Relation of Sex and Race to Outcomes in Patients Undergoing Percutaneous Intervention With Drug-Eluting Stents

Micaela Iantorno, MD, MHS, Rebecca Torguson, MPH, Paul Kolm, PhD, Deepakraj Gajanana, MD, William O. Suddath, MD, Toby Rogers, MD, PhD, Nelson L. Bernardo, MD, Itsik Ben-Dor, MD, Jiaxiang Gai, MSPH, Lowell F. Satler, MD, Hector M. Garcia-Garcia, MD, PhD, William S. Weintraub, MD, and Ron Waksman, MD*

Cardiovascular disease is the leading cause of death in men and women, black and white. However, there exists limited outcomes data for women and blacks after percutaneous coronary intervention (PCI). The aim of this study was to evaluate the 1-year major cardiovascular events in patients who underwent PCI based on gender and race. We retrospectively analyzed data that were prospectively collected over 13 years at a large tertiary hospital in the United States. There were 12,050 patients who underwent PCI for both stable disease and acute coronary syndrome from 2003 to 2016. Of those, 1,952 were black men, 6,013 white men, 1,619 black women, and 2,466 white women. Major cardiovascular events at 1 year were assessed, and proportional Cox hazard model analyses were performed to assess outcome adjusted for confounding factors (i.e., age, body mass index, presentation with acute myocardial infarction, diabetes, smoking, history of coronary artery disease, family history of coronary artery disease, hyperlipidemia, hypertension, previous cardiovascular intervention, and chronic kidney disease). At 1 year, white men had significantly lower major cardiovascular events driven by lower rate of death compared with the other groups. Adjusted for confounders, major cardiovascular events were 1.3 to 1.5 times more likely to occur in black men and women and white women than in white men. There was a significant race by gender interaction (p <0.001). **(Am J Cardiol 2019;123:913−918)**

Cardiovascular disease (CVD) is the leading cause of death for men and women, black and white, in the United States[1]; however, the burden of disease is greater in racial/gender minority groups.[2] Blacks have a higher incidence of coronary heart disease, heart failure, stroke, and overall mortality from CVD than whites.[3−7] Despite significant improvements in narrowing the US mortality difference between blacks and whites (death rate disparity declined from 27.6% in 1999 to 22.2% in 2015) and men and women, significant disparities in certain populations and communities remain.[8,9] Such disparities persist after controlling for socioeconomic factors and co-morbidities. Cardiovascular clinical trials include predominantly white men. Furthermore, outcomes from primarily white males have driven guidelines that are not gender/race specific.[10,11] Of interest, a recent pooled analysis from 2 randomized trials investigating 1-year outcomes in 4,182 patients enrolled in 52 US sites after stent implantation found no difference between women and minorities compared with that of white men in terms of major adverse cardiac events (composite of death/myocardial infarction [MI]/target vessel revascularization) after adjustment for cardiovascular risk factors.[12] The purpose of this analysis is to look the impact of sex and race on 1-year outcomes (in terms of major adverse cardiac events [MACE] including death, MI, and any target lesion revascularization [TLR]) comparing blacks and whites/women and men in a real-world retrospective analysis over 13 years in a high-volume tertiary center.

Methods

We prospectively entered clinical, procedural, and follow-up data for patients who underwent percutaneous coronary intervention (PCI) at a large single center. A retrospective analysis of 14,387 consecutive patients who underwent PCI from April 2003 to December 2016 and received 1 drug-eluting stent (DES) or bare-metal stent (BMS) was conducted. Indications for PCI included stable angina pectoris, unstable angina pectoris, and acute MI. The interventional strategy, including the type of stent implanted and anticoagulation regimen, was conducted at the operator discretion. PCI was performed according to guidelines at the time of the procedure. All patients received aspirin 325 mg and a P2Y12 inhibitor (clopidogrel, ticagrelor, or prasugrel) at the operator's discretion before the procedure. Patients were discharged on aspirin and a P2Y12 inhibitor and were encouraged to continue P2Y12 therapy for 12 months. This study was approved by the institutional review board at MedStar Washington Hospital Center and MedStar Health Research Institute

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*Corresponding author: Tel: 202-877-2812; fax: 202-877-2715.
E-mail address: ron.waksman@medstar.net (R. Waksman).

