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Original Research

Mechanical Circulatory Support in Myocardial Infarction Complicated by Cardiogenic Shock: Impact of Sex and Timing

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A B S T R A C T

Background: Sex differences in presentation, treatment, and outcomes persist in patients with acute myocardial infarction complicated by cardiogenic shock (AMICS). Sex-based outcomes of patients with AMICS undergoing percutaneous coronary intervention (PCI) with percutaneous left ventricular assist device (pLVAD) support are poorly defined.

Methods: From January 2017 to August 2019, consecutive patients undergoing PCI who received Impella support within 48 hours of myocardial infarction were enrolled in the prospective RECOVER III postmarket registry. In-hospital survival and predictors of mortality were compared by sex.

Results: A total of 358 patients (276 men and 82 women) were included. Women had lower baseline mean arterial pressure and shorter duration of pLVAD support compared with men. In-hospital adverse events were similar in women and men, including mortality (54% versus 46%, $P = .25$), major bleeding (11% versus 10%, $P = .83$), and vascular complications requiring surgery (8.5% versus 4%, $P = .10$). Women had better survival with pre-PCI versus post-PCI pLVAD implantation (59% versus 34%, $P = .03$), whereas survival in men was similar regardless of pre- versus post-PCI pLVAD support (56% versus 50%, $P = .39$). The number of inotrope/vasopressor use pre-pLVAD was the strongest predictor of mortality in women (OR 3.03, $P = .01$) but not in men (OR 1.18, $P = .25$).

Conclusions: Survival of patients with AMICS treated with PCI and Impella support was 52% at hospital discharge and was similar for women and men. Women with AMICS may derive greater benefit from early pLVAD support prior to escalation of inotrope/vasopressors and had no evidence of increased risk of access-related complications.

The Impella heart pumps (Abiomed) are percutaneous left ventricular assist devices (pLVADs) used for temporary mechanical circulatory support (MCS) in acute myocardial infarction complicated by cardiogenic shock (AMICS).[1,2] In animal models, early pLVAD implantation during acute myocardial infarction (AMI) reduces infarct size and prevents the development of heart failure through left ventricular unloading.[3,4] In randomized trials comparing pLVADs with intra-aortic balloon pumps (IABP) in patients with AMICS, pLVADs provide superior hemodynamic support and maintain higher cardiac indexes but have been associated with increased bleeding.[5,6] These early randomized studies failed to show a mortality benefit despite improved hemodynamics. Recent observational studies have suggested that pLVADs are associated with improved survival when implanted early, prior to percutaneous coronary intervention (PCI) and/or escalating inotropes or vasopressors.[7–11] In the Global cVAD registry, Basir et al[7] found that pre-PCI pLVAD implantation in patients with AMICS was associated with a significant in-hospital mortality benefit compared with post-PCI implantation (odds ratio [OR] = 0.49, $P = .04$) and survival was 68%, 46%, 35%, 35%, and 26% for patients receiving 0, 1, 2, 3, and ≥4 inotropes prior to pLVAD implantation, respectively ($P < .001$).[7] Another analysis of the Global cVAD registry found that despite older age and more risk factors, women with AMICS appeared to derive greater benefit than men from early pLVAD implantation.[8] We sought to re-evaluate sex-based outcomes of patients with AMICS undergoing PCI who received pLVAD support in the larger postmarket RECOVER III registry.

Abbreviations: AMICS, acute myocardial infarction complicated by cardiogenic shock; DBP, diastolic blood pressure; IABP, intra-aortic balloon pump; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention; pLVAD, percutaneous left ventricular assist device; SBP, systolic blood pressure.

Keywords: Percutaneous left ventricular assist device; Mechanical circulatory support; Impella; Acute myocardial infarction; Cardiogenic shock; Sex.

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Methods

Patient selection

RECOVER III is a postmarket (on-label), prospective, multicenter, single-arm, observational study of patients receiving Impella support for AMICS indication. RECOVER III is one of several indication-based post-approval studies of the Global cVAD study platform (NCT04136392) that was designed in collaboration with the US Food and Drug Administration. Details of the design and methods of the Global cVAD study have been published previously.[12] All patients ≥18 years of age with AMICS who received Impella pLVADs and underwent revascularization after diagnosis of AMICS were considered eligible. Entry criteria for AMI was defined by cardiac troponin values >2× upper limit of normal, with either new electrocardiographic changes (ST-segment changes or new Q waves) or symptoms of ischemia. Cardiogenic shock was defined as sustained hypotension lasting ≥30 minutes (systolic blood pressure [SBP] <90 mm Hg or, if available, cardiac index <2.2 L/min/m^2) deemed secondary to cardiac dysfunction or requirement of inotrope/vasopressor support to maintain hemodynamics above these prespecified levels within 48 hours of AMI. Patients were excluded if they were enrolled prior to January 2017, if the primary indication for pLVAD was not AMICS, the type of Impella device was not specified or only Impella RP was used, or if discharge status (alive/expired) was not reported.

