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Original Article

Gender disparities with the use of percutaneous left ventricular assist device in patients undergoing percutaneous coronary intervention complicated by cardiogenic shock: From pVAD Working Group

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ABSTRACT

Background: Hemodynamic support with Impella (Abiomed Inc., Danvers, MA) devices is becoming a more prevalent treatment option for patients with cardiogenic shock (CS) undergoing percutaneous coronary intervention (PCI). There exists only limited published data regarding outcome differences between male and female patients. Therefore, the objective of this paper is to analyze these gender differences between short-term survival and in-hospital outcomes in those undergoing PCI with CS.
Methods: Between January 2011 and July 2016, patients undergoing PCI with simultaneous use of Impella were identified. Only patients presenting with CS were included in the analysis. All-cause in-hospital mortality was the primary outcome. Using SAS 9.4 for propensity score matching, additional secondary outcomes were also compared.
Results: The primary outcome was comparable between males and females (39.5% vs. 26.3%, p = 0.33) in CS patients. Secondary outcomes were also comparable and included: myocardial infarction, stroke, CS, heart failure, dialysis requirement, bleeding within 72 h, blood transfusion, dysrhythmia, composite of all complications, major adverse cardiac events. Survival at 30 days was equal in both groups. A reduced mortality in males was noted for pre-PCI initiation of Impella. Additionally, both genders who received pre-PCI Impella support, experienced a significant reduction in inotrope use.
Conclusions: Despite the small number of cohorts, this study did not reveal any significant differences among gender with the use of percutaneous left ventricular assist devices for PCI in patients with acute myocardial infarction complicated by CS. However, initiation of Impella prior to PCI may be associated with improved mortality and morbidity in both genders.

1. Introduction

The incidence of cardiogenic shock (CS) in patients presenting with acute myocardial infarction (AMI) is nearly 10%.[1,2] The incidence of CS increased two-fold between 2004 and 2014.[3] Even after prompt percutaneous coronary intervention (PCI) and other adjunctive therapies, mortality rates for these patients reaches nearly 70%.[1,2] It should be noted that mortality has mildly decreased from 2004 to 2014; however, it still hovers around 50%.[3] Trans-valvular mechanical circulatory support (MCS) has been associated with improved hemodynamics and myocardial recovery by unloading the left ventricle and decreasing myocardial oxygen demand.[4] Guidelines have recommended the use of MCS, in addition to early revascularization and pharmacological management, in patients with AMI complicated by CS (AMI-CS).[5] When looking at gender differences, females are more likely to have worse comorbidities and less likely to be treated with intraaortic balloon pump (IABP) in the setting of CS due to a myriad of reasons.[6,7] Hence, females, compared to males, are likely to have higher mortality rates in the setting of CS.[8,9] However, the SHOCK registry showed no gender differences in in-hospital mortality, and revealed similar benefits for males and females after PCI for AMI-CS.[6]

Although Joseph et al compared outcomes in males and females undergoing PCI for AMI-CS with Impella 2.5 support, the conclusion reached from the investigation was limited by their lack of adjustment and by the utilization of only smaller pumps.[10]

Abbreviations: CS, cardiogenic shock; PCI, percutaneous coronary intervention; AMI, acute myocardial infarction; MCS, mechanical circulatory support; IABP, intraaortic balloon pump; pLVAD, percutaneous left ventricle assist device; EKG, electrocardiogram.

