JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 75, NO. 14, 2020

PUBLISHED BY ELSEVIER

Long-Term Outcomes in Women and Men Following Percutaneous Coronary Intervention

Ioanna Kosmidou, MD, PhD,[a,b] Martin B. Leon, MD,[a,b] Yiran Zhang, MS,[a] Patrick W. Serruys, MD, PhD,[c,d] Clemens von Birgelen, MD,[e,f] Pieter C. Smits, MD,[g] Ori Ben-Yehuda, MD,[a,b] Björn Redfors, MD, PhD,[a,b,h] Mahesh V. Madhavan, MD,[a,b] Akiko Maehara, MD,[a,b] Roxana Mehran, MD,[a,i] Gregg W. Stone, MD[a,i]

ABSTRACT

BACKGROUND Studies examining sex-related outcomes following percutaneous coronary intervention (PCI) have reported conflicting results.

OBJECTIVES The purpose of this study was to examine the sex-related risk of 5-year cardiovascular outcomes after PCI.

METHODS The authors pooled patient-level data from 21 randomized PCI trials and assessed the association between sex and major adverse cardiac events (MACE) (cardiac death, myocardial infarction [MI], or ischemia-driven target lesion revascularization [ID-TLR]) as well as its individual components at 5 years.

RESULTS Among 32,877 patients, 9,141 (27.8%) were women. Women were older and had higher body mass index, more frequent hypertension and diabetes, and less frequent history of surgical or percutaneous revascularization compared with men. By angiographic core laboratory analysis, lesions in women had smaller reference vessel diameter and shorter lesion length. At 5 years, women had a higher unadjusted rate of MACE (18.9% vs. 17.7%; p = 0.003), all-cause death (10.4% vs. 8.7%; p = 0.0008), cardiac death (4.9% vs. 4.0%; p = 0.003) and ID-TLR (10.9% vs. 10.2%; p = 0.02) compared with men. By multivariable analysis, female sex was an independent predictor of MACE (hazard ratio [HR:]: 1.14; 95% confidence interval [CI:]: 1.01 to 1.30; p = 0.04) and ID-TLR (HR: 1.23; 95% CI: 1.05 to 1.44; p = 0.009) but not all-cause death (HR: 0.91; 95% CI: 0.75 to 1.09; p = 0.30) or cardiac death (HR: 0.97; 95% CI: 0.73 to 1.29; p = 0.85).

CONCLUSIONS In the present large-scale, individual patient data pooled analysis of contemporary PCI trials, women had a higher risk of MACE and ID-TLR compared with men at 5 years following PCI. (J Am Coll Cardiol 2020;75:1631–40)

From the [a]Clinical Trials Center, Cardiovascular Research Foundation, New York, New York; [b]NewYork-Presbyterian Hospital/Columbia University Medical Center, New York, New York; [c]Imperial College of Science, Technology and Medicine, London, United Kingdom; [d]Department of Cardiology, NUIG, National University of Ireland, Galway, Ireland; [e]Department of Cardiology, Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, the Netherlands; [f]Department of Health Technology and Services Research, Technical Medical Centre, University of Twente, Enschede, the Netherlands; [g]Maasstad Ziekenhuis, Rotterdam, the Netherlands; [h]Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden; and [i]The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York. This investigator-sponsored study was funded in part by Abbott Vascular. The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. Dr. Leon has received institutional grant support from Abbott, Boston Scientific, and Medtronic. Dr. Serruys has served as a consultant to Biosensors, Sinomed, Balton sp, Philips/Volcano, Xeltis, and HeartFlow. Dr. von Birgelen has received institutional research grants from Abbott Vascular, Biotronik, Boston Scientific, and Medtronic. Dr. Smits has received institutional research grants and speaker fees from Abbott Vascular, Terumo, and St. Jude Medical. Dr. Madhavan has been supported by an institutional grant by the National Institutes of Health/National Heart, Lung, and Blood Institute to Columbia University Irving Medical Center (T32 HL007854). Dr. Maehara has received institutional grant support from Boston Scientific and Abbott; has served as a consultant to Boston Scientific and OCT Medical Imaging Inc.; and has received speaker fees from Abbott. Dr. Mehran has received institutional grant support from AstraZeneca, Bayer, Beth Israel Deaconess, Bristol-Myers Squibb, CSL Behring, Daiichi-Sankyo, Boston Scientific, Novartis Pharmaceuticals, and OrbusNeich; has received consulting fees from Medscape, Regeneron Pharmaceuticals (no fee), Sanofi, and Abbott Laboratories (personal fees for speaking engagements); has served as a consultant (paid to the institution) for Abiomed and The Medicines Company (spouse); has served on the Scientific Advisory Board/Advisory Board of PLx Opco Inc./PLx Pharma Inc. and Bristol-Myers Squibb (funding to the institution); has received equity (<1%) from Claret Medical and Elixir Medical; has served on the Executive Committee (paid to

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2020.01.056

ABBREVIATIONS AND ACRONYMS

BMS = bare-metal stents

DES = drug-eluting stents

ID-TLR = ischemia-driven target lesion revascularization

ID-TVR = ischemia-driven target vessel revascularization

IPD = individual patient data

LVEF = left ventricular ejection fraction

MACE = major adverse cardiac events

MI = myocardial infarction

PCI = percutaneous coronary intervention

Advances in percutaneous coronary intervention (PCI), including the introduction of drug-eluting stents (DES), have substantially improved long-term prognosis in patients with obstructive coronary artery disease (CAD) (1). Nevertheless, despite some evidence that utilization of DES has predominantly benefited women (2,3), most studies have yielded conflicting results on long-term sex-related outcomes following PCI (4–15), likely due to small sample sizes, lack of randomization, and use of outdated technologies. Further, whether PCI-related outcomes between women and men vary according to age, race, clinical presentation, or type of stent remains poorly understood. In the present study, we sought to determine the association between sex and 5-year cardiovascular outcomes from a large individual patient data (IPD) pooled data analysis of contemporary PCI trials.

