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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Randomized Trials of Percutaneous Microaxial Flow Pump Devices

JACC State-of-the-Art Review

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ABSTRACT

The use of mechanical circulatory support devices in cardiovascular practice has risen exponentially over the past decade. These devices are currently used for hemodynamic support in patients with cardiogenic shock, high-risk percutaneous coronary intervention, left ventricular unloading, protection of kidneys, and right ventricular failure. The Impella (Abiomed) percutaneous microaxial flow pump devices are rapidly gaining popularity. However, despite their increasing use, there are limited randomized clinical trials (RCTs) to support the benefits of the therapy and growing concern regarding complication rates. Vascular problems, including bleeding and acute limb ischemia, are associated with the devices, but published reports also highlight risks for cardiac perforations, mitral chordae rupture, and stroke. In this review, we summarize the history, mechanism of action, previously published RCT data, and upcoming RCTs on these devices. (J Am Coll Cardiol 2022;80:2028–2049) © 2022 by the American College of Cardiology Foundation.

The use of temporary mechanical circulatory support (MCS) devices has been increasing recently in cardiovascular practice. Among them, the fastest growing category is transvalvular percutaneous microaxial flow pump devices, such as the Impella (Abiomed).[1-3] These devices are currently the only percutaneous transaxial pumps approved in both the United States and Europe,[4] and all devices discussed in this paper are of this brand, unless otherwise specified. The Impella 2.5 device was first approved for use in the United States in 2008 to provide up to 6 hours of circulatory support during procedures. There have been notable improvements in the types of percutaneous microaxial flow pump devices that are currently available. The percutaneously implanted 2.5 and CP models can provide support of up to 2.5 and 3.5 to 4.0 L/min, respectively, whereas the 5.0 and 5.5 models can provide more robust hemodynamic support of 5.0 to 6.2 L/min but require a surgical cutdown for implantation.[5] Despite the sharp rise in the use of percutaneous microaxial flow pump devices, there is a lack of rigorous randomized clinical data demonstrating the benefits and safety of microaxial flow pump support for different applications. In this review, we attempt to summarize the history, mechanism of action, previously published randomized clinical trials (RCTs), and upcoming trials on microaxial flow pump devices.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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HIGHLIGHTS

- Percutaneous microaxial flow pump devices are increasingly used for mechanical circulatory support to improve hemodynamics.
- Clinical reports have noted vascular complications, including bleeding and acute limb ischemia, as well as other cardiac and extracardiac risks, such as perforation, mitral chordae rupture, and stroke.
- Rigorous data regarding the risks and benefits of these devices from randomized trials are needed, and future trials should provide guidance on appropriate use.

HISTORY

The first transvalvular microaxial flow pump was called the Hemopump (Nimbus) and was first implanted in 1988. This device consisted of a 7-inch inflow cannula connected to a 7-mm-diameter inlet axial flow pump with a maximum speed of 2,700 rpm and was able to provide flow of 3 to 4 L/min.[6] Early studies with this device showed that continuous left ventricular (LV) unloading during the entire cardiac cycle reduced the cardiac work load and improved myocardial perfusion.[7] However, the need for surgical incision and an external motor limited this device's use. Percutaneous microaxial flow pump devices improved upon this design with an intracorporeal motor that can be implanted percutaneously.

MECHANISM OF ACTION AND HEMODYNAMIC EFFECT

Percutaneous microaxial flow pump devices consist of a catheter-mounted microaxial internal motor pump, called the impeller, which provides continuous blood flow from the left ventricle across the aortic valve into the ascending aorta during both systole and diastole. The impeller pump rests within the left ventricle, with an outlet area in the aortic root and, using continuous axial flow, can provide steady output irrespective of the underlying heart rhythm or cardiac function.[8] This rapidly improves mean arterial pressure (MAP) and decreases both LV pressure and volume, resulting in cardiac unloading by lowering myocardial oxygen consumption.

The flow across the percutaneous microaxial flow pump device is inversely related to the pressure gradient across the inlet and outlet segments, which correlates to the LV pressure and aortic pressure difference, called the pressure head, and is directly related to the pump speed. Hence, the pump flow across the device depends upon both the preload and the afterload. It is important to maintain a central venous pressure of about 8 to 12 mm Hg and to recognize signs of right ventricular (RV) failure in order to prevent any suck-down events from decreased flow in the left ventricle.[9] With its ability to provide sufficient hemodynamic support and LV unloading, the transvalvular percutaneous microaxial flow pump is increasingly used in various cardiovascular conditions, as described in the **Central Illustration**. Specifically in patients with acute myocardial infarction (AMI) and cardiogenic shock (CS), myocardial perfusion is based on the difference between arterial pressure and venous pressure, which is commonly called waterfall pressure.[10] The use of percutaneous microaxial flow pumps can help improve MAP, decrease LV end-diastolic pressure, and improve systemic venous and coronary sinus congestion. This can enhance coronary perfusion and limit the amount of myocardial ischemia, a concept that is currently being studied in ongoing RCTs described later. To better understand the role of percutaneous microaxial flow pump devices in different clinical scenarios, it is important to understand the hemodynamic effects of these devices in different clinical scenarios.

PREVIOUS AND FUTURE RCTs OF PERCUTANEOUS MICROAXIAL FLOW PUMP DEVICES

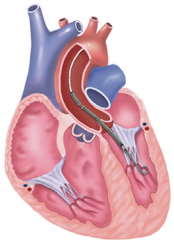
Figure 1 provides the timeline from the first approval of percutaneous microaxial flow pump devices and includes all of the RCTs available on these devices to date. We summarize all known clinical trials so far on the use of percutaneous microaxial flow pumps, divided into the following subcategories: 1) high-risk percutaneous coronary intervention (PCI) clinical trials; 2) CS; 3) LV unloading; and 4) the role of RV failure.

PERCUTANEOUS MICROAXIAL FLOW PUMP USE IN HIGH-RISK PCI. Under certain circumstances, the brief interruptions in coronary blood flow that occur

ABBREVIATIONS AND ACRONYMS

AKI = acute kidney injury
AMI = acute myocardial infarction
CS = cardiogenic shock
FDA = U.S. Food and Drug Administration
IABP = intra-aortic balloon pump
LM = left main coronary artery
LV = left ventricular
LVAD = left ventricular assist device
LVEF = left ventricular ejection fraction
MAE = major adverse event(s)
MAP = mean arterial pressure
MCS = mechanical circulatory support
MI = myocardial infarction
PCI = percutaneous coronary intervention
RCT = randomized clinical trial
RHF = right heart failure
RV = right ventricular
VA-ECMO = venoarterial-extracorporeal membrane oxygenation

CENTRAL ILLUSTRATION **Randomized Clinical Trials of the Percutaneous Microaxial Flow Pump Device**



Percutaneous Microaxial Flow Pump Devices

	High Risk PCI	Role in AMI-CS	Role in Unloading	Role in Protection of Kidneys
Mechanism of Action	• Reduce myocardial oxygen consumption • Improve myocardial blood flow • Maintain systemic perfusion	• Improve cardiac output • Decrease LVEDP • Improve systemic perfusion and BP • Prevent progressive systemic inflammation response syndrome	• Reduce myocardial oxygen-demand • Decrease LVEDP and improve collateral flow • Enhance activity of kinases limiting ischemia reperfusion injury and promote recovery • Preserve mitochondrial integrity	• Improve renal perfusion by increasing cardiac output • Decrease LVEDP resulting in renal venous decongestion
Clinical Trials	• PROTECT II *Future Trials* - PROTECT IV	• ISAR-Shock • IMPRESS • IMPELLA-STIC *Future Trials* - Dan-Ger Shock - REVERSE - RECOVER-IV	• DTU *Future Trials* - DTU-STEMI - UNLOAD-AMI - HERACLES	*Future Trials* - PROTECT KIDNEY

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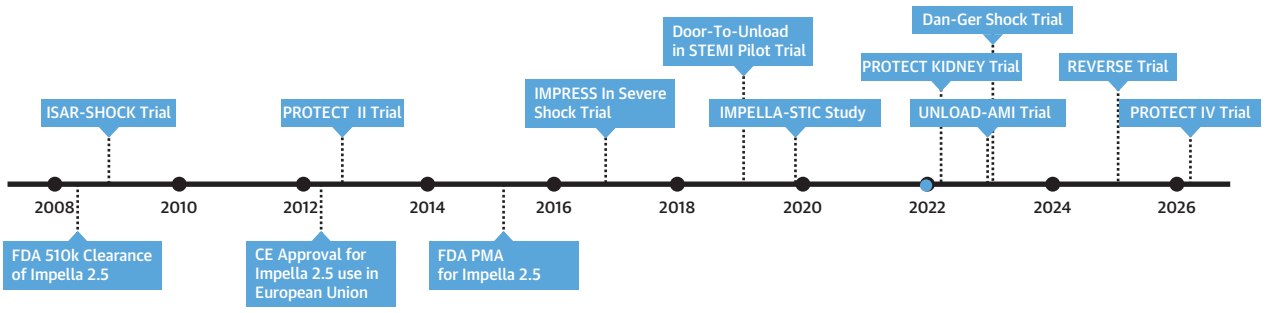
This figure shows all current and future clinical trials defining the role of percutaneous microaxial flow pump left ventricular assist devices in high-risk percutaneous coronary intervention (PCI), acute myocardial infarction (AMI) and cardiogenic shock (CS), cardiac unloading, and protection of the kidneys. Dan-Ger Shock = Danish Cardiogenic Shock Trial; DTU = Door to Unloading With Impella CP System in Acute Myocardial Infarction to Reduce Infarct Size: A Prospective Feasibility Study; DTU-STEMI = Primary Unloading and Delayed Reperfusion in ST-Elevation Myocardial Infarction: The STEMI-DTU Trial; HERACLES = Evaluation of Unloading the Heart in Patients With Cardiogenic Shock Treated With Mechanical Circulatory Support Devices; IMPELLA-STIC = Programme de Soutien aux Techniques Innovantes et Couteuses; IMPRESS = Impella Versus IABP Reduces Mortality in STEMI Patients Treated With Primary PCI in Severe Cardiogenic Shock; ISAR-Shock = Left Ventricular Assist Device [Impella LP 2.5] vs Intraaortic Balloon Counterpulsation [IABP] in Patients With Cardiogenic Shock and Acute Coronary Syndromes; LVEDP = left ventricular end-diastolic pressure; PROTECT II = A Prospective, Multi-Center, Randomized Controlled Trial of the Impella Recover LP 2.5 System Versus Intra Aortic Balloon Pump [IABP] in Patients Undergoing Non Emergent High Risk PCI; PROTECT IV = Impella-Supported PCI in High-Risk Patients With Complex Coronary Artery Disease and Reduced Left Ventricular Function; PROTECT KIDNEY = Prospective Randomized Study Comparing Impella Support Plus Optimal Medical Care Versus Optimal Medical Care Alone in Patients at High Risk for Contrast-Induced Nephropathy Undergoing Elective Percutaneous Revascularization; RECOVER IV = Early Impella Support in Patients With ST-Segment Elevation Myocardial Infarction Complicated by Cardiogenic Shock; REVERSE = A Prospective Randomised Trial of Early LV Venting Using Impella CP for Recovery in Patients With Cardiogenic Shock Managed With VA ECMO.

during PCI may result in a negative inotropic effect or hemodynamic compromise and thus lead to a bad outcome. Currently, there is no standardized definition of high-risk PCI, but in general, it incorporates 3 main categories: 1) anatomical location of the lesion and procedural techniques; 2) hemodynamic factors, such as low ejection fraction or acute decompensated heart failure; and 3) patient-specific comorbidities.[11] Currently, there is only 1 RCT with results available on the use of percutaneous microaxial flow pumps in patients with high-risk PCI, which is described later.

