JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 9, NO. 6, 2016

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2015.10.043

Sex Difference in Chest Pain After Implantation of Newer Generation Coronary Drug-Eluting Stents

A Patient-Level Pooled Analysis From the TWENTE and DUTCH PEERS Trials

Marlies M. Kok, MD,[a] Liefke C. van der Heijden, MD,[a] Hanim Sen, MD, PhD,[a] Peter W. Danse, MD, PhD,[b] Marije M. Löwik, PhD,[a] Rutger L. Anthonio, MD, PhD,[c] J. (Hans) W. Louwerenburg, MD,[a] Frits H.A.F. de Man, MD, PhD,[a] Gerard C.M. Linssen, MD, PhD,[d] Maarten J. IJzerman, PhD,[e] Carine J.M. Doggen, PhD,[e] Angela H.E.M. Maas, MD, PhD,[f] Roxana Mehran, MD,[g] Clemens von Birgelen, MD, PhD[a,e]

ABSTRACT

OBJECTIVES This study sought to assess sex differences in chest pain after percutaneous coronary intervention (PCI) with newer generation drug-eluting stents (DES).

BACKGROUND Sex-based data on chest pain after PCI with DES are scarce.

METHODS The authors performed a patient-level pooled analysis of the TWENTE and DUTCH PEERS randomized trials, in which patients were treated with newer generation permanent polymer-coated DES. At 1 and 2 years, clinical follow-up was available in 99.8% and patient-reported chest pain data in 94.1% and 93.6%, respectively.

RESULTS Among all 3,202 patients, the 871 (27.2%) women were older (67.5 ± 10.2 years vs. 62.8 ± 10.6 years; $p < 0.001$) and had more cardiovascular risk factors: diabetes (24.2% vs. 17.8%; $p < 0.001$), hypertension (63.6% vs. 51.6%; $p < 0.001$), and positive family history (54.5% vs. 50.1%; $p = 0.03$). At 1- and 2-year follow-up, women reported more clinically relevant chest pain (16.3% vs. 10.5%; $p < 0.001$, and 17.2% vs. 11.1%; $p < 0.001$, respectively). Multivariate analysis demonstrated that female sex independently predicted clinically relevant chest pain at 1- and 2-year follow-up both during daily activities and at minimum physical exertion/at rest (1 year adjusted odds ratio [OR]: 1.7; 95% confidence interval [CI]: 1.2 to 2.4; $p = 0.002$; and adjusted OR: 1.8; 95% CI: 1.3 to 2.5; $p < 0.001$; 2-year adjusted OR: 1.8; 95% CI: 1.3 to 2.6; $p < 0.001$; and adjusted OR: 1.7; 95% CI: 1.3 to 2.3; $p = 0.001$). Nevertheless, the 2-year rates of death, myocardial infarction, revascularization, stent thrombosis, and various composite clinical endpoints were similar for both sexes.

CONCLUSIONS Although the incidence of adverse cardiovascular events was low and similar for both sexes, women showed a statistically significantly higher prevalence of clinically relevant chest pain, which might be largely related to mechanisms other than epicardial coronary obstruction. (J Am Coll Cardiol Intv 2016;9:553–61)

From the [a]Department of Cardiology, Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, the Netherlands; [b]Department of Cardiology, Rijnstate Hospital, Arnhem, the Netherlands; [c]Department of Cardiology, Scheper Hospital, Emmen, the Netherlands; [d]Department of Cardiology, Ziekenhuisgroep Twente, Almelo and Hengelo, the Netherlands; [e]Health Technology and Services Research, MIRA, Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, the Netherlands; [f]Chair of Cardiology for Women, Department of Cardiology, Radboud University Medical Center, Nijmegen, the Netherlands; and [g]The Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai Heart, Mount Sinai Medical Center, New York, New York. The present study was performed without any external funding. The TWENTE and DUTCH PEERS (TWENTE II) randomized trials were supported by equal unrestricted grants from Abbott Vascular and Medtronic, and from Boston Scientific and Medtronic, respectively. Dr. Maas has received honoraria for lectures from Merck Sharp & Dohme and AstraZeneca. Dr. Mehran has received institutional research grant support from The Medicines Company, Bristol-Myers Squibb-Sanofi, Daiichi Sankyo-Lilly, and STENTYS; consulting fees from Abbott Vascular, AstraZeneca, Boston Scientific, Covidien, CSL Behring, Janssen

ABBREVIATIONS AND ACRONYMS

DES = drug-eluting stent(s)

MACE = major adverse cardiac event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

POCE = patient-oriented composite endpoint

TLR = target lesion revascularization

Women with ischemic heart disease have fewer significant stenoses of epicardial coronary arteries than men but more often have chest pain (1,2). Among patients with unstable coronary syndromes, women show, despite a lower prevalence of epicardial obstructions, more electrocardiographic changes, which suggests a higher prevalence of microvascular dysfunction in women than in men (3). This difference in microvascular disease as a mechanism of myocardial ischemia appears to be reflected in the symptoms, which in women more often comprise persistent chest pain and chest pain at rest (4,5). Evaluation of women with symptoms suggestive for myocardial ischemia is hampered by a definition of "typical angina" derived from largely male populations, where exertional components are more reflective of male patterns of presentation (6).

SEE PAGE 562

Since the introduction of the drug-eluting stent (DES) in the clinical arena, little attention has been paid to the assessment of residual symptoms after percutaneous coronary intervention (PCI) such as chest pain, the main trigger of repeat clinical assessment after successful PCI procedures (7), and the potential sex differences thereof. In current clinical practice, many patients are treated with newer generation permanent polymer-coated DES, which have been investigated in comparative stent studies with broad patient populations such as the randomized TWENTE trial (The Real-World Resolute Versus Xience V Drug-Eluting Stent Study in Twente [TWENTE]; NCT01066650) and DUTCH PEERS trial (DUrable Polymer-Based STent CHallenge of Promus Element versus ReSolute Integrity in an All Comers Population [DUTCH PEERS]; NCT01331707) (8,9). In the present patient-level analysis of pooled data from these trials, we assessed potential sex differences in patient-reported chest pain and 2-year adverse clinical events.