SEE PAGE 1641

TABLE 1 Baseline Characteristics According to Sex

	Women (n = 9,141)	Men (n = 23,736)	p Value
Age, yrs	66.0 ± 11.0	61.4 ± 10.8	<0.0001
Race			
White	89.6 (5,640/6,297)	92.9 (14,945/16,083)	<0.0001
Hispanic or Latino	2.8 (174/6,297)	1.9 (299/16,083)	<0.0001
Asian	1.5 (94/6,297)	1.9 (310/16,083)	0.03
Black or African American	6.2 (389/6,297)	3.3 (529/16,083)	<0.0001
Body mass index, kg/m^2	29.4 ± 6.5	28.8 ± 4.9	<0.0001
Diabetes mellitus	30.4 (2,779/9,130)	22.3 (5,276/23,685)	<0.0001
Insulin-treated	10.8 (990/9,130)	5.7 (1,353/23,685)	<0.0001
Current smoker, ≤30 days	24.7 (2,242/9,068)	29.5 (6,951/23,531)	<0.0001
Hypertension	73.0 (6,666/9,128)	61.2 (14,483/23,673)	<0.0001
Hyperlipidemia	64.1 (5,795/9,045)	62.0 (14,576/23,496)	0.0007
Prior coronary artery bypass grafting	7.2 (661/9,128)	10.2 (2,419/23,667)	<0.0001
Prior PCI	20.8 (1,893/9,085)	25.2 (5,929/23,573)	<0.0001
Prior myocardial infarction	20.3 (1,831/9,035)	26.4 (6,189/23,409)	<0.0001
Left ventricular ejection fraction, %	60.4 ± 11.5	58.1 ± 11.4	<0.0001
<40%	6.3 (220/3,515)	7.5 (662/8,811)	0.01
Clinical presentation			
Acute coronary syndromes	64.2 (5,547/8,646)	64.6 (14,370/22,258)	0.51
STEMI	11.6 (1,060/9,139)	14.1 (3,337/23,735)	<0.0001
NSTEMI	19.5 (1,785/9,139)	21.3 (5,053/23,735)	0.0004
Unstable angina	31.3 (2,702/8,646)	26.9 (5,980/22,258)	<0.0001
Stable coronary artery disease	35.8 (3,099/8,646)	35.4 (7,888/22,258)	0.51
Stable angina	33.8 (2,925/8,646)	32.2 (7,176/22,258)	0.007
Silent ischemia	2.0 (174/8,646)	3.2 (712/22,258)	<0.0001

Values are mean ± SD or % (n/N).

NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

METHODS

STUDY DESIGN AND ENDPOINTS. The present analysis is based on data from 21 randomized trials that enrolled patients with CAD undergoing PCI with bare-metal stents (BMS) or first- or second-generation DES. Patient-level data were pooled into a common database at the Cardiovascular Research Foundation (New York, New York). The individual study design, definitions, and endpoints used within these studies and trial methodology have been previously described (16). Each component study was approved by the institutional review board or ethics committee at each participating center, and all patients signed written informed consent. Adverse events were adjudicated by a clinical events committee in each study. The definitions and adjudicated events from each study were used in the present analysis. The primary clinical endpoint was defined as the composite outcome of cardiac death, myocardial infarction (MI), or ischemia-driven target lesion revascularization (ID-TLR) (major adverse cardiac events [MACE]) at 5 years. ID-TLR was defined as percutaneous or surgical revascularization of a target lesion with a diameter stenosis ≥50% (assessed at angiographic core laboratory) with a positive functional study, ischemic changes on an electrocardiogram, or symptoms referable to the target lesion, or with a diameter stenosis ≥70% in the absence of documented ischemia. Additional secondary endpoints included MACE at 30 days and the individual components of MACE, stent thrombosis, and ischemia-driven target-vessel revascularization (ID-TVR) at 30 days and 5 years. Median follow-up was 1,095 days (interquartile range: 395 to 1,807 days).

STATISTICAL METHODS. For this study, outcomes were analyzed according to sex. Categorical variables were compared by the chi-square test or Fisher exact test, and continuous variables were compared by the

the institution) of Janssen Pharmaceuticals; and has served as a member of the Data Safety Monitoring Board of Watermark Research Partners. Dr. Stone has received speaker or other honoraria from Cook, Terumo, QooL Therapeutics, and Orchestra Biomed; has served as a consultant to Valfix, TherOx, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, and Matrizyme; and has equity/options from Ancora, Qool Therapeutics, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, MedFocus family of funds, and Valfix. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Michelle L. O'Donoghue, MD, served as Guest Editor for this paper.

Manuscript received December 11, 2019; revised manuscript received January 25, 2020, accepted January 31, 2020.

Wilcoxon rank sum test. Event rates were estimated using the Kaplan-Meier method, with stratification by study and comparisons made using the log-rank test. Outcomes were also examined between 0 to 1 and 1 to 5 years. Multivariable Cox proportional hazard regression was used to determine whether sex was an independent predictor of adverse clinical outcomes. Two multivariable models were assessed. The following clinical covariates were included in the first model: sex, age, diabetes mellitus, hypertension, smoking, body mass index (BMI), hyperlipidemia, previous coronary artery bypass grafting or PCI, prior MI, left ventricular ejection fraction (LVEF), clinical presentation, stent type (BMS vs. DES), treated lesion in the left anterior descending artery, and number of treated lesions. The second model (clinical and angiographic) included the above covariates as well as the following angiographic variables: reference vessel diameter (RVD), minimum lumen diameter (MLD), lesion length, pre-procedure TIMI (Thrombolysis In Myocardial Infarction) flow grade 0/1 (vs. 2/3), and any American College of Cardiology (ACC) lesion class C (vs. A or B). For patients with multiple vessels or lesions, the worst TIMI flow grade, smallest MLD and RVD, and longest lesion length were used. As a sensitivity analysis, multiple imputation was used to account for missing data using the fully conditional specification method (17), and 10 imputed datasets were generated. Further analyses landmarked at 1 and 5 years were performed following adjustment for clinical and angiographic characteristics. The relative impact of sex on MACE and ID-TLR at 5 years following covariate adjustment was further tested in pre-defined subgroups according to age (>55 years vs. ≤55 years), race (Caucasian vs. non-Caucasian), clinical presentation (acute coronary syndrome vs. stable angina/silent ischemia), diabetes mellitus, LVEF (>40% vs. ≤40%), BMI (<18.5, 18.5 to 24.9, 25 to 29.9, >30 kg/m^2), and type of stent (BMS vs. first-generation DES vs. second-generation DES). All statistical models included a random effect for study to account for between-study heterogeneity. All p values were 2-sided, and $p < 0.05$ was considered statistically significant. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE AND PROCEDURAL CHARACTERISTICS. The design features of the 21 randomized PCI trials included in the present analysis are shown in Supplemental Table 1. Of 32,877 patients undergoing PCI for obstructive CAD enrolled from 2000 to 2013, 9,141 (27.8%) were women. Baseline characteristics according to sex are shown in **Table 1**. Compared with men, women were older; were less frequently Caucasian; had higher BMI and LVEF; had more frequent history of hypertension, diabetes, and hyperlipidemia; and has less frequent history of smoking, prior MI, and prior percutaneous or surgical revascularization. Women were more commonly treated for stable angina, whereas men more frequently presented with ST-segment elevation or non-ST-segment elevation MI.