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(Washington, DC). A dedicated data-coordinating center performed all data management and analyses. Prespecified clinical and laboratory data during hospitalization periods were obtained from hospital charts reviewed by independent research personnel blinded to the objectives of the study. Clinical follow-up at 30 days and 1 year was conducted by telephone contact or office visits. The occurrence of major late clinical events was recorded, including death (all-cause) and MI. All clinical events were adjudicated by source documentation of independent cardiologists who were not involved in the procedures. Patients presenting with cardiogenic shock were excluded from the analysis. Due to missing data, the number of subjects included in the analysis was reduced from 14,387 to 12,050. Patients identified themselves as African-American, Asian, Caucasian, or Hispanic and could select only 1 option. Clinical outcomes during the initial hospitalization and at 12 months were assessed. MACE included death, MI, and any TLR. TLR was defined as revascularization occurring in the lesion of the previously treated vessel. Race and gender categories were white males, black males, white females, and black females. Continuous variables are presented as means ± standard deviation, and categorical variables are presented as percentages. Standardized differences (SD) between the largest and smallest values of the race-gender covariates were calculated to indicate the largest difference between pairs of groups. SD of 0.2 indicates about 15% nonoverlap of the 2 distributions, 0.3 indicates about 23% nonoverlap, and 0.5 indicates about 33% nonoverlap. SD over 0.2 is considered meaningful. Multivariable proportional hazards regression models were used to compare race and gender categories adjusted for age, body mass index (BMI), presentation with acute MI, diabetes, smoking, history of coronary artery disease (CAD), family history of CAD, hyperlipidemia, hypertension, previous cardiovascular intervention, and chronic kidney disease (CKD) with respect to the MACE composite of death, MI, or TLR at 1-year postprocedure. Data were also adjusted for type of stent (bare-metal stent, or 1st-generation or 2nd-generation DES). Proportional hazards were assessed with Schoenfeld residuals. The models examined the race by gender interaction. The hazard distribution was modeled with Cox regression as exponentially and Weibull distributed.[13] The choice of models was determined by Akaike's and Bayesian information criteria (AIC, BIC).[14] Based on the model selected, hazard ratios (HR) were estimated for each race-gender category adjusted for the covariates. Adjusted, model-derived cumulative incidence curves were plotted for each race-gender group. Statistical analyses were performed using Stata (Version 15, College Station, TX).

Results

There were a total of 12,050 patients who underwent PCI from 2003 to 2016 with valid covariate and follow up data. Of those, 1,952 were black men, 6,013 white men, 1,619 black women, and 2,466 white women. Table 1 presents demographic and clinical characteristics for each group. White women were, on average, more than 3 years older than the other groups, whereas black women had, on average, higher BMI values. A greater percentage of blacks had experienced acute MI, a greater percentage had diabetes and CKD, particularly black women, and a greater percentage smoked compared with whites. A greater percentage of whites had a family history of CAD. Procedural characteristics are described in Table 2. There was no difference in the groups in terms of target vessel that was revascularized. Procedural length and success were similar in the 4 groups. There was no significant difference in the rate of bleeding in the groups. There was no significant difference in antiplatelet regimen at discharge. White men and women were more likely to receive a DES.

Table 3 presents the distribution of individual events and the composite at 30 days and 1 year, respectively. At 30 days and 1 year, MACE (composite of death/MI and TLR) was significantly lower in white men compared with the other groups, driven by a significantly lower death rate. There was a significant lower rate of MI in whites compared with blacks, with no gender differences. At 1 year,

Table 1
Demographic and clinical characteristics of the patient population

Variable	Black men (n = 1,952)	White men (n = 6,013)	Black women (n = 1,619)	White women (n = 2,466)	Standardized difference
Age (years)	62.9 ± 11.5	65.4 ± 11.3	65.0 ± 12.1	68.8 ± 11.9	0.520
Body mass index (kg/m^2)	29.7 ± 6.3	29.4 ± 5.5	32.2 ± 7.9	29.8 ± 7.4	0.411
Acute myocardial infarction	560 (28.7%)	1119 (18.6%)	389 (24.0%)	463 (18.8%)	0.239
Diabetes	801 (41.0 %)	1748 (29.1%)	862 (53.2%)	892 (36.2%)	0.507
Any smoking	1122 (57.5%)	3417 (56.8%)	707 (43.7%)	1142 (46.3%)	0.279
Hx coronary artery disease	694 (35.6%)	2511 (41.8%)	552 (34.1%)	883 (35.8%)	0.158
Family Hx coronary artery disease	682 (34.9%)	2888 (48.0%)	619 (38.2%)	1351 (54.8%)	0.407
Hyperlipidemia	1571 (80.5%)	5218 (86.8%)	1316 (81.3%)	2137 (86.7%)	0.171
Hypertension	1720 (88.1%)	4935 (82.1%)	1504 (92.9%)	2157 (87.5%)	0.327
Prior coronary artery bypass graft	280 (14.3%)	1260 (20.9%)	215 (13.3%)	350 (14.2%)	0.205
Prior percutaneous coronary intervention	423 (21.7%)	1551 (25.8%)	333 (20.6%)	546 (22.1%)	0.124
Chronic kidney disease	301 (15.4%)	520 (8.6%)	362 (22.4%)	332 (13.5%)	0.386