FIGURE 1 History of Percutaneous Microaxial Flow Pump Devices

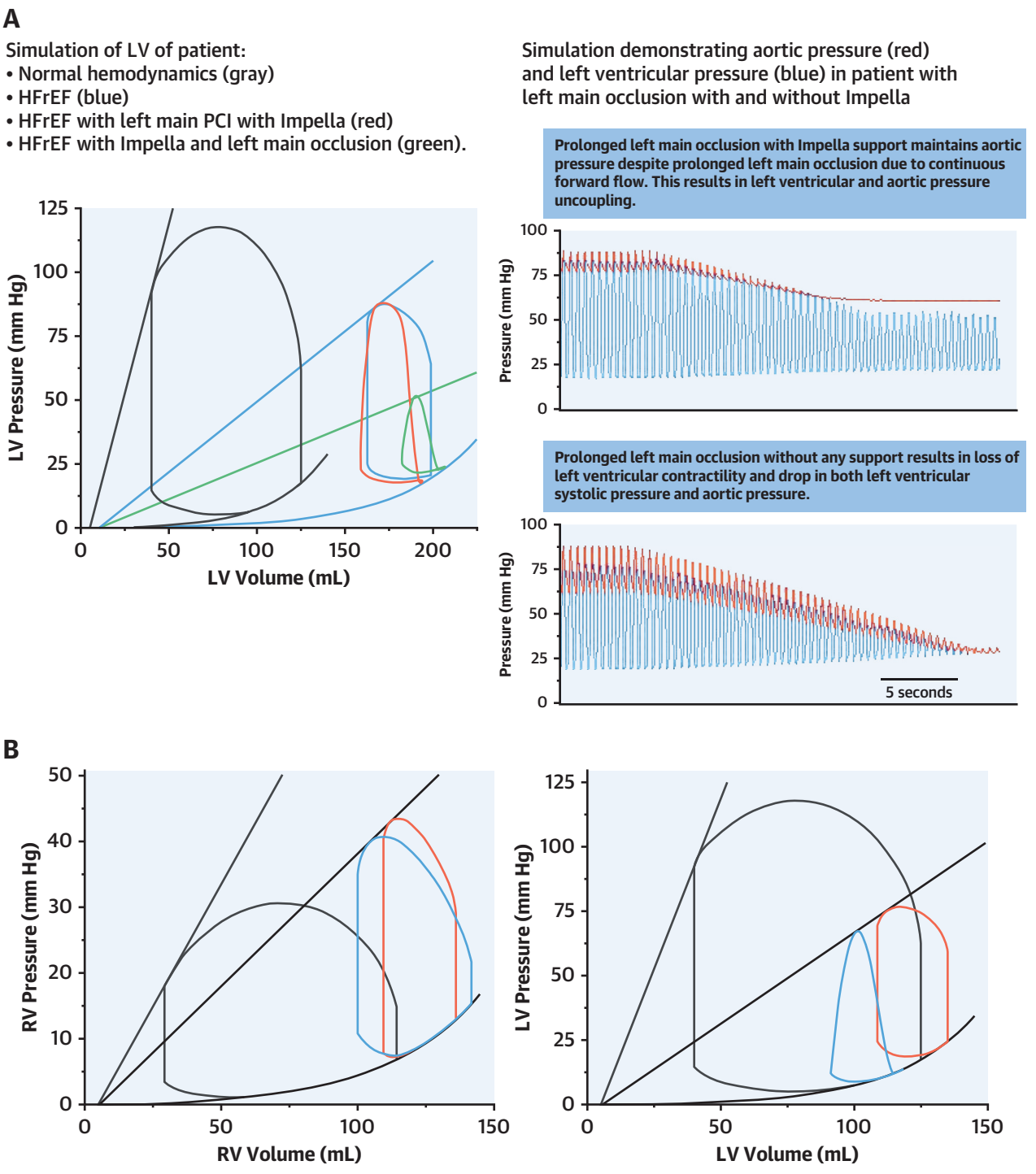


Timeline demonstrating the history and ongoing and future clinical trials on percutaneous microaxial flow pump devices. CE = Conformité Européenne; Dan-Ger Shock Trial = Danish Cardiogenic Shock Trial; FDA = U.S. Food and Drug Administration; IMPELLA-STIC = Programme de Soutien aux Techniques Innovantes et Couteuses; IMPRESS = Impella Versus IABP Reduces Mortality in STEMI Patients Treated With Primary PCI in Severe Cardiogenic Shock; ISAR-SHOCK = Left Ventricular Assist Device [Impella LP 2.5] vs Intraaortic Balloon Counterpulsation [IABP] in Patients With Cardiogenic Shock and Acute Coronary Syndromes; PMA = premarket approval; PROTECT II = A Prospective, Multi-Center, Randomized Controlled Trial of the Impella Recover LP 2.5 System Versus Intra Aortic Balloon Pump [IABP] in Patients Undergoing Non Emergent High Risk PCI; PROTECT IV = Impella-Supported PCI in High-Risk Patients With Complex Coronary Artery Disease and Reduced Left Ventricular Function; PROTECT KIDNEY = Prospective Randomized Study Comparing Impella Support Plus Optimal Medical Care Versus Optimal Medical Care Alone in Patients at High Risk for Contrast-Induced Nephropathy Undergoing Elective Percutaneous Revascularization; REVERSE = A Prospective Randomised Trial of Early LV Venting Using Impella CP for Recovery in Patients With Cardiogenic Shock Managed With VA ECMO; STEMI = ST-segment elevation myocardial infarction; UNLOAD-AMI = Attenuation of Post-Infarct Remodeling in Patients With Acute Myocardial Infarction by Left Ventricular Mechanical Unloading Using Impella-CP.

Hemodynamic effect of percutaneous microaxial flow pump devices in high-risk PCI. PCI is often performed in patients with heart failure with reduced ejection fraction, who already have depressed myocardial function. Any attempt to perform PCI in these patients is likely to result in further compromise of myocardial blood flow, which can rapidly deteriorate myocardial function and cause hypotension. As shown in **Figure 2A** and Video 1, simulation of PCI of the left main coronary artery (LM) without the percutaneous microaxial flow pump results in a sharp drop in LV pressure because of transient myocardial dysfunction coupled with a drop in systolic pressure and rapid hypotension. However, using a percutaneous microaxial flow pump device before LM occlusion results in LV and aortic decoupling, which maintains the continuous flow from the left ventricle to the aorta and the systolic pressure.

PROTECT II trial. Percutaneous microaxial flow pump LV assist devices (LVADs) can be used to provide hemodynamic support during these high-risk procedures. This was initially assessed in the PROTECT II (A Prospective, Multi-Center, Randomized Controlled Trial of the Impella Recover LP 2.5 System Versus Intra Aortic Balloon Pump [IABP] in Patients Undergoing Non Emergent High Risk PCI) trial, which was a randomized, multicenter clinical study that compared outcomes between use of the 2.5 model and the intra-aortic balloon pump (IABP) during high-risk PCI.[12] The trial enrolled 452 patients who were undergoing nonemergent PCI on an unprotected LM or last patent coronary vessel with an LV ejection fraction (LVEF) ≤35%; patients with 3-vessel disease and LVEF ≤30% were also eligible (**Table 1**). Patients were randomized in a 1:1 ratio to receive hemodynamic support during PCI with either the 2.5 model or IABP. Hemodynamic measurements, including right heart pressures and cardiac output, were obtained every 15 minutes, and hemodynamic support was discontinued in patients in stable condition immediately postprocedure, before discharge from the catheterization laboratory. Follow-up occurred for a duration of 90 days. The primary endpoint of the study was the composite rate of major adverse events (MAEs) at 30 days, as described in **Table 1**. MAEs included all-cause death, Q-wave or non-Q-wave myocardial infarction (MI), stroke or transient ischemic attack, repeat revascularization procedure, acute renal insufficiency, severe intraprocedural hypotension requiring therapy or cardiopulmonary resuscitation, ventricular tachycardia requiring cardioversion, aortic insufficiency, and angiographic failure of PCI. Secondary endpoints included in-hospital efficacy endpoints such as maximal decrease in cardiac output from baseline as a means of assessing hemodynamic support. A total of 225 patients were randomized to the percutaneous microaxial flow pump arm and 223 patients to the IABP arm. Although the trial was originally powered to enroll

FIGURE 2 Overview of Pressure-Volume Loop With Percutaneous Microaxial Flow Pump Devices



(A) Simulation of pressure-volume loop in high-risk percutaneous coronary intervention with and without the percutaneous microaxial flow pump device. **(B)** Simulation of pressure-volume of right ventricle and left ventricle in a normal patient **(gray)** and a patient with cardiogenic shock without **(red)** and with **(blue)** the percutaneous microaxial flow pump. **(C)** Simulation of the pressure-volume loop of the left ventricle with **(blue)** and without **(gray)** the percutaneous microaxial flow pump, demonstrating its role in left ventricular (LV) unloading. HFrEF = heart failure with reduced ejection fraction; MVO_2 = myocardial oxygen consumption; PE = potential energy; PVA = pressure-volume area; RV = right ventricular; SW = stroke work.