Procedural characteristics according to sex are shown in **Table 2**. Compared with men, women had smaller RVD and MLD, had shorter lesion length, and

TABLE 2 Procedural Characteristics According to Sex

	Women (v = 9,125; l = 9,106)	Men (v = 23,683; l = 23,609)	p Value
Pre-procedure			
Reference vessel diameter, mm	2.67 ± 0.60	2.80 ± 0.67	<0.0001
Minimum lumen diameter, mm	0.75 ± 0.44	0.73 ± 0.46	<0.0001
Diameter stenosis, %	72.6 ± 15.8	74.9 ± 15.9	<0.0001
Any occlusion	9.1	11.7	<0.0001
TIMI flow grade 0 or 1	13.1	16.8	<0.0001
Lesion length, mm	16.3 ± 10.8	17.0 ± 11.0	<0.0001
Tortuosity, moderate-severe	6.2	6.6	0.37
Calcification, moderate-severe	30.1	29.9	0.65
ACC class C	35.0	39.4	<0.0001
Lesion location			
Left anterior descending	50.7	50.2	0.45
Right	42.3	41.3	0.12
Left circumflex	28.8	34.3	<0.0001
Left main	1.4	1.7	0.03
Post-procedure			
Number of treated lesions	1.2 ± 0.6	1.3 ± 0.6	<0.0001
1	81.5	79.1	
2	14.8	16.1	
≥3	3.7	4.8	
Total stent length, mm	29.2 ± 20.1	30.7 ± 21.5	<0.0001
Minimum lumen diameter, mm	2.23 ± 0.69	2.32 ± 0.80	<0.0001
Diameter stenosis, %	17.1 ± 10.7	17.3 ± 11.4	0.17
TIMI flow grade 0 or 1	0.5	0.7	0.12
Type of stent			
Bare-metal	17.6	19.6	<0.0001
Drug-eluting	79.3	76.8	<0.0001
First-generation	36.4	36.0	0.44
Sirolimus-eluting	8.5	8.2	0.53
Paclitaxel-eluting	28.0	27.7	0.65
Second-generation	42.8	40.9	0.001
Zotarolimus-eluting	10.4	10.1	0.37
Fast-release	5.6	5.1	0.058
Slow-release	4.8	5.0	0.49
Everolimus-eluting	27.3	25.0	<0.0001
Biolimus-eluting	5.1	5.7	0.03

Values are mean ± SD or %.

ACC = American College of Cardiology; CoCr = cobalt-chromium; l = number of lesions treated; TIMI = Thrombolysis In Myocardial Infarction; v= number of vessels treated.

TABLE 3 Independent Predictors of 5-Year Clinical Outcomes Following Adjustment for Baseline Clinical Characteristics

	HR (95% CI)	p Value
MACE (cardiac death, MI, or ischemia-driven revascularization)		
Female sex (per 5 yrs)	1.18 (1.05–1.34)	0.008
Diabetes mellitus	1.29 (1.13–1.47)	0.0001
Previous CABG/PCI	1.28 (1.11–1.47)	0.0006
Left ventricular ejection fraction (per 1%)	0.99 (0.98–0.99)	<0.0001
Bare-metal stent	1.44 (1.26–1.65)	<0.0001
LAD lesion location	1.27 (1.13–1.42)	<0.0001
Number of treated lesions (per lesion)	1.34 (1.14–1.57)	0.0003
All-cause death		
Female sex	0.92 (0.76–1.10)	0.36
Age (per 5 yrs)	1.07 (1.06–1.09)	<0.0001
Diabetes mellitus	1.65 (1.37–1.99)	<0.0001
Current smoker	1.88 (1.51–2.33)	<0.0001
Hyperlipidemia	0.73 (0.60–0.88)	0.001
Left ventricular ejection fraction (per 1%)	0.97 (0.96–0.98)	<0.0001
Cardiac death		
Female sex	0.98 (0.74–1.29)	0.87
Age (per 5 yrs)	1.06 (1.04–1.07)	<0.0001
Diabetes mellitus	1.73 (1.31–2.28)	0.0001
Current smoker	1.56 (1.12–2.16)	0.008
Body mass index (per 1 kg/m^2)	1.03 (1.00–1.05)	0.02
Left ventricular ejection fraction (per 1%)	0.95 (0.94–0.96)	<0.0001
Acute coronary syndrome	1.50 (1.10–2.03)	0.01
LAD lesion location	1.30 (1.00–1.69)	0.05
Ischemia-driven target lesion revascularization		
Female sex	1.30 (1.11–1.52)	0.0008
Age (per 5 yrs)	0.99 (0.98–1.00)	0.01
Diabetes mellitus	1.42 (1.21–1.66)	<0.0001
Prior myocardial infarction	0.80 (0.66–0.97)	0.03
Previous CABG/PCI	1.41 (1.18–1.67)	0.0001
Bare-metal stent	1.80 (1.53–2.13)	<0.0001
LAD lesion location	1.26 (1.09–1.45)	0.001
Number of treated lesions (per lesion)	1.37 (1.12–1.67)	0.002
Ischemia-driven target vessel revascularization		
Female sex	1.15 (1.01–1.31)	0.04
Age (per 5 yrs)	0.99 (0.99–1.00)	0.02
Diabetes mellitus	1.40 (1.23–1.60)	<0.0001
Previous CABG/PCI	1.45 (1.26–1.67)	<0.0001
Bare-metal stent	1.46 (1.27–1.68)	<0.0001
Number of treated lesions (per lesion)	1.32 (1.10–1.58)	0.003
Myocardial infarction		
Female sex	1.25 (1.02–1.54)	0.03
Current smoker	1.29 (1.04–1.60)	0.02
Prior myocardial infarction	1.37 (1.09–1.74)	0.008
Previous CABG/PCI	1.53 (1.21–1.93)	0.0004
Left ventricular ejection fraction (per 1%)	0.99 (0.98–0.99)	0.0009
LAD lesion location	1.25 (1.04–1.51)	0.02
Number of treated lesions (per lesion)	1.28 (1.02–1.60)	0.04

Continued on the next page

less frequently had TIMI flow grade 0 or 1 in a treated vessel. Second-generation DES were used more frequently in women, whereas BMS deployment was more common in men.

CLINICAL OUTCOMES. At 30 days, women had increased unadjusted rates of MI, ID-TLR and the composite outcome of MACE but similar rates of all-cause and cardiac death and stent thrombosis compared with men (Supplemental Table 2). At 5 years, the unadjusted rates of all-cause death, cardiac death, MACE, and ID-TLR were higher in women compared with men, whereas the rates of MI, ID-TVR, and stent thrombosis did not differ according to sex (Supplemental Table 2). Unadjusted landmark analyses showed that the differences in the 5-year of all-cause death, cardiac death, MACE, and ID-TLR rates between women and men occurred within the first year (Supplemental Figures 1A to 1D). Conversely, women had an increased unadjusted rate of MI within the first year after PCI, whereas MI was more frequent in men after 1 year (Supplemental Figure 1E).

