			Expanded-Use		
	Women (n = 921)	Men (n = 1,777)	p Value	Women (n = 1,528)	Men (n = 3,266)	p Value
Age, yrs	65.9 ± 11.5 (921)	61.5 ± 11.2 (1,777)	<0.001	67.7 ± 11.8 (1,528)	63.7 ± 11.6 (3,266)	<0.001
Cardiac history						
Congestive heart failure	6.0% (55/921)	4.4% (79/1,777)	0.08	8.8% (135/1,528)	7.4% (242/3,266)	0.09
Previous myocardial infarction	23.6% (217/921)	28.6% (508/1,777)	0.005	37.7% (576/1,528)	43.5% (1,421/3,266)	<0.001
Previous percutaneous coronary intervention	34.1% (310/910)	35.2% (620/1,759)	0.54	34.1% (513/1,504)	39.6% (1,282/3,235)	<0.001
Previous coronary artery bypass graft	9.5% (87/919)	12.4% (220/1,772)	0.023	18.2% (277/1,520)	28.2% (918/3,260)	<0.001
Cardiac risk factors						
Current smoking	21.3% (196/921)	25.7% (456/1,777)	0.012	20.2% (309/1,528)	24.6% (803/3,266)	<0.001
Diabetes, medically treated	28.9% (266/921)	25.0% (444/1,777)	0.029	33.3% (509/1,528)	27.3% (893/3,266)	<0.001
Hypertension	80.0% (737/921)	73.0% (1,297/1,777)	<0.001	82.2% (1,256/1,528)	73.5% (2,401/3,266)	<0.001
Hypercholesterolemia	72.5% (668/921)	75.4% (1,339/1,777)	0.11	77.0% (1,176/1,528)	76.4% (2,494/3,266)	0.65
Comorbid conditions						
Previous stroke	5.9% (54/921)	4.6% (81/1,777)	0.14	9.4% (143/1,528)	5.8% (189/3,266)	<0.001
Renal disease	0.0% (0/921)	0.0% (0/1,777)	Undef	4.4% (67/1,528)	3.8% (124/3,266)	0.33
Multivessel disease	25.0% (230/921)	28.3% (503/1,777)	0.07	38.0% (581/1,528)	44.4% (1,451/3,266)	<0.001
Left main disease	0.0% (0/921)	0.0% (0/1,777)	Undef	6.3% (97/1,528)	8.0% (262/3,266)	0.04
Lesion characteristics						
Reference vessel diameter (mm)	2.92 ± 0.36 (920)	2.97 ± 0.37 (1,777)	<0.001	2.87 ± 0.45 (1,528)	2.97 ± 0.48 (3,266)	<0.001
Left anterior descending vessel location	43.2% (398/921)	38.9% (691/1,777)	0.030	47.1% (720/1,528)	40.5% (1,323/3,266)	<0.001
Modified ACC/AHA lesion type						
A	27.1% (250/921)	23.0% (409/1,777)	0.018	14.4% (220/1,528)	13.5% (441/3,266)	0.40
B1	45.8% (422/921)	47.2% (839/1,777)	0.49	38.5% (588/1,528)	38.2% (1,246/3,266)	0.83
B2	24.8% (228/921)	26.2% (466/1,777)	0.41	41.1% (628/1,528)	41.5% (1,357/3,266)	0.77
C	7.7% (71/921)	8.9% (158/1,777)	0.30	27.8% (425/1,528)	28.9% (945/3,266)	0.42
B2/C	32.0% (295/921)	34.5% (613/1,777)	0.20	64.7% (988/1,528)	66.2% (2,161/3,266)	0.31

Values are mean ± SD (n) or % (count/sample size). The p values for continuous variables were calculated by Student t test and for categorical variables were calculated by the chi-square test. Undef = undefined; other abbreviations as in Table 1.

