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WOMEN AND ISCHEMIC HEART DISEASE (P. KOHLI, SECTION EDITOR)

Mechanical Circulatory Support: a Comprehensive Review With a Focus on Women

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Abstract

Purpose of the Review The purpose of this review is to analyze the evidence for use of mechanical circulatory support (MCS) with a focus on women, namely, intra-aortic balloon pump (IABP), Impella, ventricular assist devices (VAD), and extracorporeal membrane oxygenation (ECMO).

Recent Findings There is paucity of data examining management options for cardiogenic shock (CS) in women specifically. In published data, although only a minority of MCS recipients (33%) were women, there is a trend toward even lower use in women relative to men over time. Women presenting with CS tend to have a higher risk profile including older age, greater comorbidities, higher Society of Cardiothoracic Surgery (STS) mortality scores, more hypotension and index vasopressor requirements, and longer duration of CS. Overall, women receiving mechanical support suffer increased bleeding and vascular complications and have higher 30-day readmission rates.

Summary The incidence of cardiogenic shock (CS) has been rising at a higher rate in women compared to men**.** Women in CS tend to present with an overall higher risk profile including older age, greater burden of medical comorbidities, more hypotension and index vasopressor requirements, higher STS mortality scores, and more out-of-hospital cardiac arrest. After adjusting for comorbidities and traditional cardiovascular risk factors, mortality remained higher in younger women compared to men of similar age. In spite of these facts, evidence points to the underutilization of support devices in eligible female patients. Higher complication rates, such as vascular complications requiring surgery and bleeding requiring transfusion, may be deterring factors that limit the use of MCS and hinderoperator confidence and experience with devices in women. This suggests that future research should address the sex disparities in outcomes of contemporary MCS practices.

Keywords Women · Cardiogenic shock (CS) · Mechanical circulatory support (MCS) · Intra-aortic balloon pump (IABP) · Impella · Ventricular assist device (VAD) · Extracorporeal membrane oxygenation (ECMO)

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Introduction

The incidence of cardiogenic shock (CS) complicating acute myocardial infarction (AMI) has risen in recent years at a higher rate in women compared to men [1–3, 4••, 5, 6]. Women are at increased risk of developing CS even when presenting with less extensive coronary artery disease (CAD) and smaller infarct size [7]. Women in CS tend to present with an overall higher risk profile including older age, greater comorbidities, higher STS mortality scores, more hypotension and vasopressor requirements, higher 30-day readmission rates, and a trend toward longer duration of CS [8–11]. Although female CS patients are generally older than their male counterparts, young women more commonly present with several female-predominant causes of AMI and CS such as peripartum cardiomyopathy (PPCM), Takotsubo cardiomyopathy (TC), and spontaneous coronary artery dissection (SCAD) [12, 13••, 14•].

Unadjusted in-hospital mortality is higher among women compared to men [2, 3], particularly in younger women less than 50 years of age with ST-elevation myocardial infarction (STEMI) [2]. Despite adjusting for comorbidities and traditional cardiovascular risk factors, mortality remained 15–20% higher in younger women compared to men of similar age [3]. Women with AMI also have a higher incidence of mechanical complications compared to men [15•].

Sex differences in clinical presentation and disease recognition by medical personnel may partially explain system delays in initiation of care, resulting in prolonged ischemic time, higher incidence and prolonged duration of CS, and subsequently worse mortality [5, 8, 16•, 17, 18]. Historically, women receive less evidence-based medical care, including less frequent coronary revascularization for STEMI with and without CS [3, 4••].

Evidence-guided therapy for CS is limited in both sexes, but more so in women, who are significantly underrepresented in AMI, acute decompensated heart failure (ADHF), and CS studies [3, 4••, 19, 20, 21•, 22••, 23]. Recent analyses of the US Nationwide Inpatient Sample database demonstrate a significant increase in the use of MCS devices for CS. Between 2010 and 2014, MCS utilization increased by 160%, and in-hospital mortality for CS declined. Over 30% declines were noted in MCS recipients [24]. Although only a minority of recipients (33%) were women, there was a trend toward decreasing use in women relative to men over time [25]. Furthermore, rates of CS during that period outpaced MCS utilization, further suggesting significant device underutilization in eligible female patients.

The purpose of this review is to analyze the evidence for use of mechanical circulatory support in women, namely, intra-aortic balloon pump (IABP), Impella, ventricular assist devices (VAD), and extracorporeal membrane oxygenation (ECMO).

Cardiogenic Shock Definition

Cardiogenic shock is a critical clinical status with high morbidity and mortality, generally defined as inadequate cardiac output to maintain end-organ perfusion and function. The National Cardiovascular Data Registry (NCDR) defines CS as systolic blood pressure (SBP) < 90 mmHg, cardiac index (CI) < 2.2 L/min/m2, and/or the requirement for inotropic or vasopressors or MCS to maintain SBP and cardiac index above those levels secondary to cardiac dysfunction [26]. Although useful in clinical datasets, the NCDR classification of CS is binary. Objective variables and clinical surrogates of end-organ function have been integrated by a consensus of the Society for Coronary Angiography and Interventions (SCAI) cardiology experts and endorsed by multiple professional societies, to formulate a statement and schema on classifying CS in AMI [27••].