Patient management, device selection (Impella 2.5, CP, or 5.0), and timing of pLVAD support were entirely clinically driven at the operator's discretion. The registry was performed in accordance with the Declaration of Helsinki, was approved by the institutional review board of all participating sites, and all patients provided written informed consent to conduct post-discharge follow-up.

Data collection and definitions

Patients were considered enrolled at the time of pLVAD placement. In-hospital data were collected from the time of admission through discharge and entered by into an electronic database. No additional study-specific examinations or procedures were required for this study outside of standard of care. Baseline laboratory values were those recorded prior to and nearest to pLVAD placement. Adverse events were site reported through hospital discharge and independently monitored.

Statistical analysis

Categorical variables are reported as count and percentage, continuous variables are reported as mean with standard deviation or median with interquartile range. For categorical variables, the χ^2 test or Fisher exact test was used for comparisons between groups, as appropriate, and continuous variables were compared with the 2-sample t test and the nonparametric Wilcoxon rank-sum test, as appropriate.

Univariable logistic regression models were used to identify the effects of baseline and procedural characteristics on in-hospital mortality. Variables identified with $P < .1$ in univariable analysis were included in a multivariable logistic regression model. Sex and pre-PCI pLVAD implantation were forced in the final multivariable model to assess relevance. Predictors with $P > .1$ on multivariable analysis were removed from the model, and this step was repeated until all predictors had $P < .1$. Variables in the final model were tested for significant interactions. Univariable and multivariable analyses of in-hospital mortality were performed separately by sex. Statistical analysis was performed using SAS version 9.4 (SAS Institute).

Results

Baseline and procedural characteristics

The cVAD registry enrolled a total of 4259 patients, of which 3901 (2745 men and 1100 women with 56 unknown) were excluded from the current study. Of these exclusions, 2954 did not have AMICS as a primary indication for Impella, 16 had coronary artery bypass grafting, 28 had type of Impella missing or received Impella RP only, 10 had missing discharge status, and 893 were enrolled before January 2017.

Thus, between January 2017 and August 2019, a total of 358 patients including 276 (77.1%) men and 82 (22.9%) women were enrolled in RECOVER III. Baseline characteristics are presented in Table 1. Women tended to be older with greater representation of Blacks or African Americans, but fewer Asians compared with men. Comorbidities were not different by sex. On admission, women had more hypotension with lower diastolic blood pressure and mean arterial pressure (76.3 ± 22.2 versus 83.6 ± 20.1 mm Hg, $P = .007$) compared with men and were more likely to receive initial IABP support before escalation to pLVAD (22.0% versus 13.1%, $P = .049$; Table 2). Three Impella devices were used to support the left ventricle: Impella 2.5 (8.7%), Impella CP (90.8%), and Impella 5.0 (4.5%), with 7.5% of patients receiving multiple devices, and 4.2% receiving Impella RP to support the right ventricle (Table 3). Women were significantly less likely to receive Impella CP (82.9% versus 93.1%, $P = .005$) and had significantly shorter median pLVAD support duration (26.2 versus 50.2 hours, $P = .002$) compared with men. Time to care, including shock-to-pLVAD time, door-to-balloon time, and door-to-pLVAD time, were not different by sex. While door-to-pLVAD times were similar in STEMI patients by sex, women with non–ST-segment elevation myocardial infarction tended to have longer delays than men (median 23.6 hours versus 11.3 hours, $P = .08$). There were no other significant procedural differences by sex (Table 3).

Patient outcomes

Overall survival to hospital discharge was 52.0%, with no difference in survival between women and men (46.3% versus 53.6%; $P = .25$) (Table 4). Rates of in-hospital myocardial infarction (2.0%), stroke (5.0%), repeat revascularization (0.3%), major bleeding (10.3%), and vascular complication requiring surgery (5.0%) were not significantly different by sex. Additional in-hospital adverse events are reported in Supplemental Table S1. The mean duration of hospitalization was 12.1 days (median 8 days), and 28 patients (7.9%) were hospitalized >30 days.

Impact of pLVAD timing on outcomes

Women had a significant survival benefit from early pLVAD use pre-PCI compared to post-PCI (58.5% versus 34.2%; $P = .03$), whereas pLVAD timing, specifically post-PCI, was not associated with worse survival in men (55.8% versus 50.5%, $P = .39$). Outcomes in women and men treated with pre-PCI pLVAD support were similar, whereas women treated with pLVAD support post-PCI tended to have a higher mortality compared with men ($P = .08$).