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Moreover, there is no gender difference in patients undergoing high-risk procedures using Impella; however, gender differences for patients with CS when using Impella is not clear.[11] This data sought to analyze the differences in short-term survival and in-hospital outcome between males and females undergoing PCI for AMI-CS in a "real-world" patient cohort. Our analysis included the clinical outcomes up to 30-days for both Impella 2.5 and Impella CP. Furthermore, as shown by a previous article for only left main disease, this discussion assessed whether the placement of percutaneous left ventricular assist device (pLVAD) prior to PCI was beneficial to either gender.[12]

2. Methods

2.1. Study design and data collection

Data were obtained from two high volume tertiary care centers in New York City between January 2011 and July 2016. Data were collected at both sites using the USpella registry form to record baseline, clinical and procedural characteristics. Follow-up records were also recorded and were obtained from the electronic medical records. At both sites, all patients receiving Impella 2.5 or Impella CP support during PCI for AMI-CS were identified. From the total 35,910 patients who underwent PCI, 241 were supported with Impella devices. 160 patients were considered "high-risk", but without CS, and were analyzed differently due to their different risk profiles. The remaining 81 patients who underwent PCI for AMI-CS supported with Impella were included in this study [Supplementary Fig. S1]. The timing of Impella insertion was decided by the operating physician's discretion. Crude mortality rates in patients with Impella support prior to PCI were compared to post-PCI in both genders.

Patients were treated with drug-eluting stents (DES) and/or bare metal stents (BMS) and/or percutaneous transluminal coronary angioplasty according to individual operator's discretion. Furthermore, the number of vessels and lesions treated, and the use of adjunctive therapies was also decided by the operating physician. Patients with other types of cardiac support such as tandem heart, IABP, extra-corporeal membrane oxygenation were excluded. The investigators had full access to the data and control of the data analysis. Institutional review board approval was obtained for this paper.

2.2. Endpoints and definitions

The primary endpoint was all-cause in-hospital mortality. Secondary endpoints included in-hospital AMI, stroke, CS, heart failure, dialysis requirement, bleeding within 72 h, blood transfusion, dysrhythmia, composite of all complications, major adverse cardiac events (MACE), and status of the patient at 30 days. MACE was a composite of all-cause in-hospital mortality, AMI, and stroke. AMI was defined as a creatine kinase-MB fraction greater than three times the upper limit of normal, or the development of a new pathological q wave on the electrocardiogram (EKG). Major bleeding events were defined as a hemoglobin drop of $\geq$3 g/dL, blood transfusion, or blood loss requiring a procedural intervention to stop the bleeding. The diagnosis of CS was based on the definition from the USpella registry: (1) systolic blood pressure $<$90 mmHg for $>$30 min or the need for vasopressor and/or inotropic therapy and/or IABP to maintain a systolic blood pressure greater than 90 mmHg; (2) signs of organ hypoperfusion such as oliguria/anuria, altered mental status, or cold extremities. In-hospital mortality is reported as the proportion of patients who died during their hospital stay.

2.3. Device details

The Impella 2.5 and Impella CP (Abiomed Inc., Danvers, MA) devices have been explained previously.[13,14] Briefly, Impella 2.5 is a 12 Fr pLVAD, which generates up to 2.5 L/min of forward flow into the ascending aorta. Impella CP is a 14 Fr pLVAD device, which provides a forward flow up to 3.5 L/min. Both devices are inserted through the femoral artery using a modified Seldinger technique.

2.4. Statistical analysis

Continuous data are expressed as the mean $\pm$ standard deviation (SD) and categorical data are expressed as frequencies and percentages. Continuous variables were computed using the student's *T*-test. Categorical data were evaluated using a Chi-square test. Statistical analysis was done using SAS 9.4 (SAS Institute, Cary, NC). To adjust for the baseline characteristics and procedural details, a propensity score matched analysis using logistic regression model was performed, which also reduced selection bias. First, a propensity score was generated for each patient using an automated step-wise logistic regression method. Covariates in the matching model included baseline demographics, cardiovascular risk factors, relevant comorbidities, procedural characteristics, and in-hospital outcomes. Next, patients were matched based on their propensity scores keeping the calliper width 0.2. We utilized 1:2 matching protocol without replacement. Next, unmatched patients were excluded from the analysis. Then, outcomes were compared using McNemar's test and Wilcoxon signed rank test as appropriate. The absolute standardized difference is below 10% after matching to ensure the small difference between groups after matching.[15] Statistically significant results were considered at p-value $<$ 0.05. All tests performed were two-sided.