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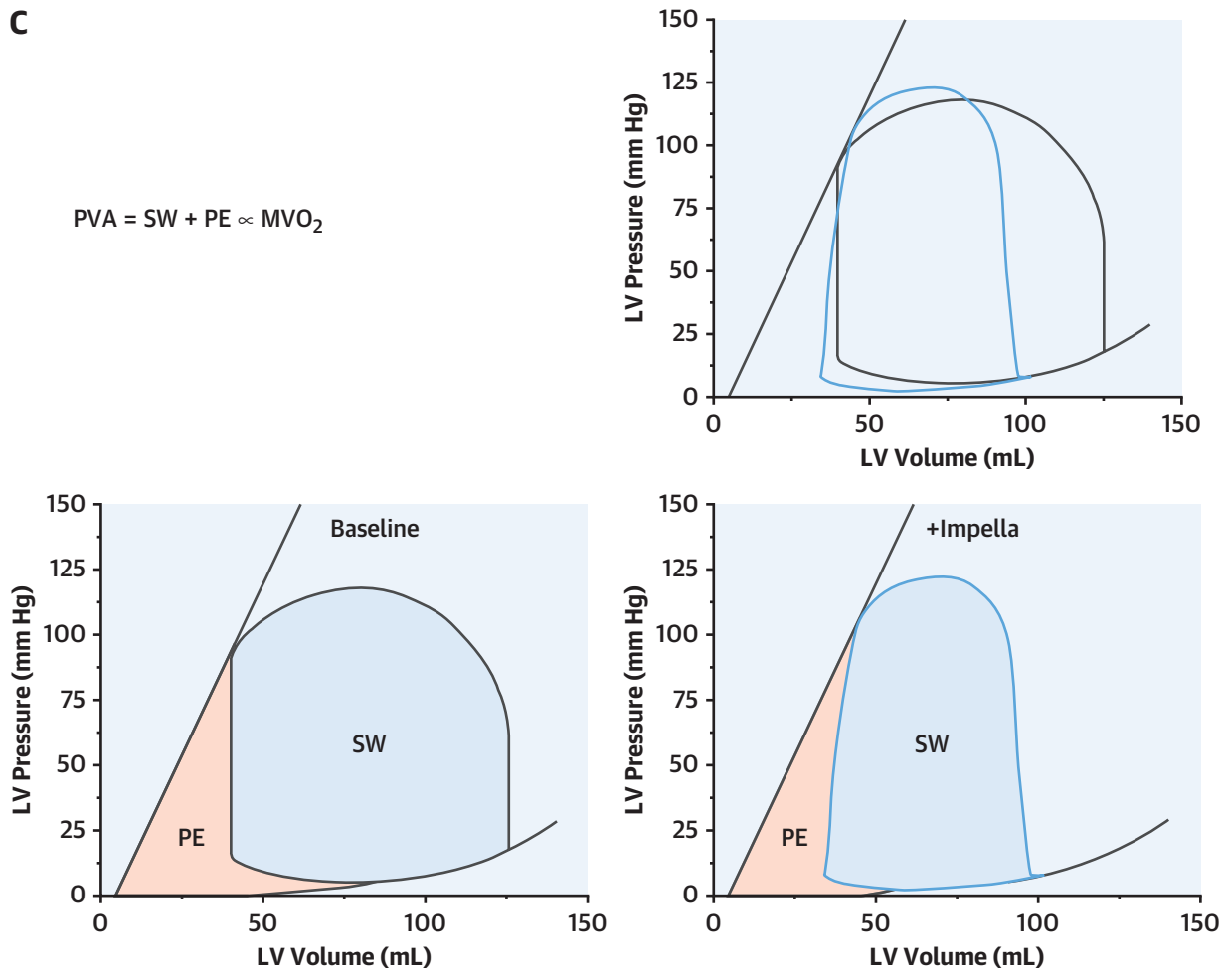
FIGURE 2 Continued



654 patients, the study was terminated early on the basis of a preplanned interim analysis that suggested futility. Baseline characteristics were similar between the 2 study groups, with the exception of a higher incidence of heart failure and of prior coronary artery bypass graft surgery in the percutaneous microaxial flow pump group (Table 2). The average LVEF in the study population was 24%. Approximately 66% of the patients were deemed to be inoperable by the study surgical consultants. The mean SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score was 30 ± 15, with a mean Society of Thoracic Surgeons mortality score of 6% ± 6%. A mean of 2.9 lesions were attempted per patient. The use of rotational atherectomy was more frequent in the percutaneous microaxial flow pump arm, whereas patients in the IABP group had a longer duration of support (8.4 hours vs 1.9 hours; $P < 0.001$). As determined by the maximal drop in cardiac power output from baseline, the 2.5 model appeared to provide better hemodynamic support than IABP during high-risk PCI (−0.04 ± 0.24 W vs −0.14 ± 0.27 W; $P = 0.001$). There was no statistically significant difference in the composite primary endpoint of MAE at 30 days between the 2.5 model and IABP groups (35.1% vs 40.1%; $P = 0.277$). At 90 days, patients supported with the percutaneous microaxial flow pump device showed a trend toward a lower MAE rate in comparison with those supported with IABP (40.6% vs 49.3%; $P = 0.06$). Prespecified subgroup analyses demonstrated that in patients not treated with atherectomy (n = 396), those who received support with the percutaneous microaxial flow pump device had a lower event rate of the primary composite outcome in comparison with those who received IABP support at 30 days (30.6% vs 39.6%; $P = 0.060$) and at 90 days (36.5% vs 48.7%; $P = 0.014$). This was

TABLE 1 Description of All RCTs on Microaxial Flow Pump Devices

Trial Name	Inclusion Criteria	Exclusion Criteria	N	Intervention vs Control	Sites	Endpoints	Results	Conclusion
PROTECT II[12]	• Subject is indicated for a nonemergent percutaneous treatment of at least 1 de novo or restenotic lesion in a native coronary vessel or bypass graft. • Patient presents with ◦ A compromised LVEF ◦ Intervention on the last patent coronary conduit ◦ Intervention on an unprotected left main artery ◦ Triple-vessel disease	• Recent MI with persistent elevation of cardiac enzymes • LV thrombus • Platelet count ≤75,000/mm^3 • Creatinine ≥4 mg/dL (patients already on dialysis were eligible) • Severe peripheral vascular disease that precluded passage of the 2.5 model device catheter or IABP	452	Percutaneous microaxial flow pump vs IABP for nonemergent high-risk PCI.	Multicenter, 112 sites in the United States, Canada, and Europe	Primary: 30-d incidence of MAE Secondary: 90-d incidence of MAE, including • All-cause death • Q-wave or non-Q-wave MI • Stroke or transient ischemic attack • Any repeat revascularization procedure • Need for a cardiac or vascular operation • Acute renal insufficiency • Severe intraprocedural hypotension requiring therapy • CPR or ventricular tachycardia requiring cardioversion • Aortic insufficiency • Angiographic failure of PCI	The percutaneous microaxial flow pump provided superior hemodynamic support in comparison with IABP. The primary endpoint (30-d MAE) was not statistically different between groups. At 90 d, a strong trend toward decreased MAE was observed in patients supported with the 2.5 model percutaneous microaxial flow pump in comparison with IABP.	The 30-d incidence of MAE was not different for patients support from an IABP or 2.5 model percutaneous microaxial flow pump hemodynamic support.
ISAR-SHOCK	AMI, CS	• Age <18 y • Prolonged resuscitation (>30 min) • Hypertrophic obstructive cardiomyopathy • Definite thrombus in left ventricle • Treatment with IABP • Severe valvular disease or mechanical heart valve • CS caused by mechanical complications of AMI such as ventricular septal defect, acute mitral regurgitation greater than second degree, or rupture of the ventricle • Predominant RV failure or the need for an RV assist device • Sepsis • Known cerebral disease • Bleeding with need for surgical intervention • Pulmonary embolism • Allergy to heparin or any known coagulopathy • Aortic regurgitation greater than second degree • Pregnancy • Inclusion in another study or trial	26	Percutaneous microaxial flow pump vs IABP.	2-center	Primary endpoint: change of cardiac index from baseline to 30 min after implantation. Secondary endpoints included lactic acidosis, hemolysis, and mortality after 30 d.	Cardiac index after 30 min of support was significantly increased in patients with the 2.5 model percutaneous microaxial flow pump compared with patients with IABP.	In patients presenting with CS caused by AMI, the use of a percutaneously placed LVAD (2.5 model percutaneous microaxial flow pump) is feasible, safe, and provides superior hemodynamic support compared with standard treatment using an IABP.

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one of the first RCTs performed on the percutaneous microaxial flow pump device. Although it did not show any benefit in the first 30 days, it did show a signal that patients supported with the percutaneous microaxial flow pump device had slightly better outcomes at 90 days.

The PROTECT II trial offered an important early examination of the role of the percutaneous microaxial flow pump device in high-risk PCI and formed the basis of the device's approval for this indication in 2015 by the U.S. Food and Drug Administration (FDA). The trial was stopped early because of the observation of similar rates of adverse events at 30 days, the prespecified primary endpoint. A significant limitation to this study was that the rate of adverse events in the percutaneous microaxial flow

TABLE 1 Continued

Trial Name	Inclusion Criteria	Exclusion Criteria	N	Intervention vs Control	Sites	Endpoints	Results	Conclusion
IMPRESS	AMI with ST-segment elevation complicated by severe CS in the setting of immediate PCI. Patients qualified only if they were mechanically ventilated before randomization.	• Severe aortoiliac arterial disease impeding placement of either IABP or pMCS • Known severe cardiac aortic valvular disease • Serious known concomitant disease with life expectancy <1 y • Known participation in this study or any other trial within the previous 30 d • CABG within the preceding week	48	pMCS device (CP model) vs IABP.	Multicenter	Primary endpoint was 30-d all-cause mortality.	At 30 d, mortality in patients treated with either IABP or pMCS was similar (50% and 46%, respectively; HR with pMCS: 0.96; 95% CI: 0.42-2.18; $P = 0.92$). At 6 mo, mortality rates for both pMCS and IABP were similar.	Routine treatment with pMCS was not associated with reduced 30-d mortality compared with IABP.
DTU	Patients aged 21-80 y presenting between 1 and 6 h from chest pain onset and with ST-segment elevation ≥2 mm in ≥2 contiguous anterior leads or ≥4 mm total ST-segment deviation sum in the anterior leads.	• Patients with prior MI or CABG • Out-of-hospital cardiac arrest requiring CPR • CS • Inability to undergo Impella CP insertion • Fibrinolysis within 72 h of presentation • Contraindications to CMR imaging	50	LV unloading with the percutaneous microaxial flow pump device followed by U-IR or LV unloading with a 30-min delay to reperfusion.	Multicenter	Primary safety outcomes: MACCE including CV mortality, reinfarction, stroke, or major vascular events at 30 d. Primary efficacy outcomes: assessment of infarct size as the percentage of total LV mass at 30 d using CMR. Secondary efficacy endpoints included infarct size by CMR at 3-5 and 30 d. Exploratory endpoints included a comparison of infarct size normalized to the area at risk at 3-5 d between groups.	MACCE rates were not statistically different between the U-IR versus delayed reperfusion groups. In comparison with the U-IR group, delaying reperfusion did not affect 30-d mean infarct size measured as a percentage of LV mass (15% ± 12% vs 13% ± 11%, U-IR vs U-DR; $P = 0.53$).	LV unloading using the CP model percutaneous microaxial flow pump device with a 30-min delay before reperfusion is feasible within a relatively short time period in anterior STEMI. The DTU-STEMI pilot trial did not identify prohibitive safety signals that would preclude proceeding to a larger pivotal study of LV unloading before reperfusion.
IMPELLA-STIC	Patients admitted with CS-AMI who had been treated with primary angioplasty within 24 h of the index AMI and required inotropic drugs and an IABP.	• Contraindication to microaxial flow pump implantation (aortic valvulopathy or mechanical valve, hypertrophic cardiopathy, LV thrombus) • Refractory CS (INTERMACS 1 or 2; high dose of norepinephrine or any dose of epinephrine) • RV failure • Resuscitated for cardiac arrest for >30 min • Septic condition	15	Surgically implanted microaxial flow pump + IABP or IABP alone.	2-center	Primary endpoint: change in CPI from baseline 12 h after implantation. Secondary endpoints • Hemodynamic and metabolic variables over 96 h • All-cause mortality at 30 d • Microaxial flow pump device–related complications (major bleeding, cerebrovascular events, and limb ischemia) • LVEF at 30 d	• 12 were available for primary endpoint analysis (IABP group, n = 6; 5.0 model microaxial flow pump + IABP group, n = 6). • Change in CPI after 12 h was not significantly different between the 2 groups.	In patients with CS and AMI stabilized by initial treatment with inotropes and IABP, the 5.0 model microaxial flow pump device did not provide additional hemodynamic support or improvement in LVEF at 1 mo; its use in this setting might be futile and possibly harmful.