METHODS

STUDY POPULATION AND DESIGN. This study assessed a broad and heterogeneous population of 3,202 patients, who participated in the TWENTE and DUTCH PEERS trials and reflect routine clinical practice. The TWENTE and DUTCH PEERS trials were performed in the Netherlands at 4 dedicated PCI centers (Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede; Rijnstate Hospital, Arnhem; Scheper Hospital, Emmen; and Medisch Centrum Alkmaar, Alkmaar) between June 2008 and August 2010, and between November 2010 and May 2012, respectively, and have previously been described in detail elsewhere (8,9).

In brief, the TWENTE and DUTCH PEERS trials were investigator-initiated, patient-blinded, randomized studies in which patients with stable or acute coronary syndromes were enrolled and treated with newer generation permanent polymer-coated DES. In both trials, the majority of patients was treated for complex target lesions and had off-label indications for DES use. After 1:1 randomization, patients in the TWENTE trial (n = 1,391) were treated with the Resolute zotarolimus-eluting stent (Medtronic Vascular, Santa Rosa, California) or the Xience V everolimus-eluting stent (Abbott Vascular, Santa Clara, California). Patients in the DUTCH PEERS trial (n = 1,811) were randomized to treatment with the Resolute Integrity zotarolimus-eluting stent (Medtronic Vascular) or the Promus Element everolimus-eluting stent (Boston Scientific, Natick, Massachusetts). Each of the two randomized, non-inferiority trials reported similar clinical outcomes for the respective zotarolimus-eluting and everolimus-eluting stents (8,9).

The TWENTE and DUTCH PEERS trials complied with the Declaration of Helsinki and were approved by the accredited Medical Ethics Committee Twente and the institutional review boards of all participating centers. All patients provided written informed consent.

CORONARY INTERVENTION AND MEDICAL THERAPY. The interventional procedures were performed according to standard techniques and routine clinical protocols that did not differ between the two trials. Details of the intervention were left at the operator's discretion. Angiographic analysts from Thoraxcentrum Twente performed off-line quantitative

Pharmaceuticals, Maya Medical, Merck, and Regado Biosciences; and serves on the advisory boards of Covidien, Janssen Pharmaceuticals, Merck, Sanofi, and Endothelix, Inc. Dr. von Birgelen has been a consultant to Abbott Vascular, Boston Scientific, and Medtronic; and has received lecture fees from AstraZeneca and Merck Sharp & Dohme; his institution has received research grants, provided by Abbott Vascular, Biotronik, Boston Scientific, Medtronic, and AstraZeneca. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received September 29, 2015; accepted October 22, 2015.

coronary angiographic analyses of all cases according to current standards using the software Qangio XA (versions 7.1 and 7.2; Medis, Leiden, the Netherlands). Medical treatment did not differ between the trials: unfractionated heparin was usually administered as an anticoagulant agent during PCI, and dual antiplatelet therapy, which commonly consisted of aspirin and clopidogrel, was generally prescribed for 12 months. Electrocardiograms and laboratory tests were systematically performed (8,9).

CLINICAL FOLLOW-UP AND EVENT ADJUDICATION. Information on clinical follow-up and chest pain at the 1- and 2-year follow-up was obtained during visits to outpatient clinics or, when in-person contact was not feasible, by telephone and/or medical questionnaire. All patients were asked to indicate, by means of a multiple-choice questionnaire, whether they experienced chest pain and to what extent this chest pain had influenced their daily activity (Online Appendix). For any potential event trigger, members of the study team gathered all clinical information from the referring cardiologist, general practitioner, and/or hospital involved.

The contract research organization Cardio Research Enschede (Enschede, the Netherlands) coordinated the trial and data management. Data monitoring was performed by an independent, external clinical research organization (Diagram, Zwolle, the Netherlands). In both trials, independent clinical research organizations processed the clinical outcome data, and independent external clinical event committees, blinded to the assigned treatment, adjudicated the adverse clinical events (Cardialysis, Rotterdam; and Diagram, Zwolle, the Netherlands).

DEFINITION OF CLINICAL ENDPOINTS. The definitions of all predefined clinical endpoints have previously been described in detail elsewhere (8,9). They were defined according to the Academic Research Consortium, including the addendum on myocardial infarction (10,11). In brief, target vessel failure, the primary endpoint of the TWENTE and DUTCH PEERS trial, is a composite endpoint of cardiac death, target vessel-related myocardial infarction (MI), or clinically indicated target vessel revascularization. Death was considered cardiac unless an unequivocal noncardiac cause could be established. A target vessel-related MI was related to the target vessel or could not be related to another vessel. Target vessel revascularization and target lesion revascularization (TLR) were considered clinically indicated if the angiographic diameter stenosis was ≥70%, or ≥50% in the presence of ischemic signs or symptoms. Stent thrombosis was classified according to the Academic Research Consortium definitions. Predefined secondary endpoints included the components of the primary endpoint, all-cause mortality, any MI, clinically indicated TLR, and stent thrombosis. Other composite parameters were patient-oriented composite endpoint (POCE), a composite of all-cause death, any MI, or any coronary revascularization; target lesion failure, a composite of cardiac death, target vessel-related MI, or clinically indicated TLR; and major adverse cardiac events (MACE), a composite of all-cause death, any MI,

TABLE 1 Characteristics of Patients, Target Lesions, and Interventional Procedures

