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EDITORIAL COMMENT: Expert Article Analysis for:
Gender disparities in high-risk angioplasty: Still room for improvement

Sex-related difference in the use of percutaneous left ventricular assist device in patients undergoing complex high-risk percutaneous coronary intervention: Insight from the cVAD registry

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Abstract

Objective: To assess the in-hospital and short-term outcome differences between males and females who underwent high-risk PCI with mechanical circulatory support (MCS).

Background: Sex differences have been noted in several percutaneous coronary intervention (PCI) series with females less likely to be referred for PCI due increased risk of adverse events. However, data on sex differences in utilization and outcomes of high-risk PCI with MCS is scarce.

Methods: Using the cVAD Registry, we identified 1,053 high-risk patients who underwent PCI with MCS using Impella 2.5 or Impella CP. Patients with cardiogenic shock were excluded. A total of 792 (75.21%) males and 261 (24.79%) females were included in the analysis with median follow-up of 81.5 days.

Results: Females were more likely to be African American, older (72.05 ± 11.66 vs. 68.87 ± 11.17, $p < .001$), have a higher prevalence of diabetes (59.30 vs. 49.04%, $p = .005$), renal insufficiency (35.41 vs. 27.39%, $p = .018$), and peripheral vascular disease (31.89 vs. 25.39%, p of .05). Women had a higher mean STS score (8.21 ± 8.21 vs. 5.04 ± 5.97, $p < .001$) and lower cardiac output on presentation (3.64 ± 1.30 vs. 4.63 ± 1.49, $p < .001$). Although women had more comorbidities, there was no difference in in-hospital mortality, stroke, MI or need for recurrent revascularization compared to males. Females were more likely to have multivessel revascularization than males. Ejection fraction improved in both males and females at the time of discharge (26.59 to 31.40% and 30.75 to 36.05%, respectively, $p < .0001$). However,

Abbreviations: AKI, acute kidney injury; BSA, body surface area; CHIP, complex high-risk indicated patients; CT scan, computed tomography scan; cVAD registry, catheter based ventricular assist device registry; MACCE, major adverse cardiovascular and cerebrovascular events; MCS, mechanical circulatory support; MI, myocardial infarction; PA, pulmonary artery; PCI, percutaneous coronary intervention; *SD*, standard deviation; STS Risk Score, society of thoracic surgery risk score.

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females had higher rate of bleeding requiring transfusion compared with males (9.58 vs. 5.30%, p = .019).

Conclusion: Female patients undergoing high PCI were older and had more comorbidities but had similar outcomes compared to males.

KEYWORDS

complex high-risk indicated patients, gender outcomes, mechanical circulatory support, percutaneous coronary intervention

1 | INTRODUCTION

Ischemic heart disease continues to be the leading cause of morbidity and mortality for both males and females.[1] Patients with complex high-risk symptomatic coronary artery disease are commonly encountered in current practice. Complex high-risk indicated patients or as also known as (CHIP) is defined by the presence of one of the following: patients undergoing percutaneous coronary intervention (PCI) of unprotected left main, last patent coronary conduit, vessel supplying a large myocardial territory with severely depressed ejection fraction (EF), or PCI of a vessel supplying a large territory in the setting of cardiogenic shock.[2] CHIP cases also include severe coronary calcification and patients who are poor surgical candidates due to their comorbidities. In such cases, PCI with adequate mechanical circulatory support has become an important part of the revascularization strategy decision-making. Indeed, protected PCI using percutaneous mechanical circulatory support has been demonstrated to be equally safe and effective as coronary artery bypass grafting.[3] Current guidelines recommend elective insertion of hemodynamic support devices in selected patients undergoing high-risk coronary interventions.[2] Further, the elective use of Impella 2.5 and Impella CP (Abiomed Inc., Danvers, MA) devices in patients having high-risk PCI have been shown to be safe and effective, and also provide a left ventricular unloading effect.[4–7]

Compared with males, females with acute coronary syndromes have higher unadjusted mortality, less use of guideline-recommended therapies and less access to revascularization therapies.[8–10] Furthermore, utilization of mechanical circulatory support (MCS) in the setting of cardiogenic shock is used less frequently in females compared to males.[11,12] Despite a higher risk-factor profile in females, there is a paucity of sex-specific safety, effectiveness, and outcomes data for mechanical support for high-risk PCI. Therefore, we sought to evaluate the sex differences in outcomes of mechanical circulatory support with Impella in patients undergoing high-risk PCI.