CAD = coronary artery disease; CABG = coronary artery bypass graft; CKD = chronic kidney disease; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Data are mean ± standard deviation for continuous variables; n (%) for categorical variables.

Table 2
Procedural characteristics and hospital stay

	Black men (n = 1,950)	White men (n = 6,013)	Black women (n = 1,619)	White women (n = 2,466)	Standardized difference
Target vessel					
Left main artery	36 (1.8%)	213 (3.5%)	30 (1.8%)	87 (4.1%)	0.105
Right coronary artery	680 (34.9%)	2077 (34.6%)	627 (38.7%)	905 (36.8%)	0.086
Left anterior descending artery	831 (42.6%)	2740 (45.6%)	690 (42.6%)	1244 (50.5%)	0.159
Left circumflex artery	687 (35.2%)	1842 (30%)	490 (30.3%)	683 (27.4%)	0.162
Proc length (min)	65.5 ± 44.1 (n = 1930)	64.9 ± 38.4 (n = 5923)	62.6 ± 36.0 (n =1592)	61.9 ± 35.8 (n = 2430)	0.079
Clinical success	1862 (95.%)	5862 (97.5%)	1552 (95.9%)	2355 (95.8%)	0.091
Bare-metal stent	609 (31.2%)	1630 (27.1%)	456 (28.1%)	711 (28.8%)	0.101
1st gen drug-eluting stent	1011 (51.8%)	4448 (74%)	953 (58.5%)	1868 (75.7%)	0.297
2nd gen drug-eluting stent	1033 (53%)	2560 (42.6%)	803 (49.6%)	962 (39%)	0.252
Length of stay (days)	3.5 ± 4.1 (n = 1,947)	2.4 ± 3.2 (n = 6,002)	3.8 ± 4.4 (n = 1,612)	3.0 ± 4.0 (n = 2,458)	0.370
Major bleeding	40 (2.0%)	111 (1.8%)	33 (2.0%)	42 (1.7%)	0.025
Arteriovenous fistula	3 (0.2%)	12 (0.2%)	10 (0.6%)	10 (0.4%)	0.075
Major hematoma	1 (0.1%)	11 (0.2%)	5 (0.3%)	10 (0.4%)	0.074
Discharge meds					
ASA	1908 (95.7%)	5950 (97.0%)	1581 (94.9%)	2416 (95.2%)	0.107
Clopidogrel	1909 (85.8%)	5946 (88.9%)	1585 (88.5%)	2415 (90.8%)	0.155
Prasugrel	1843 (6.0%)	5777 (5.1%)	1533 (4.3%)	2340 (4.1%)	0.085
Ticagrelor	1843 (5.9%)	5777 (4.5%)	1533 (4.9%)	2340 (3.1%)	0.135

AVF = arteriovenous fistula; BMS = bare-metal stent; DES = drug-eluting stent; LAD = left anterior descending artery; LCX = left circumflex artery; LM = left main artery; LOS = length of stay; RCA = right coronary artery.

Data are mean ± 1 standard deviation for continuous variables; n (%) for categorical variables.

white men had significantly lower MACE, driven by a lower rate of death compared with the other groups. Whites had a lower rate of MI compared with blacks. The number of individual events was greater than the composite because 30 patients had multiple events. All of these 30 eventually died but had an MI or TLR or both first. Six patients had TLR (but no MI) before death, 11 had MI (but no TLR) before death, and 13 had both MI and TLR before death. The hazard function was modeled as a Weibull distribution, as it provided the best fit to the data with the lowest AIC (12,983.026 compared with exponential AIC = 13,586.87 and Cox AIC = 23,300.95). Adjusted for the covariates, there was a significant race by gender interaction, indicating that the hazard functions were not the same for all groups ($p < 0.001$). Figure 1 represents the HR, 95% confidence intervals, and p values for the Weibull model. The composite event was about 1.3 to 1.5 times more likely to occur in black men and women and white women than