Patient-Based Data	Women (n = 871)	Men (n = 2,331)	p Value
Age, yrs	67.5 ± 10.2	62.8 ± 10.6	<0.001
Diabetes mellitus (any)	211 (24.2)	414 (17.8)	<0.001
Chronic renal failure before PCI*	22 (2.5)	79 (3.4)	0.21
Requiring dialysis	3 (0.3)	3 (0.1)	0.35
Serum creatinine†	74.0 ± 33.7	87.0 ± 28.2	<0.001
Arterial hypertension	554 (63.6)	1,203 (51.6)	<0.001
Hypercholesterolemia†	451 (52.3)	1,200 (52.0)	0.89
Current smoker	192 (22.0)	592 (25.4)	0.05
Family history of coronary artery disease‡	475 (54.5)	1,168 (50.1)	0.03
Previous myocardial infarction	190 (21.8)	657 (28.2)	<0.001
Previous percutaneous coronary intervention	136 (15.6)	501 (21.5)	<0.001
Previous coronary bypass surgery	66 (7.6)	255 (10.9)	0.005
Clinical syndrome at presentation			0.01
Stable angina pectoris	360 (41.3)	1,063 (45.6)	
Unstable angina pectoris	185 (21.2)	385 (16.5)	
Non-ST-segment elevation myocardial infarction	220 (25.3)	619 (26.6)	
ST-segment elevation myocardial infarction	106 (12.2)	264 (11.3)	
At least 1 small-vessel (RVD <2.75 mm)	551 (63.3)	1391 (59.7)	0.06
At least 1 lesion length >27 mm	150 (17.2)	461 (19.8)	0.10
Multivessel treatment	148 (17.0)	484 (20.8)	0.02
At least 1 chronic total occlusion	50 (5.7)	121 (5.2)	0.54
At least 1 bifurcation	189 (21.7)	638 (27.4)	<0.001
At least 1 in-stent restenosis	37 (4.2)	87 (3.7)	0.50
De novo lesions only‡	766 (87.9)	2055 (88.2)	0.87
Syntax score before PCI	12.4 ± 9.8	14.1 ± 11.0	<0.001
Smallest reference vessel diameter	2.57 ± 0.58	2.64 ± 0.59	0.002
Number of lesions treated per patient			0.05
1	625 (71.8)	1,588 (68.1)	
2	187 (18.4)	579 (24.8)	
≥3	59 (6.8)	164 (7.0)	
Number of stents per patient	1.8 ± 1.1	1.9 ± 1.1	0.17
Worst lesion complexity by ACC/AHA lesion class			0.37
A	42 (4.8)	101 (4.3)	
B1	188 (21.6)	484 (20.8)	
B2	300 (34.4)	754 (32.3)	
C	341 (39.2)	992 (42.6)	
Percent diameter stenosis			
Before PCI	69.2 ± 16.0	69.6 ± 16.7	0.52
After PCI	15.5 ± 7.9	16.1 ± 8.4	0.09

Values are mean ± SD or n (%). *Chronic renal failure defined by serum creatinine level ≥130 μmol/l. †Out of 3,168 patients. ‡Including chronic total occlusion, but not grafts or in-stent restenosis.

ACC/AHA = American College of Cardiology/American Heart Association; PCI = percutaneous coronary intervention; RVD = reference vessel diameter.

TABLE 2 Chest Pain at 1- and 2-Year Follow-Up

Follow-Up Data	Women	Men	p Value	Adjusted OR*	95% CI
1-yr	799	2,149	<0.001		
No clinically relevant chest pain					
Pain score 0–1	670 (83.9)	1,924 (89.5)			
Clinically relevant chest pain					
Pain score 2	57 (7.1)	101 (4.7)		1.7	1.2–2.4
Pain score 3	72 (9.0)	124 (5.8)		1.8	1.3–2.5
2-yr	765	2,117	<0.001		
No clinically relevant chest pain					
Pain score 0–1	634 (82.9)	1,883 (88.9)			
Clinically relevant chest pain					
Pain score 2	61 (8.0)	102 (4.8)		1.8	1.3–2.6
Pain score 3	70 (9.2)	132 (6.2)		1.7	1.3–2.3

Values are n or n (%). Women were set as reference. *Odds ratios are corrected for age, trial, previous percutaneous coronary intervention, previous coronary artery bypass grafting, and clinical syndrome.
CI = confidence interval; OR = odds ratio.

emergent coronary bypass surgery, or clinically indicated TLR.

Patient-reported chest pain was classified into scores: 0 was no chest pain at all; 1 was chest pain only during severe physical exertion; 2 was chest pain at moderate physical effort (during normal daily activities); and 3 was chest pain at mild physical effort or at rest. In analogy with previous reports (12), chest pain with a score of 2 or 3 (i.e., patients who had pain during normal daily activities or at rest) was defined as clinically relevant chest pain. Pain scores 0 to 1 (i.e., patients are free from pain or may experience chest pain only at the very maximum level of physical exertion) were considered as not clinically relevant, as these patients were not limited in their daily activities (12).

STATISTICAL ANALYSIS. Data were reported as frequencies and percentages for dichotomous and categorical variables, whereas continuous variables were expressed as mean ± SD. Differences in dichotomous and categorical variables were assessed using the chi-square and Fisher exact tests, and continuous variables were assessed with the Student *t* test or the Wilcoxon rank sum test, as appropriate. The Kaplan-Meier analysis was used to calculate the time to clinical endpoints, and the log-rank test was applied to compare between-Sex differences. Parameters were considered as potential confounders if associations were found with a $p \leq 0.15$ in univariate analyses. A multivariate Cox regression analysis was used to adjust for potential confounders, accounting for differences in clinical outcome between women and men. Age, trial, diabetes, hypertension, clinical syndrome, multivessel disease, previous MI, previous PCI or coronary artery bypass graft, and positive family history were included in the multivariate analysis. A multivariate logistic regression analysis was used to account for potential confounders in chest pain and sex. All p values and confidence intervals were two-sided, and $p < 0.05$ was considered significant. Data analysis was performed with SPSS (version 22, IBM/SPSS Inc., Chicago, Illinois).