2 | MATERIALS AND METHODS

2.1 | Study population

Using the cVAD Registry, we identified a total of 1,053 complex high-risk indicated patients who underwent PCI with MCS using Impella 2.5 or Impella CP between June 2007 and June 2015. Eligible patients were those who underwent elective or urgent PCI with the aid of hemodynamic support with an Impella 2.5 or Impella CP, placed prior to the start of PCI. Patients in cardiogenic shock were excluded from this analysis. The design and methods of cVAD registry (the catheter based ventricular assist device registry) have been previously described.[13] The cVAD Registry is an expansion of the USpella Registry to European sites during the period 2015–2016 and Japanese sites expected after 2019.[14] In brief, the cVAD Registry is an ongoing multicenter voluntary registry open to centers in the United States, Canada, and Europe. The cVAD Registry was designed by an Executive Steering Committee that oversees its ongoing conduct. The registry protocol was reviewed and approved by the Institutional Review Board at each participating site. Sites are expected to report all consecutive Impella cases without preselection of indication or patients. Patients who were identified as having received an Impella device in a separate commercial database (IQ) were expected to be reported in the cVAD Registry database; otherwise sites were notified of the obligation to enter and report the cases to ensure consecutiveness.

2.2 | Outcomes

Our study looked at cardiac, stroke, renal, and bleeding outcomes in the cVAD Registry. Acute myocardial infarction was defined by detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least one of the following: symptoms of ischemia, ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]), development of pathological Q waves in the ECG, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Revascularization was defined as any repeat revascularization based on the presence of ischemia, defined either as recurrent angina or equivalent and/or a positive functional study that involves: (a) the target lesion (the originally treated segments; for stented lesions this includes an area 5 mm proximal or distal to the stented segment), or (b) target vessel (all coronary segments in the same epicardial artery as the treated lesion if that segment may have been involved during passage of the coronary guidewire or any treatment device), or (c) nontarget vessels. This intervention could be either percutaneous or surgical bypass. Valve injury was defined as injury to the aortic valve regardless of the cause and assessed by Doppler echocardiography versus baseline or during autopsy. Aortic regurgitation was assessed by transthoracic echocardiographic measurements and defined as ≥ Grade 2 or an increase in aortic regurgitation by more than one assessment level on a 4-point scale.

Stroke is defined as an ischemic or hemorrhagic cerebrovascular accident that persists beyond 24 hr or less than 24 hr associated with infarction on an imaging study. Major adverse cardiovascular and cerebrovascular events (MACCE) is the rate of the following events occurring after the intervention until 30 days; death (all-cause mortality), cerebrovascular accident, hospitalization due to heart failure, documented nonfatal myocardial infarction, or repeat revascularization by coronary stenting or oronary artery bypass graft surgery (CABG). Acute renal dysfunction is defined as abnormal kidney function requiring dialysis (including hemofiltration) in patients who did not require dialysis prior to implant, or a rise in serum creatinine of greater than 2.5 mg/dL or greater than two times baseline.

Bleeding was defined as blood loss requiring a blood transfusion or surgical exploration for resolution. Vascular complications requiring surgical repair were defined as a pseudoaneurysm, an arteriovenous fistula, a vessel dissection/perforation, or an access site thrombosis that requires surgical intervention. Hematoma was defined as any palpable swelling ≥5 cm in maximum diameter at vascular access site diagnosed by ultrasound, computerized tomography (CT) scan, or palpation at the skin level. Hemolysis was defined by abnormal plasma free hemoglobin values greater than 40 mg/dL or presence of hematuria.

2.3 | Device

Impella 2.5 and CP devices (Abiomed Inc., Danvers, MA) are FDA-approved for up to 6 days for cardiogenic shock and up to 6 hr for high risk coronary interventions. Impella 2.5 and CP provide direct cardiac pressure and volume unloading of the left ventricle and antegrade flow in the thoracic aorta of up to 2.5 and 4.0 L/min, respectively. The catheter-based device is typically inserted through a peripheral access using a single arterial access of 13Fr and 14Fr, respectively. From a pathophysiologic standpoint, unloading leads to decreased wall stress of the left ventricle by reducing left ventricular end-diastolic volume, pressure, and oxygen demand.[15–18] In addition, the pump flow from the Impella increases the mean arterial pressure, diastolic pressure, and cardiac output. The result is enhanced coronary and end organ perfusion.[16]

2.4 | Data collection

Data were abstracted retrospectively from the medical record to a standard electronic case report form by the sites' study coordinators who were centrally trained. Information was collected on patient's demographic characteristics, medical history, clinical presentation, hemodynamic, echocardiographic, angiographic characteristics, and treatment during hospitalization, hospital discharge status, and follow up status when available at the time of data collection. Data were monitored against source documentation to maximize accuracy. All patients reported in the registry that met the listed inclusion criteria of protected PCI were included in the current analysis without preselection of patients or sites.