Five progressive stages of clinical deterioration comprise the schema from A to E (Table 1). A is for the patient who is "at risk" of shock from an AMI, with acute chronic CHF symptoms. B is for "beginning CS" with relative hypotension or tachycardia without hypotension. C is for "classic CS" comprised of hypoperfusion requiring intervention such as pressors or MCS. D is a "deteriorating" condition from stage C with the added requirement of additional pressors or escalation of MCS. E is for "extremis" in the patient in cardiac arrest undergoing cardiopulmonary resuscitation (CPR) and/or extracorporeal membrane oxygenation (ECMO) due to no systolic BP without resuscitation, PEA, or refractory VT/VF [21•, 27••].

Unique to the SCAI document on CS in AMI is the incorporation of lab values such as BNP, BMP, lactate, liver enzymes, and pH. Similar to the protocol adopted by National Cardiogenic Shock Initiative assessing early MCS intervention in patients presenting with AMI and CS; the SCAI document advocates for the utility of pulmonary-artery catheter (PAC) monitoring for standard hemodynamics of cardiac index and pulmonary capillary wedge pressure (PCWP) and the variables of pulmonary artery pulsatility index (PAPI) and cardiac power output (CPO) [21•]. Evidence for the use of minimally invasive continuous cardiac monitors is conflicting. Qualified cardiac output trends guide management in critical care areas and are clinically more useful than absolute figures.

Hemodynamics of CS is understood as a parameter of ventricular filling pressures (low, normal, or elevated) against a vascular resistance to determine whether systemic perfusion is adequate or inadequate. This was first described as a two-by-two system (Fig. 1) on the presence or absence of congestion vs. low perfusion at rest in the management of patients presenting with heart failure [28]. Classic CS would be best classified as "cold and wet" with poor systemic perfusion and pulmonary congestion, evidenced as a low cardiac index and high PCWP, respectively. The function of the ventricle with respect to filling pressures and efficiency is hemodynamically best illustrated with the tracings of pressure/volume loops (PVL) for cardiac cycles [29].

Table 1 Descriptors of shock stages: physical exam, biochemical markers and hemodynamics

Stage	Description	Physical exam/bedside findings	Biochemical markers	Hemodynamics
A At risk	A patient who is not currently experiencing signs or symptoms of CS but is at risk for its development. These patients may include those with large acute myocardial infarction or prior acute and/or acute on chronic heart failure symptoms	Normal JVP Lung sounds clear Warm and well perfused • Strong distal pulses • Normal mentation	Normal labs • Normal renal function • Normal lactic function	Normotensive (SBP≥100 or normal for pt) If hemodynamics done • Cardiac index ≥2.5 • CVP < 10 • PA sat ≥65%
B Beginning CS	A patient who has clinical evidence of relative hypotension or tachycardia without hypoperfusion	Elevated JVP Rales in lung fields Warm and well perfused • Strong distal pulses • Normal mentation	Normal lactate Minimal renal function impairment Elevated BNP	SBP < 90 *OR MAP* < OR > 30 mmHG drop from baseline Pulse ≥100 If hemodynamics done • Cardiac index ≥2.2 PA sat ≥65%
C Classic CS	A patient that manifest with hypoperfusion that requires intervention (inotrope pressor or mechanical support including ECMO) beyond volume resuscitation to restore perfusion. This patients typically present with relative hypotension	*May include any of the following:* Looks unwell Panicked Ashen, mottled, dusky Volume overload Extensive rales Kill ip Class 3 or 4 BiPap or mechanical ventilation Cold, clammy Acute alteration in mental status Urine output < 30 mL/h	*May include any of the following:* Lactate < 2 Creatinine doubling OR > 50% drop in GFR Increased LFTs Elevated BNP	*May include any of the following:* SBP < 90 OR MAP < OR > 30 mmHG drop from baseline *AND* drugs/device use to maintain BP above these targets Hemodynamics • Cardiac index < 2.2 • PCWP > 15 • RAP/PCWP ≥0.8 PAPI < 1.85 • Cardiac power output ≤0.6
D Deteriorating/doom	A patient that is similar to category C but are getting worse. They have failure to respond to initial interventions	*Any of stage C*	*Any of stage C AND* Deteriorating	*Any of stage C AND* Requiring multiple pressors OR addition of mechanical circulatory support devices to maintain perfusion
E Extremis	A patient that is experiencing cardiac arrest with ongoing CPR and/or ECMO, being supported by multiple interventions	Near pulselessness Cardiac collapse Mechanical ventilation Defribelator used	"Trying to die" CPR (A–modifier) pH ≤ 7.2 Lactate ≥5	No SBP without resuscitation PEA or refractory VT/VF Hypotension despite maximal support

SCAI clinical expert consensus statement 2019 on the classification of cardiogenic shock. The schema describes five stages of shock A–E (Reprinted from: Naidu, et al. Catheterization and Cardiovascular Interventions. 2019; 94 (1). doi:https://doi.org/10.1002/ccd.28329; with permission from John Wiley and Sons)