RESULTS

CHARACTERISTICS OF PATIENTS, LESIONS, AND INTERVENTIONS. Among the 3,202 patients enrolled in the TWENTE and DUTCH PEERS trials, there were 871 (27.2%) women and 2,331 (72.8%) men. The women were on average older than the men (67.5 ± 10.2 years vs. 62.8 ± 10.6 years; $p < 0.001$) and had more cardiovascular risk factors such as diabetes mellitus (24.2% vs. 17.8%; $p < 0.01$), arterial hypertension (63.6% vs. 51.6%; $p < 0.001$), or a positive family history of cardiovascular disease (54.5% vs. 50.1%; $p = 0.03$) (Table 1). In addition, the women had less often a history of PCI (15.6% vs. 21.5%; $p < 0.001$) or MI (21.8% vs. 28.2%; $p = 0.001$), and they were less often treated for bifurcated target lesions (21.7% vs. 27.4%; $p < 0.01$) or for lesions in multiple vessels (17.0% vs. 20.8%; $p = 0.02$). In the women, the smallest reference vessel diameter was on average somewhat smaller than in the men (2.57 ± 0.58 mm vs. 2.64 ± 0.59 mm; $p = 0.002$).

SEX AND PATIENT-REPORTED CHEST PAIN. Information on the presence and/or absence of chest pain was provided at the 1-year follow-up by a total of 2,948 patients (94.1% of 3,134 surviving patients) and at the 2-year follow-up by 2,882 patients (93.6% of 3,078 surviving patients). At both times of assessment, the vast majority of women and men were free from chest pain or had chest pain only during maximum physical exertion (i.e., pain scores 0 to 1) (Table 2, Figure 1). At the 1-year follow-up, the women had clinically relevant chest pain more often than the men (score 2: 7.1% vs. 4.7%; score 3: 9.0% vs. 5.8%; $p < 0.001$). At the 2-year follow-up, the prevalence of clinically relevant pain was also higher in women versus men (score 2: 8.0% vs. 4.8%; score 3: 9.2% vs. 6.2%; $p < 0.001$) (Figure 1).

Multivariate analysis demonstrated that sex was an independent predictor of clinically relevant chest pain. At the 1-year follow-up, women showed a 1.7-fold increased risk for having chest pain during normal daily activities (adjusted odds ratio [OR]: 1.7; 95% confidence interval [CI]: 1.2 to 2.4; $p = 0.002$) and a 1.8-fold increased risk for having chest pain at rest (adjusted OR: 1.8; 95% CI: 1.3 to 2.4; $p < 0.001$) (Table 2). At 2-year follow-up, these increased risks

for women were 1.8 (adjusted OR: 1.8; 95% CI: 1.3 to 2.6; $p < 0.001$) and 1.7 (adjusted OR: 1.7; 95% CI: 1.3 to 2.3; $p = 0.001$) respectively.

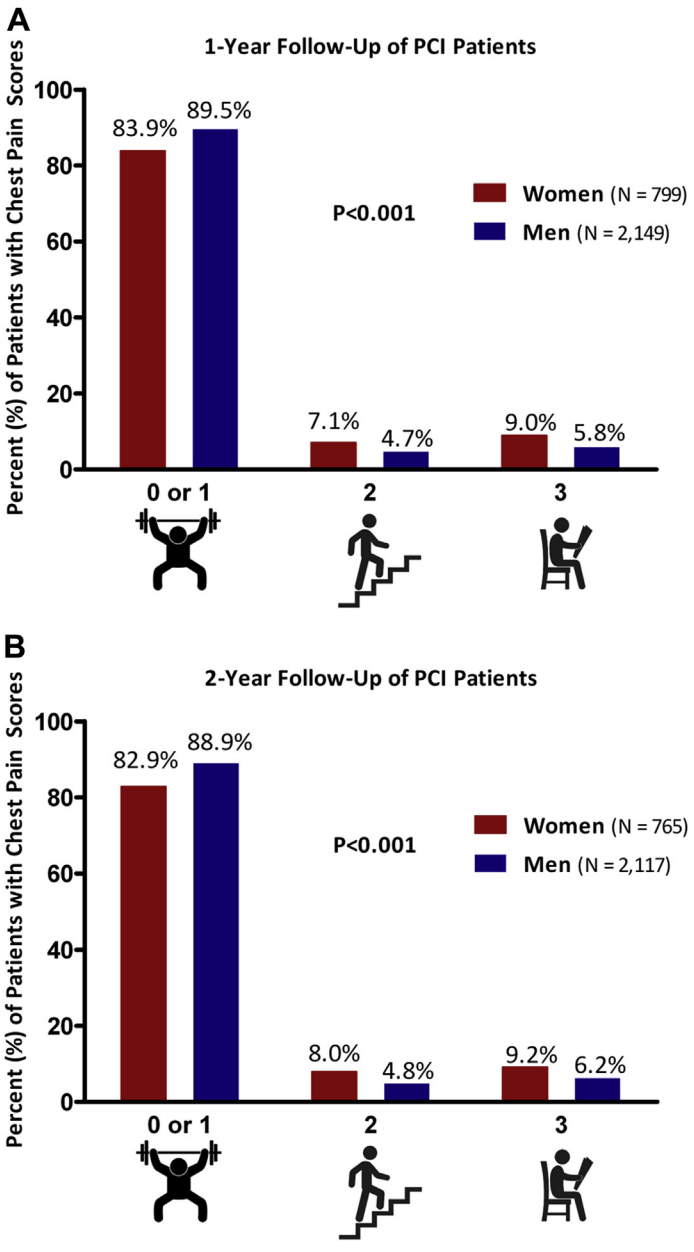
SEX AND CLINICAL EVENTS. The 2-year clinical follow-up data (n = 3,197, 99.8%) were obtained from all but five patients, who withdrew consent. Table 3 presents the clinical event rates for patients of both sexes. In addition, Figure 2 presents the Kaplan-Meier event curves for POCE and its individual components in the women and men. At the 2-year follow-up, the rate of the composite endpoint POCE was similar for women and men (14.8% vs. 14.2%; $p = 0.68$) (Table 3). In addition, for women and men the incidence of the individual components of POCE were similar: any death (4.5% vs. 3.4%; $p = 0.16$), any MI (3.7% vs. 3.9%; $p = 0.72$), and any revascularization (8.5% vs. 8.6%; $p = 0.91$). The 2-year definite stent thrombosis rates were low and did not show a statistically significant sex difference (0.5% vs. 0.8%; $p = 0.34$).