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CMR = cardiac magnetic resonance; CPI = cardiac power index; CPR = cardiopulmonary resuscitation; CS = cardiogenic shock; DTU = Door to Unloading With Impella CP System in Acute Myocardial Infarction to Reduce Infarct Size: A Prospective Feasibility Study; IABP = intra-aortic balloon pump; IMPELLA-STIC = Impella Programme de Soutien aux Techniques Innovantes et Couteuses; IMPRESS = Impella Versus IABP Reduces Mortality in STEMI Patients Treated With Primary PCI in Severe Cardiogenic Shock; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; ISAR-SHOCK = Left Ventricular Assist Device (Impella LP 2.5) vs. Intraaortic Balloon Counterpulsation (IABP) in Patients With Cardiogenic Shock and Acute Coronary Syndromes; LV = left ventricular; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MACCE = major adverse cardiovascular and cerebrovascular event(s); MAE = major adverse event(s); MI = myocardial infarction; PCI = percutaneous coronary intervention; pMCS = percutaneous mechanical circulatory support; PROTECT II = A Prospective, Multi-Center, Randomized Controlled Trial of the Impella Recover LP 2.5 System Versus Intra Aortic Balloon Pump (IABP) in Patients Undergoing Non Emergent High Risk PCI; RCT = randomized clinical trial; RV = right ventricular; STEMI = ST-segment elevation myocardial infarction; U-IR = immediate reperfusion.

TABLE 2 Baseline Characteristics and Hemodynamic Variables in Available RCTs

	PROTECT II		ISAR-SHOCK		IMPRESS		DTU		IMPELLA-STIC	
	IABP (n = 223)	2.5 Model Percutaneous Microaxial Flow Pump (n = 2,250)	IABP (n = 13)	2.5 Model Percutaneous Microaxial Flow Pump (n = 13)	IABP (n = 24)	CP Model Percutaneous Microaxial Flow Pump (n = 24)	Delayed Reperfusion (n = 25)	Immediate Reperfusion (n = 25)	IABP (n = 6)	Percutaneous Microaxial Flow Pump + IABP (n = 7)
Baseline characteristics										
Age, y	67 ± 11	68 ± 11	67	65	59 ± 11	58 ± 9	60.6 ± 10.7	58.8 ± 11.4	53.5 ± 8.1	60.3 ± 12.3
Male	81.2	80.0	85.0	62.0	83.0	75.0	84.0	68.0	100.0	85.7
CHF	83.4	91.1								
Arterial hypertension			69	54	29	20	56	48		
Hyperlipidemia			54	62	24	20	36	56		
Diabetes mellitus	50.7	52	23	39	13	9	24	28.6	0	28.6
Current smoking			54	62	32	61	32	20		
Prior MI					4	5			0	14.3
History of stroke					4	0	0	4		
CAD			77	69						
Peripheral vascular disease	26.5	25.7			0	9	0	0		
Renal insufficiency	30.2	23.1					0	0		
Hemodynamic status										
MAP, mm Hg			72 ± 17	78 ± 16	66 ± 15	66 ± 15	108 ± 20	116 ± 20	69.9 ± 7.8	67.7 ± 12.3
LVEF, %	24.1 ± 6.3	23.4 ± 6.3	31 ± 16	28 ± 14	28 ± 16	30 ± 16	32.7 ± 12.7	41.9 ± 12.3	30 ± 8	29 ± 6
Cardiac index, L/min/m^2			1.73 ± 0.59	1.71 ± 0.45					2.3 ± 0.4	2.4 ± 0.8
LVEDP/PCWP, mm Hg			22 ± 7	22 ± 8			25.0 ± 9.6	24.0 ± 8.1	15.8 ± 6.1	17.4 ± 2.3
CVP/RA pressure, mm Hg			12 ± 6	13 ± 7					8.0 ± 2.8	11.5 ± 3.15
PAP, mm Hg			28 ± 9	28 ± 8					24	26.8
Laboratory assessment										
Creatinine, mg/dL					102 ± 22	96 ± 29				
Hb, g/dL					8.6 ± 1.2	8.6 ± 1.2				
Lactate, mmol/L					8.9 ± 6.6	7.5 ± 3.2			1.3 ± 0.3	1.7 ± 0.4

Values are mean ± SD or %.

CAD = coronary artery disease; CHF = congestive heart failure; CVP = central venous pressure; Hb = hemoglobin; LVEDP = left ventricular end-diastolic pressure; MAP = mean arterial pressure; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RA = right atrial; other abbreviations as in Table 1.

pump group may have been falsely elevated by clinically insignificant periprocedural MIs that were associated with rotational atherectomy.

PROTECT II laid the foundation for the future studies, including PROTECT III (Protected PCI Study: A Prospective Clinical Trial for Patients Undergoing Protected Percutaneous Coronary Intervention With Impella 2.5 System) and the ongoing PROTECT IV (Impella-Supported PCI in High-Risk Patients With Complex Coronary Artery Disease and Reduced Left Ventricular Function) trials.

The PROTECT III retrospective study included 1,143 participants who underwent elective nonemergent PCI with the 2.5 and CP models of the percutaneous microaxial flow pump. The study showed that the primary endpoint of mortality, MI, stroke, and repeat procedures at 90 days was lower in patients who underwent percutaneous microaxial flow pump-supported PCI compared with similar patients from the PROTECT II RCT. The patients enrolled in PROTECT III were older and received longer support with more complex procedures, as more vessels were treated in comparison with PROTECT II. These important findings laid the foundation for the development of the PROTECT IV trial.[13] Recent retrospective studies showed that percutaneous microaxial flow pump device use in patients undergoing high-risk PCI or who have AMI and CS did not show any benefit and were associated with higher rates of complications such as bleeding or limb ischemia in comparison with IABP use.[1,14,15] Hence, PROTECT IV will be important as the first RCT to look at the role of the percutaneous microaxial flow pump device in comparison with IABP for performing high-risk PCI.

PROTECT IV trial. A major limitation of the PROTECT II trial was the short follow-up duration, 30 days, for the primary composite outcome, as this time period was not sufficient to demonstrate a significant improvement in outcomes in this patient population. On 90-day follow-up, it was observed that the percutaneous microaxial flow pump arm

had fewer MAE compared with the IABP arm. Additionally, further subgroup analysis looking at major adverse cardiovascular events using the definition of a troponin or creatine kinase-MB increase of more than 8 times the normal value, instead of 3 times the normal value in the PROTECT II trial, showed a 29% unadjusted reduction in events in the percutaneous microaxial flow pump arm.[16] This led to the development of the ongoing PROTECT IV study, which aims to investigate similar patient populations over a longer follow-up period (Table 3). The PROTECT IV investigators aim to enroll 1,252 patients to assess whether the use of predominantly the CP or 2.5 models of the percutaneous microaxial flow pump during high-risk PCI in patients with reduced LV systolic function will result in improved outcomes compared with the use of IABP during high-risk PCI. The primary outcome is a composite of all-cause death, stroke, MI, durable LVAD implantation or heart transplantation, and hospitalization for cardiovascular causes. Follow-up will occur for 3 years.[17] The results of this study will likely provide data as to the safety and efficacy of the percutaneous microaxial flow pump device and will guide clinical decision making and improve patient care.

One of the major complications of high-risk PCI is kidney damage in patients with chronic kidney disease. Longer procedure times with greater volumes of contrast medium are thought to increase the risk for contrast-induced acute kidney injury (AKI) during high-risk PCI. This risk may ultimately limit procedural quality and/or complete revascularization. Current strategies to mitigate the risk for AKI include intravascular volume expansion with intravenous hydration, but these strategies have shown only modest reductions in the incidence of AKI. The percutaneous microaxial flow pump device, with its ability to enhance forward cardiac flow, is proposed to provide a new strategy to minimize AKI risk during PCI. This was demonstrated in multiple studies in which patients undergoing high-risk PCI with percutaneous microaxial flow pump support experienced a 5-fold reduction in the incidence of AKI compared with patients who did not receive percutaneous microaxial flow pump support, despite longer procedure times and greater contrast medium volume in the percutaneous microaxial flow pump-supported group.[18,19] Subgroup analyses of the PROTECT III trial also demonstrated a lower incidence of AKI in the percutaneous microaxial flow pump-supported group during high-risk PCI. However, many of the percutaneous microaxial flow pump devices can result in hemolysis, which can further worsen AKI, hence suggesting the need for further RCTs of percutaneous microaxial flow pump devices for renal-sparing effects.

