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CLINICAL RESEARCH

Impact of Sex on Clinical and Angiographic Outcomes Among Patients Undergoing Revascularization With Drug-Eluting Stents

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Objectives The goal of this study was to investigate sex-based differences in long-term clinical and angiographic outcomes after coronary revascularization with drug-eluting stents (DES).

Background The impact of sex on clinical and angiographic outcomes following revascularization with DES is not well established.

Methods Individual patient data from 3 all-comers randomized DES trials (SIRTAX, LEADERS, RESOLUTE All-Comers) were pooled. Of 5,011 patients, 4,885 (97.5%) completed 2-year follow-up (1,164 women, 3,721 men). Protocol-mandated angiographic follow-up was available for 1,561 lesions (351 among women, 1,210 among men). The primary endpoint was the composite of cardiac death and myocardial infarction (MI) at 2 years.

Results At baseline, women, as compared with men, were older, more frequently had diabetes, obesity, and hypertension, less frequently had smoking habits, previous MI, and previous surgical revascularization, and had a smaller reference diameter of the target vessel as well as a lower SYNTAX score. After adjustment for baseline differences, women and men had a similar risk of cardiac death or MI (odds ratio [OR]: 1.13, 95% confidence interval [CI]: 0.82 to 1.56, p = 0.44), cardiac death (OR: 1.04, 95% CI: 0.61 to 1.80, p = 0.87), and MI (OR: 1.07, 95% CI: 0.75 to 1.53, p = 0.71) at 2 years. Similarly, risks of target lesion revascularization (OR: 1.09, 95% CI: 0.77 to 1.54, p = 0.62), target vessel revascularization (OR: 0.88, 95% CI: 0.63 to 1.22, p = 0.43), and definite or probable stent thrombosis (OR: 0.73, 95% CI: 0.38 to 1.38, p = 0.33) were comparable for women and men. Follow-up angiography showed no differences in terms of in-stent late loss (0.18 ± 0.54 mm vs. 0.20 ± 0.99 mm, p = 0.76) and in-segment binary restenosis (8.5% vs. 8.5%, p = 0.76).

Conclusions The unrestricted use of DES is associated with similar long-term safety and efficacy among women and men with coronary artery disease. (Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization [SIRTAX]; NCT00297661, LEADERS Trial Limus Eluted From A Durable Versus ERodable Stent Coating [LEADERS]; NCT00389220, RESOLUTE-III All-comers Trial: A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention [RESOLUTE All-Comers]; NCT00617084) (J Am Coll Cardiol Intv 2012; 5:301–10) © 2012 by the American College of Cardiology Foundation

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More than 1 million percutaneous coronary interventions (PCI) are performed each year in the United States with one-third of procedures performed in women (1). Female patients differ from their male counterparts in terms of age (2), cardiovascular risk factors (3), clinical presentation (4,5), and angiographic characteristics, including vessel size and extent of disease (4,6). Early studies during the balloon angioplasty era reported a lower procedural success, a higher in-hospital mortality, and impaired long-term clinical outcomes among women compared with men (2,3,7,8).

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Bare-metal stents improved outcomes after PCI among women (4,9–12) in terms of safety and efficacy. The advent of drug-eluting stents (DES) has led to important reductions in restenosis and repeat revascularization rates compared with bare-metal stents (13), and DES are used in more than 80% of patients undergoing PCI in the United States (1). However, sex-related differences in clinical and angiographic outcomes after revascularization with DES are not well established (14–17). We therefore pooled individual patient data from 3 recent all-comers randomized clinical trials with the unrestricted use of DES (Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization [SIRTAX]; LEADERS Trial Limus Eluted From A Durable Versus ERodable Stent Coating [LEADERS]; RESOLUTE-III All-comers Trial: A Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention [RESOLUTE All-Comers]) (18–20) and compared clinical and angiographic outcomes between women and men during long-term follow-up through 2 years.

Abbreviations and Acronyms

CI = confidence interval
DES = drug-eluting stent(s)
MI = myocardial infarction
OR = odds ratio
PCI = percutaneous coronary intervention

Methods

Study population. Individual data were pooled for 5,011 patients from 3 large randomized clinical trials investigating the unrestricted use of DES for coronary revascularization: the SIRTAX trial (18), the LEADERS trial (19), and the RESOLUTE All-Comers trial (20). All trials were conducted between 2004 and 2009 at European institutions, with the exclusive use of DES and an all-comers study design. Inclusion criteria were broad to reflect routine clinical practice. Patients with either stable coronary artery disease or acute coronary syndrome (including patients with unstable angina, non–ST-segment elevation and ST-segment elevation myocardial infarction) were eligible, if they had at least 1 lesion with diameter stenosis of 50% or more in a vessel with reference diameter of 2.25 to 4.0 mm (SIRTAX and RESOLUTE All-Comers) and 2.25 to 3.5 mm (LEADERS) (18–20). None of the trials had any restriction with respect to number of treated lesions, treated vessels, lesion length, or number of stents implanted. Exclusion criteria were few and included known intolerance to the study drugs, metal alloys, or contrast media, planned surgery within 6 months after the index procedure, and participation in another study. Angiographic follow-up was planned at 8 months among patients included in SIRTAX, at 9 months among 25% of patients included in LEADERS, and at 13 months among 20% of patients in RESOLUTE All-Comers. The trials complied with the provisions of the Declaration of Helsinki, and the study protocols were approved by the institutional review board at each study center. All patients provided written informed consent for participation in the study.