By multivariable analysis adjusting principally for clinical covariates, female sex was an independent predictor of MACE, ID-TLR, ID-TVR, and MI at 5 years, but not of all-cause death, cardiac death, or stent thrombosis (**Table 3**). After accounting for both clinical and angiographic characteristics, female sex remained an independent predictor for MACE (hazard ratio [HR]: 1.14; 95% confidence interval [CI]: 1.01 to 1.30; p = 0.04), ID-TLR (HR: 1.23; 95% CI: 1.05 to 1.44; p = 0.009) and MI (HR: 1.24; 95% CI: 1.01 to 1.53; p = 0.04) but not ID-TVR (**Table 4**, Supplemental Figure 2). Imputation models confirmed female sex as an independent predictor of MACE (HR: 1.09; 95% CI: 1.02 to 1.16; p = 0.009) and ID-TLR (HR: 1.13; 95% CI: 1.04 to 1.24; p = 0.004). In addition, female sex was also an independent predictor of all-cause death when missing values were imputed (Supplemental Table 3). Landmark analyses showed that the adjusted differences in the risk of MACE, ID-TLR, and MI between women and men were observed within the first year (Supplemental Table 4) with a statistically significant interaction between sex and time for MACE (p interaction = 0.005) and ID-TLR (p interaction = 0.04). Unadjusted and adjusted associations between sex and MACE or ID-TLR at 5 years are shown in the **Central Illustration**.

SUBGROUP ANALYSES. In unadjusted analyses, the impact of sex on ID-TLR was consistent on all subgroups, except for age (HR: 1.43; 95% CI: 1.22 to 1.68 vs. HR: 1.04; 95% CI: 1.04 to 1.14 for ≤55 years vs. >55 years; p interaction = 0.009); similarly, the impact of sex on MACE was consistent on all subgroups, except for age (HR: 1.27; 95% CI: 1.11 to 1.45 vs. HR: 1.06; 95% CI: 0.99 to 1.14 for ≤55 years vs. >55 years; p interaction = 0.02). However, the impact of sex on

the adjusted 5-year risk of MACE (Figure 1A) and ID-TLR (Figure 1B) was consistent across pre-specified groups.

DISCUSSION

The major findings from the present IPD pooled analysis, in which the prognostic impact of sex on clinical outcomes was examined in 32,877 patients undergoing PCI in 23 randomized trials, are as follows: 1) compared with men, women had a higher unadjusted rate of the composite outcome of cardiac death, MI, or ID-TLR (MACE); all-cause death; cardiac death; and ID-TLR at 5 years; 2) the higher risk of adverse outcomes in women was predominantly observed within the first year following the index PCI; 3) in adjusted analyses, female sex was an independent predictor of MACE, ID-TLR, and MI but not all-cause death or cardiac death; and 4) in adjusted analyses, the impact of sex on MACE and ID-TLR was similar across pre-specified subgroups.

Prior studies evaluating the impact of sex on PCI-related outcomes have produced disparate results (5,9,11,18–21), contributing to the ongoing debate as to whether CAD management should vary according to sex (21–23). However, few reports have examined long-term sex-based outcomes after PCI, and those that have were largely based on registry or observational data (12,13,24). Similarly, despite rigorous efforts to increase enrollment of women in contemporary clinical trials, women remain underrepresented, as evidenced in the present study, in which only one-fourth of enrolled patients were women. As such, the present IPD analysis from contemporary randomized PCI trials, which enrolled patients across the spectrum of CAD presentations and which utilized a variety of stent platforms, offers a unique opportunity for a comprehensive assessment of both short- and long-term risks associated with sex. Drawn from randomized trials, this dataset is particularly robust given the detailed capture of clinical, angiographic, and procedural characteristics; adjudication of clinical outcomes; and large sample size.

In the present study, women were older and had more extensive comorbidities and different angiographic characteristics compared with men, consistent with previous reports (5,10,25). Notably, women had a lower atherosclerotic disease burden and reduced target lesion complexity compared with men, other than smaller diameter epicardial vessels. Nevertheless, we observed a persistently increased adjusted risk for MACE, MI, as well as ID-TLR and ID-TVR at 5 years in women compared with men. Importantly, in the present study, event rates were adjusted not only for well-established clinical risk factors that frequently vary between men and women, but also for core laboratory–assessed angiographic characteristics that are typically not considered in most meta-analyses or registry-based studies. Even after accounting for these differences, the 5-year ID-TLR and MACE rates were higher in women than men.

Several plausible explanations that may underlie the increased risk of adverse events in women should be considered. First, racial and socioeconomic disparities have been shown to affect clinical outcomes following PCI (5); in the present study, we did not find a significant interaction between race- and sex-related outcomes, although this analysis was limited given the Caucasian predominance of the pooled study population. Second, younger age has been reported as an important factor in sex-related outcomes, implicating a more aggressive atherosclerotic phenotype in young women (7,26). Consistent with these observations and extending the period of observation up to 5 years, we showed that younger age was associated with a higher risk of long-term adverse outcomes in women compared with men; however, the interaction between age and sex was no longer present following adjustment. Third, the low inclusion rate of women in randomized trials (27), as observed in the current pooled analysis, has resulted in device-based techniques being optimized for men. The extent to which procedural factors, such as less rigorous lesion preparation, suboptimal treatment of smaller vessels, or more conservative antithrombotic therapy in women contribute to the worse prognosis in the female population deserves further study. Interestingly, we did not observe any significant interactions on the effect of sex on MACE or ID-TLR according to diabetic status, cardiac function,

TABLE 3 Continued

	HR (95% CI)	p Value
Stent thrombosis		
Female sex	1.34 (0.95–1.88)	0.09
Current smoker	1.43 (1.02–2.03)	0.04
Previous CABG or PCI	1.87 (1.23–2.85)	0.003
Left ventricular ejection fraction (per 1%)	0.98 (0.97–1.00)	0.02

The full list of covariates tested in the main models appears in the Methods section. Covariates not appearing in the table were not statistically significant in the final models.

CABG = coronary artery bypass grafting; CI = confidence interval; HR = hazard ratio; LAD = left anterior descending; MACE = major adverse cardiac events; MI = myocardial infarction; PCI = percutaneous coronary intervention.