Table 3
Outcomes at 30 days and 1 year

Outcomes at 30 days						
Outcome	Black men (n = 1,952)	White men (n = 6,013)	Black women (n = 1,619)	White women (n = 2,466)	p value	Differences
Major adverse cardiovascular events	93 (4.8%)	139 (2.3%)	71 (4.4%)	100 (4.1%)	<0.001	White men < all others
Target lesion revascularization	17 (0.9%)	30 (0.5%)	17 (1.0%)	18 (0.7%)	0.062	NS
Myocardial infarction	17 (0.9%)	17 (0.3%)	14 (0.9%)	11 (0.4%)	0.001	White < Black
Death	70 (3.6%)	102 (1.7%)	53 (3.3%)	79 (3.2%)	<0.001	White men < all others
Unadjusted outcomes at 1 year						
Outcome	Black men (n = 1952)	White men (n = 6,013)	Black women (n = 1,619)	White women (n = 2,466)	p value	Differences
Death	156 (8.0%)	284 (4.7%)	133 (8.2%)	212 (8.6%)	< 0.001	White men < all others
Myocardial infarction	71 (3.6%)	91 (1.5%)	54 (3.3%)	42 (1.7%)	< 0.001	White < Black
Target lesion revascularization	98 (5.0%)	233 (3.9%)	87 (5.4%)	111 (4.5%)	0.024	White men < Black
Major adverse cardiovascular events	289 (14.8%)	567 (9.4%)	241 (14.9%)	336 (13.6%)	< 0.001	White men < all others

Data are n (%) where the percent is of the number of individual patients in each race/gender category.

MACE: major adverse cardiovascular events; MI: myocardial infarction; TLR: target lesion revascularization; WM: White men.

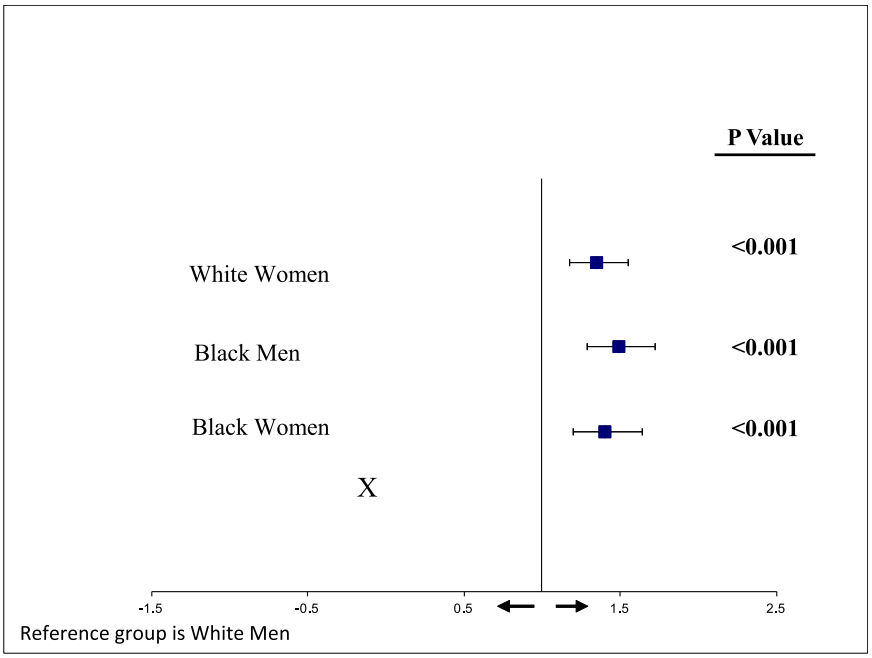

Figure 1. Hazard ratios and 95% confidence intervals from multivariable analysis. MACE
White women, black men and black women all had higher MACE rates than white men. MACE rates did not differ between white women, black men and black women (all p >0.1).