Procedures. Randomization was done after diagnostic angiography and before PCI in all 3 trials. In the SIRTAX trial (18), patients were randomly allocated to receive sirolimus-eluting stents (Cypher, Cordis, Johnson & Johnson, Miami Lakes, Florida) or paclitaxel-eluting stents (Taxus, Boston Scientific, Natick, Massachusetts); in the LEADERS trial (19), patients were randomly allocated to receive biolimus-eluting stents (BioMatrix, Biosensors, Newport Beach, California) or sirolimus-eluting stents (Cypher, Cordis); and in the RESOLUTE All-Comers trial (20), patients were randomly allocated to receive zotarolimus-eluting stents (Resolute Endeavor, Medtronic, Santa Rosa, California) or everolimus-eluting stents (Xience V, Abbott Vascular, Santa Clara, California). Balloon angioplasty and stent implantation were performed according to standard techniques and in accordance with guidelines; direct stenting was allowed. Full lesion coverage was attempted by implanting 1 or several stents. No mixture of type of stents was permitted for a given patient unless the operator was unable to insert the study stent, in which case crossover to another device of the operator's choice was possible. In case of unplanned revascularization procedures requiring stent implantation, it was recommended that physicians use the same type as the initially allocated study stent. Procedural anticoagulation was achieved with unfractionated heparin at a dose of 5,000 IU or 70 to 100 IU/kg of body weight; the use of glycoprotein IIb/IIIa inhibitors was left to the operator's discretion. Dual antiplatelet therapy consisting of acetylsalicylic acid of at least 75 mg once daily and the thienopyridine clopidogrel 75 mg daily was prescribed for at least 12 months in the SIRTAX and LEADERS trials, and for at least 6 months in the RESOLUTE All-Comers trial.

Definitions. The primary endpoint of the present study was the composite of cardiac death and myocardial infarction (MI) at 2 years. Secondary clinical endpoints were the individual components of the primary endpoint as well as all-cause death, the composite of all-cause death and MI, clinically indicated target lesion and target vessel revascularization, and definite and definite or probable stent thrombosis according to the Academic Research Consortium criteria (21).

For each trial, a blinded clinical events committee independently adjudicated all adverse events. Endpoint definitions were comparable across the 3 trials. Cardiac death was defined as death from cardiac causes or any death from unknown causes in SIRTAX and LEADERS, and as any death unless an undisputed noncardiac cause was present in RESOLUTE All-Comers. MI was defined—in SIRTAX and LEADERS trials—as the presence of new Q waves in at least 2 contiguous leads and an elevated creatine kinase-MB fraction, or—in the absence of significant Q waves—as an increase in the creatine kinase level to more than twice the upper limit of the normal range with an elevated level of creatine kinase-MB or troponin (18,19). In the RESOLUTE All-Comers trial, MI was defined according to an "extended historical" definition (20,22), consistent with the 1 used in SIRTAX and LEADERS. Target lesion revascularization was defined as any revascularization for a stenosis within the stent or within a 5-mm border proximal and distal to the stent in all 3 trials. A revascularization was considered clinically indicated in the presence of angiographic diameter stenosis of at least 50% and ischemic signs or symptoms, or with angiographic diameter stenosis of at least 70% regardless of ischemic signs or symptoms (18–20).

Secondary angiographic endpoints were late lumen loss (i.e., difference between the post-procedure and follow-up minimal lumen diameter), rate of binary restenosis (i.e., % diameter stenosis of at least 50%), percent diameter stenosis (i.e., reference vessel diameter − minimal lumen diameter/reference vessel diameter × 100), and minimal lumen diameter. Angiographic endpoints were considered for both the in-stent (i.e., within the stent) and in-segment (i.e., within the stent and a 5-mm border proximal and distal) analysis. For a detailed description of quantitative coronary angiography methods, we refer to the principal publications of the 3 trials (18–20). SYNTAX score was assessed by a central core laboratory (Cardialysis, Rotterdam, the Netherlands) in all 3 trials.

Statistical analysis. Of 5,011 patients randomized in the 3 trials, 4,885 (97.5%) patients completed 2 years of follow-up according to the pre-specified definition (i.e., last medical contact 720 days after the index procedure, with a 30-day window) and were included in the present analysis. Comparison between women and men were carried out using mixed models with random effects specified as type of randomized clinical trial as random intercept, and treatment arms as random coefficients. Mixed maximum logistic regression models were used to derive differences between female and male patients for binary and continuous outcomes, respectively. The percentages were predicted probabilities derived from mixed maximum logistic regression models. Means and standard deviations were predicted values derived from mixed maximum likelihood regression models. Odds ratios (ORs) and confidence intervals (CIs) were adjusted for stent type in the crude analysis, whereas the adjusted