Table 1
Baseline characteristics in cardiogenic shock patients with Impella use: stratified by gender (unmatched cohorts).

Variable name	Male (N = 62)	Female (N = 19)	P value
Age (years)	61.1 $\pm$ 13.1	67.3 $\pm$ 15.1	0.08
Body mass index (kg/m^2)	28.2 $\pm$ 5.6	25.6 $\pm$ 5.4	0.08
Race:			
White	30 (48.4%)	9 (47.4%)	0.71
Black	6 (9.7%)	4 (21.1%)	
Asian	17 (27.4%)	4 (21.1%)	
Other	9 (14.5%)	2 (10.5%)	
Baseline characteristics:			
Hypertension	47 (75.8%)	16 (84.2%)	0.44
Renal failure	7 (11.3%)	1 (5.3%)	0.44
Dialysis	2 (3.2%)	1 (5.3%)	0.68
Diabetes mellitus	24 (38.7%)	9 (47.4%)	0.50
Smoker	19 (30.6%)	2 (10.5%)	0.08
Peripheral vascular disease	5 (8.1%)	1 (5.3%)	0.68
Myo/endocarditis	2 (3.2%)	0 (0%)	0.43
Hyperlipidemia	32 (51.6%)	9 (47.4%)	0.75
Chronic lung disease	2 (3.2%)	2 (10.5%)	0.20
Prior myocardial infarction	14 (22.6%)	4 (21.1%)	0.89
Dysrhythmia	4 (6.4%)	1 (5.3%)	0.85
Cerebrovascular disease	1 (1.6%)	0 (0%)	0.58
Prior coronary artery disease	30 (48.4%)	10 (52.6%)	0.75
Congestive heart failure	25 (40.3%)	7 (36.8%)	0.79
Valvular disease	4 (6.4%)	0 (0%)	0.26
Ischemic cardiomyopathy	20 (32.3%)	1 (5.3%)	0.02
Prior CABG	11 (17.7%)	1 (5.3%)	0.18
Prior PCI	19 (30.6%)	4 (21.1%)	0.42

CABG – coronary artery bypass grafting, PCI – Percutaneous Coronary Intervention. Frequencies are in number (%) or mean $\pm$ standard deviation.

Table 2
Procedural details in cardiogenic shock patients with Impella use: stratified by gender (unmatched cohorts).

Variable name	Male (N = 62)	Female (N = 19)	P value
STS mortality	12.0 ± 11.4	12.1 ± 11.8	0.98
STS morbidity	50.2 ± 21.9	47.0 ± 20.8	0.58
LVEDP (%)	28.7 ± 8.7	26.9 ± 7.7	0.42
Grace score	137.1 ± 32.8	152.6 ± 30.6	0.07
Ejection fraction (%)	20.2 ± 9.3	22.5 ± 11.0	0.36
Total CCU stay (days)	10.6 ± 14.4	11.4 ± 18.9	0.85
Lesion length (mm)	17.4 ± 3.4	18.9 ± 3.6	0.10
Lesion diameter (mm)	2.5 ± 0.3	2.6 ± 0.2	0.27
Ultrasound guided access	26 (41.9%)	4 (21.1%)	0.10
Left main stenosis	15 (24.2%)	5 (26.3%)	0.85
>1 vessels treated	20 (32.3%)	4 (21.1%)	0.35
Atherectomy	3 (4.8%)	2 (10.5%)	0.37
Impella 2.5	26 (41.9%)	10 (52.6%)	0.41
Impella CP	36 (58.1%)	9 (47.4%)	

STS – Society of Thoracic Surgeons, LVEDP – Left Ventricle End Diastolic Pressure, CCU – Coronary Care Unit. Frequencies are in number (%) or mean ± standard deviation.

Table 3
In-hospital outcomes in cardiogenic shock patients with Impella use: stratified by gender (unmatched cohorts).