2.5 | Statistical analysis

Data are expressed as mean ± *SD* or median as appropriate. Qualitative data are presented as proportion. Categorical variables were tested using Pearson's Chi-square test for contingency tables or Fisher Exact test, as appropriate. Continuous variables were analyzed by an independent *t*-test or paired *t*-test. All statistical tests and/or confidence intervals, as appropriate, were performed with a two-sided *p* value of .05. Kaplan–Meier estimates of the cumulative incidence of MACCE and of survival through 30 days were performed, and a Log-rank test was used to compare the curves between the two groups at this time point. Statistical analysis was performed using SAS Software v10 (SAS Institute Inc., Cary, NC).

3 | RESULTS

A total of 1,053 consecutive patients in the cVAD registry (mean age 69.66 ± 11.37, African American 17.83%) underwent high-risk PCI assisted with MCS using Impella 2.5 or CP. Baseline characteristics stratified by sex are presented in Table 1. Of the 1,053 patients, 261 (24.79%) were females and 792 (75.21%) were males. Both genders were similar in terms of prevalence of hypertension, stroke, existing heart failure, prior myocardial infarction (MI), and prior PCI. Women were older (72.05 ± 11.66 vs. 68.87 ± 11.17, $p < .001$), and had a lower body surface area (BSA) (1.80 vs. 2.02, $p < .001$). Females also had a higher prevalence of diabetes (59.3 vs. 49.04%, *p* of .005), renal insufficiency (35.41 vs. 27.39%, *p* of .018), peripheral vascular disease (31.89 vs. 25.39%, *p* of .05), lower hemoglobin (11.00 ± 1.73 vs. 13.08 ± 9.07, $p < .001$) and valvular disease (18.02 vs. 11.44%, $p < .001$). In contrast, females had a lower prevalence of tobacco use (29.03 vs. 40.18%, *p* of .002), arrhythmia (22.22 vs. 33.38%, $p < .001$) and prior CABG (19.07 vs. 32.70%, $p < .001$) (Table 1).

Despite having a higher left ventricular ejection fraction on presentation (33.18 ± 17.75 vs. 28.04 ± 15.37, $p < .001$), females overall were at greater risk of death as indicated by Society of Thoracic Surgeons (STS) mortality scores (8.21 ± 8.21 vs. 5.04 ± 5.97, $p < .001$) and morbidity scores (34.72 ± 17.75 vs. 27.85 ± 16.74, $p < .001$) (Table 1). Women were more likely to be seen by the surgical team (51.57 vs. 39.43%, $p < .001$) and to be considered for CABG (38.89 vs. 29.11%, *p* of .005).

Impella 2.5 was more used than Impella CP. Impella 2.5 was used in 94% of cases for females and 89% of cases for males. Less than one third of the patients presented with an acute MI and the majority of them had non-ST segment elevation myocardial infarctions (NSTEMI) (87%) with no difference between females and males (Table 2). Only 26.30% of the patients were transfers from a different hospital. None of the patient had cardiogenic shock on presentation as this was one of the exclusion criteria. However, a total of 71% females and 70% of males presented with New York Heart Association (NYHA) Class