Multivariate analysis, however, showed that this observed increase in mortality in women in the expanded-use patients was attributable to their higher baseline comorbidities (including age and diabetes), making sex per se a marker of a more severe clinical profile rather than a variable that directly affects the outcome. This observation is in alignment with previous studies that reported no differences in short- or long-term differences in mortality between men and women after adjustment for baseline covariates in the modern era of PCI with DES in patients with de novo lesions (22,23).

A more interesting finding of this study is the increase in TLR for women in the expanded-use registry population. Our finding is supported by a previous report wherein female sex has been reported as an independent predictor of restenosis following sirolimus-eluting stent implantation in high-risk patients (24). Also a recent pooled sex-based analysis comparing the everolimus-eluting stent and PES demonstrated that irrespective of the stent type, a higher 2-year TLR rate was observed in women than in men (7.3 vs. 4.2, p = 0.03) (25). Sex differences in intravascular ultrasound measures of neointimal hyperplasia have been reported previously (26). The fact

that increases in the rate of repeat revascularization were limited to the expanded-use registry population in the PES registries suggests that this slightly greater level of neointimal hyperplasia may only become clinically relevant in more complex lesions. Unlike the increase in death rate, the increase in TLR for women persisted after multivariate adjustment, suggesting a fundamental biologic difference or perhaps the effect of other unmeasured confounders.

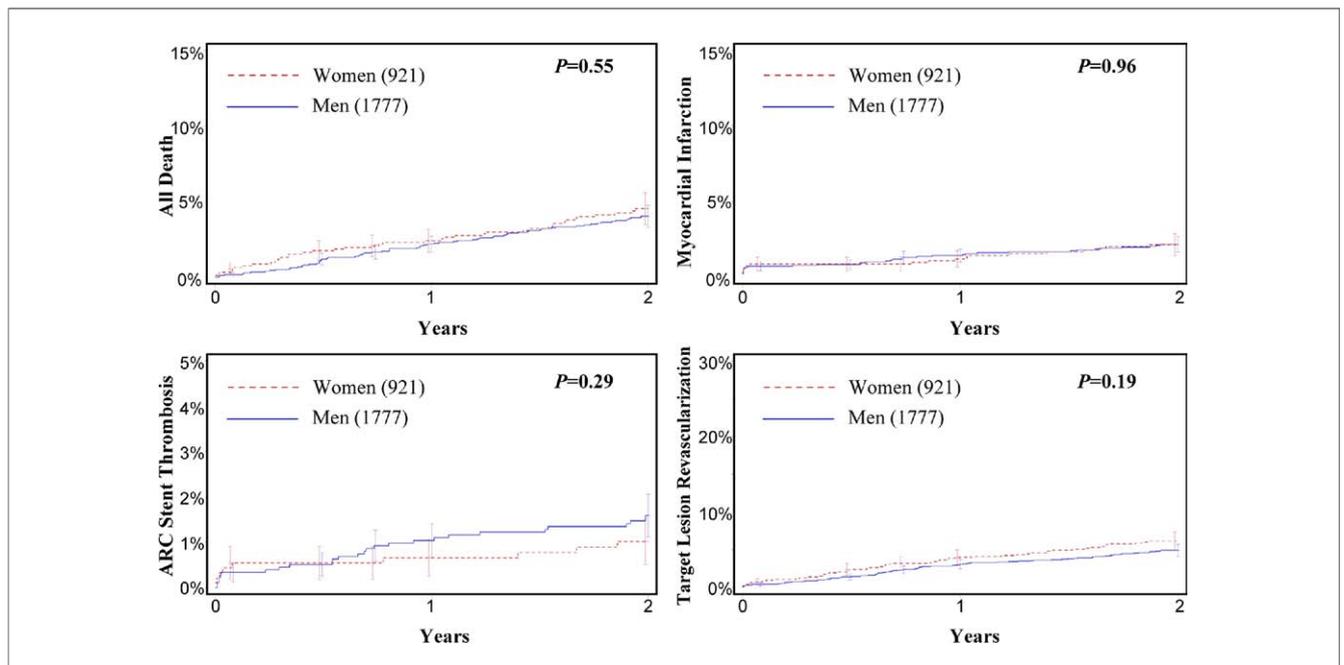
Some concerns have been raised about the potential for increased very late (after 1 year) rates of stent thrombosis with DES versus BMS (27). It has been postulated that DES might be more vulnerable to this complication due to potential suppression of neointimal hyperplasia and the altered vascular responses by the antiproliferative effects responsible for the desired reduction in restenosis. Although this event occurs with low frequency, it is associated with significant morbidity and mortality. In that context, it is of interest that a moderately significant reduction in stent thrombosis at 12 months in favor of women was observed in both the trial and simple-use registry patients. However, this initial benefit in terms of stent thrombosis was not sustained to 5 years, nor did it persist after