Table 1. Baseline Clinical Characteristics

	Women (n = 1,164)	Men (n = 3,721)	Difference (95% CI)	p Value
Age, yrs	67.1 (10.5)	63.0 (10.7)	4.09 (3.39 to 4.79)	<0.001
Cardiac risk factors				
Diabetes	315 (27.1)	804 (21.6)	5.46 (2.66 to 8.25)	<0.001
Insulin-requiring diabetes	134 (42.6)	253 (31.5)	11.08 (4.86 to 17.31)	<0.001
Obese	336 (28.9)	903 (24.4)	4.52 (1.64 to 7.40)	<0.001
Hypertension	889 (76.4)	2,531 (68.0)	8.36 (5.28 to 11.44)	<0.001
Hypercholesterolemia	751 (64.5)	2,426 (65.2)	−0.68 (−3.37 to 2.01)	0.62
Serum creatinine >2.0 mg/l	15 (1.3)	57 (1.6)	−0.26 (−1.08 to 0.55)	0.52
Current smoking	272 (23.4)	1,067 (28.7)	−5.31 (−8.33 to −2.29)	<0.001
Clinical history				
Previous MI	285 (24.7)	1,186 (32.2)	−7.51 (−10.55 to −4.46)	<0.001
Previous PCI	338 (29.0)	1,173 (31.5)	−2.49 (−5.21 to 0.23)	0.07
Previous CABG	73 (6.3)	428 (11.5)	−5.23 (−7.25 to −3.21)	<0.001
Clinical indication to PCI				0.29
Stable coronary artery disease	540 (46.4)	1,738 (46.7)	−0.32 (−0.90 to 0.27)	
Non–ST-segment elevation acute coronary syndromes	444 (38.1)	1,321 (35.5)	2.64 (−2.22 to 7.50)	
ST-segment elevation MI	180 (15.5)	662 (17.8)	−2.33 (−6.61 to 1.95)	
Left ventricular ejection fraction <0.50	167 (21.1)	581 (22.5)	−1.43 (−4.70 to 1.84)	0.39
SYNTAX score	12.9 ± 8.4	13.8 ± 8.7	−0.95 (−1.55 to −0.34)	<0.001
Multivessel disease	280 (24.1)	980 (26.3)	−2.25 (−5.37 to 0.87)	0.39

Values are mean ± SD or n (%).
CABG = coronary artery bypass graft; CI = confidence interval; MI = myocardial infarction; PCI = percutaneous coronary intervention.

analysis was performed using multivariable models, adjusting for baseline variables showing differences ($p < 0.2$) between women and men, including: stent type, age, diabetes, body mass index, hypertension, current smoking, previous MI, previous PCI, previous coronary artery bypass surgery, SYNTAX score, lesion length, pre-procedural reference vessel diameter, and pre-procedural stenosis.

Results

Of 5,011 patients randomized in the 3 trials, 4,885 (97.5%) patients completed 2 years of follow-up and were included in the present analysis: 1,164 (23.8%) women and 3,721 (76.2%) men. At baseline, women, as compared with men, were older (67.1 ± 10.5 years vs. 63.0 ± 10.7 years, $p < 0.001$), more frequently had diabetes (27.1% vs. 21.6%, $p < 0.001$), obesity (28.9% vs. 24.4%, $p < 0.001$), and hypertension (76.4% vs. 68.0%, $p < 0.001$), less frequently had smoking habits (23.4% vs. 28.7%, $p < 0.001$), prior MI (24.7% vs. 32.2%, $p < 0.001$), and prior coronary artery bypass surgery (6.3% vs. 11.5%, $p < 0.001$), and had a lower angiographic complexity as assessed by the SYNTAX score (12.9 ± 8.4 vs. 13.8 ± 8.7, $p < 0.001$) (Table 1). Angiographic and procedural characteristics are shown in Table 2. Women had a smaller reference diameter of the

Table 2. Angiographic Characteristics and Procedural Results

	Women (n = 1,164)	Men (n = 3,721)	Difference (95% CI)	p Value
No. of vessels treated per patient	1.2 (0.5)	1.2 (1.0)	−0.03 (−0.06 to 0)	0.10
Allocated stent type				0.09
Sirolimus-eluting stent	336 (28.9)	1,001 (26.9)	1.96 (−0.34 to 4.26)	
Paclitaxel-eluting stent	108 (9.3)	397 (10.7)	−1.39 (−3.02 to 0.24)	
Biolimus-eluting stent	208 (17.9)	630 (16.9)	0.94 (−0.16 to 2.04)	
Zotarolimus-eluting stent	260 (22.3)	838 (22.5)	−0.18 (−0.40 to 0.03)	
Everolimus-eluting stent	252 (21.6)	855 (23.0)	−1.33 (−2.88 to 0.23)	
No. of lesions	1,615	5,448		
Target vessel				0.62
Left main	23 (1.4)	83 (1.5)	−0.10 (−0.50 to 0.30)	
Left anterior descending	678 (42.0)	2,175 (39.9)	2.06 (−6.16 to 10.28)	
Left circumflex	377 (23.3)	1,331 (24.4)	−1.09 (−5.43 to 3.25)	
Right coronary artery	521 (32.3)	1,710 (31.4)	0.87 (−2.61 to 4.35)	
Bypass graft	16 (1.0)	149 (2.7)	−1.74 (−8.71 to 5.22)	
Lesion characteristics				
De novo lesions	1,500 (93.6)	5,056 (93.3)	0.29 (−1.10 to 1.68)	0.68
Total occlusion	203 (12.7)	705 (13.1)	−0.46 (−2.34 to 1.42)	0.63
Moderate or severe calcification	337 (21.1)	1,108 (20.6)	0.50 (−1.76 to 2.76)	0.66
Lesion length, mm	12.24 ± 10.30	12.60 ± 17.05	−0.36 (−0.86 to 0.14)	0.16
Stent characteristics				
No. of stents per lesion	1.2 (0.7)	1.2 (1.5)	0.01 (−0.03 to 0.05)	0.49
Average stent diameter, mm	2.84 ± 0.52	2.93 ± 0.95	−0.09 (−0.11 to −0.06)	<0.001
Total stent length per lesion, mm	19.93 ± 13.00	20.79 ± 23.83	−0.86 (−1.50 to −0.22)	0.01
Angiographic findings				
Pre-procedure				
RVD, mm	2.60 ± 0.66	2.71 ± 1.21	−0.11 (−0.15 to −0.08)	<0.001
MLD, mm	0.79 ± 0.60	0.79 ± 1.10	0.00 (−0.03 to 0.03)	0.94
Stenosis, %	69.3 ± 21.0	70.5 ± 38.5	−1.26 (−2.30 to −0.23)	0.02
Post-procedure				
MLD, mm				
In-stent	2.40 ± 0.59	2.48 ± 1.08	−0.07 (−0.10 to −0.04)	<0.001
In-segment	2.17 ± 0.63	2.25 ± 1.17	−0.08 (−0.12 to −0.05)	<0.001
Stenosis, %				
In-stent	11.6 ± 11.3	12.32 ± 20.6	−0.71 (−1.26 to −0.16)	0.01
In-segment	18.3 ± 13.0	18.26 ± 24.1	0.05 (−0.62 to 0.72)	0.89