TABLE 1 Baseline characteristics stratified by sex

Characteristics	Total (*N* = 1,053)	Female (*N* = 261)	Male (*N* = 792)	*p*-value
Age, mean ± *SD*(N)	69.66 ± 11.37	72.05 ± 11.66	68.87 ± 11.17	<.001
Asian	2.48%	2.31%	2.53%	.99
African American	17.83%	25.77%	15.21%	<.001
Caucasian	69.49%	61.92%	71.99%	.003
BSA (m^2), mean ± *SD*(*N*)	1.97 ± 0.26	1.80 ± 0.25	2.02 ± 0.24	<.001
BMI (kg/m^2), mean ± *SD*(*N*)	28.99 ± 7.06	30.21 ± 8.26	28.59 ± 6.57	.005
Hyperlipidemia	74.50%	71.37%	75.51%	.187
Hypertension	90.10%	93.10%	89.11%	.072
Diabetes mellitus	51.59%	59.30%	49.04%	.005
CAD	85.50%	83.04%	86.27%	.233
Smoker	37.46%	29.03%	40.18%	.002
Stroke/TIA	5.82%	6.42%	5.63%	.623
Cerebrovascular disease	18.11%	19.84%	17.54%	.450
Renal insufficiency	29.39%	35.41%	27.39%	.018
Dialysis	26.13%	34.12%	22.77%	.056
Liver insufficiency	2.78%	3.21%	2.64%	.658
COPD	22.64%	22.31%	22.75%	.931
Arrhythmia	30.63%	22.22%	33.38%	<.001
PVD	27.01%	31.89%	25.39%	.050
CHF	54.91%	51.12%	56.10%	.217
NYHA class				
I	7.49%	8.97%	7.03%	.623
II	19.76%	17.95%	20.31%	.746
III	44.61%	35.90%	47.27%	.091
IV	28.14%	37.18%	25.39%	.046
III/IV	72.75%	73.08%	72.66%	.99
Valvular disease	13.01%	18.02%	11.44%	.016
Cardiomyopathy	42.38%	33.78%	45.07%	.003
Prior MI	46.93%	45.82%	47.29%	.716
Hours between MI onset and start of PCI, mean ± *SD*(*N*)	166.8 ± 246.0	230.6 ± 42.2	143.6 ± 132.7	.252
Prior AICD/pacer implanted	22.63%	15.35%	25.00%	.001
Prior PCI	47.04%	41.67%	48.78%	.050
Prior CABG	29.34%	19.07%	32.70%	<.001
Surgical consultation was requested	42.43%	51.57%	39.43%	<.001
CABG was considered for treatment	31.51%	38.89%	29.11%	.005
LVEF (%), mean ± *SD*(*N*)	29.3 ± 15.8	33.18 ± 16.68	28.04 ± 15.37	<.001
STS mortality score, mean ± *SD*(*N*)	5.8 ± 6.7	8.21 ± 8.21	5.04 ± 5.97	<.001
STS morbidity score, mean ± *SD*(*N*)	29.59 ± 17.25	34.72 ± 17.75	27.85 ± 16.74	<.001
Hgb (g/dL), mean ± *SD*(*N*)	12.56 ± 7.95	11.00 ± 1.73	13.08 ± 9.07	<.001
Platelet count ($10^3/\mu l$), mean ± *SD*(*N*)	200.6 ± 69.8	218.77 ± 78.17	194.61 ± 65.7	<.001
Creatinine (mg/dL), mean ± *SD*(*N*)	1.49 ± 1.1	1.53 ± 1.36	1.48 ± 1.10	.570
GFR ($ml\ min^{-1}\ m^{-2}$), mean ± *SD*(*N*)	57.53 ± 27.5	46.92 ± 23.27	61.30 ± 27.99	<.001
AST (U/L), mean ± *SD*(*N*)	46.94 ± 72.0	51.81 ± 87.33	45.00 ± 65.01	.484
ALT (U/L), mean ± *SD*(*N*)	41.50 ± 62.9	37.36 ± 55.84	43.10 ± 65.56	.444

Abbreviations: AICD, automated implantable cardioverter defibrillator; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; Hgb, hemoglobin; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; STS, society of thoracic surgery; TIA, transient ischemic attached.