	Simple-Use		p Value	Expanded-Use		p Value
	Women	Men		Women	Men	
	(n = 921)	(n = 1,777)		(n = 1,528)	(n = 3,266)	
<b>All-cause death</b>						
0-1 yr	2.47%	2.22%	0.68	5.37%	3.82%	0.02
1-2 yrs	2.19%	1.92%	0.65	4.21%	3.64%	0.39
0-2 yrs	2.34%	2.07%	0.55	4.82%	3.74%	0.02
<b>Myocardial infarction</b>						
0-1 yr	1.25%	1.47%	0.65	2.95%	2.51%	0.41
1-2 yrs	0.98%	0.83%	0.72	1.23%	1.53%	0.46
0-2 yrs	1.12%	1.14%	0.96	2.15%	1.99%	0.64
<b>ARC stent thrombosis (definite/probable)</b>						
0-1 yr	0.68%	1.06%	0.34	2.51%	2.21%	0.54
1-2 yrs	0.37%	0.64%	0.39	1.00%	1.31%	0.41
0-2 yrs	0.53%	0.80%	0.29	1.77%	1.74%	0.93
<b>Target lesion revascularization</b>						
0-1 yr	4.13%	3.14%	0.20	8.06%	5.69%	0.004
1-2 yrs	2.84%	2.46%	0.59	4.15%	3.86%	0.67
0-2 yrs	3.27%	2.60%	0.19	5.82%	4.60%	0.02

Abbreviations as in Tables 1, 2, and 3.

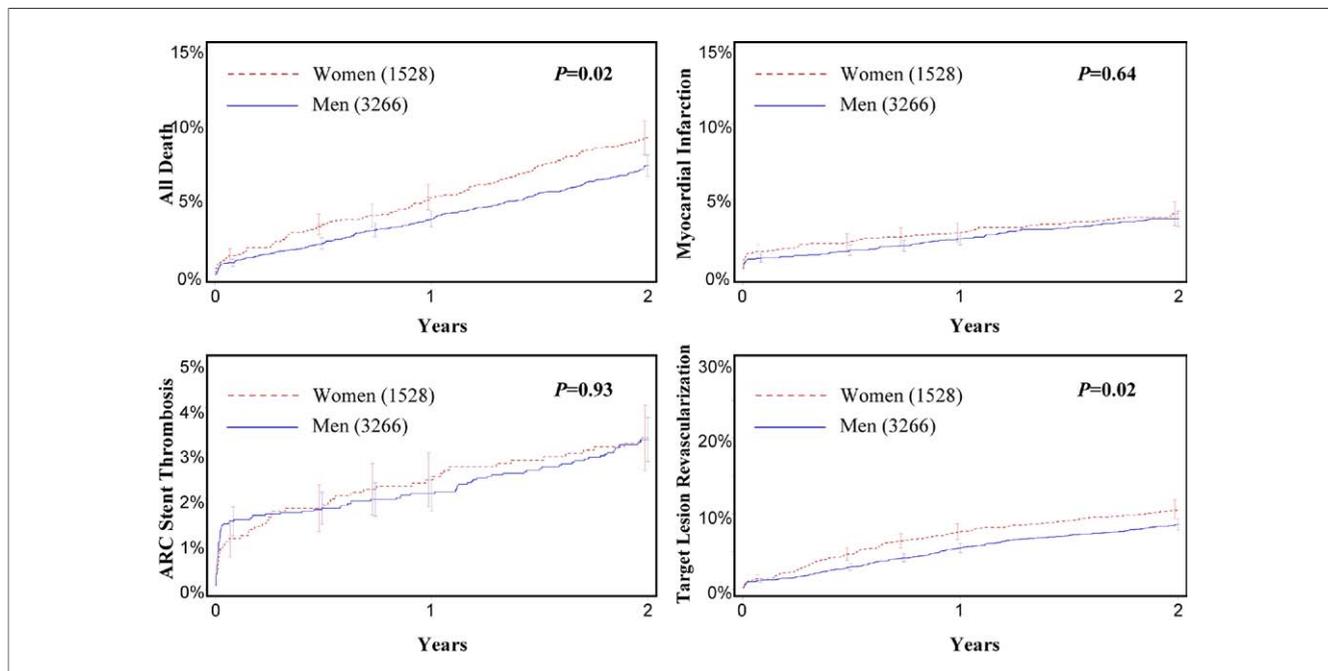
multivariate adjustment for other baseline differences. It was also not explicable by women being more likely to adhere to dual antiplatelet therapy, given similar rates of medication compliance over time, for men and women. It is possible