Women receiving post-PCI pLVAD support were more likely to present with shock on admission than women with pre-PCI implantation (61.0% versus 26.8%, $P = .002$); however, they had fewer vessels treated on average (1.3 versus 1.7, $P = .01$) (Supplemental Tables S2-S7). Men receiving pre-PCI pLVAD support were more likely to undergo left main revascularization (28.1% versus 11.3%, $P = .001$) and were less likely to have anoxic brain damage (7.7% versus 19.0%, $P = .007$), cardiac arrest (46.3% versus 60.4% , $P = .02$), cardiopulmonary resuscitation (39.5% versus 56.6%; $P = .006$), or require inotrope support (62.6% versus 77.6%; $P = .009$) compared with post-PCI pLVAD. Both women and men with pre-PCI support had longer door-to-balloon times (Supplemental Tables S2-S7).

Impact of inotrope usage on outcomes

Both women and men had worsening survival the more inotropes/vasopressors were required prior to escalation to pLVAD support. Women

Table 1
Baseline characteristics.

Characteristic	All ($N = 358$)	Women ($n = 82$)	Men ($n = 276$)	P value
Age, y	64.3 ± 11.6 (358)	66.2 ± 11.8 (82)	63.7 ± 11.6 (276)	.09
Race				
American Indian or Alaska Native	0.3% (1/358)	0.0% (0/82)	0.4% (1/276)	1.00
Asian	3.9% (14/358)	0.0% (0/82)	5.1% (14/276)	.04
Black or African American	12.3% (44/358)	20.7% (17/82)	9.8% (27/276)	.008
Caucasian	69.6% (249/358)	65.9% (54/82)	70.7% (195/276)	.41
Native Hawaiian or other Pacific Islander	0.3% (1/358)	0.0% (0/82)	0.4% (1/276)	1.00
Other	2.0% (7/358)	1.2% (1/82)	2.2% (6/276)	.58
Unknown	11.7% (42/358)	12.2% (10/82)	11.6% (32/276)	.88
Body surface area, m^2	2.0 ± 0.3 (353)	1.8 ± 0.3 (82)	2.1 ± 0.2 (271)	<.001
Medical history				
Smoker	58.8% (190/323)	54.0% (41/76)	60.3% (149/247)	.32
Hyperlipidemia	59.6% (196/329)	58.6% (41/70)	59.9% (155/259)	.85
Hypertension	79.7% (271/340)	86.5% (64/74)	77.8% (207/266)	.10
Diabetes mellitus	48.5% (161/332)	51.4% (38/74)	47.7% (123/258)	.58
Stroke/transient ischemic attack	8.7% (29/332)	12.3% (9/73)	7.7% (20/259)	.22
Renal insufficiency	17.6% (58/329)	22.2% (16/72)	16.3% (42/257)	.25
Peripheral vascular disease	11.0% (36/326)	11.4% (8/70)	10.9% (28/256)	.91
NYHA class				
I	0.0% (0/63)	0.0% (0/13)	0.0% (0/50)	—
II	12.7% (8/63)	7.7% (1/13)	14.0% (7/50)	.54
III	17.5% (11/63)	30.8% (4/13)	14.0% (7/50)	.16
IV	69.8% (44/63)	61.5% (8/13)	72.0% (36/50)	.46
III/IV	87.3% (55/63)	92.3% (12/13)	86.0% (43/50)	.54
Prior myocardial infarction	24.5% (78/319)	24.3% (17/70)	24.5% (61/249)	.97
Prior percutaneous coronary intervention	26.2% (88/336)	24.3% (18/74)	26.7% (70/262)	.68
Prior coronary artery bypass grafting	8.5% (29/341)	6.5% (5/77)	9.1% (24/264)	.47
Left ventricular ejection fraction, %	26.5 ± 13.1 (172)	29.5 ± 15.7 (45)	25.4 ± 12.0 (127)	.11

Continuous data are reported as mean ± standard deviation (N); categorical data are reported as % (n/N).
NYHA, New York Heart Association.

Table 2
Admission characteristics and pre-pLVAD hemodynamics.