Variable name	Male (N = 62)	Female (N = 19)	P value
In-hospital mortality	22 (35.5%)	5 (26.3%)	0.46
Myocardial infarction	6 (9.7%)	0 (0%)	0.16
Congestive heart failure	6 (9.7%)	1 (5.3%)	0.55
Stroke	1 (1.6%)	0 (0%)	0.58
Dialysis	1 (1.6%)	0 (0%)	0.58
Bleeding within 72 h	3 (4.8%)	0 (0%)	0.33
Blood transfusion	12 (19.3%)	2 (10.5%)	0.37
Dysrhythmia	3 (4.8%)	2 (10.5%)	0.37
MACE[a]	29 (46.8%)	5 (26.3%)	0.11
Any complications[b]	44 (71%)	9 (47.4%)	0.05
Alive at 30 Days	33 (53.2%)	10 (52.6%)	0.96

MACE – major adverse cardiac event. Frequencies are in number (%) or mean ± standard deviation.
[a] MACE included all-cause in-hospital mortality, myocardial infarction or stroke.
[b] Any complication is a presence of any complications describe above.

3. Results

3.1. Analysis prior to propensity score matching

A total of 81 patients presented for AMI-CS were included (Table 1). Patients were critically ill as 100% of patients had CS on admission or 24 h prior to the procedure. Females presented with higher age compared to males but was statistically non-significant (67.3 vs. 61.1 years, p = 0.08). Body mass index was higher in males compared to females but was also statistically non-significant (28.2 vs. 25.6 kg/m^2, p = 0.08). Much of the population was white (48.1%) followed by Asian (25.9%). No differences existed in any baseline or procedural characteristics except for ischemic cardiomyopathies, which was significantly higher in males (32.3% vs 5.3%, p = 0.02). Impella CP was used more frequently (55.5%) compared to Impella 2.5 (Table 2). Systolic, diastolic, and mean arterial blood pressure was illustrated before PCI and during Impella support. Systolic blood pressure in males and females increased significantly after Impella Support. Diastolic blood pressure and mean blood pressure increased in males after Impella support (Fig. 1). All-cause in-hospital mortality was seen in 27 (33.3%) patients. A total of 22 (35.5%) males and 5 (26.3%) females died on discharge (Table 3). In-hospital mortality was nearly 50% higher in males. Patients were divided into two groups: one group received Impella support prior to PCI (Pre-PCI) and the other received Impella support during or after PCI (Post-PCI). In-hospital mortality was significantly lower when using Impella pre-PCI in males (58.3% vs. 21%, p = < 0.01); whereas, a statistically