PROTECT KIDNEY trial. The PROTECT KIDNEY (Prospective Randomized Study Comparing Impella Support Plus Optimal Medical Care Versus Optimal Medical Care Alone in Patients at High Risk for Contrast-Induced Nephropathy Undergoing Elective Percutaneous Revascularization) trial is a randomized controlled, open-label, parallel study that aims to investigate the potential renoprotective benefit of percutaneous microaxial flow pump device use during high-risk PCI compared with standard medical care, including periprocedural hydration (Table 3).[20] Patients at high risk for contrast-induced nephropathy will be randomized to undergo high-risk PCI with periprocedural hydration either with or without the use of a percutaneous microaxial flow pump device during PCI. The investigators aim to enroll 224 participants, who will be followed for 6 months. The primary outcome is the incidence rate of AKI over 2 days after PCI. Secondary outcomes will include change in estimated glomerular filtration rate, incidence rate of AKI over 3 days after PCI, initiation of dialysis, length of hospital stay, hospitalization for renal dysfunction, and all-cause mortality. Patients will be eligible for enrollment if they are deemed to be at high risk for contrast-induced AKI as indicated by a preliminary Mehran score ≥10.

PERCUTANEOUS MICROAXIAL FLOW PUMP USE IN CS.

Another indication for percutaneous microaxial flow pump placement that is under active investigation is in patients with CS, a state defined by inadequate tissue perfusion secondary to impaired myocardial function.[21] Catecholamines and other inotropic agents are widely used to treat CS; however, these agents do not always provide adequate circulatory support and are associated with arrhythmia and increased myocardial oxygen consumption.[22] As such, alternative treatment strategies have been investigated. One such strategy is MCS, which uses a mechanical pump to assist the myocardium in circulating blood. MCS therapies theoretically provide benefit by increasing circulatory support without the threat of myocardial ischemia and decreased myocardial oxygen demand.[21] That being said, several recently published observational studies did not show any benefit of using percutaneous microaxial flow pump devices in comparison with IABP, which was shown to be associated with increased complications.[14,15,23] All of the studies performed propensity-matched analyses among patients

TABLE 3 Upcoming RCTs on Microaxial Flow Pump Devices

Trial Name	Inclusion Criteria	Exclusion Criteria	N	Intervention vs Control	Single Center vs Multicenter	Endpoints	Remarks
PROTECT IV[17]	• Ages 18-90 y • Clinical presentation and baseline LV function either has CCS or NSTEMI with LVEF ≤40% • STEMI ≥24 h and <30 d after symptom onset with LVEF ≤30% (LVEF must be demonstrated to be ≤30% by quantitative echocardiography after the primary PCI procedure [if performed] and within 72 h before the planned randomization) • Local heart team has determined the need for PCI is indicated and the most important management • Meets the anatomical criteria for complex PCI as listed in the study	• STEMI ≤24 h from the onset of ischemic symptoms • Cardiogenic shock (SBP <80 mm Hg for ≥30 min) • Presently or recently intubated for the current admission • Cardiorespiratory arrest related to the current admission • Iliofemoral stents placed within 6 mo of enrollment • Incessant ventricular arrhythmias that would likely preclude stable percutaneous microaxial flow pump device positioning • Severe aortic stenosis or severe aortic insufficiency • Any contraindication or inability to place percutaneous microaxial flow pump device • Known LV thrombus • Prior mechanical valve or self-expanding TAVR • Any prior CABG or PCI within 12 mo • Prior placement of any other MCS device • Known severe pulmonary hypertension or RV dysfunction • Platelet count <75,000, active bleeding • On dialysis • Prior stroke with any permanent neurologic deficit • Taking any chronic anticoagulant that cannot be safely discontinued • Pregnancy • Any noncardiac condition with life expectancy <3 y	1,252	Percutaneous microaxial flow pump placement before high-risk PCI vs PCI with or without an IABP.	Multicenter	Primary endpoints at 3 y include composite of • All-cause death • Stroke • MI • LVAD placement or heart transplantation • Hospitalization for CV causes	• Follow-up at 1, 6, 12, 24, and 36 mo • Baseline and serial echocardiogram, KCCQ score, 6MWD, biomarkers • Plan for substudies looking at right heart catheterization, renal function, viability (using CMR at baseline and 6 mo)
Dan-Ger Shock[27]	• 18 y or older • STEMI of <36 h duration, confirmed by new-onset ST-segment elevation, or emergency angiography demonstrating acute occlusion of coronary artery • CS of <24 h duration, defined as: ◦ Signs of hypoperfusion with lactate ≥2.5 mmol/L ◦ Persistent (<30 min) SBP <100 mm Hg and/or need for vasoactive therapy • LVEF < 45% visually estimated or by wall motion score index >1.6	• Other causes of shock • Shock due to mechanical complication of MI • Severe aortic valve regurgitation/stenosis • Predominant RV failure. • Out-of-hospital cardiac arrest with persistent Glasgow Coma Scale score <8 after return of spontaneous circulation • Shock duration >24 h • Known heparin intolerance • Already established MCS • Do-not-resuscitate order	360	Conventional circulatory support (used according to the enrolling site's usual management) vs percutaneous microaxial flow pump.	Multicenter	Primary endpoint: all-cause mortality at 180 d after randomization Secondary endpoints • Composite of CV events (death, cardiac transplantation, escalation to MCS device, rehospitalization for HF) • Combined safety (major bleeding, vascular complications, and significant hemolysis) • Renal function • Number and doses of inotropes and vasopressors at 24, 48, and 72 h after randomization • LV function at 180 d • SIRS • Health economics • Hemodynamics parameters (CPO and lactate clearance for first 48 h)	Patients with CS are at higher risk for severe complications such as infection, bleeding, electrolyte abnormalities, and arrythmias. The study plans to collect significant degree of adverse events throughout the ICU period. A data and safety monitoring board consisting of 2 independent cardiologists and 1 biostatistician will monitor this.

Continued on the next page

TABLE 3 Continued

Trial Name	Inclusion Criteria	Exclusion Criteria	N	Intervention vs Control	Single Center vs Multicenter	Endpoints	Remarks
REVERSE[31]	• Ages 18-65 y • CS including refractory to conventional therapy • Post-AMI cardiogenic shock excluding mechanical complications requiring surgical intervention after ECMO • Drug overdose–induced CS • Early graft failure: post-orthotopic heart transplantation CS, excluding immediate intraoperative failure • Acute or chronic cardiomyopathy with progressive shock and decompensation unresponsive to medical therapies	• Recent significant pulmonary embolism • Moderate to severe AI • Ongoing significant sepsis • Severe pulmonary hypertension and shock • Hypothermia • Postcardiotomy CS • Continuous CPR >20-30 min, except if neurologic status is satisfactory • Transfer from outside hospital on VA-ECMO or with history of CPR • Listed for cardiopulmonary transplantation or being evaluated for cardiopulmonary transplantation or permanent MCS • Known or suspected CHF with echocardiogram documenting LV diastolic diameter >6.5 cm • Known or suspected CHF with echocardiogram documenting LVEF <25% • Mechanical aortic valve replacement • Presence of LV thrombus • Preexisting 2.5, CP, 3.5, or 5.0 model microaxial flow pump • CS due to primary respiratory failure • Mechanical complications requiring surgical intervention after ECMO such as postischemic VSD • Severe liver failure • Active malignancy • Acute aortic dissection • Intracranial hemorrhage • Neurologic injury, including recent cerebrovascular accident or suspected severe neurologic injury	96	VA-ECMO alone vs VA-ECMO with early institution (within 10 h of institution of VA-ECMO) of CP model percutaneous microaxial flow pump device LV venting.	Multicenter	Primary endpoint: recovery from CS shock at 30 d (defined as survival free from MCS, heart transplantation, or inotropic support). Secondary endpoint: survival to hospital discharge (time frame: at discharge from hospital, an average of 60 d).	
RECOVER IV (currently under development)	As per current information similar to the investigator-initiated NCSI study, which includes • AMI symptoms with ECG changes and/or biomarker evidence of STEMI or NSTEMI • Presence of CS, defined as ◦ Hypotension ◦ Signs of end-organ hypoperfusion ◦ Hemodynamic criteria represented by cardiac index <2.2 L/min/m^2 or CPO <0.6 W • Patients undergoing PCI	As per current information, similar to the investigator-initiated NCSI study, as follows • Evidence of anoxic brain injury • Unwitnessed out-of-hospital cardiac arrest in which return of spontaneous circulation is not achieved within 30 min • Septic, anaphylactic, hemorrhagic and neurologic causes of shock • Nonischemic causes of shock/hypotension (pulmonary embolism, pneumothorax, myocarditis, tamponade, etc) • Active bleeding for which mechanical circulatory support is contraindicated • Recent major surgery for which MCS is contraindicated • Mechanical complications of AMI • Known LV thrombus • Mechanical aortic prosthetic valve • Contraindication to intravenous systemic anticoagulation	Currently under development	5.5 model microaxial flow pump pre-PCI/RP model RP oxygenation escalation vs PCI with other treatment protocol, including any kind of circulatory support devices from a different brand with AMI and CS.	Multicenter	Not available	

Continued on the next page

TABLE 3 Continued

Trial Name	Inclusion Criteria	Exclusion Criteria	N	Intervention vs Control	Single Center vs Multicenter	Endpoints	Remarks
UNLOAD-AMI[34]	• Large anterior wall AMI with estimated ischemia of <24 h • At risk of the beginning of cardiogenic shock (SCAI A/B) • Blood pressure <160/100 mm Hg • No previous AMI based on the patient's history • No previously known LV systolic dysfunction • Assumed new LV dysfunction documented by echocardiography or LVG (LVEF <45%), • Infarct culprit lesion at the proximal LAD, LMCA, or equivalent, with TIMI flow grade ≤ 2 • LV end-diastolic pressure ≥18 mm Hg measured invasively	• History of chronic LV dysfunction • Chronic anticoagulation therapy • Need for GP IIb/IIIa blockers at PCI • Inadequate femoral vein access (peripheral artery disease) • Significant valve disease or valve prosthesis • CPR >5 min before PCI • LV thrombus • Periprocedural AMI (obliteration of large nonculprit artery during PCI)	80	LV mechanical unloading by CP model percutaneous microaxial flow pump (patients will receive the CP device for 36-48 h; pump speed and LV unloading will be guided by PCWP).	Single center	Primary • Difference in LV end-systolic volume (measured during the index hospitalization [days 5-7] and at 3 mo) • Occurrence of LV remodeling (defined by increase of LVESV >20%) • Extent of post-infarct scar (measured by Tc-SPECT) Secondary: CV complications, HF	
HERACLES[35]	• Patients aged 18 y or older with CS of any etiology • On VA-ECMO support • Undergoing clinically indicated cardiac catheterization	• Postcardiotomy CS • Confirmed LV thrombus on imaging • Age <18 y • Pregnancy or peripartum cardiomyopathy • Contraindication to either IABP or pLVAD insertion (more than moderate aortic regurgitation, severe peripheral vascular disease prohibiting insertion of either device) • Current treatment with either IABP or pLVAD • Mechanical aortic valve replacement					
PROTECT KIDNEY[20]	• Age 18-85 y • Clinical indication for coronary angiogram with potential high-risk PCI • Patients at high risk for contrast-induced AKI, as indicated by a preliminary Mehran score ≥10	• Patients with contraindications to use of a percutaneous microaxial flow pump (mural thrombus in the left ventricle; presence of a mechanical aortic valve or aortic valve stenosis; moderate to severe aortic insufficiency [echocardiographic assessment graded as ≥+2]); severe peripheral arterial disease precluding placement of a percutaneous microaxial flow pump system • Patients who are deemed to potentially require hemodynamic support for PCI • Patients needing emergency PCI • Patients with acute CS • Patients diagnosed with AKI within the last 7 d before screening or incipient AKI	224	Standard-of-care PCI vs percutaneous microaxial flow-protected PCI in patients at high risk for contrast-induced nephropathy undergoing elective percutaneous revascularization.	Single center	Primary: incidence rate of contrast-induced AKI (2 d after PCI) Secondary • Change in eGFR • AKI 3 d or more after PCI • Incidence of dialysis (within 6 mo) • Rehospitalization for renal dysfunction • Mortality up to 6 mo after PCI • Length of hospital stay	