DISCUSSION

After PCI with the implantation of the newer generation DES, statistically significantly more women than men reported clinically relevant chest pain, both at 1-year (16.3% vs. 10.5%) and 2-year follow-up (17.2% vs. 11.1%) evaluations. However, the rates of various composite clinical endpoints, such as POCE and target vessel failure, were similar for both sexes, suggesting that chest pain was partly related to mechanisms other than the obstruction of epicardial coronary arteries. Similar to previous studies (13–15), women in the TWENTE and DUTCH PEERS trials were older and had higher rates of cardiovascular risk factors than men. Arterial hypertension and diabetes, which were more prevalent in women, are known to be associated with more microvascular disease and left ventricular hypertrophy that are related to a more frequent occurrence of chest pain (16). Nevertheless, multivariate analysis demonstrated that female sex was an independent predictor of clinically relevant chest pain at both times of assessment.

CHEST PAIN IN WOMEN. Although significant stenoses of epicardial coronary arteries are less often found in women with coronary atherosclerosis than in men, women more often have chest pain (1,2). Chest pain is considered the key symptom of angina and the main trigger for patients to consult medical professionals after successful PCI (17,18). In women with chest pain after PCI or acute MI, the symptoms are more often persistent and lead more often to office visits and hospitalizations than in men (5,19). In addition, the

FIGURE 1 Chest Pain Score at 1 and 2-Year Follow-Up in Men and Women



Women **(red)** versus men **(blue)** treated with a newer generation permanent polymer-coated drug-eluting stent are compared. Patient-reported chest pain was classified into scores: 0 = no chest pain at all; 1 = chest pain only during most severe physical exertion; 2 = chest pain at moderate physical effort (during moderate/normal daily activities); 3 = chest pain during mild physical exertion or at rest. Pain scores of 2 and 3 are considered clinically relevant. Information about the presence and extent (i.e., pain score) of chest pain at 1-year **(A)** and 2-year **(B)** follow-up in all (surviving) patients who provided chest pain information at the two individual time points (n = 2,948 and 2,882, respectively).

TABLE 3 2-Year Clinical Outcome Between Men and Women

	Women (n = 871)	Men (n = 2,326)	Difference (95% CI)	Adjusted HR* (95% CI)	p Value
Death					
Any cause	39 (4.5)	80 (3.4)	1.0 (−0.4 to 2.5)	1.02 (0.69-1.52)	0.92
Cardiac cause	23 (2.6)	46 (2.0)	0.7 (−0.5 to 1.8)	1.11 (0.66-1.88)	0.69
POCE†	129 (14.8)	331 (14.2)	0.6 (−2.1 to 3.3)	1.02 (0.83-1.26)	0.82
MI					
Any MI	32 (3.7)	92 (3.9)	−0.3 (−1.8 to 1.2)	0.99 (0.66-1.48)	0.95
Target vessel-related MI	30 (3.4)	84 (3.6)	−0.2 (−1.6 to 1.3)	1.00 (0.66-1.52)	0.99
Revascularization					
Any revascularization	74 (8.5)	201 (8.6)	−0.1 (−2.3 to 2.1)	1.07 (0.81-1.40)	0.64
TVR	38 (4.4)	122 (5.2)	−0.9 (−2.6 to 0.8)	0.97 (0.67-1.41)	0.88
TLR	31 (3.6)	87 (3.7)	−0.2 (−1.6 to 1.3)	1.12 (0.74-1.71)	0.59
TVF‡	82 (9.4)	222 (9.5)	−0.1 (−2.4 to 2.2)	1.03 (0.79-1.34)	0.82
TLF§	76 (8.7)	196 (8.4)	0.3 (−1.9 to 2.5)	1.10 (0.85-1.45)	0.44
Major adverse cardiac events‖	91 (10.4)	236 (10.1)	0.3 (−2.0 to 2.7)	1.04 (0.81-1.33)	0.78
Stent thrombosis					
Definite	4 (0.5)	18 (0.8)	−0.3 (−1.0 to 0.3)	0.76 (0.25-2.28)	0.63
Definite or probable	11 (1.3)	27 (1.2)	0.1 (−0.7 to 0.9)	1.19 (0.59-2.41)	0.62

Values are n (%). *HR adjusted for age, clinical syndrome, trial (i.e., TWENTE or DUTCH PEERS), diabetes, hypertension, previous percutaneous coronary intervention or coronary artery bypass grafting, and previous MI using a Cox regression model. †POCE is a composite of all cause death, any MI, or any revascularization. ‡TVF is a composite of cardiac death, target vessel-related MI, or clinically indicated TVR. §TLF is a composite of cardiac death, target vessel-related MI, or clinically indicated TLR. ‖Major adverse cardiac events is a composite of all cause death, any MI, emergent coronary-artery bypass surgery, or clinically indicated TLR.

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; POCE = patient-oriented composite endpoint; TLF = target lesion failure; TLR = target lesion revascularization; TVF = target vessel failure; TVR = target vessel revascularization.

women with chest pain experienced more limitations in their abilities to perform daily activities (5). In women, the presence of chest pain after successful PCI with newer generation DES often does not indicate a failure of interventional treatment. Instead, mechanisms other than epicardial obstruction are more often responsible for the residual chest pain. Microvascular dysfunction, which is known to be more prevalent in women, might account for this sex difference.

Female patients with unstable coronary syndromes show more electrocardiographic changes despite having a lower prevalence of epicardial obstructions than men, which suggests a higher prevalence of microvascular dysfunction in women (3,20). Microvascular disease may result from oxidative stress in the presence of endothelial dysfunction and from microvascular damage as a consequence of aging, arterial hypertension, and inflammatory processes (20). In addition, hormonal changes throughout a woman's life may contribute to the development of microvascular disease (5,21), which is characterized by intimal thickening, medial hyperplasia, hyalinization, and sclerosis (22). The sex-specific differences in patient-reported clinical symptoms reflect the greater role of microvascular disease as a cause of ischemia and persistent chest pain in women (4,5).