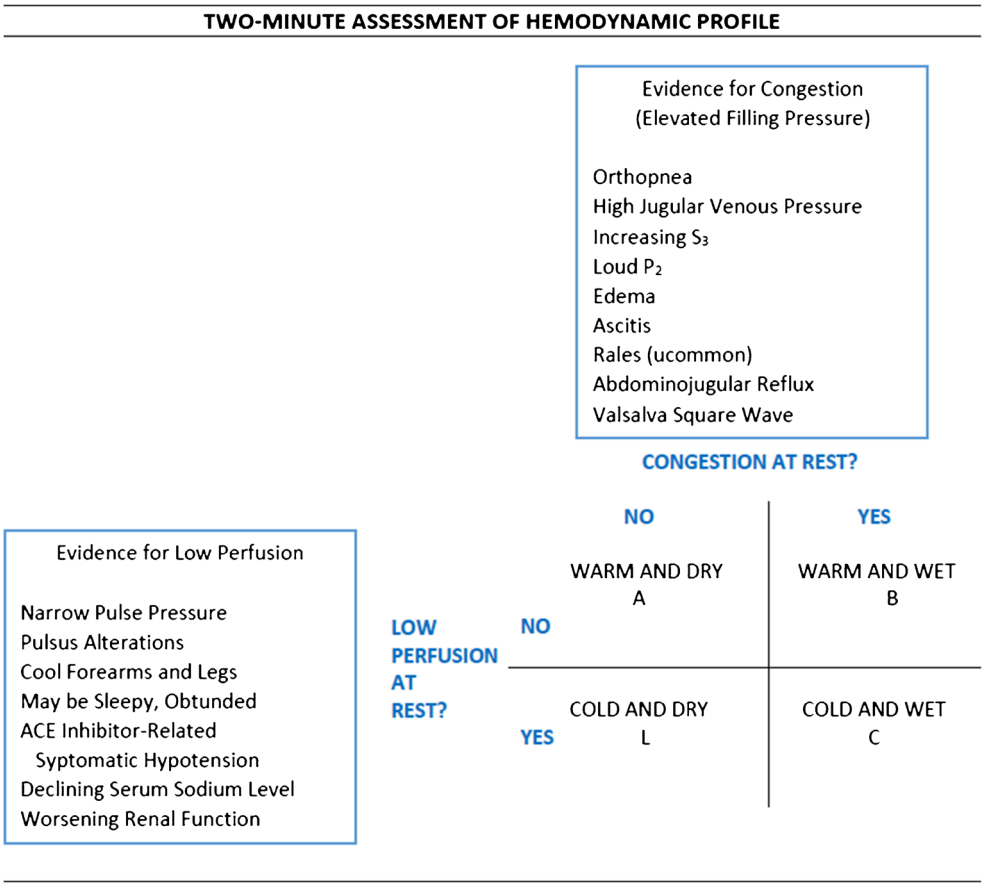

Fig. 1 Two-minute assessment of hemodynamic profile. Hemodynamics of CS are understood as parameters of ventricular filling pressures (low, normal, or elevated) against a vascular resistance to determine whether systemic perfusion is adequate or inadequate. This was first described as a two-by-two system on the presence or absence of congestion vs. low perfusion at rest in the management of patients presenting with heart failure. (Reproduced with permission from JAMA. 2002. 287 (5): doi:https://doi.org/10.1001/jama.287.5.628. Copyright©(2002) American Medical Association. All rights reserved)

Pressure volume loops are influenced by several factors intrinsic and extrinsic to the myocardium. Preload, afterload, and inotropy are the major factors in the changing nature of PV loops. Animal models have greatly assisted in understanding the independent effects of these variables on filling pressure and stroke volume. However, the passive and active interplay of the ventricle and valves are highly variable for the myriad etiologies, stages, and treatments of CS, particularly acute CS. Guiding principles of PV loop analysis for congestive heart failure center on maintaining preload at an adequate, but not too large of a volume to fill the LV, reducing afterload improve ejection fraction and maintaining inotropy for the heart to contract sufficiently [30]. While impractical to derive pressure-volume loops at the bedside for patients with CS, it is important to remember the goal of maximizing stroke volume while minimizing myocardial work.

Inotrope and vasopressor therapies offer inadequate circulatory support in severe CS. Furthermore, their short-term stabilizing effects are offset by adverse impacts on afterload, oxygen demand, impaired tissue microcirculation, and arrhythmogenicity, translating into cardiotoxicity and end-organ dysfunction [5, 31, 32]. Mechanical circulatory support options offer alternatives to overcome these adverse effects.

Intra-Aortic Balloon Pump

IABP support was initially described in 1980 in a patient suffering from cardiogenic shock [33, 34]. The mechanism was assumed to be through augmentation of the diastolic blood pressure to improve coronary perfusion with a positive effect on cardiac output. It was not until 2001 when the Benchmark Counterpulsation Outcomes Registry was published documenting the indications, technique, outcomes, hemodynamics, and complications [35]. This report included 17,540 records from June 1996 to August 2000. Of the total, 31.2% were females with a mean age of 65.9 years; 25.6% were diabetic; and 11.9% had peripheral vascular disease. Only 18.8% of IABP use was in cardiogenic shock; 12.3% were for unstable refractory angina and 13% for high-risk preoperative patients. In their analysis, the investigators concluded that female gender, small body surface area, older age, and peripheral vascular disease were all independent predictors of a serious complication.