white men after categories were adjusted for age, BMI, presentation with acute MI, diabetes, smoking, history of CAD, family history of CAD, hyperlipidemia, hypertension, previous cardiovascular intervention and CKD. When looking at outcomes based on presentation with stable angina versus unstable angina/acute MI, we noted similar outcomes in the 4 groups when presenting with stable angina and worse outcomes in black women and men and white women compared with white men (p = 0.014), indicating that presentation with acute coronary syndrome was associated with worse outcomes, especially in black men and women and white women. Figure 2 presents the adjusted cumulative hazard for each race-gender category. White men had a significantly lower hazard rate than the other race-gender groups with a curve divergence that appears pretty early on time and continue to expand over the 12-month follow-up. However, none of the other groups, black men, black women and white women, were significantly different from each other with respect to hazard rates (p >0.1 for all comparisons). On average, the 1-year hazard rate for white men was 2.5% compared with 4.1% for blacks, both men and women, and 3.7% for white women. Including type of stent in the multivariable model did not have a significant effect on the hazard for males/females (p = 0.244) or race (p = 0.620). Independently, 2nd-generation DES reduced the hazard of MACE by 20% (HR = 0.805, 95% confidence interval = 0.693 to 0.936, p = 0.005).

Discussion

Our main finding was increased MACE, mainly driven by mortality, in black men and women and white women compared with white men after adjusting for baseline differences, with significant interaction of race and gender. Disparities are complex and include a variety of factors, including socioeconomic differences, income, health insurance, site of care, education on prevention, prevalence of cardiometabolic risk factors, prevention behavior, medication adherence compliance, response to medications, and rate of hospitalizations, as well as genetic background.[15,16] Blacks, both men and women, have been reported to have a higher incidence of coronary heart disease, heart failure, stroke, and overall mortality for CVD than whites.[3] Although, we also found a higher prevalence of co-morbidities in blacks, the increased mortality/MACE remains significantly increased in both black men and women, but also white women, after adjusting for baseline differences. The reasons for this are uncertain but probably multifactorial and may also relate to socioeconomic differences. Access to care and atypical clinical presentation might also play a significant role in worse outcomes, especially in women. Despite significant improvements, narrowing the US mortality difference between blacks and whites (death-rate disparity declined from 27.6% in 1999 to 22.2% in 2015), significant disparities in certain populations and communities remain.[9] Such disparities include not only the prevalence of cardiovascular risk factors but also hospitalization rate, coronary intervention procedures, cardiovascular medical therapy, and mortality.[17] A systematic review of published trials found a significant under-representation of women and minorities in randomized controlled trials.[15] Interestingly, a recently published pooled analysis of 2 prospective, multicenter, observational studies collected PCI outcomes in women and minorities compared with white men and showed comparable adjusted risks of 1-year MACE and