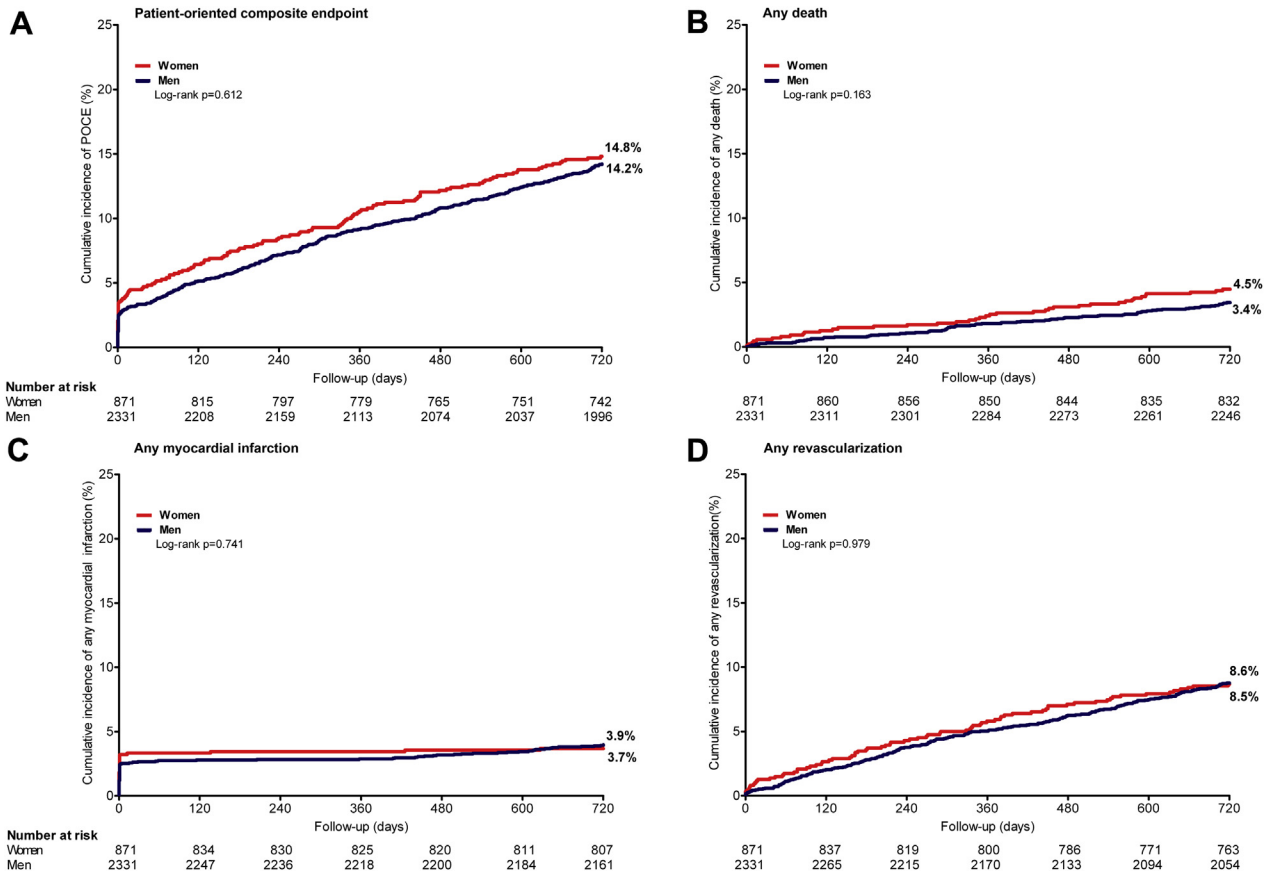
PREVIOUS SEX ANALYSES OF PCI WITH DES. The present study in patients treated with newer generation DES shows clinical event rates that, despite the relatively high patient and lesion complexity, were low and similar in women and men. Although a mechanistic study with intravascular ultrasound assessment of neointimal hyperplasia suggested that women benefit from DES even more than men (23), previous clinical studies on sex-based differences in outcome after PCI (MACE and mortality) reported conflicting results (24–29).

Several large registry studies reported that the rates of MACE and mortality after PCI were higher among women than men, but after adjusting for differences in baseline characteristics these findings lost statistical significance (24–26). Other studies found female sex to be a significant predictor of MACE even after multivariate adjustment for confounders (27). In addition, as women with coronary disease are more likely to present with more vague symptoms than men, studies without systematic long-term follow-up may show false low event rates for women (28).

Sex-based analyses of prospective randomized trials with second-generation DES in broad patient populations have suggested similar clinical outcomes for both sexes (29–31). In addition, a large meta-analysis recently demonstrated that the use of newer generation DES is associated with an improved safety profile as compared with the early DES (32). This was suggested to be related to thinner struts, which are associated with more rapid strut endothelialization and with less vessel wall damage and inflammation (33).

Intravascular ultrasound studies in heart transplant patients demonstrated that coronary arteries are, independent of body size, inherently smaller in women, and such smaller coronary arteries may be associated with an increased risk of subsequent coronary events (34). The smaller vessel size in women has been associated with a higher procedural complexity of PCI, an increased risk of restenosis and recurrent intervention, and with vascular injury (7). However, in the present study, outcome measures did not differ between women and men, which is consistent with several previous DES studies that found a similar procedural success in both sexes (35–37), although with earlier PCI material and devices vascular bleeding complications were increased in women (6).

FIGURE 2 Kaplan-Meier Curves for POCE and Individual Components at 2-Year Follow-Up



Kaplan-Meier cumulative incidence curves for **(A)** the composite endpoint patient-oriented composite endpoint (POCE), a composite of any death, any myocardial infarction, or any revascularization. **(B)** Any death, **(C)** any myocardial infarction, and **(D)** any revascularization for women **(red)** versus men **(blue)** treated with newer generation drug-eluting stent.