TABLE 4 Independent Predictors of 5-Year Clinical Outcomes Following Adjustment for Baseline Clinical and Angiographic Characteristics

	HR (95% CI)	p Value
MACE (cardiac death, MI, or ischemia-driven revascularization)		
Female sex	1.14 (1.01–1.30)	0.04
Diabetes mellitus	1.26 (1.10–1.43)	0.0006
Body mass index (per 1 kg/m^2)	1.01 (1.00–1.02)	0.050
Previous CABG/PCI	1.24 (1.07–1.42)	0.003
Left ventricular ejection fraction (per 1%)	0.99 (0.98–0.99)	<0.0001
Bare-metal stent	1.44 (1.25–1.65)	<0.0001
Left anterior descending lesion location	1.23 (1.09–1.38)	0.0005
Number of treated lesions	1.27 (1.08–1.50)	0.004
Baseline reference vessel diameter (per mm)	0.74 (0.65–0.84)	<0.0001
Total lesion length (per mm)	1.02 (1.01–1.02)	<0.0001
All-cause death		
Female sex	0.91 (0.75–1.09)	0.30
Age (per 5 yrs)	1.07 (1.06–1.09)	<0.0001
Diabetes mellitus	1.64 (1.36–1.98)	<0.0001
Current smoker	1.86 (1.50–2.31)	<0.0001
Hyperlipidemia	0.72 (0.60–0.88)	0.0009
Left ventricular ejection fraction (per 1%)	0.97 (0.96–0.98)	<0.0001
Baseline minimum lumen diameter (per mm)	1.33 (1.01–1.76)	0.05
Cardiac death		
Sex (female vs. male)	0.97 (0.73–1.29)	0.85
Age (per 5 yrs)	1.06 (1.04–1.07)	<0.0001
Diabetes mellitus	1.73 (1.31–2.29)	0.0001
Current smoker	1.57 (1.13–2.18)	0.007
Body mass index (per 1 kg/m^2)	1.03 (1.00–1.05)	0.02
Left ventricular ejection fraction (per 1%)	0.95 (0.94–0.96)	<0.0001
Acute coronary syndrome	1.50 (1.10–2.04)	0.01
Ischemia-driven target lesion revascularization		
Female sex	1.23 (1.05–1.44)	0.009
Age (per 5 yrs)	0.99 (0.98–1.00)	0.02
Diabetes mellitus	1.36 (1.15–1.60)	0.0002
Prior myocardial infarction	0.80 (0.66–0.98)	0.03
Previous CABG/PCI	1.35 (1.13–1.61)	0.0008
Bare-metal stent	1.84 (1.56–2.18)	<0.0001
Left anterior descending lesion location	1.20 (1.04–1.39)	0.01
Number of treated lesions	1.28 (1.04–1.58)	0.02
Baseline reference vessel diameter (per 1 mm)	0.65 (0.56–0.77)	<0.0001
Total lesion length (per 1 mm)	1.02 (1.01–1.03)	<0.0001
Ischemia-driven target vessel revascularization		
Female sex	1.09 (0.95–1.24)	0.22
Age (per 5 yrs)	0.99 (0.99–1.00)	0.02
Diabetes mellitus	1.36 (1.19–1.55)	<0.0001
Previous CABG/PCI	1.38 (1.20–1.59)	<0.0001
Bare-metal stent	1.47 (1.28–1.70)	<0.0001
Number of treated lesions	1.26 (1.05–1.52)	0.01
Baseline reference vessel diameter (per 1 mm)	0.70 (0.61–0.80)	<0.0001
Total lesion length (per 1 mm)	1.01 (1.01–1.02)	0.001
Myocardial infarction		
Female sex	1.24 (1.01–1.53)	0.04
Current smoker	1.30 (1.04–1.61)	0.02
Previous CABG/PCI	1.39 (1.10–1.75)	0.006
Left ventricular ejection fraction (per 1%)	1.50 (1.18–1.90)	0.0009
Left anterior descending lesion location	0.99 (0.98–1.00)	0.002
Total lesion length (per 1 mm)	1.01 (1.00–1.02)	0.02

Continued on the next page

clinical presentation, or type of stent used, further supporting the hypothesis that other confounders adversely affect prognosis in women following PCI.

The difference in 5-year MACE was partially driven by an increased risk of ID-TLR in women compared with men after adjusting for clinical characteristics, suggesting a higher rate of in-stent restenosis and more aggressive lesion progression within the target vessel. Prior reports have yielded conflicting results regarding the sex-related risk of restenosis (7,28–30); increased revascularization rates, both TLR and TVR, have been reported predominantly in younger women compared with men, and differences in angina prevalence resulting in increased rates of surveillance angiography have been suggested as potential causes (10,11). In contrast to prior reports, we specifically assessed ischemia-driven revascularization, minimizing the risk that the increased rates were confounded by oculo-stenotic treatment of nonischemic lesions. Furthermore, the association between female sex and ID-TLR persisted even following adjustment for angiographic confounders, suggesting that unaccounted factors, such as differences in acute lesion gain (25) or intraprocedural and long-term pharmacotherapy, potentially contribute to the increased risk of ID-TLR in women. In contrast, women no longer had an increased risk of ID-TVR following inclusion of pertinent angiographic factors, suggesting that the observed unadjusted differences in non-TLR–related ID-TVR procedures are predominantly related to anatomic variability and likely differences in procedural and postprocedural management rather than sex-related differences in the atherosclerotic substrate. This hypothesis is further supported by the fact that, in the present IPD, the sex-related risk for ID-TLR was confined within the first year following PCI. Finally, we cannot exclude unmeasured biological reasons that may promote intimal hyperplasia in women. Given the correlation between ID-TLR and long-term mortality (16), further exploration of the factors contributing to sex-related differences in ID-TLR is warranted.

Last, the overall unadjusted rate of MI at 5 years did not differ between men and women; nevertheless, a higher risk was noted in women following adjustment, further suggesting that women have an increased susceptibility to ischemic events compared with men (5). Similar to ID-TLR, the increased risk of MI was predominantly observed within the first year following PCI, but not thereafter.