Continued on the next page

TABLE 3 Continued

Trial Name	Inclusion Criteria	Exclusion Criteria	N	Intervention vs Control	Single Center vs Multicenter	Endpoints	Remarks
		• Unwitnessed cardiac arrest or ≥30 min of CPR before screening or any impairment in mental status, cognition, or any global or focal neurologic deficit • Patients on mechanical ventilation • Patients diagnosed with AKI within the last 7 d before screening or incipient AKI (in cases in which AKI cannot be ruled out as a cause for elevated serum creatinine, a rise or fall above 30% of a second serum creatinine measurement obtained within 12-24 h is indicative of AKI) • Patients with eGFR <20 mL/min/1.73 m^2 • Suspected or known pregnancy • Patients with comorbidities that, in the investigator's opinion, would limit life expectancy to <6 mo • Patients with other medical, social, or psychological problems that, in the opinion of the investigator, preclude them from undergoing percutaneous microaxial flow pump-protected PCI or the study-related procedures, evaluations, and follow-up • Patients with severe anemia, as indicated by Hb concentrations <8.5 g/dL at the time of screening • Patients who were exposed to contrast media in the last 7 d before the time of screening • Mental incapacity, unwillingness, or language barriers precluding adequate understanding or cooperation • Participation in the active treatment or follow-up phase of another clinical study of an investigational drug or device that has not reached its primary endpoint					

6MWD = 6-minute walk distance; AI = aortic valve insufficiency; AKI = acute kidney injury; CCS = Canadian Cardiovascular Society; CPO = cardiac power output; Dan-Ger Shock = Danish Cardiogenic Shock Trial; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; GP = glycoprotein; HERACLES = Evaluation of Unloading the Heart in Patients With Cardiogenic Shock Treated With Mechanical Circulatory Support Devices; HF = heart failure; ICU = intensive care unit; KCCQ = Kansas City Cardiomyopathy Questionnaire; LAD = left anterior descending; LMCA = left main coronary artery; LVESV = left ventricular end-systolic volume; MCS = mechanical circulatory support; NCSI = National Cardiogenic Shock Initiative; NSTEMI = non-ST-segment myocardial infarction; pLVAD = percutaneous left ventricular assist device; PROTECT IV = Impella-Supported PCI in High-Risk Patients With Complex Coronary Artery Disease and Reduced Left Ventricular Function; PROTECT KIDNEY = Prospective Randomized Study Comparing Impella Support Plus Optimal Medical Care Versus Optimal Medical Care Alone in Patients at High Risk for Contrast-Induced Nephropathy Undergoing Elective Percutaneous Revascularization; RECOVER IV = Early Impella Support in Patients With ST-Segment Elevation Myocardial Infarction Complicated by Cardiogenic Shock; REVERSE = A Prospective Randomised Trial of Early LV Venting Using Impella CP for Recovery in Patients With Cardiogenic Shock Managed With VA ECMO; SBP = systolic blood pressure; SCAI = Society for Cardiovascular Angiography and Interventions; SIRS = systemic inflammatory response syndrome; Tc-SPECT = technetium single-photon emission computed tomography; TIMI = Thrombosis In Myocardial Infarction; UNLOAD-AMI = Attenuation of Post-Infarct Remodeling in Patients With Acute Myocardial Infarction by Left Ventricular Mechanical Unloading Using Impella-CP; VA = venoarterial; VSD = ventricular septal defect; other abbreviations as in Tables 1 and 2.

receiving percutaneous microaxial flow pump devices and IABP from a large multicenter database. One of these studies matched patients with AMI and CS from multiple tertiary care centers in Europe from the IABP-SHOCK II (Randomized Clinical Study of Intra-aortic Balloon Pump Use in Cardiogenic Shock Complicating Acute Myocardial Infarction) trial. Of 237 patients who were matched, the study did not show any mortality difference at 30 days.[15] Similarly, a study performed from the American College of Cardiology's National Cardiovascular Data Registry among 1,680 propensity-matched patients with AMI and CS showed higher in-hospital mortality with an intravascular microaxial LVAD pump such as the percutaneous microaxial flow pump device in comparison with an IABP (absolute risk difference 10.9 percentage points; 95% CI: 7.6-14.2; $P < 0.001$), which may have been related to increased bleeding complications. The advent of new MCS devices, including the percutaneous microaxial flow pump, appears promising for improving hemodynamic status; however, because of a lack of RCT data, questions regarding their relative efficacy have been raised.

Hemodynamic effect of the percutaneous microaxial flow pump device in CS. Figure 2B and Video 2 demonstrate the hemodynamic effect of a percutaneous microaxial flow pump device in a patient with CS. As shown in the simulation, patients with CS often have high LV end-diastolic pressure and volume. The use of a transvalvular microaxial flow pump such as this decreases both LV end-diastolic pressure and volume by continuous forward flow from the left ventricle to the aorta. It also improves systemic aortic pressure by continuous flow in both systole and diastole. This results in a decrease in left-sided filling pressure, improves RV stroke volume, and results in RV unloading.

ISAR-SHOCK trial. The ISAR-SHOCK (Left Ventricular Assist Device [Impella LP 2.5] vs Intraaortic Balloon Counterpulsation [IABP] in Patients With Cardiogenic Shock and Acute Coronary Syndromes) trial was a multicenter RCT that compared IABP with the percutaneous microaxial flow pump device in 25 patients with CS secondary to AMI.[4] The devices were implanted after treatment with inotropes, revascularization, and measurement of hemodynamic parameters. Follow-up hemodynamic measurements were taken 30 minutes after device placement. The primary endpoint of this study was change in cardiac index at the 30-minute mark. Secondary endpoints included other hemodynamic and metabolic parameters, all-cause mortality at 30 days, and various device-related complications (Table 1). Baseline characteristics and hemodynamic data from the patients in each arm are detailed in Table 2. The change in cardiac index at 30 minutes was found to be statistically significant ($P = 0.02$), with percutaneous microaxial flow pump patients benefiting more (change in cardiac index 0.49 ± 0.46 L/min/m^2) than IABP patients (change in cardiac index = 0.11 ± 0.31 L/min/m^2). The MAP also increased more in percutaneous microaxial flow pump patients than in IABP patients. However, the most significant difference was in diastolic arterial pressure, which increased by 9.2 ± 12.1 mm Hg in percutaneous microaxial flow pump patients, whereas it decreased in IABP patients (−8.0 ± 13.1 mm Hg; $P = 0.002$). There were no differences in mortality between the 2 groups, and device placement was successful in >90% of patients in each arm. Serum lactate was also lower in percutaneous microaxial flow pump patients during the first 48 hours, with an area under the curve of 123 ± 87 h · mmol/L in percutaneous microaxial flow pump patients vs 180 ± 147 h · mmol/L in IABP patients. Hemolysis, as measured by free hemoglobin, was higher in percutaneous microaxial flow pump patients, so they were given more packed red blood cells and fresh frozen plasma; however, this was only transient. The study showed that cardiac index, cardiac output, and MAP were significantly improved 30 minutes after implantation in the percutaneous microaxial flow pump arm, but there was no mortality difference. Endogenous cardiac work load was lower at all time points in the percutaneous microaxial flow pump group, which could explain why hemodynamic improvement was limited to the first hours after implantation. Additionally, it was noted that the use of inotropes and vasopressors did not differ between the groups. At discharge, LVEF was not significantly different between the groups, and improvements in hemodynamic parameters were not significantly different at 30 days. The results of this study are limited by the small sample size and the early time point used for primary endpoint assessment.

A major limitation of the ISAR-SHOCK trial was that it left the time to initiation of the intervention, as well as device removal, to the clinical judgment of the treating physician, which creates an unaccounted-for variable in the study. Additionally, in this study, MCS devices were implanted after revascularization, which may have limited the observed benefits because of mechanical unloading.

IMPRESS trial. The IMPRESS (Impella Versus IABP Reduces Mortality in STEMI Patients Treated With Primary PCI in Severe Cardiogenic Shock) trial was a

multicenter RCT that compared IABP with the CP model of the percutaneous microaxial flow pump. The study was conducted in 48 patients with CS (defined as systolic pressure <90 mm Hg) after AMI.[24] To study an even sicker patient population, this study included only patients who were mechanically ventilated before randomization. The primary endpoint was 30-day all-cause mortality, and the secondary endpoint was 6-month mortality (Table 1). MCS placement occurred after treatment with catecholamines and revascularization, except in 8 patients (3 with IABP and 5 with the CP model) who underwent revascularization after MCS placement. All statistics were performed by intention-to-treat analysis. The study revealed no significant difference in mortality rates at 30 days between the cohorts. There was also identical mortality at the 6-month mark (50% in both groups; $P = 0.92$). The mean patient age was 58 years, and 21% were women. Further baseline characteristics of the patients enrolled in this trial are described in Table 2.

The lack of benefit in this study could be due to the extremely sick study population, as 48% of the enrollees had return of spontaneous circulation times longer than 20 minutes, 100% of participants were on ventilators, 92% of patients had resuscitated cardiac arrest, and the median lactate level was 8 mmol/L. As the CP model uses a 14-F sheath, compared with the 8-F sheath used for IABP, there was a higher rate of vascular complications in the percutaneous microaxial flow pump arm. Additionally, a minority of patients in this study underwent device placement before reperfusion. Early MCS use for hemodynamic support may play an important factor in such patients presenting with refractory CS. The majority of patients died of anoxic brain injury. Hence, it may be difficult to suggest a benefit from the MCS device in this futile group of patients.