The persistence of a metallic stent indefinitely prevents compensatory vascular enlargement in response to positive arterial remodeling and may, in the long-term, impair the function of the endothelium in the treated segment, which may contribute to the recurrence (or persistence) of chest pain after successful PCI (38). The relatively thicker polymer struts of bioresorbable vascular scaffolds show a superior compliance to the dynamics of the vessel wall and cause less vessel stretch than contemporary metallic DES. Finally, these devices permit the return of vasomotion, which might reduce chest pain (39). The data of our present study suggest that when comparing chest pain data from patients treated with contemporary metallic DES versus patients treated with bioresorbable vascular scaffolds, it is very important to take the proportion of female patients into account. In addition, in randomized trials that assess the recurrence of chest pain or angina after PCI, stratification for sex during the process of randomization should be considered as this will guarantee a balanced distribution of sexes between the treatment arms. In addition, when comparing chest pain data of different clinical trials, the proportion of female patients should be taken into account.

STUDY LIMITATIONS. The present analysis of pooled, prospectively collected data from the randomized TWENTE and DUTCH PEERS trials, which used similar trial designs, study procedures (e.g., systematic assessment of cardiac markers), concomitant medications, and clinical endpoints, is a nonpredefined study. The pooled TWENTE and Dutch Peers trial

database was not powered to detect outcome differences between women and men. Although patient characteristics and enrollment rates suggest that both clinical trials assessed patients with complex and diffuse coronary artery disease that reflects routine clinical practice, the event rates in routine daily practice might be somewhat higher. The relatively low rate of residual chest pain after PCI in this study might be the result of the thorough embrace of the principle of ischemia-driven PCI in Dutch hospitals. Nevertheless, the lack of data on both the antianginal medication and the completeness of revascularization represents a limitation of the present study. In addition, in this study no routine angiographic follow-up data or data on stress testing were available, which limits the interpretation of our findings to some extent. The collection of data on ischemia testing and cardiac assessment after PCI by future trials is highly desirable, as such data will provide further insights into the relations between chest pain, sex, and microvascular disease.

We decided not to use a validated questionnaire, such as the Seattle Angina Questionnaire. Such questionnaires require patients to answer a considerable number of questions, which might have had a negative effect on trial adherence and completeness of clinical follow-up (which was 99.8% in this study). In addition, in the ABSORB II study, the results of the angina evaluation on the basis of the Seattle Angina Questionnaire were statistically significantly different from the site-diagnosed angina or chest pain; nevertheless, the latter was considered a clinically valuable parameter (39).

In the present study, no routine angiographic follow-up data or data on stress testing were present, which is why the results should be considered hypothesis generating. Future studies should focus on collecting these data to provide objective evidence on the presence of microvascular disease in relation to the persistence of chest pain in women.

CONCLUSIONS

Although the incidence of adverse cardiovascular events was low and similar for both sexes after PCI with newer generation DES, women showed a statistically significantly higher prevalence of clinically relevant chest pain that might be largely related to mechanisms other than the obstruction of epicardial coronary arteries.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. C. von Birgelen, Thoraxcentrum Twente and University of Twente, Medisch Spectrum Twente, Department of Cardiology, Postbus 50.000, 7500 KA Enschede, the Netherlands. E-mail: c.vonbirgelen@mst.nl.

PERSPECTIVES

WHAT IS KNOWN? Sex-based analyses of prospective randomized trials with second-generation DES in broad patient populations have suggested similar clinical outcomes for both sexes, yet little attention has been paid to the assessment of residual symptoms after PCI.

WHAT IS NEW? Women showed a statistically significantly higher prevalence of clinically relevant chest pain at 1- and 2-year follow-up after PCI, although the incidence of adverse cardiovascular events was low and similar for both women and men.

WHAT IS NEXT? In future randomized clinical trials that assess chest pain or angina, researchers should account for sex differences or (ideally) perform a stratification for sex. In addition, further research on objective evidence of microvascular disease in patients with or without persistence of chest pain after PCI is of interest.

REFERENCES

1. Hemingway H, Langenberg C, Damant J, et al. Prevalence of angina in women versus men. A systematic review and meta-analysis of international variations across 31 countries. Circulation 2008;117:1526–36.

2. Tamis-Holland JE, Lu J, Korytkowski M, et al. Sex differences in presentation and outcome among patients with type 2 diabetes and coronary artery disease treated with contemporary medical therapy with of without prompt revascularizaion. J Am Coll Cardiol 2013;61:1767–76.

3. Mega JL, Hochman JS, Scirica BM, et al. Clinical features and outcomes of women with unstable ischemic heart disease. Observations from metabolic efficiency with ranolazine for less ischemia in non-ST-elevation acute coronary syndromes: Thrombolysis in Myocardial infarction 36 (MERLIN-TIMI 36). Circulation 2010;121:1809–17.

4. Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: an update. Eur Heart J 2014;35:1101–11.

5. Shaw LJ, Bugiardini R, Bairey Merz CN. Women and ischemic heart disease: evolving knowledge. J Am Coll Cardiol 2009;54:1561–75.

6. Douglas PS, Ginsburg GS. The evaluation of chest pain in women. N Engl J Med 1996;16:1311–5.

7. Jaworski R, Jankowska EA, Ponikowski P, et al. Costs of management of patients with coronary artery disease in Poland: the multicenter RECENT study. Pol Arch Med Wewn 2012;122:599–607.

8. von Birgelen C, Basalus MW, Tandjung K, et al. A randomized controlled trial in second-generation zotarolimus-eluting resolute stents versus everolimus-eluting Xience V stents in real-world patients: the TWENTE trial. J Am Coll Cardiol 2012;59:1350–61.

9. von Birgelen C, Sen H, Lam MK, et al. Third-generation zotarolimus-eluting and everolimus-eluting stents in all-comer patients requiring a

percutaneous coronary intervention (DUTCH PEERS): a randomised, single-blind, multicentre, non-inferiority trial. Lancet 2014;383:413–23.

10. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.

11. Vranckx P, Cutlip DE, Mehran R, et al. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. EuroIntervention 2010;5:871–4.

12. Sen H, Lam MK, Löwik MM, et al. Clinical events and patient-reported chest pain in all-comers treated with Resolute Integrity and Promus Element stents: two-year follow-up of the randomized DUTCH PEERS (TWENTE II) trial. J Am Coll Cardiol Intv 2015;8:889–99.