that the lower body weight of women compared with the body weight of men could lead to higher dosing of clopidogrel (milligrams per kilograms body weight), and thus more effective antiplatelet effect during the first year, but



**Figure 4. Sex-Based Clinical Outcomes in the Registries (Simple-Use)**

Kaplan-Meier estimates of 2-year cumulative rates of death (A), myocardial infarction (B), Academic Research Consortium (ARC)-defined definite/probable stent thrombosis (C), and target lesion revascularization (D) for women versus men in simple-use patients receiving paclitaxel-eluting stent(s) in the registries. **Error bars** are ±1.5 SE.



**Figure 5. Sex-Based Clinical Outcomes in the Registries (Expanded-Use)**

Kaplan-Meier estimates of 2-year cumulative rates of death (A), myocardial infarction (B), Academic Research Consortium (ARC)-defined definite/probable stent thrombosis (C), and target lesion revascularization (D) for women versus men in expanded-use patients receiving paclitaxel-eluting stents in the registries. **Error bars** are ±1.5 SE.

recent data suggest that sex is a significant predictor of heightened platelet reactivity despite dual antiplatelet therapy in patients undergoing PCI (28). Hence, we cannot exclude that this observation of reduced first-year stent thrombosis in women was the result of a type 2 error, making further clarification from a larger prospective study warranted before concluding that there is a real difference in early stent thrombosis for women.

**Study limitations.** This study based on a large cohort of PES-treated women was subjected to careful ascertainment of follow-up events. However, as a post hoc subset analysis of prospective trials and registries it still must be considered as an observational and hypothesis-generating study. In addition, although the results of this analysis cannot be applied directly to women with more diffuse disease, acute MI, or those requiring multivessel intervention, the inclusion of expanded-use conditions in the real-world registries may provide insight into sex differences when DES are used in such high-risk patients. Finally, it remains to be determined whether DES other than Taxus would show the same relative results in women compared with men.

## Conclusions

These data indicate that the overall beneficial effects of PES in reducing revascularization compared with BMS are generalizable to women. There were no sex-based

differences in key adverse outcomes such as death, MI, TLR, or stent thrombosis in the randomized trial and simple-use registry patients. However, a slightly higher rate of TLR was observed in women in the overall expanded-use registry patients, across the subgroups usually associated with an increased risk of restenosis. Nonetheless, this large sex-based analysis demonstrates that PCI with PES is a safe and effective treatment option for women with coronary artery disease suitable for revascularization with DES.

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**Key Words:** coronary disease ■ drug-eluting stent(s) ■ revascularization ■ sex.