Characteristic	All ($N = 358$)	Women ($n = 82$)	Men ($n = 276$)	P value
Patient transferred from another hospital	32.4% (116/358)	24.4% (20/82)	34.8% (96/276)	.08
Patient supported with IABP prior to pLVAD	15.1% (54/357)	22.0% (18/82)	13.1% (36/275)	.049
Cardiogenic shock present on admission	46.4% (166/358)	43.9% (36/82)	47.1% (130/276)	.61
Duration of cardiogenic shock				
<6 hours	80.8% (252/312)	79.5% (58/73)	81.2% (194/239)	.74
6-12 hours	7.1% (22/312)	8.2% (6/73)	6.7% (16/239)	.66
12-24 hours	4.5% (14/312)	4.1% (3/73)	4.6% (11/239)	.86
>24 hours	7.7% (24/312)	8.2% (6/73)	7.5% (18/239)	.85
Anoxic brain damage	11.3% (38/335)	8.1% (6/74)	12.3% (32/261)	.32
End-organ hypoperfusion	18.6% (57/306)	21.7% (15/69)	17.7% (42/237)	.45
Cardiac arrest	50.6% (180/356)	45.1% (37/82)	52.2% (143/274)	.26
Mechanical ventilation	43.5% (155/356)	39.0% (32/82)	44.9% (123/274)	.35
Cardiopulmonary resuscitation	45.5% (162/356)	42.7% (35/82)	46.4% (127/274)	.56
Acute myocardial infarction	100.0% (358/358)	100.0% (82/82)	100.0% (276/276)	—
ST-segment elevation myocardial infarction	72.4% (249/344)	71.8% (56/78)	72.6% (193/266)	.90
Non–ST-segment elevation myocardial infarction	27.6% (95/344)	28.2% (22/78)	27.4% (73/266)	.90
Patient required inotropes/pressors prior to pLVAD	69.0% (247/358)	70.7% (58/82)	68.5% (189/276)	.70
If yes, maximum no. of different inotropes[a]	1.9 ± 1.0 (247)	2.0 ± 1.1 (58)	1.9 ± 1.0 (189)	.30
Heart rate, bpm	97.4 ± 26.8 (320)	97.9 ± 29.6 (74)	97.2 ± 25.9 (246)	.84
Systolic blood pressure, mmHg	108.9 ± 25.8 (318)	106.3 ± 25.1 (75)	109.6 ± 26.0 (243)	.33
Diastolic blood pressure, mmHg	68.3 ± 18.3 (318)	62.0 ± 18.6 (75)	70.3 ± 17.8 (243)	<.001
Mean arterial pressure, mmHg	81.9 ± 20.8 (323)	76.3 ± 22.2 (78)	83.6 ± 20.1 (245)	.007
Cardiac index, $L/min/m^2$	2.1 ± 0.7 (115)	2.1 ± 0.7 (27)	2.1 ± 0.8 (88)	.68
Cardiac output, L/min	4.1 ± 1.6 (115)	3.8 ± 1.1 (27)	4.2 ± 1.7 (88)	.12
Pulmonary capillary wedge pressure, mmHg	26.7 ± 9.0 (47)	25.3 ± 6.2 (13)	27.2 ± 9.8 (34)	.52
Left ventricular end diastolic pressure, mmHg	29.7 ± 12.5 (41)	38.2 ± 20.7 (6)	28.3 ± 10.4 (35)	.30
Hematology and blood chemistry				
Hemoglobin, g/dL	12.8 ± 2.6 (298)	11.7 ± 2.4 (70)	13.2 ± 2.5 (228)	<.001
Bilirubin, mg/dL	0.8 ± 1.1 (143)	0.5 ± 0.3 (35)	0.9 ± 1.2 (108)	.002
Creatinine, mg/dL	1.8 ± 3.8 (293)	1.8 ± 1.8 (71)	1.9 ± 4.3 (222)	.85
Lactate, mmol/dL[a]	4.9 (2.2-9.9; 125)	4.5 (2.1-9.3; 21)	4.9 (2.3-10.1; 104)	.89

Continuous data are reported as mean ± standard deviation (N); categorical data are reported as % (n/N).
IABP, intra-aortic balloon pump; pLVAD, percutaneous left ventricular assist device.
[a] Provided as median (interquartile range; denominator), with P values generated with the Wilcoxon rank-sum test.

Table 3
Procedural characteristics.