Values are mean ± SD or n (%).
CI = confidence interval; MLD = minimal lumen diameter; RVD = reference vessel diameter.

Table 3. Clinical Outcomes at 30 Days

	Women (n = 1,164)	Men (n = 3,721)	Crude		Adjusted	
			OR (95% CI)	p Value	OR (95% CI)	p Value
Death	13 (1.1)	20 (0.5)	2.10 (1.04–4.23)	0.04	2.53 (0.84–7.67)	0.10
Cardiac death	10 (0.9)	18 (0.5)	1.79 (0.82–3.90)	0.14	2.21 (0.65–7.57)	0.21
MI	52 (4.5)	132 (3.6)	1.27 (0.91–1.76)	0.16	1.06 (0.71–1.60)	0.77
Q-wave	10 (0.9)	23 (0.6)	1.39 (0.66–2.93)	0.39	0.96 (0.36–2.56)	0.93
Non–Q-wave	42 (3.6)	110 (3.0)	1.22 (0.85–1.76)	0.28	1.07 (0.69–1.68)	0.75
Clinically indicated TVR	22 (1.9)	59 (1.6)	1.18 (0.72–1.94)	0.51	0.69 (0.34–1.40)	0.31
Percutaneous	20 (1.7)	52 (1.4)	1.22 (0.72–2.05)	0.46	0.70 (0.34–1.48)	0.35
Surgical	2 (0.2)	8 (0.2)	0.82 (0.17–3.86)	0.80	0.61 (0.06–5.87)	0.67
Clinically indicated TLR	21 (1.8)	53 (1.4)	1.26 (0.75–2.09)	0.38	0.76 (0.37–1.57)	0.46
Percutaneous	19 (1.6)	46 (1.2)	1.31 (0.76–2.24)	0.33	0.71 (0.33–1.54)	0.39
Surgical	2 (0.2)	7 (0.2)	0.91 (0.19–4.41)	0.91	0.71 (0.07–6.99)	0.77
Cardiac death or MI	59 (5.1)	147 (4.0)	1.29 (0.95–1.76)	0.10	1.07 (0.72–1.59)	0.75
Cardiac death, MI, clinically indicated TVR	66 (5.7)	171 (4.6)	1.24 (0.93–1.67)	0.14	1.02 (0.69–1.49)	0.93
Cardiac death, MI, clinically indicated TLR	66 (5.7)	166 (4.5)	1.28 (0.96–1.72)	0.10	1.06 (0.72–1.55)	0.78

Values are n (%).
OR = odds ratio; TLR = target-lesion revascularization; TVR = target-vessel revascularization; other abbreviations as in Table 1.

target vessel than men (2.60 ± 0.66 mm vs. 2.71 ± 1.21 mm, $p < 0.001$), and had a smaller percent stenosis of the target lesion (69.3 ± 21.0% vs. 70.5 ± 38.5%, $p = 0.02$). The randomly allocated type of stent was comparable between women and men.

Clinical outcomes at 30 days and 2 years are reported in Tables 3 and 4. At 2 years of follow-up, women, as compared with men, had a similar risk of cardiac death or MI (8.3% vs. 6.6%, adjusted OR: 1.13, 95% CI: 0.82 to 1.56, $p = 0.44$) in adjusted analyses. The individual components of the primary endpoint cardiac death (2.9% vs. 2.5%, adjusted OR: 1.04, 95% CI: 0.61 to 1.80, $p = 0.87$) and MI (5.8% vs. 4.7%, adjusted OR: 1.07, 95% CI: 0.75 to 1.53, $p = 0.71$) did not show differences between women and men. The risk of clinically indicated repeat interventions was comparable between women and men with respect to target lesion (6.1% vs. 6.0%, adjusted OR: 1.09, 95% CI: 0.77 to 1.54, $p = 0.62$) and target vessel revascularization (6.4% vs. 7.5%, adjusted OR: 0.88, 95% CI: 0.63 to 1.22, $p = 0.43$). Adjusted risks of the primary endpoint and its components, as well as target lesion and target vessel revascularization at 2 years are displayed in Figure 1.