STUDY LIMITATIONS. First, imbalances in baseline clinical and angiographic characteristics were

apparent between men and women; however, these were accounted for in multivariable models. Accounting for missing data in imputed models confirmed the association between female sex and MACE and, in fact, strengthened the conclusion that female sex is a risk factor as the relationship between sex and all-cause death became significant. Second, immediate procedure-related complications, stroke, and bleeding events were not consistently captured and are thus not reported. Third, baseline laboratory data; procedural details, such as lesion preparation and use of intravascular imaging and physiological lesion assessment; and data on pharmacotherapy prescription and adherence were not routinely available from the 21 randomized trials in the present IPD. As such, we cannot exclude a potential effect of these and other unmeasured confounders. Furthermore, whether ID-TLR was driven by worsening symptoms or objective demonstration of ischemia was not available. Thus, whether the frequency or severity of

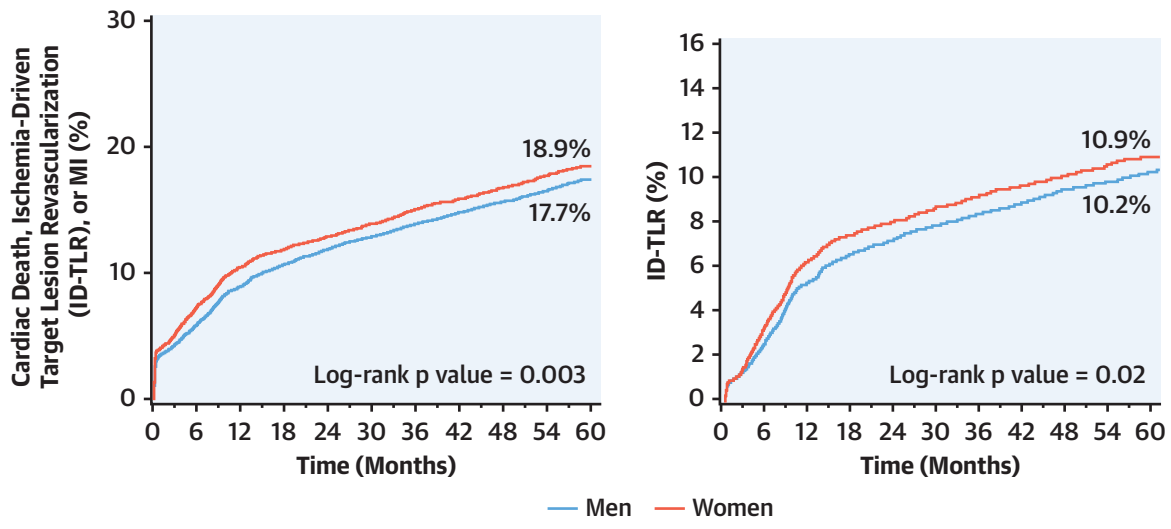
TABLE 4 Continued

	HR (95% CI)	p Value
Stent thrombosis		
Female sex	1.31 (0.92–1.85)	0.13
Current smoker	1.49 (1.05–2.11)	0.02
Previous CABG or PCI	1.86 (1.21–2.84)	0.004
Left ventricular ejection fraction (per 1%)	0.98 (0.97–1.00)	0.02

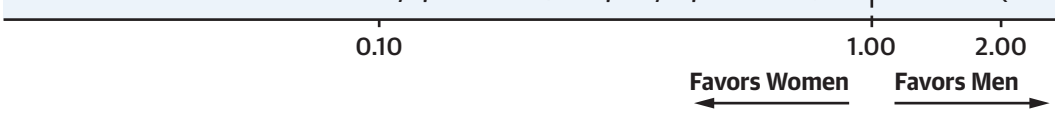
The full list of covariates tested in the main models appears in the Methods section. Covariates not appearing in the table were not statistically significant in the final models.

Abbreviations as in Table 3.

CENTRAL ILLUSTRATION Percutaneous Coronary Interventions and Sex-Related Outcomes at 5 Years



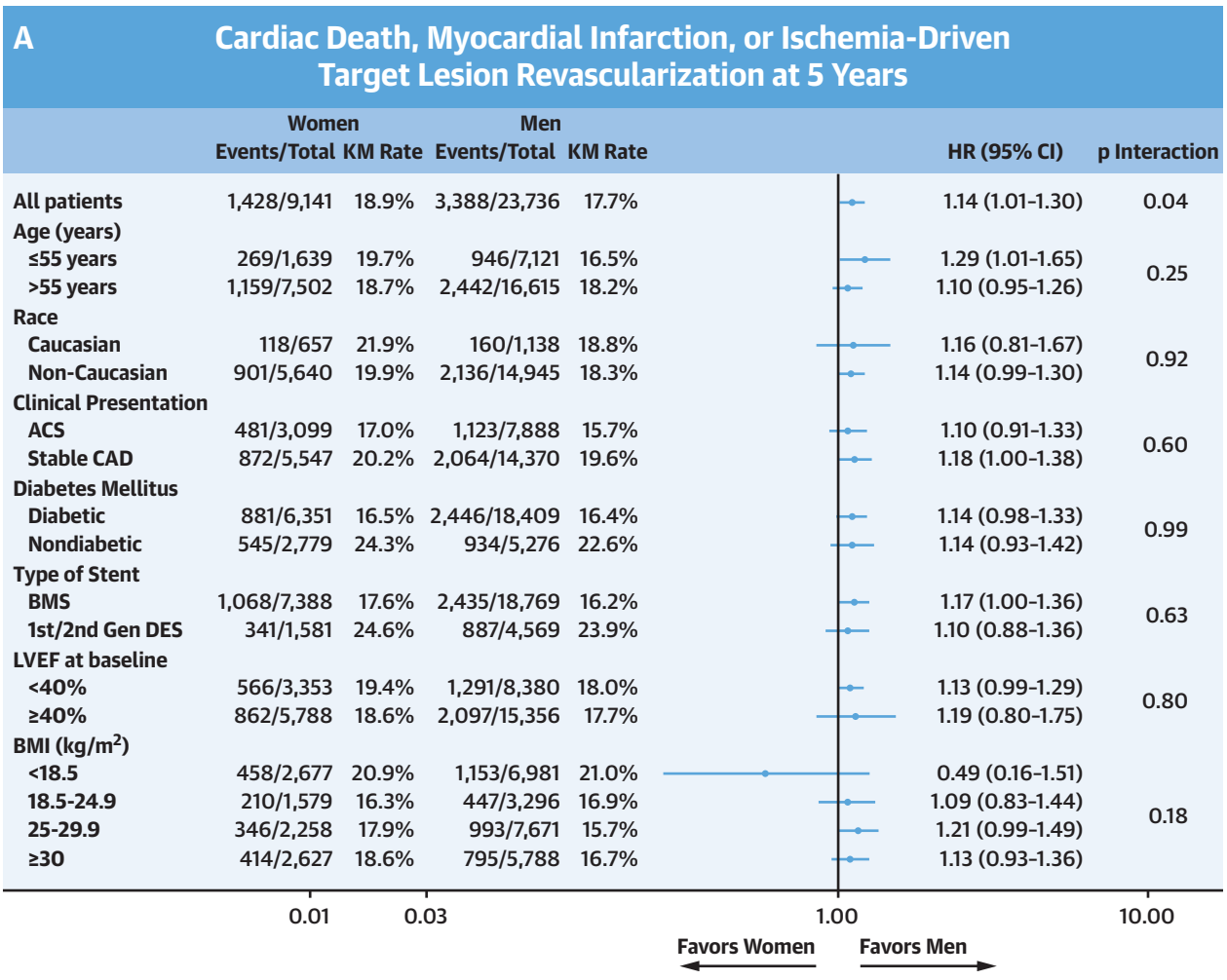
	Women Events/Total	Women KM Rate	Men Events/Total	Men KM Rate	HR (95% CI)	p Value
Cardiac Death, ID-TLR, or MI	1,428/9,141	18.9%	3,388/23,736	17.7%	1.14 (1.01 to 1.30)	0.04
ID-TLR	823/9,141	10.9%	1,946/23,736	10.2%	1.23 (1.05 to 1.44)	0.009



Kosmidou, I. et al. J Am Coll Cardiol. 2020;75(14):1631–40.