Characteristic	All (N = 358)	Women (n = 82)	Men (n = 276)	P value
Number of vessels treated	1.6 ± 0.8 (353)	1.5 ± 0.7 (82)	1.6 ± 0.8 (271)	.26
1	55.2% (195/353)	62.2% (51/82)	53.1% (144/271)	.15
2	28.9% (102/353)	23.2% (19/82)	30.6% (83/271)	.19
3	15.9% (56/353)	14.6% (12/82)	16.2% (44/271)	.73
Number of lesions treated	2.0 ± 1.2 (352)	1.9 ± 1.3 (82)	2.1 ± 1.2 (270)	.32
pLVAD access				
Femoral	96.6% (342/354)	97.5% (79/81)	96.3% (263/273)	.60
Subclavian or axillary	5.9% (21/354)	3.7% (3/81)	6.6% (18/273)	.33
Direct (aorta)	0.6% (2/354)	0.0% (0/81)	0.7% (2/273)	1.00
pLVAD used (can have multiple)				
Impella 2.5	8.7% (31/358)	15.9% (13/82)	6.5% (18/276)	.008
Impella CP	90.8% (325/358)	82.9% (68/82)	93.1% (257/276)	.005
Impella 5.0	4.5% (16/358)	4.9% (4/82)	4.4% (12/276)	.84
Impella RP	4.2% (15/358)	3.7% (3/82)	4.4% (12/276)	.78
Subjects with >1 pLVAD device type	7.5% (27/358)	7.3% (6/82)	7.6% (21/276)	.93
pLVAD use before PCI	58.0% (204/352)	50.0% (41/82)	60.4% (163/270)	.10
Door-to-balloon time, h[a]	2.5 (1.2-16.9; 320)	2.7 (1.1-20.9; 73)	2.5 (1.3-15.7; 247)	.81
Door-to-pLVAD time, h[a]	3.0 (1.5-21.7; 314)	4.2 (1.6-24.0; 74)	3.0 (1.5-17.0; 240)	.33
Door-to-pLVAD time when STEMI, h[a]	2.1 (1.3-5.9; 214)	2.3 (1.3-6.0; 51)	2.0 (1.3-5.2; 163)	.55
Door-to-pLVAD time when NSTEMI, h[a]	16.3 (4.5-69.0; 87)	23.6 (13.6-90.1; 19)	11.3 (4.3-52.3; 68)	.08
Duration of device support, h[a]	48.0 (23.1-95.0; 331)	26.2 (7.1-72.0; 73)	50.2 (24.0-95.4; 258)	.002
Onset of cardiogenic shock to pLVAD start, h[a]	2.3 (1.1-6.9; 314)	2.5 (1.2-6.0; 74)	2.3 (1.1-7.5; 240)	.95
Intensive care unit stay, d[a]	6.0 (3.0-12.0; 332)	6.0 (2.0-11.0; 70)	6.5 (3.0-12.0; 262)	.25
Duration of index hospitalization, d[a]	8.1 (3.6-15.1; 353)	6.3 (3.1-13.7; 80)	8.3 (3.7-15.5; 273)	.22
Vessel location				
Left anterior descending	74.3% (263/354)	70.7% (58/82)	75.4% (205/272)	.39
Left main	22.0% (78/354)	24.4% (20/82)	21.3% (58/272)	.55
Left circumflex	44.6% (158/354)	37.8% (31/82)	46.7% (127/272)	.17
Right	39.3% (139/354)	42.7% (35/82)	38.2% (104/272)	.52
Graft	4.0% (14/354)	4.9% (4/82)	3.7% (10/272)	.75
TIMI flow before PCI[b]				
0	39.0% (213/546)	43.4% (53/122)	37.7% (160/424)	.26
1	7.5% (41/546)	8.2% (10/122)	7.3% (31/424)	.74
2	18.1% (99/546)	17.2% (21/122)	18.4% (78/424)	.77
3	35.4% (193/546)	31.2% (38/122)	36.6% (155/424)	.27
TIMI flow after PCI[b]				
0	2.3% (14/598)	4.8% (6/126)	1.7% (8/472)	.04
1	1.0% (6/598)	0.8% (1/126)	1.1% (5/472)	1.00
2	5.0% (30/598)	3.2% (4/126)	5.5% (26/472)	.29
3	91.6% (548/598)	91.3% (115/126)	91.7% (433/472)	.87

Continuous data are reported as mean ± standard deviation (N); categorical data are reported as % (n/N).
NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; pLVAD, percutaneous left ventricular assist device; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.
[a] Time-based variables reported as median (interquartile range; denominator), with P values generated with the Wilcoxon rank-sum test.
[b] Vessel-based.

with 0, 1-2, or >2 inotropes/vasopressors pre-pLVAD had survival rates of 70.8%, 42.9%, and 18.8%, respectively (P = .001), whereas men had survival rates of 64.4%, 54.2%, and 31.1%, respectively (P = .004). There was no difference in survival between women and men on 0-1 inotropes (64.6% versus 60.2%, P = .58), but women on ≥2 inotropes had significantly lower survival than their male counterparts (20.6% versus 42.0%, P = .03) (Central Illustration). Additional details on differences between groups based on inotrope/vasopressor use are in Supplemental Tables S8-S13.

