EuroIntervention 2021;17:e274-e286 published online ahead of print May 2021 ■ published online e-edition July 2021

Joint EAPCI/ACVC expert consensus document on percutaneous ventricular assist devices

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJY21M05_01

KEYWORDS

- Mechanical circulatory support
- Acute coronary syndromes
- High-risk percutaneous coronary intervention
- Intra-aortic balloon pump
- ECMO
- Impella

Abstract

There has been a significant increase in the use of short-term percutaneous ventricular assist devices (pVADs) as acute circulatory support in cardiogenic shock and to provide haemodynamic support during interventional procedures, including high-risk percutaneous coronary interventions. Although frequently considered together, pVADs differ in their haemodynamic effects, management, indications, insertion techniques, and monitoring requirements. This consensus document summarizes the views of an expert panel by the European Association of Percutaneous Cardiovascular Interventions (EAPCI) and the Association for Acute Cardiovascular Care (ACVC) and appraises the value of short-term pVAD. It reviews the pathophysiological context and possible indications for pVAD in different clinical settings and provides guidance regarding the management of pVAD based on existing evidence and best current practice.

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SUBMITTED ON 03/01/2021 - REVISION RECEIVED ON 11/02/2021 - ACCEPTED ON 04/03/2021

DOI: 10.4244/EIJY21M05_01

Preamble

This consensus document summarizes the views of an expert panel endorsed by the European Association of Percutaneous Cardiovascular Interventions (EAPCI) and the Association for Acute Cardiovascular Care (ACVC) and appraises the importance of short-term percutaneous ventricular assist device (pVAD). It reviews the pathophysiological context, initiation, and indications for pVAD in different clinical settings and provides guidance regarding the management of pVAD based on existing evidence and best current practice.

Introduction

There has been a significant increase in the implementation of short-term percutaneous ventricular assist device (pVAD) in recent years, aiming to improve outcomes in cardiogenic shock (CS) and high-risk percutaneous coronary intervention (HR-PCI). These devices aim to reduce cardiac stroke work and myocardial oxygen demand whilst maintaining systemic and coronary perfusion.[1,2] Although frequently considered interchangeable, the indications, management and evidence supporting the use of various types of pVAD differ significantly.[3] This Joint European Association of Percutaneous Cardiovascular Interventions (EAPCI)/Association for Acute Cardiovascular Care (ACVC) expert consensus document reviews the pathophysiological context and indications for pVAD in different clinical settings and provides guidance regarding the clinical management of patients requiring pVAD.

Pathophysiology of shock and haemodynamic response to pVADs

Understanding the pathophysiological background of haemodynamic changes during disease and in response to support is vital for selection and monitoring, troubleshooting, and assessment of pVAD performance. Different options for pVAD are currently available (see **Figure 2** for their possible selection based on left and right ventricular (RV) support; **Supplementary material online, Table S1** for comparison among different pVAD). The phenotype and severity of CS additionally dictate device selection, including RV and/or left ventricular (LV) support, with/without oxygenation.[4] The position and shape of ventricular pressure-volume (PV) loops are preload and afterload-dependent[5] with normal PV loops bound by the end-systolic PV relationship (ESPVR) and enddiastolic PV relationship (EDPVR) **(Figure 1)**. The ESPVR is relatively linear, with the slope Ees (end-systolic elastance) and the volume-axis intercept (Vo), shifting with changes in contractility. The EDPVR is non-linear and defines the diastolic properties of the ventricle. Afterload can additionally be depicted on the PV plane by the 'effective arterial elastance' (Ea) line. The Ea line starts on the volume axis at the end-diastolic volume intersecting the ESPVR at the ventricular end-systolic PV point of the PV loop **(Figure 1A)**.[6] Based on pulmonary artery catheter measurements, numerous haemodynamic parameters can be measured, allowing calculation of cardiac index, systemic vascular resistance, pulmonary vascular resistance, and pulmonary artery pulsatility index, all of which may contribute to device selection. Several different haemodynamic variables are associated with worse outcome in RV dysfunction which may also assist in device selection **(Table 1)**.

Current models of left-sided pVAD comprise three different circuit configurations: right atrium to aorta (e.g. veno-arterial extracorporeal membrane oxygenation, VA-ECMO); left atrium to aorta (e.g. the TandemHeart, LivaNova London, UK); or left ventricle to aorta (Impella, Abiomed, Danvers, MA, USA; PulseCath iVAC2L, PulseCath BV, Amsterdam, The Netherlands; HeartMate PHPTM, St. Jude Medical/Abbott Vascular, St. Paul, MN, USA)