Unadjusted **(top panel)** and adjusted **(bottom panel)** outcomes for the primary composite major adverse cardiac events (MACE) endpoint of cardiac death, myocardial infarction (MI), or ischemia-driven target lesion revascularization (ID-TLR) **(upper left graph)** and the endpoint of ID-TLR **(upper right graph)** at 5 years. Women had a higher unadjusted and adjusted risks of MACE and ID-TLR at 5 years following percutaneous coronary intervention, compared with men. CI = confidence interval; HR = hazard ratio; KM = Kaplan-Meier.

FIGURE 1 Adjusted 5-Year Risk for MACE and ID-TLR in Women Versus Men Across Pre-Specified Subgroups

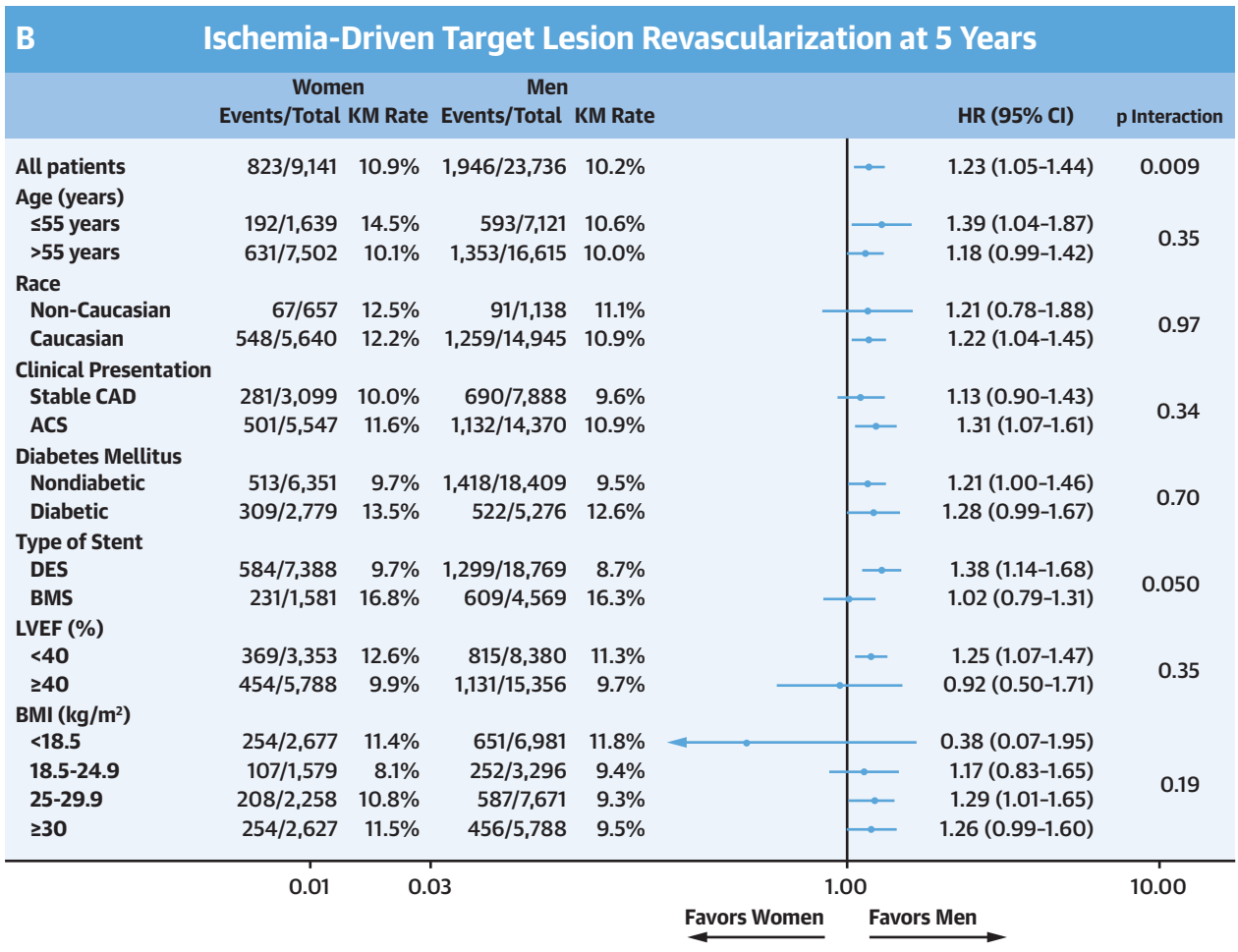


Adjusted subgroup analysis for the **(A)** primary composite major adverse cardiac events (MACE) endpoint of cardiac death, myocardial infarction, or ischemia-driven target lesion revascularization (ID-TLR) and **(B)** the endpoint of ID-TLR at 5 years, according to sex. The impact of sex on MACE and ID-TLR at 5 years was consistent across prespecified subgroups. Data are shown as the number of primary endpoint events per total number of patients in that subgroup and the event rate at 5 years. Event rates were based on Kaplan-Meier (KM) estimates in time-to-first-event analyses. ACS = acute coronary syndrome; BMI = body mass index; BMS = bare-metal stents; CAD = coronary artery disease; CI = confidence interval; DES = drug-eluting stents; HR = hazard ratio; LVEF = left ventricular ejection fraction.

Continued on the next page

recurrent symptoms versus ischemia varied in women versus men could not be addressed in the present study. Fourth, definitions of periprocedural MI varied somewhat across trials, potentially introducing imprecision in the assessment of sex-related MI risk. Finally, as the IPD was drawn from randomized trial datasets, our results are not necessarily generalizable to higher-risk patients who are often excluded from such trials. Finally, spontaneous coronary artery dissection (SCAD) is more common in women than men and may respond poorly to PCI (31,32). Although angiographically evident SCAD would have been excluded from most of the component studies of the present IPD, absent routine imaging, the possibility that a greater frequency of SCAD may have contributed to the higher adverse event rates in women cannot be excluded.