Thereafter, the use of an IABP in high-risk interventions was primarily described through case series [36–38]. In 2012, Curtis et al. provided insight on IABP use in those undergoing high risk PCI [39] by analyzing the CATH PCI NCDR from 2005 to 2007. A total of 181, 599 patient records were

reviewed. High risk was defined as having at least one of the following: unprotected left main artery as the target vessel, cardiogenic shock, severely depressed left ventricular function, or ST segment elevation myocardial infarction. The overall use of IABP was 10.5% and varied significantly across hospitals. A multivariable analysis adjusted for hospital and patient characteristics demonstrated no difference in in-hospital mortality or complications. Of note, there are limitations to this review. It is a retrospective analysis that may not capture confounding parameters that are not measured in the NCDR database. Additionally, a power calculation was not performed to definitely determine whether the data could detect significant differences in morality across hospitals. Females constituted 28.9% of the total studied population accounting for 30.4% of those who received an IABP.

The IABP Shock Trials I and II [23, 40] provide more contemporary data. These were randomized controlled trials with 1:1 assignment. The IABP SHOCK I trial was a small study that included 45 consecutive patients with AMI and shock. IABP use was associated with only modest reduction of Acute Physiology and Chronic Health Evaluation II (APACHE II) score, improvement of cardiac index, or reduction of BNP biomarker status compared with medical therapy alone. The small sample size precluded any definitive conclusion, and the investigators recommended a larger prospective, randomized, multicenter trial. As such, the IABP SHOCK II trial was conducted between 2009 and 2012. A total of 300 patients in the IABP and 298 in the control group were enrolled. Inclusion criteria included AMI (with or without ST segment elevation) complicated by cardiogenic shock and if early revascularization (by means of PCI or CABG) was planned. At 30 days, mortality was 119 patients in the IABP (39.7%) and 123 patients in the control group (41.3%) ($p = 0.69$). There were no significant differences in the time to hemodynamic stabilization, length of stay, serum lactate levels, dose of catecholamine therapy, and renal function. There was no significant difference in the rates of major bleeding (3.3 and 4.4%, $p = 0.51$), peripheral ischemic complications (4.3 and 3.4%, $p = 0.53$), or stroke (0.7 and 1.7%, $p = 0.28$) between the two groups.

In the IABP-SHOCK II trial, Thiele et al. furnished us with the results of the longest follow-up (6 years) of any randomized trial [41]. There was no mortality difference between the IABP and the control group (66.3 versus 67.0%; $p = 0.98$). There were also no differences in recurrent myocardial infarction, stroke, repeat revascularization, or re-hospitalizations. In a further analysis stratified by IABP-SHOCK II score, the long-term mortality demonstrated no differences between the two groups. Multivariable modeling revealed that increasing age, history of stroke, baseline arterial lactate, creatinine level, oliguria (< 30 ml/h), and multivessel disease were strong predictors of long-term mortality. Sex, however, was not a predictor in this analysis.

An unpublished sub-analysis from the IABP SHOCK II trial studied the 187 female patients who were enrolled in the total population (31%). Women were significantly older than men (74 vs. 68 years) and had a significantly lower systolic (88 vs. 90 mmHg; $p = 0.04$) and diastolic (53 vs. 60 mmHg; $p < 0.001$) at presentation. Diabetes mellitus and hypertension were more frequent in women, whereas smoking was more frequent in men. PCI was lower in women (86 vs. 92%; $p = 0.04$). A patent culprit vessel after PCI was less often achieved in female patients (TIMI 3 flow after PCI, 77 vs. 84%; $p = 0.04$). Women showed an unadjusted significant higher mortality within the first day after randomization (18 vs. 9%; $p = 0.004$). There was no significant difference in acute mortality after multivariable adjustment. At 1, 6, and 12 months of follow-up (women vs. men 46 vs. 42%, $p = 0.36$; 54 vs. 47%, $p = 0.12$; 57 vs. 50%; $p = 0.14$, respectively), no significant differences were noted in the unadjusted and in multivariable analyses. In this large series, although women had a higher risk profile and underwent suboptimal treatment, mortality rates in short- and long-term follow-up for women were similar to men. This, however, was not a pre-specified analysis.

Another trial providing long-term follow-up is the Balloon Pump–Assisted Coronary Intervention Study (BCIS-1) [42]. Three hundred one patients with an ejection fraction < 30% and severe coronary disease were randomized to receive PCI with elective IABP support ($n = 151$) or without ($n = 150$). Median follow-up was 51 months. Long-term all-cause mortality was assessed by tracking the databases held at the Office of National Statistics (in England and Wales) and the General Register Office (in Scotland). All-cause mortality was 33% in the overall cohort, with significantly fewer deaths in the IABP group ($p = 0.039$). There was a 34% relative reduction in all-cause mortality. Another major limitation of this study was that it was designed to address in-hospital major adverse cardiac or cerebrovascular event (MACCE) (capped at 28 days). It is therefore not prospectively powered for all-cause mortality in the short term. The high event rate over longer-term follow-up provides reasonable power for the comparison of outcomes in the two arms. Disappointingly, women constituted less than 20% of the studied cohort limiting any inferences.