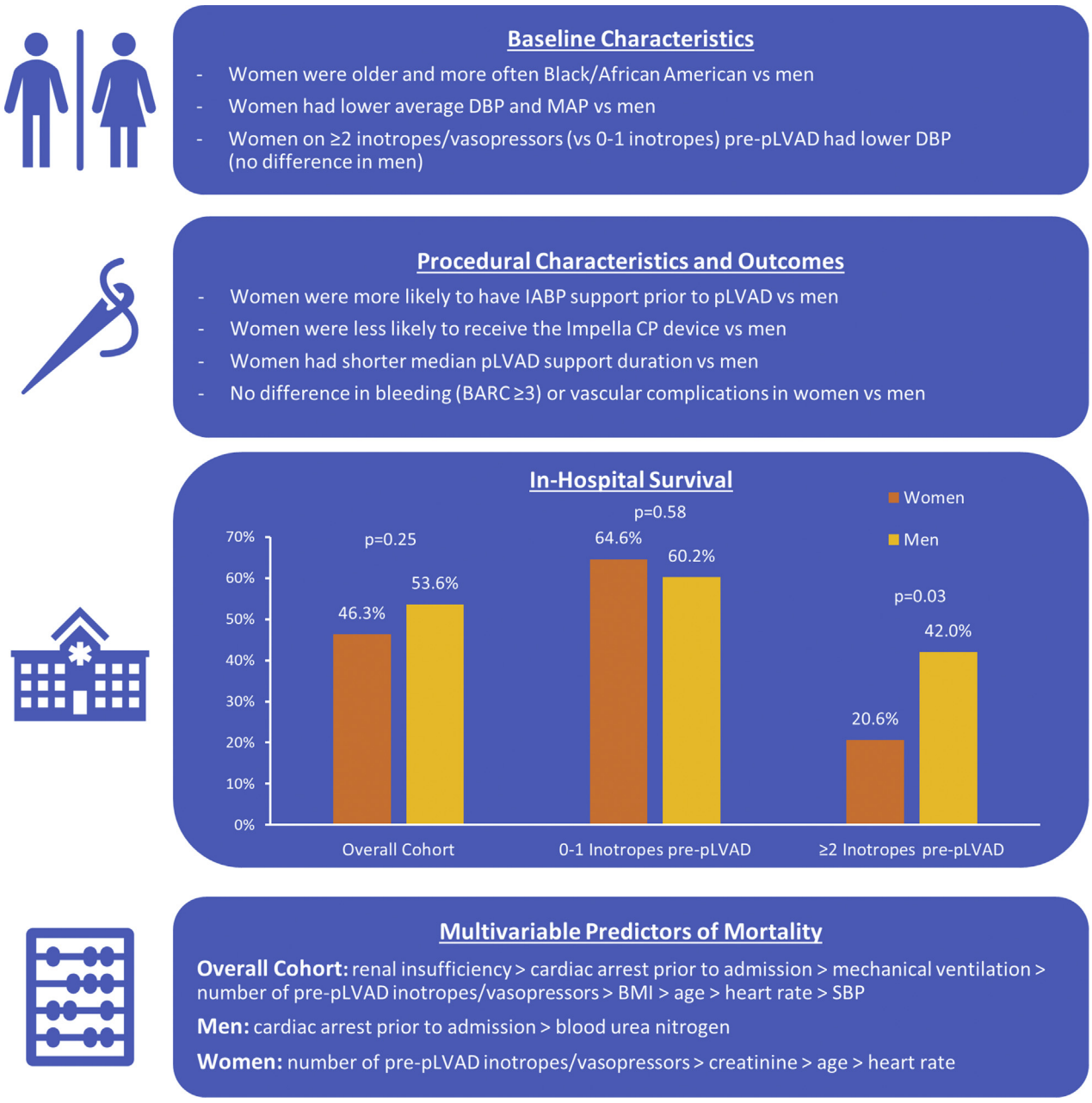
Multivariable predictors of mortality

Multivariable predictors of mortality are listed in Table 5. Sex, pre-PCI pLVAD support, and type of Impella device were not independent

Table 4
In-hospital outcomes.

Outcome	All (N = 358)	Women (n = 82)	Men (n = 276)	P value
Death	48.0% (172/358)	53.7% (44/82)	46.4% (128/276)	.25
Repeat myocardial infarction	2.0% (7/358)	2.4% (2/82)	1.8% (5/276)	.72
Cerebrovascular accident/stroke	5.0% (18/358)	3.7% (3/82)	5.4% (15/276)	.52
Transient ischemic attack	0.6% (2/358)	0.0% (0/82)	0.7% (2/276)	1.00
Revascularization (coronary)	0.3% (1/358)	0.0% (0/82)	0.4% (1/276)	1.00
Bleeding (≥BARC 3)	10.3% (37/358)	11.0% (9/82)	10.1% (28/276)	.83
Blood transfusion	8.9% (32/358)	9.8% (8/82)	8.7% (24/276)	.77
Vascular complication requiring surgery	5.0% (18/358)	8.5% (7/82)	4.0% (11/276)	.10
Vascular complication without surgery	5.3% (19/358)	4.9% (4/82)	5.4% (15/276)	.84
Acute renal dysfunction/failure	21.2% (76/358)	15.9% (13/82)	22.8% (63/276)	.18
New renal replacement therapy required	4.5% (16/358)	2.4% (2/82)	5.1% (14/276)	.31

Data are reported as % (n/N).
BARC, Bleeding Academic Research Consortium.