FIGURE 1 Continued



CONCLUSIONS

In the present IPD analysis of 32,877 patients from 21 randomized trials, women had an increased 5-year risk of MACE, ID-TLR, and MI compared with men. Further studies are warranted to address whether sex-specific pharmacological therapies or procedural approaches may improve the long-term prognosis of women undergoing PCI.

ADDRESS FOR CORRESPONDENCE: Dr. Gregg W. Stone, Mount Sinai Medical Center, Cardiovascular Research Foundation, 1700 Broadway, 9th Floor, New York, New York 10019. E-mail: gregg.stone@mountsinai.org. Twitter: @GreggWStone, @Drroxmehran.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: After adjustment for clinical and angiographic characteristics, women face a higher risk of adverse cardiac outcomes than men do following PCI. The heightened risk occurs mainly during the first year post-PCI.

TRANSLATIONAL OUTLOOK: Future studies should assess whether specific factors, such as differences in intraprocedural or post-procedural management or adherence to pharmacotherapy explain the increased risk of adverse outcomes in women.

REFERENCES

1. Palmerini T, Benedetto U, Biondi-Zoccai G, et al. Long-term safety of drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. J Am Coll Cardiol 2015;65:2496–507.

2. Kornowski R, Vaknin-Assa H, Assali A, et al. A comparative analysis of major clinical outcomes with drug-eluting stents versus bare metal stents in male versus female patients. EuroIntervention 2012;7:1051–9.

3. 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.

4. Anderson ML, Peterson ED, Brennan JM, et al. Short- and long-term outcomes of coronary stenting in women versus men: results from the National Cardiovascular Data Registry Centers for Medicare & Medicaid services cohort. Circulation 2012;126:2190–9.

5. Batchelor W, Kandzari DE, Davis S, et al. Outcomes in women and minorities compared with white men 1 year after everolimus-eluting stent implantation: insights and results from the PLATINUM Diversity and PROMUS Element Plus Post-Approval Study Pooled Analysis. JAMA Cardiol 2017;2:1303–13.

6. de Boer SP, Roos-Hesselink JW, van Leeuwen MA, et al. Excess mortality in women compared to men after PCI in STEMI: an analysis of 11,931 patients during 2000-2009. Int J Cardiol 2014;176:456–63.

7. Epps KC, Holper EM, Selzer F, et al. Sex differences in outcomes following percutaneous coronary intervention according to age. Circ Cardiovasc Qual Outcomes 2016;9:S16–25.

8. Giustino G, Baber U, Aquino M, et al. Safety and efficacy of new-generation drug-eluting stents in women undergoing complex percutaneous coronary artery revascularization: from the WIN-DES collaborative patient-level pooled analysis. J Am Coll Cardiol Intv 2016;9:674–84.

9. Glaser R, Selzer F, Jacobs AK, et al. Effect of gender on prognosis following percutaneous coronary intervention for stable angina pectoris and acute coronary syndromes. Am J Cardiol 2006;98:1446–50.

10. Gudnadottir GS, Andersen K, Thrainsdottir IS, James SK, Lagerqvist B, Gudnason T. Gender differences in coronary angiography, subsequent interventions, and outcomes among patients with acute coronary syndromes. Am Heart J 2017;191:65–74.

11. Heer T, Hochadel M, Schmidt K, et al. Sex differences in percutaneous coronary intervention-insights from the Coronary Angiography and PCI Registry of the German Society of Cardiology. J Am Heart Assoc 2017;6:e004972.

12. 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.

13. Kunadian V, Qiu W, Lagerqvist B, et al. Gender differences in outcomes and predictors of all-cause mortality after percutaneous coronary intervention (data from United Kingdom and Sweden). Am J Cardiol 2017;119:210–6.

14. Lichtman JH, Wang Y, Jones SB, et al. Age and sex differences in inhospital complication rates and mortality after percutaneous coronary intervention procedures: evidence from the NCDR. Am Heart J 2014;167:376–83.

15. Pendyala LK, Torguson R, Loh JP, et al. Comparison of adverse outcomes after contemporary percutaneous coronary intervention in women versus men with acute coronary syndrome. Am J Cardiol 2013;111:1092–8.

16. Palmerini T, Della Riva D, Biondi-Zoccai G, et al. mortality following nonemergent, uncomplicated target lesion revascularization after percutaneous coronary intervention: an individual patient data pooled analysis of 21 randomized trials and 32,524 patients. J Am Coll Cardiol Intv 2018;11:892–902.

17. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res 2007;16:219–42.

18. Berger JS, Elliott L, Gallup D, et al. Sex differences in mortality following acute coronary syndromes. JAMA 2009;302:874–82.

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

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

21. 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.

22. Lansky AJ, Hochman JS, Ward PA, et al. Percutaneous coronary intervention and adjunctive pharmacotherapy in women: a statement for healthcare professionals from the American Heart Association. Circulation 2005;111:940–53.

23. Vaccarino V, Badimon L, Corti R, et al. Presentation, management, and outcomes of ischaemic heart disease in women. Nat Rev Cardiol 2013;10:508–18.

24. King KM, Ghali WA, Faris PD, et al. Sex differences in outcomes after cardiac catheterization: effect modification by treatment strategy and time. JAMA 2004;291:1220–5.

25. Lansky AJ, Ng VG, Maehara A, et al. Gender and the extent of coronary atherosclerosis, plaque composition, and clinical outcomes in acute coronary syndromes. J Am Coll Cardiol Img 2012;5:S62–72.

26. Champney KP, Frederick PD, Bueno H, et al. The joint contribution of sex, age and type of myocardial infarction on hospital mortality following acute myocardial infarction. Heart 2009;95:895–9.

27. Coakley M, Fadiran EO, Parrish LJ, Griffith RA, Weiss E, Carter C. Dialogues on diversifying clinical trials: successful strategies for engaging women and minorities in clinical trials. J Womens Health 2012;21:713–6.

28. Lansky AJ, Costa RA, Mooney M, et al. Gender-based outcomes after paclitaxel-eluting stent implantation in patients with coronary artery disease. J Am Coll Cardiol 2005;45:1180–5.

29. Mehilli J, Kastrati A, Bollwein H, et al. Gender and restenosis after coronary artery stenting. Eur Heart J 2003;24:1523–30.

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

31. Hayes SN, Kim ESH, Saw J, et al. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. Circulation 2018;137:e523–57.

32. Tweet MS, Hayes SN, Pitta SR, et al. Clinical features, management, and prognosis of spontaneous coronary artery dissection. Circulation 2012;126:579–88.

KEY WORDS mortality, outcomes, percutaneous coronary intervention, sex

APPENDIX For supplemental tables and figures, please see the online version of this paper.