TABLE 2 Admission and procedural characteristics stratified by sex

Characteristics	Total (*N* = 1,053)	Female (*N* = 261)	Male (*N* = 792)	*p*-value
Patient was transferred from another hospital	26.30%	31.02%	24.73%	.055
Patient was supported with an IABP prior to Impella support	4.67%	6.76%	4.01%	.101
Acute myocardial infarction	28.80%	35.63%	26.55%	.006
STEMI	13.10%	18.89%	10.50%	.060
NSTEMI	86.90%	81.11%	89.50%	.060
Number of diseased vessels (≥50% stenosis), mean ± *SD*(N)	1.74 ± 0.76	1.90 ± 0.71	1.69 ± 0.77	<.001
Number of vessels treated, mean ± *SD*(*N*)	1.58 ± 0.71	1.71 ± 0.67	1.54 ± 0.72	<.001
Patients with 1 vessel treated	38.43%	29.34%	41.47%	<.001
Patients with 2 vessels treated	48.21%	58.30%	44.83%	<.001
Patients with 3 vessels treated	7.84%	8.49%	7.62%	.689
SVG intervention (at least one SVG lesion attempted)	7.94%	3.47%	9.43%	.001
Number of lesions treated, mean ± *SD*(*N*)	1.71 ± 0.77	1.77 ± 0.81	1.69 ± 0.75	.172
Number of stents used, mean ± *SD*(*N*)	2.20 ± 1.17	2.29 ± 1.2	2.18 ± 1.15	.187
Impella access				
Femoral	99.56%	99.54%	99.56%	.99
Subclavian or axillary	0.44%	0.46%	0.44%	.99
Impella pump flow (L/min), mean ± *SD*(*N*)	2.23 ± 0.81	2.16 ± 0.41	2.26 ± 0.9	.051
Vessel location				
LAD	35.50%	35.42%	35.53%	.965
Left Main	16.43%	18.67%	15.64%	.056
LCx	27.82%	27.75%	27.85%	.99
RCA	15.97%	16.50%	15.78%	.650
Graft	4.28%	1.66%	5.20%	<.001
LIMA	0.47%	0.13%	0.59%	.133
SVG	3.81%	1.53%	4.61%	<.001
Lesion location				
Proximal	45.51%	44.02%	46.07%	.368
Mid	27.81%	27.99%	27.74%	.920
Distal	18.50%	18.51%	18.49%	.99
Ostial	8.19%	9.48%	7.70%	.164
TIMI flow 0/1 pre PCI	9.02%	7.50%	9.49%	.292
TIMI flow 0/1 post PCI	1.76%	1.40%	1.89%	.558

Abbreviations: LAD, left anterior descending; LCx, left circumflex crater; LIMA, left internal mammary artery; NSTEMI, Non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; *SD*, standard deviation; STEMI, ST-elevation myocardial infarction; SVG, saphenous vein graft; TIMI, thrombolysis in myocardial infarction.

III/IV. After the procedure, 50% of females and 55% males of had NYHA Class III/IV. Females had high coronary artery disease burden compared to males (number of vessels 1.90 ± 0.71 vs. 1.69 ± 0.77, $p < .001$). Overall, there was a statistically significant difference in the number of vessels treated between the genders. Specifically, males had a higher rate of 1 vessel treatment and females had a higher rate of 2 vessel treatment. There was no statistical significance in the rate of 3 vessel treatment. Females had similar rates of left main disease compared to males (18.67 vs. 15.64% *p* of .056). Consistent with the higher CABG rates in males, there was higher occurrence of graft intervention. The majority of the coronary lesions were in proximal segments with no difference between females and males. Impella access sites, pump flow and pressure levels were similar between groups (Table 2).

Right heart catheterization data were available in a small subset of patients. The data suggest a disparity in pulmonary artery (PA) catheter placement between females and males: 24% of females and 75% of males. Baseline hemodynamic characteristics prior to device placement were similar for both females and males prior to insertion and initiation of Impella device (Table 3). Women had lower diastolic blood pressure compared to men and slightly lower cardiac output.

Survival rates at the time of discharge were comparable for females and males (95.02 vs. 96.84%, *p* of 0.18). Myocardial infarction

TABLE 3 Baseline Hemodynamics Prior to Impella Placement

	HRPCI (*N* = 1,053)	Females (*N* = 261)	Males (*N* = 792)	*p*-value
HR (bpm), mean ± *SD*(*N*)	72.93 ± 17.00	73.29 ± 16.89	72.81 ± 17.05	.696
Systolic blood pressure (mmHg), mean ± *SD*(*N*)	122.73 ± 25.01	125.48 ± 27.26	121.81 ± 24.16	.055
Diastolic blood pressure (mmHg), mean ± *SD*(*N*)	69.40 ± 14.94	64.94 ± 15.40	70.88 ± 14.50	<.001
Mean arterial pressure (mmHg), mean ± *SD*(*N*)	87.57 ± 16.89	85.53 ± 18.45	88.25 ± 16.29	.037
Cardiac index (L min^{-1} m^{-2}), mean ± *SD*(*N*)	2.24 ± 0.75	2.11 ± 0.80	2.27 ± 0.73	.293
Cardiac output (L/min), mean ± *SD*(*N*)	4.41 ± 1.50	3.64 ± 1.30	4.63 ± 1.49	.001
PCWP (mmHg), mean ± *SD*(*N*)	20.90 ± 9.96	21.58 ± 10.79	20.68 ± 9.71	.624
PAP (mmHg), mean ± *SD*(*N*)	24.15 ± 12.24	23.55 ± 12.92	24.35 ± 12.05	.709

Abbreviations: HR, heart rate; PCWP, pulmonary capillary wedge pressure; PAP, peripheral artery pressure; *SD*, standard deviation.