Recently, further analysis of these patients at the 5-year follow-up showed that the primary endpoint of major adverse cardiac and cerebrovascular events occurred in 12 of 24 percutaneous microaxial flow pump patients (50%) and 19 of 24 IABP patients (79%) ($P = 0.07$). Although we do see some signals of benefit of the percutaneous microaxial flow pump device over a long-term period, the study failed to show any significant differences, which could be due to the small sample size.[25]

IMPELLA-STIC trial. IMPELLA-STIC (Programme de Soutien aux Techniques Innovantes et Couteuses) was another randomized study that included 15 patients with AMI and CS to test the hypothesis that the surgically implanted 5.0 model may provide hemodynamic benefits and improve LVEF in patients already being managed with an IABP.[26] Two patients from the IABP group were excluded, as 1 had nonischemic dilated cardiomyopathy and the other withdrew consent. For analysis, 6 patients were included in the IABP group and 7 patients in the microaxial flow pump group. The patients were enrolled into the study 60.8 ± 39.9 hours after the index AMI admission and 48.1 ± 38.5 hours after the initial IABP insertion. The hemodynamic status of the patients was stable, as shown in Table 2. The 5.0 model of the microaxial flow pump was placed 4.4 ± 2.3 hours after randomization through the axillary artery. The study demonstrated no additional benefit with the use of the 5.0 model, and the primary endpoint of change in the cardiac power index was comparable between the 2 groups (IABP: change in cardiac power index 0.08 ± 0.08 W/m^2; 5.0 model plus IABP: change in cardiac power index −0.02 ± 0.25 W/m^2; $P = 0.40$). There was a greater number of patients on mechanical ventilation in the 5.0 model group than in the IABP arm (4 vs 0). The LVEF at baseline was similar in both groups (28% with IABP vs 29% with microaxial flow pump), and there was no difference in the improvement of LVEF at 1 month (40.6% ± 12.5% with microaxial flow pump vs 38.6% ± 14.4% with IABP). It was also observed that, similar to previous studies, vascular complications such as bleeding were higher in the microaxial flow pump arm.

The study's initial plan was to enroll 60 patients, but because of changes in guidelines and slow recruitment, only 15 were enrolled, of whom 13 were included in the analysis. The study was largely underpowered, and it can be considered only a feasibility trial. The study compared IABP vs IABP plus microaxial flow pump, making it difficult to assess the benefit of the microaxial flow pump device alone. Additionally, a majority of the patients enrolled in the study had pulmonary capillary wedge pressures <18 mm Hg and cardiac indexes more than 2.2. This raises the concern as to whether these patients even needed the 5.0 model microaxial flow pump for support, and the benefits might have been outweighed by the overall vascular complication events. The primary endpoint of the study was to look at the change in cardiac power index, and hemodynamic variables and all-cause mortality were secondarily examined. The morbidity data were excluded from the analysis, which obscures the clinical picture and restricts accurate interpretation of patient outcomes.

Ongoing and future trials. Currently, IABPs have been insufficient in showing any benefit in patients with AMI and CS. This has resulted in increased use of

more advanced MCS devices such as venoarterial extracorporeal membrane oxygenation (VA-ECMO) and microaxial flow pump devices. Among these devices, the microaxial flow pump appears to be more promising because of its ability to be rapidly inserted percutaneously and provide a wide range of flow (2.5-6.0 L/min), depending upon the type of device. However, as mentioned previously, the initial studies of the use of microaxial flow pumps in patients with CS are limited by small sample sizes. Hence, future RCTs are currently ongoing or proposed to include a greater number of patients and are discussed later (Table 3).

Dan-Ger Shock trial. Dan-Ger Shock (Danish Cardiogenic Shock Trial) is an ongoing multicenter RCT that will compare conventional circulatory support (according to the enrolling sites' routine management) with the percutaneous microaxial flow pump device in patients with ST-segment elevation MI and CS.[27,28] The investigators plan to enroll 360 patients, and randomization will be allowed pre-PCI or, in the case of CS, up to 12 hours after PCI. The primary endpoint will be all-cause death at 6 months, and secondary outcomes will include major adverse cardiovascular events, combined safety (comprising bleeding, vascular complications, and hemolysis), renal function, use of inotropes or pressors, LV function, systemic inflammatory response syndrome, health economics, and hemodynamic status (Table 3). Some of the major exclusion criteria are listed in Table 3. The study also plans to include a data and safety monitoring board comprising 2 cardiologists and 1 biostatistician to monitor and collect all data regarding severe complications, such as infection, bleeding, electrolyte disturbance, or arrhythmias, which are expected to be seen in the intensive care unit irrespective of the MCS device.

REVERSE trial. VA-ECMO is increasingly used as the rescue strategy for complete circulatory support in patients with CS, irrespective of the underlying etiology. The complete circulatory support can improve end-organ function and coronary perfusion and can also be used as a bridge to advanced therapies.[29] However, one of the major drawbacks of using VA-ECMO is that it worsens the afterload on the left ventricle, resulting in worsening of LV recovery. Recent studies have shown that the addition of a percutaneous microaxial flow pump device to VA-ECMO can help reduce ventricular loading and improve survival.[30] The REVERSE (A Prospective Randomised Trial of Early LV Venting Using Impella CP for Recovery in Patients With Cardiogenic Shock Managed With VA ECMO) trial is an ongoing single-center RCT in 96 patients that compares VA-ECMO alone with VA-ECMO in combination with the CP model of the percutaneous microaxial flow pump (Table 3).[31] The primary outcome will be recovery from CS, defined as survival free from MCS, heart transplantation, or inotropic support. The secondary outcome will be survival to hospital discharge. Exclusion criteria are listed in Table 3. The results of this and other ongoing trials are anticipated to provide high-powered evidence for whether there is a role for the percutaneous microaxial flow pump in CS.

RECOVER IV trial. The RECOVER IV (Early Impella Support in Patients With ST-Segment Elevation Myocardial Infarction Complicated by Cardiogenic Shock) RCT is designed to determine whether the use of the 5.5 model pre-PCI during AMI in patients with CS facilitates myocardial recovery and decreases subsequent development of heart failure. This trial is still in the development phase and is planned to start in the next 1 to 2 years and to involve sites both within and outside of the United States. According to currently available information, the inclusion and exclusion criteria will be very similar to those used for patients enrolled in the National Cardiogenic Shock Initiative prospective registry (Table 3). RECOVER IV will be one of the largest RCTs to date on the use of the microaxial flow pump device in patients with AMI and CS and is designed to include all current best practices related to rapid revascularization, culprit vs nonculprit PCI, the role of early (pre-PCI) support, hemodynamic guidance, and escalation and weaning strategies, as well as vascular safety.

PERCUTANEOUS MICROAXIAL FLOW PUMP DEVICES IN LV UNLOADING.

LV unloading is a more recent indication for the use of the percutaneous microaxial flow pump device. The fundamental idea in LV unloading is that percutaneous assist devices that decrease afterload could facilitate myocardial recovery and reduce the area of ischemic myocytes by improving blood supply from the collateral circulation, decreasing LV end-diastolic pressure, preventing remodeling of the myocardium, and reducing oxygen demand, a concept that underlies many of the treatments used in heart failure patients around the world.[32] This method makes sense from a physiological standpoint; however, research on this technique is still being conducted in order to examine its applicability to humans.

Hemodynamic effect of the percutaneous microaxial flow pump device on LV unloading.

Before we discuss the role of the percutaneous microaxial flow pump in LV unloading, it is important to understand the

hemodynamic effect of the device on LV unloading. **Figure 2C** and Video 3 show a simulation of a pressure-volume loop at baseline without a microaxial flow pump device in comparison with the pressure-volume loop with a percutaneous microaxial flow pump device. The pressure-volume area has been shown to correlate with myocardial oxygen consumption, which represents the sum of myocardial stroke work and the potential energy of the myocardium and is related to the underlying wall tension. In patients with AMI and CS and those on extracorporeal membrane oxygenation, the pressure-volume loop shifts toward the right side and increases the overall pressure-volume area. By drawing blood from the left ventricle into the systemic circulation, the percutaneous microaxial flow pump device decreases the overall LV filling pressure and volume. This moves the pressure-volume loop toward the left side, resulting in decreased stroke volume and reduced LV end-diastolic pressure and volume, which improves myocardial perfusion and results in decreased microvascular resistance, reducing the potential energy of the myocardium.

DTU clinical trial. The DTU (Door to Unloading With Impella CP System in Acute Myocardial Infarction to Reduce Infarct Size: A Prospective Feasibility Study) trial was a multicenter RCT conducted in 50 patients with anterior ST-segment elevation MIs that compared percutaneous microaxial flow pump device placement followed by either immediate reperfusion or by reperfusion after 30 minutes of unloading with the percutaneous microaxial flow pump device.[33] Providers were permitted to shorten the time between percutaneous microaxial flow pump placement and reperfusion if it was deemed clinically necessary. Patients presenting up to 6 hours from the initial onset of chest pain and with ST-segment elevation in 2 contiguous anterior leads were eligible. Pertinent exclusion criteria included prior MI, prior coronary artery bypass graft surgery, out-of-hospital cardiac arrest requiring cardiopulmonary resuscitation, and CS (**Table 1**). The primary safety endpoint of this study was major adverse cardiac and cerebrovascular events. The primary efficacy endpoint was the size of the myocardial infarct at 30 days as a percentage of total LV mass, which was measured using cardiac magnetic resonance. Baseline characteristics of the patients are described in **Table 2**. Notably, the baseline LVEF was lower in the delayed reperfusion group than in the immediate reperfusion group (respectively, 32.7% ± 12.7% and 41.9% ± 12.3%; $P = 0.02$). The average time from percutaneous microaxial flow pump placement to angiography was 13.8 ± 10.3 minutes in the delayed reperfusion group and 1.7 ± 6.9 minutes in the immediate reperfusion group. Infarct size, the primary efficacy outcome, was not statistically different between the 2 groups (13.1% ± 11.3% in the delayed group vs 15.3% ± 11.5% in the immediate reperfusion group; $P = 0.53$). The incidence of major adverse cardiac and cerebrovascular events, the primary safety outcome, was also not statistically different between the groups (12% in the delayed reperfusion group vs 8% in the immediate reperfusion group; $P = 0.99$). The results of this study demonstrate the safety of a delayed reperfusion approach for anterior ST-segment elevation MI and warrant further investigation into treatment strategies that unload the left ventricle. Major limitations to this study are the small sample size, lack of comparison with standard treatment guidelines, and the relatively short assessment and follow-up time points.

The DTU trial was designed on the basis of preclinical studies that demonstrated beneficial reductions in myocardial infarct size when the left ventricle was mechanically unloaded for 30 minutes before reperfusion. Although the average time to reperfusion in this trial was 97 minutes in the delayed reperfusion group and 72 minutes in the immediate reperfusion group, the symptom onset time for the immediate reperfusion group happened to be 24 minutes longer than in the other arm purely by chance of randomization. This unfortunately limits the generalizability of this study because the ischemic time, a key variable for this study's research question, was not adequately controlled. Additionally, this trial did not include a study arm for standard-of-care treatment. As such, it is difficult to assess the safety and efficacy of this approach. Still, this study will be key for future examination of mechanical unloading of the left ventricle.