Table 4. Clinical Outcomes at 2 Years

	Women (n = 1,164)	Men (n = 3,721)	Crude		Adjusted	
			OR (95% CI)	p Value	OR (95% CI)	p Value
Death	47 (4.0)	138 (3.7)	1.08 (0.77–1.52)	0.65	0.99 (0.63–1.56)	0.97
Cardiac death	34 (2.9)	92 (2.5)	1.18 (0.79–1.75)	0.43	1.04 (0.61–1.80)	0.87
MI	68 (5.8)	175 (4.7)	1.25 (0.94–1.67)	0.13	1.07 (0.75–1.53)	0.71
Q-wave	12 (1.0)	32 (0.9)	1.20 (0.62–2.34)	0.59	1.02 (0.44–2.38)	0.97
Non–Q-wave	56 (4.8)	146 (3.9)	1.23 (0.90–1.69)	0.20	1.04 (0.70–1.54)	0.85
Clinically indicated TVR	75 (6.4)	280 (7.5)	0.85 (0.65–1.10)	0.22	0.88 (0.63–1.22)	0.43
Percutaneous	67 (5.8)	250 (6.7)	0.85 (0.64–1.12)	0.25	0.85 (0.59–1.20)	0.35
Surgical	11 (1.0)	46 (1.2)	0.77 (0.40–1.50)	0.45	0.98 (0.47–2.07)	0.96
Clinically indicated TLR	71 (6.1)	222 (6.0)	1.03 (0.78–1.36)	0.84	1.09 (0.77–1.54)	0.62
Percutaneous	63 (5.4)	194 (5.2)	1.04 (0.78–1.40)	0.78	1.08 (0.74–1.55)	0.70
Surgical	8 (0.7)	36 (1.0)	0.72 (0.33–1.54)	0.39	0.84 (0.35–2.03)	0.70
Cardiac death or MI	96 (8.3)	244 (6.6)	1.27 (1.00–1.63)	0.05	1.13 (0.82–1.56)	0.44
Cardiac death, MI, clinically indicated TVR	141 (12.1)	456 (12.3)	0.99 (0.81–1.21)	0.89	0.98 (0.75–1.26)	0.85
Cardiac death, MI, clinically indicated TLR	139 (11.9)	403 (10.8)	1.12 (0.91–1.37)	0.29	1.13 (0.87–1.47)	0.35

Values are n (%).
Abbreviations as in Tables 1 and 3.

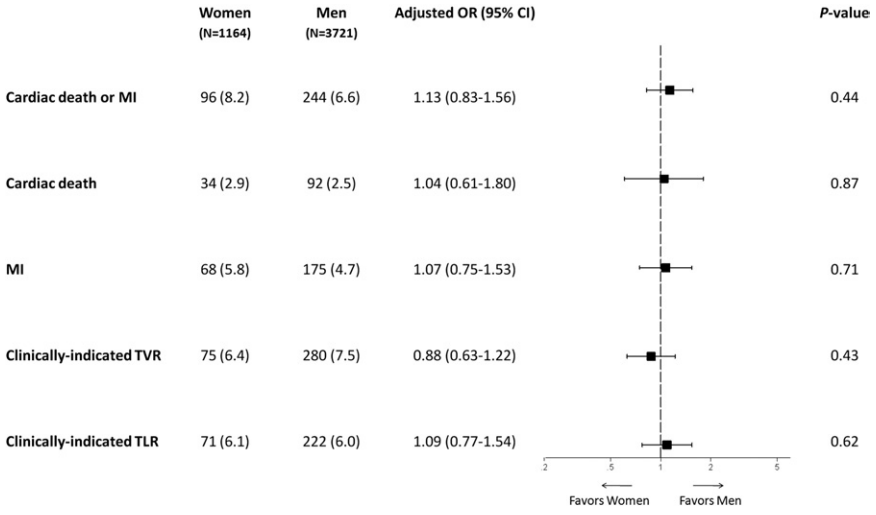

Figure 1. Clinical Outcomes Among Women and Men

Adjusted odds ratios (OR) and 95% confidence intervals (CI) for cardiac death or myocardial infarction (MI), cardiac death, MI, clinically indicated target lesion revascularization (TLR), and target vessel revascularization (TVR) at 2 years.

Cumulative events curves for definite and definite or probable stent thrombosis stratified according to sex are shown in Figure 2. There was no difference in the risk of stent thrombosis between women and men in terms of definite (1.7% vs. 1.7%, adjusted OR: 0.68, 95% CI: 0.33 to 1.39, $p = 0.29$) and definite or probable stent thrombosis (2.2% vs. 2.2%, adjusted OR: 0.73, 95% CI: 0.38 to 1.38, $p = 0.33$) at any time point (Table 5).

Angiographic outcomes. Protocol-mandated angiographic follow-up was available for 1,561 lesions: 351 lesions among 260 women and 1,210 lesions among 876 men. With respect to baseline clinical characteristics, patients with, as compared to those without, angiographic follow-up were younger (62.6 ± 10.7 vs. 64.3 ± 10.8, $p < 0.001$), more frequently smokers (32.7% vs. 26.1%, $p = 0.05$), and less frequently treated with previous coronary artery bypass graft (4.1% vs. 10.6%, $p < 0.001$). Crude and adjusted results of angiographic outcomes according to sex are presented in Table 6. There were no differences in terms of in-stent late lumen loss (0.18 ± 0.54 mm vs. 0.20 ± 0.99 mm, $p = 0.76$) and in-segment binary restenosis (8.5% vs. 8.5%, $p = 0.76$) (Fig. 3) between women and men during follow-up angiography. Paired angiographic findings for in-stent minimal lumen diameter at baseline, immediately after the intervention and at the time of angiographic follow-up showed no differences between women and men (Fig. 4).

Discussion

The present analysis represents the largest investigation of sex-based clinical and angiographic outcomes in a population pooled from 3 large randomized clinical trials with the unrestricted use of DES and follow-up through 2 years. Our findings can be summarized as follows:

1. Women undergoing PCI with the unrestricted use of DES differ from their male counterparts and are typically older, have more cardiovascular risk factors except for smoking, and a lower degree of angiographic complexity as assessed by the SYNTAX score.
2. After controlling for baseline differences, women undergoing PCI with DES have a similar risk of cardiac death and MI as compared with men through 2 years of follow-up.
3. DES achieve equivalent safety and efficacy in women and men with similar results in terms of stent thrombosis, repeat revascularization, and angiographic outcomes through 2 years of follow-up.