The aforementioned studies did not examine the impact of sex on outcomes specifically. Beiras-Fernandez et al. retrospectively studied 57 consecutive females (mean age, 73 ± 9 years) requiring an IABP undergoing cardiac surgery compared with 182 male patients from 2007 to 2010 [43]. Baseline differences revealed that female patients were older (73 ± 9 vs. 67 ± 10 years), had a higher ejection fraction (45% ± 24% vs. 36% ± 14%), and had a higher EuroSCORE (25% ± 20% vs. 19% ± 17%; $p < 0.05$); catecholamine support was significantly higher, prolonged length of stay (10.64 ± 9.7 vs. 7.6 ± 7.6 days), higher incidence of renal replacement therapy, and a higher mortality (19.4% vs. 33.9%; $p < 0.05$) in the IABP arm.

Wilczyński et al. conducted a randomized trial of 502 high-risk patients (351 men, 151 women) with 1:1 assignment of preoperative IABP vs. control group [44]. The primary endpoint was MACCE. There was a significant reduction of MACCE rate in patients with the preoperative IABP counterpulsation in comparison to the control group ($p = 0.001$) and in the female subgroup ($p = 0.005$). After adjustment for baseline characteristics, the hazard ratio for MACCE was 0.7 ($p = 0.005$) in the total population; 0.6 ($p = 0.01$) for females; and 0.8 ($p = 0.1$) for males. This is the only trial that has demonstrated benefit in women who receive preoperative IABP.

The current body of evidence did not demonstrate a benefit of IABP use in terms of mortality in the short or long term. Therefore, the European guidelines have downgraded IABP use for cardiogenic shock from a previous Class I to a Class III B, and the US guidelines downgraded its use to a Class IIb B [45, 46].

Impella

The Impella percutaneous ventricular assist device (PVAD) is a catheter-based non-pulsatile micro-axial continuous flow pump with a flexible pigtail loop, designed to propel blood from the left ventricle into the ascending aorta. There is also a right-sided Impella device, the Impella RP, designed to support right ventricular function, which aspirates blood from the inferior vena cava and expels it into the pulmonary artery. Impella devices are implanted via percutaneous access or surgical cut down and can provide forward flow of 2.5–5.0 L/min depending on the specific device. Similar to permanent ventricular assist devices, the Impella is designed to match blood flow to hemodynamic need. The left ventricular Impella devices are all contraindicated in patients with mechanical aortic valves and left ventricular thrombus and require systemic anticoagulation during implantation and use. Impella uniquely offers a combination of circulatory support, ventricular support, and left ventricular unloading to restore stable hemodynamics, minimize myocardial ischemia, reduce cardiac workload, and maintain vital organ perfusion to either facilitate follow-on therapies or native heart recovery. It may also serve as an effective adjunctive unloading strategy with concomitant venoarterial extracorporeal membrane oxygenation (VA ECMO) [47, 48•].

Pre-clinical evidence exists demonstrating that decreasing afterload of the heart with transvalvular axial flow devices such as the Impella enhances myocardial salvage [49–51]. Animal data indicates that mechanically reducing LV work before coronary reperfusion with a transvalvular pump may both reduce infarct size and improve cardiac function [52, 53]. This hypothesis will further be tested more definitively in humans in the upcoming Primary Unloading and Delayed Reperfusion in ST-Elevation Myocardial Infarction: STEMI-DTU Trial (DTU-STEMI). Patients with STEMI will be randomized to primary LV unloading and a 30-minute delay to reperfusion versus current standard of care to demonstrate safety and effectiveness in reducing infarct size and heart failure-related clinical events. Safety and feasibility have been reported in the STEMI-DTU pilot trial [54].

While initially implemented as adjunctive therapy after revascularization and maximal pharmacologic therapy, there is increasing data to suggest that first-line up-front use of the Impella percutaneous MCS devices may lead to superior outcomes in AMI CS [14•, 21•, 55, 56]. There is increasing registry evidence that survival in AMI-CS may be improved with earlier MCS use [56]. In a published analysis of 15,259 patients from a large national Impella Registry, up-front use of Impella device pre-PCI was associated with a 59% survival rate compared with 52% when used as a salvage strategy ($p < 0.001$) [14•]. In the most recent report of the National Cardiogenic Shock Initiative (NCSI) outcomes in 171 patients across 35 sites, survival to discharge with a pre-PCI Impella strategy for hemodynamically confirmed CS was 72%, compared to 50% for similar historical controls [21•, 57]. Taken together, these findings suggest the possibility of improved survival in both women and men through earlier identification of CS and more prompt initiation of hemodynamic support with short-term Impella MCS.

Women who received Impella support pre-PCI demonstrated significant reductions in inotrope use, greater overall survival, and a greater magnitude of survival benefit compared to men (women, 68.8% survival with Impella pre-PCI versus 24.2% post-PCI, $p = 0.05$; men, 54.2% survival with Impella pre-PCI vs. 40.3% with Impella post-PCI, $p = 0.1$) [15•]. This benefit occurred despite a higher predicted risk of mortality by STS score and more cardiac arrest in women versus men [15•]. There is less evidence for Impella RP right ventricular support for right ventricular failure and no sex-specific studies. The limited available data suggests rapid hemodynamic improvement with reversal of shock and favorable survival in appropriately selected patients [58].