Ongoing and future trials. ***STEMI-DTU trial.*** STEMI-DTU (Primary Unloading and Delayed Reperfusion in ST-Elevation Myocardial Infarction) is a currently ongoing randomized trial that is planned to enroll a larger cohort of 668 patients and will test the hypothesis that LV unloading with the CP model for 30 minutes before revascularization will reduce myocardial damage from heart attack and subsequently will reduce adverse events. The primary endpoint is infarct size (3-5 days postprocedure, evaluated using cardiac magnetic resonance), and secondary endpoints are: 1) infarct size as a percentage of LV mass (3-5 days postprocedure); 2) percutaneous microaxial flow

pump device-related major bleeding and vascular complications at 30 days; and 3) CS, cardiovascular mortality, heart failure, LVAD placement or heart transplantation, and implantable cardioverter-defibrillator placement within 12 months.

UNLOAD-AMI trial. The UNLOAD-AMI (Attenuation of Post-Infarct Remodeling in Patients With Acute Myocardial Infarction by Left Ventricular Mechanical Unloading Using Impella-CP) study is an ongoing multicenter RCT in 80 patients with anterior wall AMI that compares mechanical unloading by percutaneous microaxial flow pump on top of standard treatment after PCI with standard treatment for AMI alone.[34] Major inclusion and exclusion criteria are listed in **Table 3**. Primary outcomes will be the difference in LV end-systolic volume, occurrence of LV remodeling, and extent of postinfarct scar (all of which will be measured at 5 to 7 days and then again at 3 months). Secondary outcomes include cardiovascular complications or heart failure during the first 5 days of hospitalization.

HERACLES trial. HERACLES (Evaluation of Unloading the Heart in Patients With Cardiogenic Shock Treated With Mechanical Circulatory Support Devices) is another upcoming RCT that is currently in the development phase in patients with CS undergoing treatment with VA-ECMO that will compare the physiological effects of LV unloading by percutaneous microaxial flow pump vs IABP on myocardial oxygen supply and demand.[35] Eligible patients have CS of either ischemic or nonischemic etiology and are either are on VA-ECMO or are being considered for treatment with VA-ECMO, including undergoing clinically indicated cardiac catheterization. Major exclusion criteria will include postcardiotomy CS, LV thrombus confirmed on imaging, contraindication to IABP or percutaneous microaxial flow pump placement, current treatment with IABP or percutaneous microaxial flow pump, and mechanical aortic valve placement. Primary outcomes include measuring coronary flow reserve using a coronary guidewire after LV unloading. Secondary outcomes include early effects of LV unloading, minimal microvascular resistance after LV unloading, time to VA-ECMO decannulation, and days alive and out of the intensive care unit (at 30 days postrandomization) (**Table 3**). The results of these studies will provide greater insight into the safety of LV unloading using percutaneous microaxial flow pump vs IABP, guiding the approach in patients on VA-ECMO.

ROLE OF PERCUTANEOUS MICROAXIAL FLOW PUMP RP DEVICES FOR RV FAILURE. Right heart failure (RHF) is often encountered in patients with AMI, after cardiotomy or heart transplantation or LVAD implantation. Irrespective of the underlying cause, management of RHF is often challenging and carries high morbidity and mortality.[36] Initial management of these patients involves medical therapy, which comprises: 1) optimization of RV preload; 2) decreasing RV afterload using pulmonary vasodilators; and 3) inotropic therapy to improve cardiac output. Patients who continue to deteriorate despite medical therapy often require temporary MCS for stabilization. The RP model of the percutaneous microaxial flow pump is a percutaneous MCS device that displaces blood directly from the right atrium to the pulmonary artery, bypassing the right ventricle. It includes a 22-F microaxial flow pump device mounted on an 11-F catheter and is delivered using a 23-F venous peel-away sheath. RECOVER-RIGHT (The Use of Impella RP Support System in Patients With Right Heart Failure: A Clinical and Probable Benefit Study) was the first prospective study using this device in 30 patients with refractory RHF; it showed 73% survival at 30 days.[37] Its clinical benefit was further confirmed with another premarket clinical study in 60 patients with RV failure.[38] No RCTs to date show benefit for any temporary MCS device, including the RP model. However, the increasing recognition of the challenges involved in management of RHF suggests the need to perform RCTs of right-sided MCS devices.

COMPLICATIONS WITH PERCUTANEOUS MICROAXIAL FLOW PUMP DEVICES

All MCS devices are associated with bleeding risk, vascular complications, stroke, infections, and mechanical complications.[39-41] In patients with CS, this risk is further heightened because of concomitant treatment with vasopressors, anticoagulant agents, and antiplatelet agents and the need for other devices such as pulmonary artery catheters or arterial lines. The use of large-bore access, along with continuous anticoagulant agents, is often associated with increased risk for bleeding and limb ischemia. Hemolysis can also occur from the impeller pump, which increases shear stress on blood cells and can result in acute renal dysfunction. There have been case reports on the risk for mitral stenosis and severe mitral regurgitation from chordal rupture due to improper placement of percutaneous microaxial flow pump devices.[42,43] RCTs will be needed to evaluate the frequency of these complications and to determine the risks and benefits of using them in comparison

with early-generation percutaneous microaxial flow pump devices. The FDA Manufacturer and User Facility Device Experience database continues to collect reports on complications related to the device, and those should be followed carefully.[44] The percutaneous microaxial flow pump manufacturer launched robust educational efforts to mitigate these complications, but data are lacking to substantiate a significant reduction of serious events related to the device.

It is worth looking more closely at bleeding and vascular complications in the clinical studies discussed in this review. The PROTECT II trial showed that 1.4% of patients required vascular or cardiac operations at 30 days in the IABP group vs 0.9% in the percutaneous microaxial flow pump group; at 90 days, the rates were 1.8% in the IABP group vs 1.3% in the percutaneous microaxial flow pump group. In the IMPRESS trial, which had 48 participants, there was a 33% occurrence of major bleeding events in the percutaneous microaxial flow pump group vs 8% in the IABP group and a 4% occurrence of major vascular complications vs 0% in the IABP group. The ISAR-SHOCK trial, which had 26 participants, encountered no major bleeding complications in either comparison group, but 1 of 12 patients (8%) assigned to the percutaneous microaxial flow pump encountered a major vascular complication vs none in the IABP group. The DTU trial, which was performed on 50 patients, showed a 4% rate of vascular events in the percutaneous microaxial flow pump–delayed reperfusion group and 0% in the immediate reperfusion group. This trial also demonstrated bleeding complications in 16% of delayed-reperfusion patients and in 12% of the immediate-reperfusion group. The IMPELLA-STIC trial, which had 12 patients, had a 71.4% occurrence of major bleeding events in the percutaneous microaxial flow pump group vs 0% in the IABP group and a 28.6% occurrence of vascular events in the percutaneous microaxial flow pump group vs 0% in the IABP group.

FUTURE DIRECTIONS

Bleeding and vascular complications remain an important consideration for patients requiring the percutaneous microaxial flow pump device.[14,41] Hemolysis is more challenging to control and may require shortening the dwelling of the device in the heart. Very recently, the FDA granted breakthrough device designation to the ECP model on the basis of reassuring clinical outcomes of an initial cohort of 21 patients as part of an FDA regulatory early feasibility study.[45] This expandable device is the world's smallest heart pump, needing small-bore access and closure. The ECP model's pump diameter is 9-F (3 mm), and it is delivered through a slender-profile sheath. It is unsheathed in the descending aorta and expands to 18-F, providing hemodynamic support >3.5 L/min. Another unique feature of this device is a soft polyurethane cannula that sits across the aortic valve and opens only when the pump is working. The cannula relaxes if the pump stops for any reason, permitting the valve leaflets to close around it without interrupting its competency. The pump is intended for short-term mechanical support in patients requiring high-risk PCI. It is resheathed postprocedure and removed through the same profile. Further studies are warranted to test its safety and effectiveness in high-risk PCI.

The ability to combine pharmacologic, structural and electric device therapy, along with fully implantable transvalvular pumps such as the percutaneous microaxial flow pump devices, provides future promise of improving myocardial recovery and remission. The clinical trials mentioned in this review provide better insight into the role of percutaneous microaxial flow pump devices in the field of high-risk PCI, CS, and LV unloading. Although there is currently no consensus regarding the optimal timing of initiation of MCS with percutaneous microaxial flow pump devices, the available evidence suggests that early initiation of hemodynamic support before PCI may be associated with more complete revascularization and improved survival when used in the correct patient population.[46] Selection of the appropriate patient for this level of support remains difficult, though several algorithms are currently being studied that suggest that features such as LVEF <25%, SYNTAX score >22, and LV end-diastolic pressure >20 mm Hg indicate a likely benefit from percutaneous microaxial flow pump device use during PCI.[47] In patients with CS, the new 5.0 and 5.5 models of microaxial flow pumps provide a promising future, with the ability to provide full hemodynamic support similar to that achieved by VA-ECMO. These devices can play a significantly important role in myocardial unloading with the goal of recovery and remission. Furthermore, we suggest early evaluation of patients using the collaborative effort of a CS team, including input from advanced heart failure cardiologists, interventional cardiologists, cardiothoracic surgeons, intensivists, and other clinical support staff members to optimize timing and patient selection for this level of MCS, as these teams have demonstrated feasibility and shown benefits with early use of these devices.[48]

CONCLUSIONS

Although the potential indications for the use of the percutaneous microaxial flow pump devices have been identified, there is still a considerable lack of RCTs to substantiate their use. Currently, there are not sufficient clinical data to demonstrate benefit and reasonable safety for the proposed indications. Nevertheless, the device design does appear to have the potential to improve hemodynamics and provide sufficient circulatory support in patients with high-risk PCI, CS, and for LV unloading. The data reported from registries lack control groups, are driven by case selection bias, and are not sufficient to draw definitive conclusions. The ongoing RCTs are critical to determine when, in whom, and how these devices should be used. The challenge of conducting clinical trials for these indications is enormous, and the studies may take years to complete before definitively determining when it would be appropriate to use these devices. It is up to regulators, industry, and academicians to work together to establish interim recommendations concerning the use of these devices until data from the RCTs are available to substantiate or refute these recommendations. Studies such as PROTECT IV and RECOVER IV should provide essential evidence and guidance on treating these complex patients with MCS and should be the focus of future investigations, rather than small, uncontrolled registries.

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APPENDIX For supplemental videos, please see the online version of this paper.