Early studies evaluating sex-based differences in outcomes after PCI in the balloon angioplasty era reported disparate results, but in general showed worse in-hospital and long-term clinical outcomes among women compared with men, with higher rates of in-hospital mortality and more frequent recurrent angina during long-term follow-up (2,3,7,8,23). This "gender gap" did largely decrease with the advent of bare-metal stents. Indeed, advances in technology leading to smaller guiding and balloon catheters resulted in more favorable outcomes in women with similar angiographic and procedural success rates despite smaller vessel size (10). Moreover, the use of bare-metal stents improved long-term outcomes among women (4,9–12), particularly as related to the risk of repeat revascularization. However, women still showed a higher risk of mortality during the short term (30 days) that persisted after adjustment for baseline clinical dif-

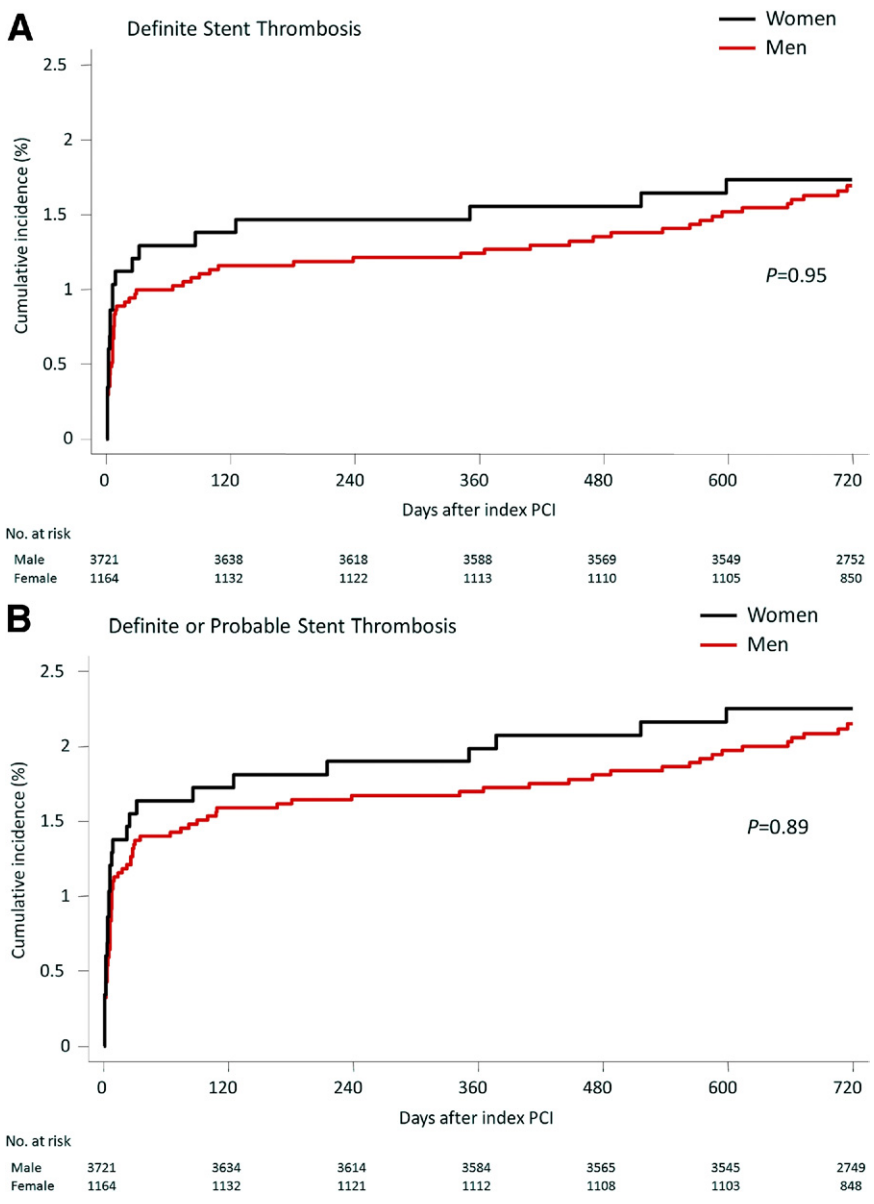

Figure 2. Stent Thrombosis

Cumulative event rates of definite **(A)** and definite or probable **(B)** stent thrombosis in women and men through 2 years. PCI = percutaneous coronary intervention.

ferences (4), and tended to have more symptoms of angina as compared with men during follow-up to 1 year (24). Only a few studies are available related to sex-based differences using DES (14–17). Lansky et al. (14) and Solinas et al. (15) observed a similar benefit among women and men in terms of angiographic outcomes and rates of revascularization in 2 cohorts of patients undergoing PCI with paclitaxel-eluting stents (14) (187 women and 475 men) and sirolimus-eluting stents (15) (249 women and 629 men) in the setting of "on-label" indications. Onuma and coauthors reported comparable rates of death, MI, and target vessel revascularization in 798 women and 2,007 men treated with sirolimus-eluting or paclitaxel-eluting stents within the RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) registries during 3-year follow-up (16), and showed a similar benefit of DES as compared with bare-metal stents in terms of repeat revascularization among women and men. Similar