Women undergoing cardiac catheterization, percutaneous coronary intervention, and other cardiac interventions have a significantly higher risk of vascular complications and bleeding than men, leading to significant morbidity and mortality [59]. Vascular complications with large-bore access for MCS use are common in both sexes and occur more frequently compared to non-large-bore procedures. In a matched-pair mortality analysis of 237 Impella-treated vs. 237 IABP-treated CS patients, high rates of severe bleeding (8.5%, $p < 0.01$) and peripheral vascular complications (9.8%, $p = 0.01$) were observed with the Impella device, which increase with decreasing vessel size [60, 61]. Another study of 90 patients (40% female) receiving Impella 2.5 device between 2010 and 2013 for both planned, urgent, and emergent procedures demonstrated a 17% rate of vascular complications, with the most important clinical

predictors being CS and female sex [61]. Sex-influenced size limitations may influence MCS utilization decision-making and complication rates, as women often have smaller iliofemoral vessels compared to men, even after controlling for height, weight, and other comorbidities known to affect vascular anatomy [62]. In the cVAD Registry, despite possible increased clinical benefits to MCS employment in women versus men, women had more vascular complications requiring surgery (18.4% vs. 9.2%, $p = 0.09$) and bleeding requiring transfusion (22.5 vs. 12.9%, $p = 0.12$) [15•]. Even higher vascular complications rates than these might be expected in the presence of female-predominant extra-coronary arteriopathies such as are seen with SCAD [63]. Aside from increased vascular risks, women also have smaller hearts than men and more frequently develop concentric hypertrophy with larger wall thickness and smaller internal cavity diameters, which might also theoretically complicate Impella selection, placement, and functioning [64].

Recent single-center reports suggest that MCS devices such as the Impella axial flow catheter may offer particular benefit in both men and women, not only when used early but also when employed in conjunction with hemodynamic guidance and established care protocols and at specialized cardiac facilities [13••, 14•, 21•, 65].

Ventricular Assist Devices

VAD have emerged as the mainstay of treatment for patients with advanced heart failure. In its most recent release, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) reported 14,195 isolated LVAD implantations between 2012 and 2017, of which 21.3% were placed in female patients [66]. Although their total number has increased over time, the representation of women remains grossly disproportionate.

No recent study has substantiated significant mortality differences between men and women in the current era [67, 68]. In comparison to their male counterparts, females are younger [67–70], have more dilated cardiomyopathy [68, 69], INTERMACS 1 or 2 classification [68, 69, 71•], less atrial fibrillation [67, 68], and more anemia [68, 70]. Through these reports and others, several sex-specific adverse effects [72] associated with current continuous flow devices have been observed.

Female gender has been identified as a pre-implantation risk factor for ischemic and hemorrhagic strokes [73], particularly when using continuous axial flow devices [67]. The findings of these studies were further substantiated in a recent meta-analysis, which demonstrated higher axial device stroke risk compared to men [74]. Moreover, a few reports have highlighted concern for right heart dysfunction and increased need for RV support in women. Both intraoperative placement and post-implant RV dysfunction requiring RVAD have been described [68, 69, 74]. These findings are often attributed to the increased prevalence of dilated cardiomyopathy [69], although differences in preoperative RV dysfunction were not consistent [68]. It remains to be seen if RVAD implantation is preventable. Sex differences in the overall common complications were evaluated in several studies. Women had higher rates of major bleeding 30 days after LVAD implantation [69, 70]. Other adverse effects such as device-related infection and renal dysfunction were either insignificant [69, 74] or not reported [67, 70, 73].

While the focus of disparity research in the VAD population is often limited to INTERMACS outcomes, other sex-specific differences exist. VADs have been employed for refractory peripartum cardiomyopathy with promising results [75]. In addition, female patients have been found to report increased depression, pain, and functional limitations at 6 months and 1 year following implantation in both unstable (INTERMACS 1–3) and ambulatory (INTERMACS 4–7) populations [76, 77].

In 2018 and 2019, two studies were released from the Multicenter Study of MagLev Technology in Patients Undergoing MCS Therapy with HeartMate 3 (MOMENTUM-3) trial in which continuous fully magnetically levitated centrifugal flow devices demonstrated superiority to the axial flow HeartMate II device, with substantial improvements in 2-year survival and freedom from stroke or device replacement [78, 79]. While these studies were not designed to evaluate sex differences, it is likely that generalized reduction of VAD-associated complications will improve outcome disparities.

Extracorporeal Membrane Oxygenation

ECMO provides hemodynamic support, pulmonary gas exchange, and end-organ perfusion to critically ill patients in cardiogenic shock. Venoarterial (VA) ECMO is the modality of support and has seen unparalleled growth in cardiogenic shock [80].

Venoarterial (VA) ECMO is a modified form of cardiopulmonary bypass. Blood is withdrawn from a major vein via a cannula (or large bore biocompatible plastic tube) and pumped through a gas exchange device to oxygenate the blood and remove carbon dioxide to provide support for the heart and lungs. Oxygenated decarboxylated blood is then reinfused via an additional cannula into an artery, thus partially bypassing the failing and diseased heart. This bypass support provides richly oxygenated blood to failing or diseased organs [81].