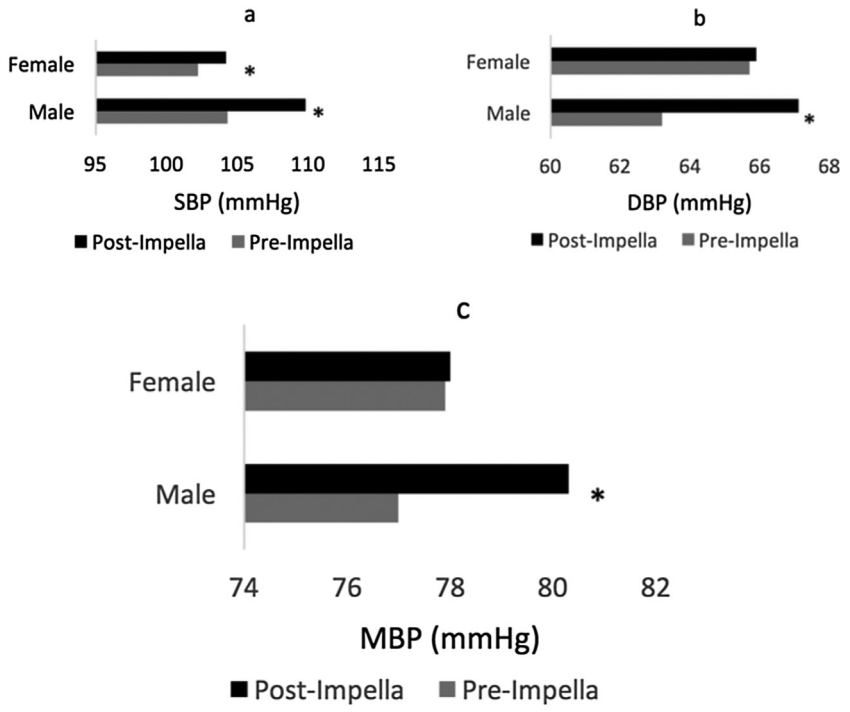

Fig. 1. (a) Systolic blood pressure values pre- and post-Impella support. (b) Diastolic blood pressure values pre- and post-Impella support. (c) Mean blood pressure values pre- and post-Impella support.
SBP – Systolic blood pressure, DBP – Diastolic blood pressure, MBP – Mean blood pressure Values described here are either immediately before the procedure and at least 3 h after the removal of Impella device. An asterisk (*) indicates P values below 0.05.

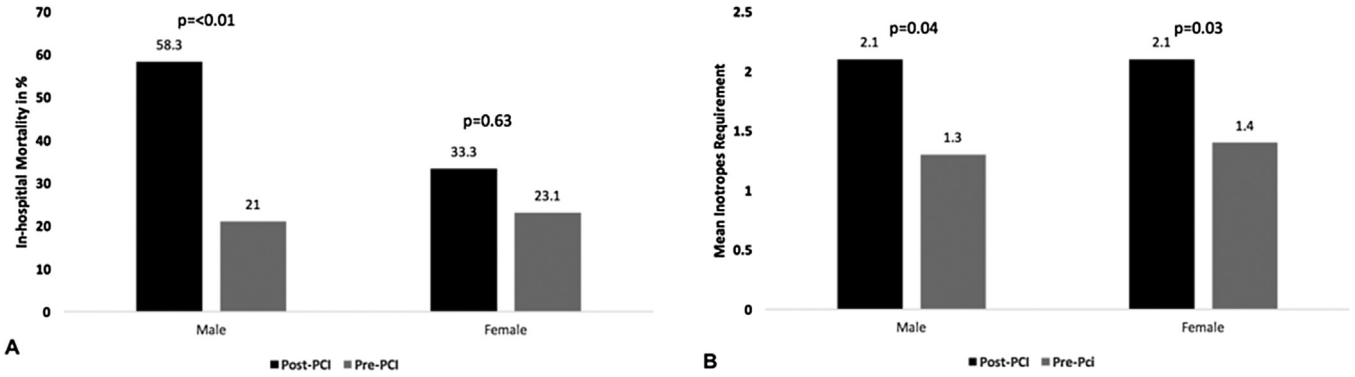

Fig. 2. (a) In-hospital mortality decreases in males when using Impella before PCI. (b) Inotropes requirements reduced in both gender when using Impella before PCI. PCI – Percutaneous coronary intervention.

non-significant reduction was noted in females (33.3% vs. 23.1%, p = 0.63) (Fig. 2a). When using Impella pre-PCI, the mean number of inotropes requirement was significantly reduced in both males (2.1 vs. 1.3, p = 0.04) and females (2.1 vs. 1.4, p = 0.03) (Fig. 2b).

3.2. Analysis after propensity score matching

After propensity score matching, 57 patients were in the CS group: among them, 38 males and 19 females (Table 4). No difference in the primary outcome existed between males and females (39.5% vs 26.3%, p = 0.3265). Furthermore, no differences were noted with in any of the secondary outcomes such as AMI, CS, congestive heart failure, stroke, dialysis, bleeding, transfusion, dysrhythmia, MACE or composite of all complications. Finally, the survival rate at 30 days was equal in both groups.