Central Illustration. Sex differences in characteristics, treatments, and outcomes in patients with AMICS treated with pLVAD. AMICS, acute myocardial infarction complicated by cardiogenic shock; BARC, Bleeding Academic Research Consortium; BMI, body mass index; DBP, diastolic blood pressure; IABP, intra-aortic balloon pump; MAP, mean arterial pressure; pLVAD, percutaneous left ventricular assist device; SBP, systolic blood pressure.

predictors of mortality. For men, the strongest predictor was cardiac arrest prior to admission (OR = 2.3, $P = .01$), and for women it was the maximum number of inotropes/vasopressors prior to pLVAD implantation (OR = 3.0, $P = .01$) (Table 6).

Discussion

In this sex-based analysis of the RECOVER III registry, patients with AMICS treated with PCI and Impella support continue to have poor survival (52%) to hospital discharge, with no apparent survival differences between women and men. This study does, however, provide important insights into different treatment approaches and outcomes for women and men and potential opportunities for improved outcomes for women. Escalation of inotropes and delayed pLVAD support post-PCI rather than immediately pre-PCI were factors associated with significantly worse mortality overall but were more pronounced in women. In fact, the strongest predictor of mortality for women was the maximum number of inotropes/vasopressors administered prior to pLVAD support. Our analysis suggests that in women every additional pre-pLVAD inotrope/vasopressor used is associated with greater harm than in men. Notably after adjustment, pre-PCI pLVAD implantation was not a significant predictor of mortality. This suggests that the timing of pLVAD pre-PCI *per se* may not improve mortality, but rather early pLVAD utilization before worsening hemodynamic compromise, manifested by escalating number of inotropes/vasopressors, can have a significant survival benefit, especially in women. Sustained hypoperfusion together with the inherent effects of inotropes and vasopressors on increasing myocardial oxygen consumption and afterload, thereby increasing the

Table 5
Multivariable analysis for in-hospital mortality.

Variable	Odds ratio estimate	Lower 95% confidence limit for odds ratio	Upper 95% confidence limit for odds ratio	*P* value
Renal insufficiency	2.72	1.31	5.68	.008
Cardiac arrest	2.15	1.18	3.90	.01
Mechanical ventilation	1.93	1.08	3.45	.03
Maximum number of inotropes/ vasopressors before pLVAD	1.38	1.09	1.74	.008
Body mass index, kg/m^2	1.05	1.01	1.10	.02
Age, y	1.04	1.01	1.06	.01
Heart rate, bpm	1.01	1.00	1.02	.01
Systolic blood pressure, mmHg	1.01	1.00	1.02	.03
Male sex	0.85	0.44	1.64	.62
Pre-PCI pLVAD	0.78	0.44	1.38	.39
Number of vessels treated	0.74	0.51	1.08	.12

Multivariable analysis was performed on 275 patients with available data (154 survivors, 121 nonsurvivors). Covariates with $P < .1$ in the univariable analysis were included in the multivariable model, as well as pre-PCI pLVAD, and sex. Age, heart rate, systolic blood pressure, the maximum number of inotropes/vasopressors, body mass index, and the number of vessels treated were continuous variables.

PCI, percutaneous coronary intervention; pLVAD, percutaneous left ventricular assist device.

Table 6
Multivariable analysis for in-hospital mortality in male- and female-specific models.

Variable	Odds ratio estimate	Lower 95% confidence limit	Upper 95% confidence limit	*P* value
Male model[a]				
Prior coronary artery bypass grafting	2.50	0.85	7.32	.10
Cardiac arrest	2.33	1.20	4.49	.01
Mechanical ventilation	1.66	0.87	3.19	.13
Maximum number of inotropes/vasopressors pre-pLVAD	1.18	0.89	1.56	.25
Blood urea nitrogen, mg/dL	1.02	1.00	1.05	.04
Age, y	1.01	.99	1.04	.37
Pre-PCI pLVAD	0.88	0.46	1.69	.70
Female model[b]				
Mechanical ventilation	5.94	0.84	41.82	.07
Maximum number of inotropes/vasopressors before pLVAD	3.03	1.26	7.29	.01
Creatinine, mg/dL	1.81	1.03	3.19	.04
Age, y	1.09	1.01	1.19	.04
Heart rate, bpm	1.06	1.02	1.09	.003
Number of vessels treated	0.37	0.11	1.25	.11
Pre-PCI pLVAD	0.30	0.05	1.94	.21

PCI, percutaneous coronary intervention; pLVAD, percutaneous left ventricular assist device.