ECMO comes with risk. Complications include bleeding, thromboembolic events, infection, cardiac distention, loss of limb, and even the potential for death [80, 82]. In ACS, the delay before seeking medical help is prolonged in females [83,

Table 2 Summary of available data on mechanical support: IABP, Impella, VAD, and ECMO with highlighting of the differences observed in women

Mechanical support	Study (year)	Type of study	Inclusion criteria	Total enrolled	Endpoints	Results
IABP	Curtis JP et al. 2012 CATH PCI NCDR	Observational data from the CATH PCI NCDR Registry	High-risk PCI (unprotected left main artery as the target vessel, cardiogenic shock, severely depressed left ventricular function, or STEMI)	181,599	In-hospital mortality or complications	Overall use of IABP 10.5%, varied significantly No difference in in-hospital mortality/complications Females constituted 28.9% of total study population; 30.4% of those who received IABP
	Thiele H et al. 2019 IABP SHOCK II	Randomized controlled open-label multicenter	AMI (with or without ST segment elevation) complicated by cardiogenic shock and early revascularization was planned	600: 301 in the IABP group 299 in the control group	30-day all-cause mortality Major bleeding, peripheral ischemic complications, sepsis, and stroke	No significant reduction in 30-day mortality in patients with cardiogenic shock complicating AMI (early revascularization strategy) No difference in complication rates Women significantly older (74 vs. 68 y), lower systolic BP (88 vs. 90 mmHg; $p = 0.04$) and diastolic BP (53 vs. 60 mmHg; $p < 0.001$) at presentation DM and HTN more frequent in women PCI lower in women (86 vs. 92%; $p = 0.04$); Patent culprit vessel after PCI less often achieved in females Women higher unadjusted mortality (18 vs. 9%; $p = 0.004$) Women with higher risk profile, underwent suboptimal treatment, mortality rates in short and long term were similar to men
	Perera D et al2012 BCIS-1	Randomized controlled multicenter	Poor LV function (EF < 30%) and severe coronary disease (BCIS-1 jeopardy score ≥ 8; maximum possible score = 12)	301	Long-term all-cause mortality	Significantly fewer deaths in elective IABP group ($n = 42$) vs. underwent PCI without IABP ($n = 58$) (hazard ratio, 0.66; 95% confidence interval, 0.44–0.98; $p = 0.039$) Female patients older (73 ± 9 vs. 67 ± 10 years), higher ejection fraction (45% ± 24% vs. 36% ± 14%), and had a higher EuroSCORE (25% ± 20% vs. 19% ± 17%; $p < 0.05$), catecholamine support significantly higher, prolonged length of stay (10.64 ± 9.7 vs. 7.6 ± 7.6 days), higher incidence of renal replacement therapy, and higher mortality (19.4% vs. 33.9%; $p < 0.05$) in the IABP arm
	Wilczyński et al. 2010	Randomized controlled	High-risk CABG patients	502	Major adverse cardiac or cerebrovascular event (MACCE)	Significant reduction of MACCE rate in patients with preoperative IABP counterpulsation vs. control group ($p = 0.001$) in female subgroup ($p = 0.005$)
Impella	O'Neill et al. 2018	Observational (multicenter registry)	CS complicating AMI treated with Impella (2.5, CP, 5.0) devices	15,259 (27% female)	Survival to device explant	Up-front Impella device pre-PCI associated with 59% survival to explant rate vs. 52% when used as salvage strategy ($p < 0.001$) Possible improved survival in both women and men through earlier identification of CS and more prompt initiation of Impella MCS
	Joseph et al. 2016	Observational (multicenter registry)	CS complicating AMI treated with Impella 2.5 device	180 (100% female)	Survival to hospital discharge	Women with Impella support pre-PCI with significant reductions in inotrope use, greater overall survival, greater magnitude of survival benefit compared to men (Women: 68.8% survival with Impella pre-PCI versus 24.2% post-PCI, $p = 0.05$) (Men: 54.2% survival with Impella pre-PCI vs. 40.3% with Impella post-PCI, $p = 0.1$).
	Abaunza et al. 2015	Single-center observational	Consecutive patients undergoing insertion of Impella 2.5 device	90 (40% female)	Vascular complications	17% rate of vascular complications, with the most important clinical predictors being CS and female sex
	Regitz-Zagrosek V et al. 2016	Review (EUGenMed Cardovascular Clinical Study Group position paper)	Not applicable	Not applicable	Not applicable	Women have smaller hearts than men and more frequently develop concentric hypertrophy with larger wall thickness and smaller internal cavity diameters (theoretically can complicate Impella selection, placement, functioning)
VAD	Meeteren JV et al. 2017	Single-center observational	All patients who underwent primary LVAD implantation	734	Outcome analysis	Females younger with higher incidence of dilated cardiomyopathy
		Observational	Patients with LVAD support from the European Registry for Mechanically	966	Mortality, complications	Women with worse 1-year survival (75.5 vs. 83.2% in men); unstable condition at VAD implantation (INTERMACS 1 or 2

Table 2 (continued)