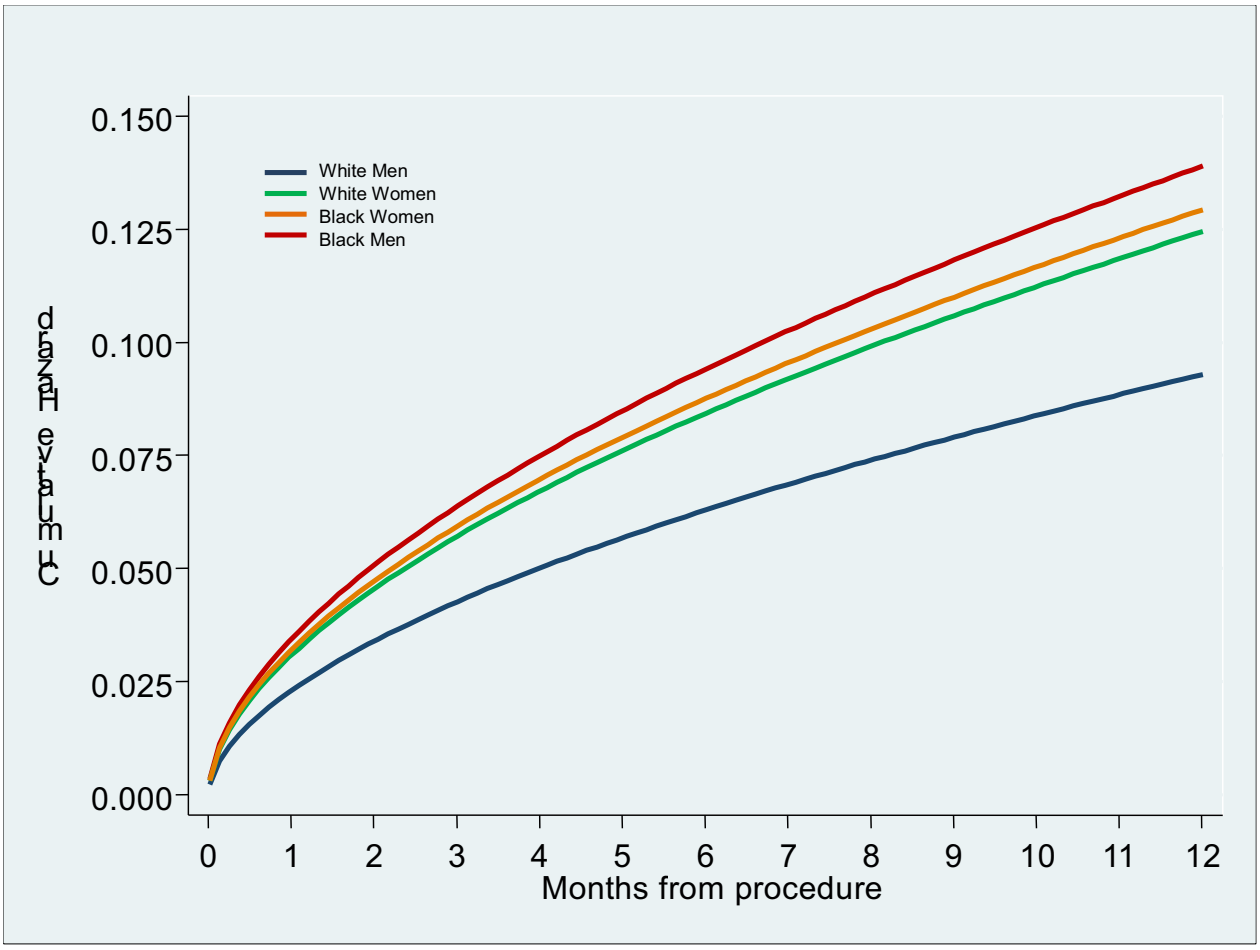

Figure 2. Adjusted cumulative hazard functions for black men, black women, white women, and white men.

death supporting the concept of improvement in cardiovascular care of women and minorities in the era of 2nd-generation DES.[12] However, data from this analysis might carry the risk of selection bias and observer expectancy bias. In our "real-world analysis," whereas 2nd-generation DES decreased the hazard of MACE by 20%, it did not affect the disparity compared with white men. Our data include all-comers (excluding only patients presenting with cardiogenic shock), in a real-world analysis of a large tertiary center in the District of Columbia area over the course of 13 years in the DES era. In our cohort, white and black women were older and black women had more co-morbidites, suggesting later presentation that might have affected outcomes. Black men had a higher chance to present with an acute MI, indicating lack of preventive cardiovascular care in this population. One of the reasons might be related to the use of clopidogrel in the majority of our cohort. Previous studies have demonstrated that carriers of a reduced-function CYP2C19 allele have significantly lower levels of the active metabolite of clopidogrel, diminished platelet inhibition, and an increased rate of cardiovascular events.[18,19] Homozygosity for loss of function for the CYP2C19*2 has been seen in 2% of whites, 4% of blacks, and 14% of East Asians.[20] Heterozygosity for CYP2C19*2 was described in 30% of whites, 40% of blacks, and up to 50% of East Asians and 18% in Mexican-Americans.[21,22] This study was a retrospective analysis and is therefore prone to the shortcomings of any retrospective study; however, the observational real-world data do not carry the risk of uncertain generalizability of clinical trials. Furthermore, any confounding variables not represented in the model could potentially affect outcomes. Race was self-reported, which is the preferred method in federal guidelines. Our study reported race in mutually exclusive categories and might not account for patients who may identify with more than 1 race or ethnicity. Finally, we had no data for socioeconomic status. In summary, we found significant disparities related to both race and gender in outcomes after PCI in our large cohort. Efforts are needed to identify and better characterize the factors underlying and contributing to racial and gender disparities in the era of personalized medicine.

Disclosures

Toby Rogers: Consultant: Medtronic; Proctor: Edwards Lifesciences.

Nelson L. Bernardo: Conducts training for Cook Medical; Speakers Bureau for Medtronic.

Ron Waksman: Advisory Board: Abbott Vascular, Amgen, Boston Scientific, Medtronic, Philips Volcano, Pi-Cardia Ltd., Cardioset; Consultant: Abbott Vascular, Amgen, Biosensors, Biotronik, Boston Scientific, Medtronic, Philips Volcano, Pi-Cardia Ltd., Cardioset; Grant **Support:** Abbott Vascular, AstraZeneca, Bio sensors, Biotronik, Boston Scientific, Chiesi; Speakers Bureau: AstraZeneca, Chiesi; Investor: MedAlliance.

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