Table 5. Stent Thrombosis Through 2 Years

	Women (n = 1,164)	Men (n = 3,721)	Crude		Adjusted	
			OR (95% CI)	p Value	OR (95% CI)	p Value
Definite						
Early (0–30 days)	15 (1.3)	37 (1.0)	1.27 (0.69–2.32)	0.44	0.54 (0.21–1.34)	0.18
Late (31 days-12 months)	3 (0.3)	9 (0.2)	1.05 (0.28–3.89)	0.94	1.85 (0.39–8.76)	0.44
Very late (>12 months)	2 (0.2)	16 (0.4)	0.40 (0.09–1.77)	0.23	0.47 (0.05–4.57)	0.52
Overall	20 (1.7)	62 (1.7)	1.02 (0.61–1.69)	0.95	0.68 (0.33–1.39)	0.29
Definite or probable						
Early (0–30 days)	19 (1.6)	51 (1.4)	1.18 (0.69–2.01)	0.54	0.52 (0.22–1.20)	0.13
Late (31 days-12 months)	4 (0.3)	12 (0.3)	1.05 (0.34–3.26)	0.94	1.68 (0.44–6.39)	0.45
Very late (>12 months)	3 (0.3)	17 (0.5)	0.57 (0.17–1.95)	0.37	0.98 (0.18–5.45)	0.98
Overall	26 (2.2)	80 (2.2)	1.03 (0.66–1.62)	0.89	0.73 (0.38–1.38)	0.33

Values are n (%).
Abbreviations as in Tables 2 and 3.

observations came from the TAXUS Woman analysis (17), comparing outcomes between 665 women and 1,606 men treated with paclitaxel-eluting or bare-metal stents included into 5 randomized clinical trials in an "on-label" setting, as well as 1,528 women and 3,266 men with an "expanded" indication within 2 large "real-world" registries. The present study extends the available evidence to a large and homogenous cohort of women and men who were treated with the unrestricted use of DES in an all-comers patient population, including ST-elevation MI, and a high prevalence of "off-label" indications. The similar outcomes in terms of cardiac death, MI, and stent thrombosis are reassuring and reinforce the lack of a sex gap in terms of patient and device safety. Along the same line, the present study provides robust evidence that DES achieve comparable efficacy in women and men. Rates of clinical revascularization showed no difference despite a somewhat lower baseline reference vessel diameter among women. Moreover, detailed angiographic analysis showed similar acute and long-term performance of DES irrespective of sex as evidenced by comparable post-procedural and follow-up minimal lumen diameter dimensions (Fig. 4). Finally, the results confirm similar potency of DES in the suppression of neointimal hyperplasia as evidenced by the in-stent late loss and in-segment restenosis. Mehilli et al. have previously described a lower risk of clinical and angiographic restenosis in women as compared with men undergoing PCI using bare-metal stents (6). Conversely, we observed a similar risk of angiographic and clinical restenosis

Table 6. Angiographic Follow-Up

	Women	Men	Crude		Adjusted	
			Difference (95% CI)	p Value	Difference (95% CI)	p Value
Lesions, n	351	1,210				
RVD, mm	2.76 ± 0.60	2.76 ± 1.11	−0.01 (−0.08 to 0.05)	0.72	0.00 (−0.07 to 0.06)	0.88
MLD, mm						
In-stent	2.30 ± 0.73	2.29 ± 1.36	−0.01 (−0.09 to 0.07)	0.83	−0.01 (−0.09 to 0.07)	0.80
In-segment	2.09 ± 0.75	2.10 ± 1.40	−0.03 (−0.11 to 0.05)	0.46	−0.02 (−0.10 to 0.06)	0.60
Stenosis, %						
In-stent	18.1 ± 19.9	18.3 ± 37.0	0.24 (−1.87 to 2.35)	0.82	0.72 (−1.60 to 3.05)	0.54
In-segment	24.4 ± 21.2	23.9 ± 39.4	1.09 (−1.15 to 3.34)	0.34	1.26 (−1.30 to 3.82)	0.33
Late loss, mm						
In-stent	0.18 ± 0.54	0.20 ± 0.99	−0.01 (−0.07 to 0.05)	0.76	0.00 (−0.06 to 0.07)	0.97
In-segment	0.16 ± 0.56	0.18 ± 1.04	0.00 (−0.06 to 0.06)	0.98	0.00 (−0.07 to 0.06)	0.93
Binary restenosis						
In-stent	21 (6.1)	64 (5.4)	0.72 (−1.38 to 2.82)	0.50	1.47 (−2.05 to 4.99)	0.41
In-segment	29 (8.5)	100 (8.5)	0.01 (−4.65 to 4.67)	0.76	0.49 (−5.89 to 6.87)	0.65

Values are mean ± SD or n (%).
Abbreviations as in Tables 2 and 3.