Mechanical support	Study (year)	Type of study	Inclusion criteria	Total enrolled	Endpoints	Results
	Magnussen C et al. 2018		Assisted Circulatory Support (EUROMACS)			classification) (51.7% vs. 41.6% in men; more major bleeding (events per patient year [PY] 0.3 in women vs. 0.14 in men, $p = 0.0012$); higher rate of arrhythmias (events per PY 0.08 in women vs. 0.03 in men, $p = 0.022$); right ventricular (RV) failure (events per PY 0.11 in women vs. 0.03 in men, $p < 0.001$) with need for additional RV support
	Grady K et al. 2017	Observational	Patients from INTERMACS received a continuous flow LVAD as a primary implant at 133 U.S. hospitals	7353	health-related quality of life early after LVAD	Increased depression, pain, and functional limitations at 6 months and 1 year following implantation in both unstable (INTERMACS 1–3) and ambulatory (INTERMACS 4–7) populations
ECMO	Zhang R et al. 2014	Single-center retrospective	patients supported on veno-arterial (VA) ECMO for AMI-induced CS	41	Mortality, complications	Females with higher in-hospital mortality with adjusted HR 2.86 (1.16–7.14, 95%CI, $p = 0.02$), Lower survival to discharge (11.1 vs. 53.1%, $p = 0.05$), more bleeding complications while on ECMO (66.7 vs. 25.0% $p = 0.04$).

Hemodynamics of CS are understood as parameters of ventricular filling pressures (low, normal, or elevated) against a vascular resistance to determine whether systemic perfusion is adequate or inadequate. This was first described as a two-by-two system on the presence or absence of congestion vs. low perfusion at rest in the management of patients presenting with heart failure (Reproduced with permission from JAMA. 2002. 287 (5): doi:https://doi.org/10.1001/jama.287.5.628. Copyright©(2002) American Medical Association. All rights reserved)

84]. There is increasing evidence that a gender-specific threshold for troponin may aid healthcare workers in more rapid detection of myocardial infarction in women.

In a single-center survey consisting of 41 patients supported with venoarterial ECMO, the comparison between males and females yielded a substantial difference in their ability to be successfully decannulated from ECMO (11.1 vs. 53.1% $p = .05$) and discharged from the hospital [84]. The comparison of the two groups saw no correlation in other parameters such as AKI requiring dialysis, transaminitis, or even lactate, which could potentially elude to the increased mortality. Interestingly, the data also yielded that woman had a much greater propensity to suffer from bleeding complications while on ECMO (66.7 vs. 25.0% $p = 0.04$) [84]. Bleeding is an independent predictor of mortality following intervention for an acute coronary syndrome and for all patients supported with ECMO [84].

Bleeding is the single most prevalent complication while undergoing extracorporeal support [84]. However, why women are more likely to have complications from bleeding [81] remains speculative. There are several hypotheses, and it is likely multifaceted. Women have smaller vessels and are at a greater risk for receiving multiple sticks, or even more posterior wall sticks, which then increase the risk of bleeding post-intervention [83]. While ECMO is not a curative percutaneous intervention such as a coronary artery stent or angioplasty, the cannulas are introduced in the body in much the same way. Another hypothesis is that women's hormonal balance may result in greater vascular fragility. As women are more likely to suffer vessel dissections due to estrogen levels, their vessels may be inherently structurally weaker [83]. A third thought is related to anticoagulant/antiplatelet dosing. Many of the anticoagulants on the market do not take the possibility of a smaller women's body weight and volume of distribution into consideration. Institutions are moving to weight-based heparin and direct thrombin inhibitor dosing, which rule out many of the anticoagulant dosing arguments.

Conclusion

Until recently, shock definition and management pathways had not been universally outlined, making trial design and interpretation confounded. Yet the uptake of individualized protocols that included MCS has been steadily rising. Despite increasing clinical use, no adequately powered randomized trials exist to support the routine use of mechanical circulatory support in CS [85]. Supportive data are primarily derived from small randomized trials with hemodynamic endpoints and observational studies or registries with survival rates higher than historical controls (Table 2) [13••, 21•, 85–87]. There is even less sex-specific safety, effectiveness, and outcomes data for MCS in women in the setting of CS

[10, 88]. Currently there is only one prospective randomized clinical trial, DanGer Shock, designed to address whether mechanical circulatory support with Impella CP can improve survival in AMI CS, which is actively recruiting in both Denmark and Germany [89]. It remains to be seen whether women will be equally represented in this trial.

In addition, despite the improved safety profile of modern mechanical support systems, reports have cited concerns for increased risk of stroke, major bleeding, need for RV support, and worse quality of life metrics in females. Understanding of sex-specific differences in MCS outcomes remains poor and outpaced by technological development. Whether further device improvements ultimately eliminate sex-specific differences in the future remains speculative and warrants randomized controlled trials that employ the recently elaborated SCAI definition and streamlined center-specific treatment pathways.

Compliance with Ethical Standards

Conflict of Interest Manal Alasnag, Holli Williams, Sara C. Martinez, Syeda Kashfi Qadri, John P Skendelas, William A Jakobleff, and Mirvat Alasnag each declare that they have no conflict of interest. Alexander G. Truesdell reports serving as a consultant and on the Speakers Bureau for Abiomed Inc. outside the submitted work.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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