TABLE 4 In-hospital adverse events stratified by sex

Adverse events	Total (*N* = 1,053) (%)	Females (*N* = 261) (%)	Males (*N* = 792) (%)	*p*-value
Death	3.61	4.98	3.16	.181
Myocardial infarction	0.85	1.15	0.76	.698
CVA/stroke	0.09	0.00	0.13	.99
TIA	0.00	0.00	0.00	–
Valve injury	0.00	0.00	0.00	–
Acute renal dysfunction	4.65	6.51	4.04	.126
Revascularization	0.66	0.77	0.63	.686
Hemolysis	0.00	0.00	0.00	–
Acute hepatic failure	0.19	0.38	0.13	.434
Bleeding requiring surgery	0.66	0.77	0.63	.686
Bleeding requiring transfusion	6.36	9.58	5.30	.019
Device malfunction	0.09	0.00	0.13	.99
Hematoma	3.80	4.60	3.54	.456
Vascular complication requiring surgery	1.23	2.30	0.88	.100
Vascular complication without surgery	2.18	2.68	2.02	.475
Aortic valve regurgitation > = 2 grades from baseline	0.00	0.00	0.00	–
Need for cardiac, thoracic or abdominal vascular operation or femoral artery bypass graft (not isolated femoral artery)	0.28	0.38	0.25	.575
Infection	2.09	3.07	1.77	.215
Cardiopulmonary resuscitation or ventricular arrhythmia	3.61	4.21	3.41	.567
Failure to achieve angiographic success (as residual stenosis <30% after stent implant)	0.38	0.77	0.25	.258

Abbreviations: CVA, cerebrovascular accidence; TIA, transient ischemic attacked.

(1.15 vs. 0.76%, *p* of .70), need for repeat revascularization (0.77 vs. 0.63%, *p* of .69), and stroke (0.00 vs. 0.13%, *p* of .99) were infrequent and similar in females and males (Table 4). There were no differences in terms of vascular complications, cardiac arrhythmias, acute kidney injury, or dialysis requirements between two groups. However, females had higher rate of bleeding requiring blood transfusion compared to males (9.5 vs. 5.3%, *p* of .019). In addition, survival rate and MACCE to 30 days was comparable in both groups (93 vs. 94%, *p* of .441, 9.8 vs. 9.3%, *p* of .434, respectively) (Figures 1 and 2). Ejection fraction improved in both males and females at the time of discharge (26.59 to 31.40% and 30.75 to 36.05%, respectively, $p < .0001$). Specifically, both females (mean difference 5.30, 95% CI 9.74 to 0.87, $p < .001$) and males (mean difference 4.8, 95% CI 7.40 to 2.21, $p < .001$) improved their left ventricular ejection fraction (LVEF) (Table 5).

4 | DISCUSSION

We performed a retrospective analysis of a multicenter prospective registry. Based on our study, the differences between females and males in the treatment of high-risk PCI from the cVAD Registry are[1]; symptomatic females with complex high-risk coronary disease have higher comorbidities and are at greater risk of death with CABG as indicated by STS score compared to males.[2] Females were equally likely as males to survive to hospital discharge after high-risk PCI with MCS support despite having higher STS mortality risk scores.[3] Myocardial infarction, stroke, AKI, repeat revascularization, and vascular complications rates were also similar in both sexes.[4] Females were equally likely to develop hematoma and bleeding as males, they required more blood transfusions compared to their male counterparts.