[a] Multivariable analysis was performed on 194 male patients with available data for all variables included in the model (109 survivors, 85 nonsurvivors).

[b] Multivariable analysis was performed on 65 female patients with available data for all variables included in the model (33 survivors, 32 nonsurvivors). Age, heart rate, systolic blood pressure, the maximum number of inotropes/vasopressors, blood urea nitrogen, creatinine, and the number of vessels treated were continuous variables.

risk of myocardial ischemia and arrhythmias,[1,13] likely contribute to the observed staggering mortality rates. Thus, implanting pLVAD devices for hemodynamic support prior to starting these potentially cardiotoxic agents (or as soon as possible) in patients with CS may provide a mortality benefit, especially in women. This is consistent with a recent matched analysis comparing IABP with pLVAD, which found that pLVAD was superior to IABP only in CS patients who received MCS before catecholamine medications.[11]

While there was no survival difference by sex in patients on 0-1 inotropes/vasopressors, in the more critically ill patients on ≥2 inotropes/vasopressors, women had significantly worse survival. Potential reasons may relate to the established differences in cellular response to stress and beta-adrenergic stimulation by sex, particularly in patients with heart disease.[14,15] Second, women may be more predisposed to cardiac ischemia secondary to inotropes/vasopressors due to higher rates of microvascular dysfunction and/or greater coronary vessel wall thickness and diffusion radius relative to cardiomyocyte width.[16] Similarly, women with AMICS tend to have lower rates of smoking and prior myocardial infarction than men, which may limit their ischemic preconditioning and collateral circulation.[17] Indeed, in our study, women on ≥2 inotropes/vasopressors pre-pLVAD had significantly lower DBP (and consequently less coronary perfusion) than women on 0-1 inotropes, which was not seen for men. It is possible that earlier pLVAD support before inotrope/vasopressor escalation may offset these effects in women. Other procedural factors more commonly seen in women, including greater initial use of IABP prior to pLVAD escalation and shorter total duration of pLVAD support, may contribute to the observed mortality trends and may represent an opportunity to standardize care between the sexes and improve outcomes. Ultimately, the reason for this sex-specific survival discrepancy in critically ill patients merits further exploration.

Some predictors identified in our multivariable analysis were also identified as risk factors of similar magnitude in pLVAD-treated cardiogenic shock patients in the IMP-IT registry,[18] including age, body mass index, mechanical ventilation, and inotropic support. The association of increased body mass index with mortality suggests that smaller patients receiving more support per kilogram may have better outcomes.

Although it is well established that pLVADs provide superior hemodynamic support compared with IABP,[5,6] it generally comes at the cost of increased rates of major bleeding—as high as 25-30% in some studies.[6,19,20] In our study, the rate of major bleeding was 10.3%, and the rate of vascular complications requiring surgery was 5.0%. This compares favorably to the prior sex analysis from the cVAD registry in 2016,[8] which reported rates of bleeding requiring transfusion and vascular site complications requiring surgery of 15.6% and 11.7%, respectively, without significant excess bleeding in women. In our study, rates of major bleeding and vascular complications are lower for both sexes, but more so for women, even with the larger Impella CP device. This reflects improved operator experience with large bore insertion techniques since initial approval of the Impella 2.5, improved devices, and patient selection that has evolved over the last decade. This should mitigate fears of increased access site and bleeding complications in women receiving pLVAD devices and likely explains in part why women are less likely to be treated with MCS[21,22] and why women received Impella CP less often than men in our study.

Limitations

This analysis has the inherent limitations of observational studies that cannot control for unmeasured confounders despite multivariable adjustment. All events were site reported and not adjudicated by an independent committee. The analysis was limited by the relatively small number of female patients. Systematic under-utilization of more aggressive therapies in female patients in this area has been widely reported in the literature.[21–25] Until such time as these treatment disparities are addressed, the majority of sex-stratified analyses in clinical trials and real-world studies will suffer from a smaller female cohort. Finally, the results of this study are intended to be hypothesis generating.

Conclusion

In RECOVER III, survival of patients with AMICS treated with PCI and Impella support was 52% at hospital discharge and was similar for men and women. Women with AMICS may derive greater survival benefit than men from early pLVAD support prior to escalation of inotropes/vasopressors without evidence of an increased risk of access-related complications.

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Declaration of competing interest

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Supplementary material

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Peer review statement

Given their roles as Associate Editor and Editor in Chief, Cindy Grines and Alexandra Lansky had no involvement in the peer review of this article and have no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Dean J. Kereiakes.

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