13. Berger JS, Sanborn TA, Sherman W, et al. Influence of sex on in-hospital outcome and long-term survival after contemporary percutaneous coronary intervention. Am Heart J 2006;151:1026–31.

14. Solinas E, Nikolsky E, Lansky AJ, et al. Gender-specific outcomes after sirolimus-eluting stent implantation. J Am Coll Cardiol 2007;50:2111–6.

15. Jacobs AK, Johnston JM, Haviland A, et al. Improved outcomes for women undergoing contemporary percutaneous coronary intervention: a report from the National Heart, Lung, and Blood Institute Dynamic Registry. J Am Coll Cardiol 2002;39:1608–14.

16. Camici PG, Crea F. Coronary microvascular dysfunction. N Engl J Med 2007;356:830–40.

17. Wasfy JH, Strom JB, O'Brien C, et al. Causes of readmission after percutaneous coronary intervention. Circ Cardiovasc Interv 2014;7:97–103.

18. Stone GW. Demonstration of clinical superiority with a bioresorbable vascular scaffold: the ABSORB III + IV Clinical Trial Program. Presented at EuroPCR. May 20, 2014, Paris.

19. Shaw LJ, Bairey Merz CN, Pepine CJ, et al. The economic burden of angina in women with suspected ischemic heart disease: results from the national institutes of health—National Heart, Lung, and Blood Institute–sponsored women's ischemia syndrome evaluation (WISE). Circulation 2006;114:894–904.

20. Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: a changing philosophy. JAMA 2005;293:477–84.

21. Pepine CJ, Kerensky RA, Lambert CR, et al. Some thoughts on the vasculopathy of women with ischemic heart disease. J Am Coll Cardiol 2006;47:30–5.

22. Wong TY, Klein R, Nieto FJ, et al. Retinal microvascular abnormalities and 10-year cardiovascular mortality: a population-based case-control study. Ophthalmology 2003;110:933–40.

23. Nakatani D, Ako J, Tremmel JA, et al. Sex differences in neointimal hyperplasia following endeavor zotarolimus-eluting stent implantation. Am J Cardiol 2011;108:912–7.

24. Peterson ED, Dai D, DeLong ER, et al. Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588, 398 procedures in the National Cardiovascular Data Registry. J Am Coll Cardiol 2010;55:1923–32.

25. Kovacic JC, Mehran R, Karajgikar R, et al. Female gender and mortality after percutaneous coronary intervention: results from a large registry. Catheter Cardiovasc Interv 2012;80:514–21.

26. Fath-Ordoubadi F, Barac Y, Abergel E, et al. Gender impact on prognosis of acute coronary syndrome patients treated with drug-eluting stents. Am J Cardiol 2012;110:636–42.

27. Yu J, Mehran R, Grinfeld L. Sex-based differences in bleeding and long term adverse events after percutaneous coronary intervention for acute myocardial infarction: three year results from the HORIZONS-AMI trial. Catheter Cardiovasc Interv 2015;85:359–68.

28. Ng VG, Lansky AJ, James B, et al. Three-year results of safety and efficacy of the everolimus-eluting coronary stent in women (from the SPIRIT III Randomized Clinical Trial). Am J Cardiol 2011;107:841–8.

29. Tandjung K, Basalus MW, Sen H, et al. Women treated with second-generation zotarolimus-eluting Resolute stents and everolimus-eluting Xience V stents: insights from the gender-stratified, randomized, controlled TWENTE trial. Catheter Cardiovasc Interv 2013;82:396–405.

30. Jacobs AK. The efficacy of drug-eluting stents in women: a window of opportunity. J Am Coll Cardiol Intv 2009;2:611–3.

31. Signh M, Rihal CS, Gersh BJ, et al. Mortality differences between men and women after percutaneous coronary interventions: a 25-year, single centre experience. J Am Coll Cardiol 2008;51:2313–20.

32. Stefanini GG, Baber U, Windecker S, et al. Safety and efficacy of drug-eluting stents in women: a patient-level pooled analysis of randomised trials. Lancet 2013;382:1879–88.

33. Joner M, Nakazawa G, Finn AV, et al. Endothelial cell recovery between comparator polymer-based drug-eluting stents. J Am Coll Cardiol 2008;52:333–42.

34. Herity NA, Lo S, Lee DP, et al. Effect of a change in gender on coronary arterial size: a longitudinal intravascular ultrasound study in transplanted hearts. J Am Coll Cardiol 2003;41:1539–46.

35. Onuma Y, Kukreja N, Daemen J, et al. Impact of sex on 3-year outcome after percutaneous coronary intervention using bare-metal and drug-eluting stents in previously untreated coronary artery disease: insights form the RESEARCH and T-SEARCH Registries. J Am Coll Cardiol Intv 2009;2:603–10.

36. Mikhail GW, Gerber RT, Cox DA, et al. Influence of sex on long-term outcomes after percutaneous coronary intervention with the paclitaxel-eluting coronary stent: results of the "TAXUS Woman" analysis. J Am Coll Cardiol Intv 2010;3:1250–9.

37. Thompson CA, Kaplan AV, Friedman BJ, et al. Gender-based differences of percutaneous coronary intervention in the drug-eluting stent era. Catheter Cardiovasc Interv 2006;67:25–31.

38. Ormiston JA, Serruys PW, Regar E, et al. A bioresorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. Lancet 2008;371:899–907.

39. Serruys PW, Chevalier B, Dudek D, et al. A bioresorbable everolimus-eluting scaffold versus a metallic everolimus-eluting stent for ischaemic heart disease caused by de-novo native coronary artery lesions (ABSORB II): an interim 1-year analysis of clinical and procedural secondary outcomes from a randomised controlled trial. Lancet 2015;385:43–54.

KEY WORDS chest pain, sex analysis, newer generation drug-eluting stent(s), percutaneous coronary intervention, randomized clinical trial, second-generation drug-eluting stent(s)

APPENDIX For supplemental material, please see the online version of this article.