4. Discussion

This study compares short-term in-hospital outcomes between males and females undergoing PCI complicated with CS and treated with Impella devices. No significant baseline differences were noticed between males and females. This study showed males and females to have similar short-term in-hospital outcomes when undergoing PCI complicated by CS. Additionally, the data revealed equal survival rates on discharge at 30-days post-procedure when supported by Impella device during PCI procedure. When choosing patients early and appropriately for the use of Impella after identification of CS in patients undergoing PCI, males and females showed no differences, despite having slight baseline differences.

Compared to a previously reported article on patients with CS treated with Impella, this study revealed a lower all-cause in-hospital mortality (33.3%).[13] Other in-hospital outcomes such as CS, congestive heart failure, bleeding, transfusion, and dysrhythmia were noted to be lower as well. Post-procedural AMI was 5.3% and post-procedural stroke was 1.7% in patients with CS. The safety and efficacy have been explained earlier in several articles.[13,16,17] Thus, this study demonstrates the ability of Impella 2.5 and Impella CP devices to provide equally effective therapy for both male and female patients with AMI-CS undergoing PCI.

Previous studies showed worse outcomes with women compared to men when PCI is complicated by CS.[18,19] Mcllvennan et al showed higher in-hospital mortality in females compared to males.[20] However, results from the SHOCK registry revealed that males and females benefitted equally from the revascularization procedure complicated with CS.[6] A total of 115 females and 176 males underwent PCI in the SHOCK registry and showed similar (49.6% vs. 43.8%, p = 0.33) in-hospital mortality. The IABP SHOCK II-trial showed no gender-related differences in patients with CS undergoing PCI, even after multivariate analysis.[7] A recent study by Joseph et al showed no differences (46.6% vs. 38.8%, p = 0.3) in outcomes when using Impella 2.5 in patients with CS.[10] Another study by Meeteren et al showed similar outcomes in males and females after LVAD support.[21] Several other articles reported no differences in outcomes between males and females with CS.[22–24] This study supports these results by revealing no differences after using Impella 2.5 or Impella CP as a bridge to PCI complicated by CS. Operators at this institute are highly skilled due to the high volume of devices utilized annually and the standardized approach used to treat those patients. Also, the present study did not display significant differences in baseline or procedural characteristics due to the small sample size, which may account for the similar outcomes observed. The use of Impella 2.5 and Impella CP prior to PCI can show further benefits when used appropriately.[10,12] The benefit of pre-PCI pLVAD was demonstrated as well. Although the mortality benefit was seen in both males and females, only males had a significant difference; additionally, the reduction of inotropes utilized significantly decreased in both males and females.

Several limitations should be recognized as this is a retrospectively analyzed observational study. The small numbers of patients in each group may be the culprit for not finding gender differences. In unmatched cohorts, overall complication rates were 71% in males compared to 47.4% in females (p = 0.05). If the power of the study increases slightly, better overall outcomes for females, including in-hospital mortality, may have been observed. For most patients, the time spanning from onset of symptoms to revascularization was not recorded, and was thus not included as a study variable. This is an experience from two tertiary-care centres in New York City; therefore, more data is needed to generalize if any differences exist in larger cohorts. However, this study did not subselect patients, included all comers with AMI complicated with CS, and all patients were treated with Impella 2.5 or Impella CP. Although this is an association and hypothesis generating, a conclusion regarding the use of Impella prior to PCI cannot be made from this study as there is no control group.

In conclusion, short-term outcomes are not significantly different among males and females undergoing PCI complicated with CS and supported by Impella. Although there is a trend toward better outcomes in females compared to males, a larger study cohort may have demonstrated such significance. In this study, pre-PCI initiation of pLVAD when treating AMI-CS has demonstrated benefits in both males and females.

Table 4
Impella in patient with acute myocardial infarction complicated by cardiogenic shock: stratified by gender (propensity score-matched analysis).