The use of MCS for high-risk PCI has increased in recent years.[19] This is due, in part, to patient demographic changes including increased comorbidities, older age, and greater impairments of LV systolic function of patients referred to the cath lab for coronary intervention. In addition, technological improvements in the Impella platform with enhanced ease of use and increasing operator skill and familiarity with Impella and protected PCI have also contributed to increased utilization. The randomized controlled clinical trial PROTECT II compared Impella 2.5 with intra-aortic balloon pump (IABP) during high-risk PCI and showed that the use of the Impella 2.5 is not superior to IABP in reducing adverse events at 30 and 90 days. Although there was no difference in in-hospital death, stroke, myocardial infarction, or the composite of death/stroke/MI between Impella 2.5 and IABP, fewer irreversible MACCE of death/stroke/ MI (7.0 vs. 12.9%, p = .042) and of death/stroke/ MI/repeat revascularization (9.8 vs. 18.6%, p = .009) occurred after hospital discharge in the Impella 2.5 arm in comparison with the IABP arm. Furthermore, it showed superior hemodynamic support with Impella allowing more vessels to be treated, more stents used, and more lesion modification with atherectomy.[7] The ability to perform high-risk PCI safely has been attributed to decreasing left ventricular wall stress from unloading the left ventricle, reducing left ventricular end-diastolic volume, and lowering ventricular pressure and oxygen demand.[15–18] Furthermore, Impella use during PCI has been shown to enhance coronary and end organ perfusion and may reduce the risk of AKI.[16,20] These findings and others have led to increased utilization of MCS, especially Impella, during CHIP cases.

Complete revascularization of coronary disease has been shown to improve overall outcomes when compared with incomplete revascularization. Both females and males, had better outcomes in terms of mortality, MACE and overall complications when complete revascularization was performed.[21–24] In addition, 90-day follow-up data from the PROTECT II trial showed a significant decrease in major adverse events (37 vs. 49% p of .014) and major adverse cardiac and cerebral events (22 vs. 31%, p of .034) in the Impella group, driven by more complete revascularization. In our study, both females and males had similar in-hospital mortality, stroke, MI and need for revascularization regardless of the number of vessels and lesions treated. Myocardial ischemia associated with treatment of left main coronary disease and multi-vessel PCI are better tolerated with circulatory support. Similar findings were reported in a recent study by Doshi et al. They analyzed gender differences by looking at short-term survival and in-hospital outcomes in those undergoing Impella assisted PCI in the setting of cardiogenic shock. They showed that men and women who had complete revascularization with Impella support had no sex difference in clinical outcomes. There was no difference in in-hospital mortality or

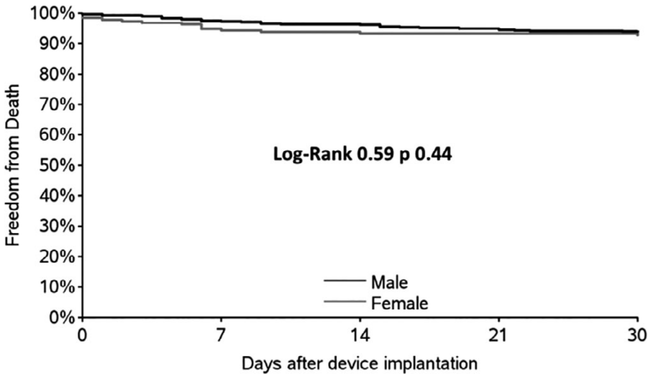

FIGURE 1 Freedom from death at 30 days

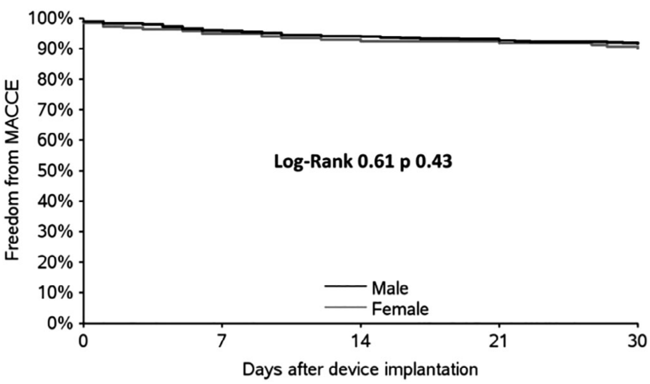

FIGURE 2 Freedom from major adverse cardiac events (MACE) at 30 days

TABLE 5 Ejection fraction (%) at baseline and at longest follow-up

All patients	At baseline(N = 1,053 patients)	At longest follow-up(N = 1,053 patients)	Difference [95% CI]	p-value
LVEF (%) mean ± *SD* (*N*)	27.70 ± 14.82	32.64 ± 15.45	−4.94[−7.19, −2.69]	<.0001
Males (N = 792)				
LVEF (%), mean ± *SD* (*N*)	26.59 ± 14.51	31.40 ± 15.32	−4.80[−7.40, −2.21]	<.0001
Females (N = 261 patients)				
LVEF (%), mean ± *SD* (*N*)	30.75 ± 15.32	36.05 ± 15.38	−5.30[−9.74,−0.86]	<.0001

Abbreviations: CI, confidence interval; LVEF, left ventricular ejection fraction; *SD*, standard deviation.