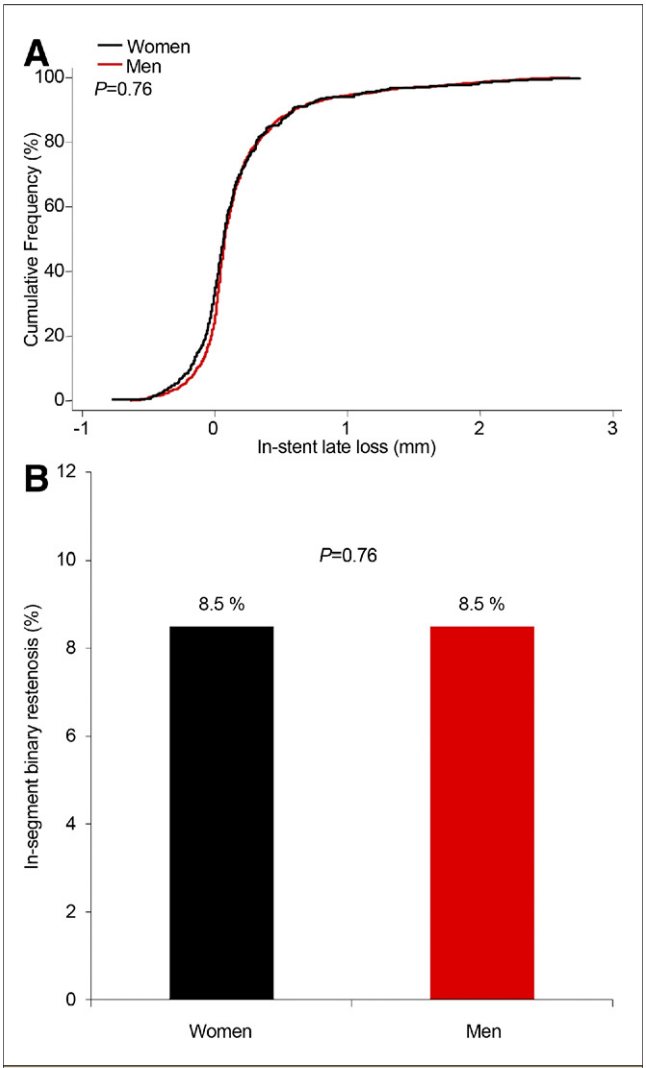

Figure 3. Angiographic Outcomes Among Women and Men

Cumulative frequency of in-stent late loss **(A)** and rates of in-segment binary restenosis **(B)** among women and men at the time of follow-up angiography.

among women and men irrespective of the type of DES used, indicating that DES efficacy is largely independent of patient sex.

Recently, 2 large investigations underscored sex differences in delivery of evidence-based therapies and clinical outcomes among patients with coronary artery disease (25,26). In the present study, women presented with more advanced age and a greater prevalence of diabetes and hypertension, resulting in an overall higher clinical risk profile at baseline. The latter contributed to higher crude event rates among women, which were no longer apparent following adjustment for differences in baseline characteristics. The present study does not address why women present later and have a higher clinical risk profile at the time of revascularization. However, it is notable that the angiographic risk as assessed by the SYNTAX score was lower among female than male patients, suggesting that the extent of coronary artery disease was less severe despite the more unfavorable clinical characteristics.

Study limitations. First, this is an analysis of individual patient data pooled from 3 randomized clinical trials not primarily intended to investigate sex-based differences in outcomes. However, the large number of included patients provides sufficient precision to evaluate differences between women and men in a large spectrum of patients. Second, 5 different types of DES were used for implantation in 3 different studies. However, we analyzed differences by the use of mixed models accounting for the different studies included in the present analysis as well as treatment arms. Moreover, the use of different types of DES provides a certain degree of generalizability of our findings to DES as a class treatment effect. Finally, the angiographic follow-up was not available for all included patients. Nevertheless, the consistency of angiographic results and the correlation with clinical efficacy support our findings of equivalent efficacy of DES in women and men undergoing PCI.

Conclusions

The unrestricted use of DES is associated with similar long-term safety and efficacy among women and men with coronary artery disease requiring revascularization.

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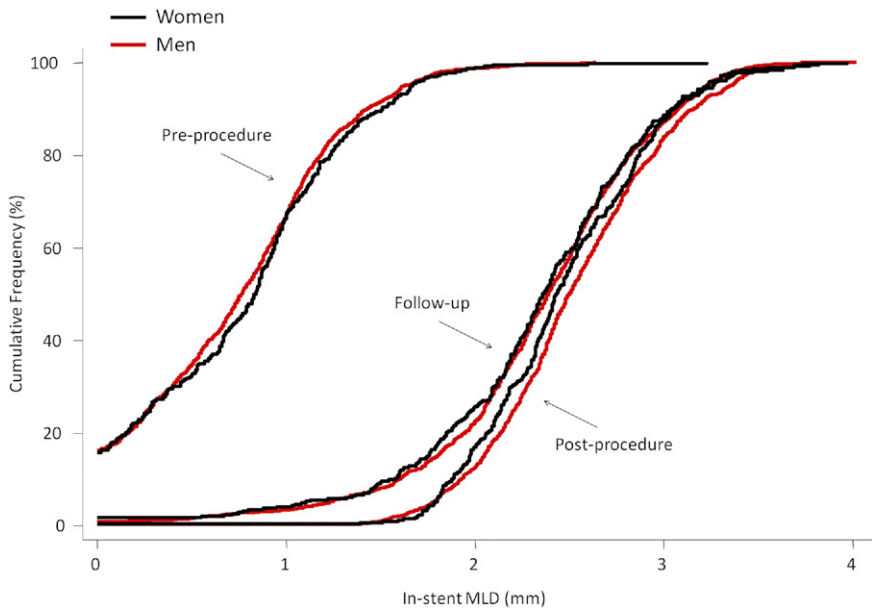

Figure 4. Minimal Lumen Diameter

Cumulative curves of minimal lumen diameter (MLD) at baseline (pre-procedure), immediately after the intervention (post-procedure), and at the time of follow-up angiography (follow-up) among women and men.

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Key Words: coronary artery disease ■ drug-eluting stent(s) ■ restenosis ■ sex disparities ■ women.