Variable name	Male (N = 38)	Female (N = 19)	P value
Age (years)	61.5 ± 12.6	67.3 ± 15.1	0.14
Body mass index (kg/m^2)	28.1 ± 4.8	25.6 ± 5.4	0.07
Race:			
White	21 (55.3%)	9 (47.4%)	0.19
Black	3 (7.9%)	4 (21%)	
Asian	9 (23.7%)	4 (21%)	
Other	5 (12.1%)	2 (10.5%)	
Baseline characteristics:			
Hypertension	29 (76.3%)	16 (84.2%)	0.49
Renal failure	3 (7.9%)	1 (5.3%)	0.71
Dialysis	1 (2.6%)	1 (5.3%)	0.61
Diabetes mellitus	18 (47.4%)	9 (47.4%)	1.00
Smoker	10 (26.3%)	2 (10.5%)	0.17
Peripheral vascular disease	1 (2.6%)	1 (5.3%)	0.61
Myo/endocarditis	2 (5.3%)	0 (0%)	0.32
Hyperlipidemia	22 (57.9%)	9 (47.4%)	0.45
Chronic lung disease	1 (2.6%)	2 (10.6%)	0.21
Prior myocardial infarction	6 (15.8%)	4 (21%)	0.62
Dysrhythmia	1 (2.6%)	1 (5.3%)	0.61
Cerebrovascular disease	0 (0%)	0 (0%)	N/A
Prior coronary artery disease	16 (42.1%)	10 (52.6%)	0.45
Congestive heart failure	11 (28.9%)	7 (36.8%)	0.54
Valvular disease	1 (2.6%)	0 (0%)	0.48
Ischemic cardiomyopathy	2 (5.3%)	1 (5.3%)	1.00
Prior coronary artery bypass grafting	4 (10.5%)	1 (5.3%)	0.51
Prior percutaneous coronary intervention	11 (28.9%)	4 (21%)	0.52
Procedural Characteristics:			
STS mortality	14 ± 12.5	12.1 ± 11.8	0.57
STS morbidity	54.1 ± 22.8	47 ± 20.8	0.26
LVEDP (%)	29.8 ± 9.4	26.9 ± 7.7	0.25
Grace score	136.5 ± 34.4	152.6 ± 30.6	0.09
Ejection fraction (%)	20.9 ± 8.4	22.5 ± 11	0.55
Total CCU stay (days)	10.7 ± 12.1	11.4 ± 18.9	0.86
Lesion length (mm)	17.5 ± 3.5	18.9 ± 3.6	0.14
Lesion diameter (mm)	2.5 ± 0.4	2.6 ± 0.2	0.40
Ultrasound guided access	15 (39.5%)	4 (21%)	0.16
Left main stenosis	9 (23.7%)	5 (26.3%)	0.83
>1 vessel treated	11 (28.9%)	4 (21%)	0.41
Atherectomy	1 (2.6%)	2 (10.5%)	0.21
Impella 2.5	12 (31.6%)	10 (52.6%)	0.12
Impella CP	26 (68.4%)	9 (47.4%)	
In-hospital outcomes:			
In-hospital mortality	15 (39.5%)	5 (26.3%)	0.33
Myocardial infarction	3 (7.9%)	0 (0%)	0.22
Congestive heart failure	4 (10.5%)	1 (5.3%)	0.51
Stroke	1 (2.6%)	0 (0%)	0.48
Dialysis	0 (0%)	0 (0%)	N/A
Bleeding within 72 h	2 (5.3%)	0 (0%)	0.32
Blood transfusion	7 (18.4%)	2 (10.5%)	0.44
Dysrhythmia	1 (2.6%)	2 (10.5%)	0.21
MACE[a]	19 (50%)	5 (26.3%)	0.09
Alive at 30 days	19 (50%)	10 (52.6%)	0.85

STS – society of thoracic surgeons, LVEDP – left ventricle end diastolic pressure, CCU – coronary care unit, MACE – major adverse cardiac event. Frequencies are in number (%) or mean ± standard deviation.

[a] MACE included all-cause in-hospital mortality, myocardial infarction or stroke.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ihj.2018.04.009.

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