30-day survival rates Secondary outcomes such as major adverse cardiac events, dialysis requirement, bleeding within 72 hr, blood transfusion, dysrhythmia were similar in both cohorts.[25]

Complete revascularization is often achieved with CABG surgery and has been shown to be associated with long-term mortality benefits.[26,27] However, CHIP population patients are often turned down for surgical intervention given the severity of their CAD with low LV function and comorbidities that put the patient at high or extreme surgical risk. In addition, patients may decline surgery because of personal preference. In this study, there were more CABG consultations for females than males (51.57 vs. 39.43%, $p < .001$) which may indicate higher CAD burden or coronary lesion complexity compared to males. However, more female patients were deemed ineligible for CABG surgery than males due to concomitant comorbidities that precluded them from CABG (18.62 vs. 9.59%, p of .002). Furthermore, females had on average higher STS mortality scores and higher STS morbidity scores, making them poor surgical candidates. Based on these findings, protected PCI represents a useful alternative to CABG based on in-hospital adverse events. Similarly, in another trial, complex multivessel CAD patients who underwent protected PCI with the Impella 2.5 device experienced similar in-hospital major adverse cardiac and cerebrovascular event rates when compared to CABG. However, patients undergoing CABG experienced significantly more peri-procedural additional adverse events (28.6 vs. 3.8%; $p < .05$).[3] In our cohort, women had higher rates of renal insufficiency than men at baseline and despite this, the clinical outcome including worsening renal failure or renal failure requiring dialysis was similar in females and males. This finding is consistent with a study by Flaherty et al. who examined the impact of Impella MCS on renal function after high-risk PCI. This study demonstrated that MCS with Impella was associated with a significant reduction in AKI despite the presence of CKD or severely reduced left ventricular ejection fraction.[20]

Previous studies have shown that females with acute coronary syndrome are treated less aggressively than males despite presenting with higher risk characteristics and having higher in-hospital risk.[10] In the PROTECT II trial, only 20% were females, which is an underrepresentation in the overall population undergoing complex high-risk PCI. In our study, females had higher rate of comorbidities such as diabetes, renal insufficiency, and PVD that confer greater risk of adverse events during high-risk PCI. Yet, females were found to have equal survival and clinical outcomes to hospital discharge. Of note, a prior study among patients with cardiogenic shock by Joseph et al., demonstrated that female patients derived a greater benefit from Impella supported high-risk PCI.[28]

Females are known to have higher risk of access site complications and the use of transradial route in percutaneous coronary intervention has been shown to reduce access site bleeding.[29] Although females had lower baseline hemoglobin and experienced more bleeding that required blood transfusion they were not at increased risk of vascular complications compared with males. However, the difference in bleeding events was not significant after adjusting for baseline hemoglobin levels suggesting that patient baseline condition/anemia was mainly responsible. Continued advances in best practices for safe femoral access may further improve this hazard for both females and males.

5 | LIMITATIONS

Our study using the cVAD registry study has several limitations. The data analyzed were retrospectively collected and included Impella treated patients only. Causality regarding the impact of Impella on outcomes cannot be inferred, and residual confounding factors cannot be excluded. Second, women constituted only 24.79% of our study population. Consequently, this could be underpowered to detect sex differences in clinical outcomes. Therefore, this study should be used to generate further prospective data to elucidate whether sex-related differences exist in a larger sample size of protected PCI patients. However, this study included all comers with no exclusion criteria at participating sites, and all patients were treated with Impella 2.5 or Impella CP. Therefore, this study reflects real-world practice.

6 | CONCLUSION

Only 25% of the patients referred for high risk PCI are females, which suggest that females may encounter barriers to access to highly specialized medical care. Also, despite being older and sicker, females had favorable outcomes after high risk PCI that were not different compared to males.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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