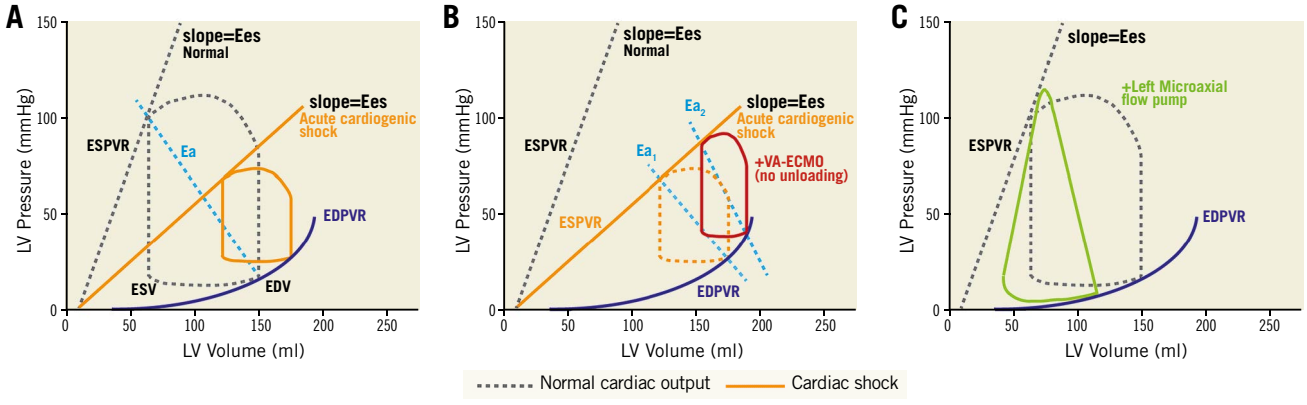

Figure 1. *Pressure-volume loops. (A) Normal PV-loop and PV-loop in acute cardiogenic shock, the slope (Ees) shifts with changes in contractility. (B) PV-loop in VA-ECMO supported cardiogenic shock. PV-loop becomes narrower and is associated with an increase in EDPVR. (C) PV-loop in a left ventricular microaxial flow pump supported configuration, resulting in loss of normal isovolumetric periods, reduced EDPVR and conversion of the typical PV-loop to a triangular shape. Ea: arterial elastance; EDPVR: end-diastolic pressure-volume relationship; EDPVR: end-diastolic pressure-volume relationship; EDV: end-diastolic volume; Ees: end-systolic elastance; ESPVR: end-systolic pressure-volume relationship; ESV: end-systolic volume*

Table 1. Haemodynamic parameters assisting device selection.

Deteriorating shock (SCAI-C and D) – failure to respond to initial therapy. Consider mechanical support. Clinical signs of (relative) hypoperfusion: mottled, cold, clammy, volume overload, extensive rales, (non)-invasive ventilation, alteration in mental status	
RV failure	**LV failure**
Central venous pressure (CVP) ≥15 mmHg	Systolic blood pressure (SBP) ≤90 mmHg or mean arterial pressure (MAP) <60 or >30 mmHg drop and inotropes/ vasopressors
Pulmonary artery pulsatility index (PAPi) ≤1.85 [7]	Cardiac index (CI) <2.2 L/min/m^2 Cardiac power output (CPO) <0.6 W [8]
Right atrial to pulmonary capillary wedge pressure ratio (RA/PCWP) ≥0.8 [7]	Left ventricular end-diastolic pressure (LVEDP) >15 mmHg

Table 2. Indication for pVAD-support in HR-PCI[a].

Device	Indication	Evidence
IABP	Should not be used	BCIS-1[10]
AFP	May be considered in highly selected patients undergoing HR-PCI in case of acceptable femoral access (>6 mm diameter common femoral artery, no severe tortuosity)	PROTECT II [11] and cohort studies[12-15]
VA-ECMO	Should not be used	No data available

AFP: microaxial flow pump; HR-PCI: high-risk percutaneous coronary intervention; IABP: intra-aortic balloon pump; VA-ECMO: veno-arterial extracorporeal membrane oxygenation. [a]There is no common definition of HR-PCI. PCIs might be considered as high risk in patients satisfying the followings clinical and/or anatomical high-risk criteria: clinical characteristics [stable/decompensated LVEF <35%, haemodynamic instability, diabetes mellitus, acute coronary syndromes (ACS), previous cardiac surgery, chronic kidney disease] angiographic characteristics (diffuse CAD, multivessel disease, unprotected left main coronary disease involving bifurcation, severe coronary total occlusion, severely calcified lesions needing rotational atherectomy, last patent conduit).[2]

(Figure 2).[5,9] Peak flow rates range between 2.0 and 7.0 L/min, depending on the circuit and cannula(e) diameter(s). Devices may be used alone, in combination, and some allow/mandate concomitant use of an oxygenator within the circuit.

The haemodynamic response to different pVADs is discussed in the **Supplementary material online**.

pVAD in high-risk PCI

The rationale and indications **(Table 2)** for pVAD in high-risk percutaneous coronary intervention (PCI) are described in the **Supplementary material online**. The aims of pVAD in the setting of HR-PCI are to initiate haemodynamic support in very high-risk patients before the intervention, to prevent profound hypotension/ low cardiac output (CO) episodes, and allow sufficient time to achieve optimal and complete revascularization **(Table 2)**.[1,16]

pVAD in high-risk myocardial infarction without cardiogenic shock

The rationale and indications **(Table 3)** for pVAD in high-risk acute myocardial infarction (AMI) without CS are described in the **Supplementary material online**. In high-risk AMI, unloading of the left ventricle can be initiated prior to reperfusion in order to rapidly reduce wall tension and potentially reduce myocardial damage.[19,20] No data from randomized trials or long-term outcomes of a pre-emptive unloading strategy are available, however, the DTU (Door to Unload) trial is currently enrolling patients **(Table 3)**.

Left-sided pVAD in cardiogenic shock

The rationale and indications **(Table 4)** for pVAD in CS are described in the **Supplementary material online**. Left-sided

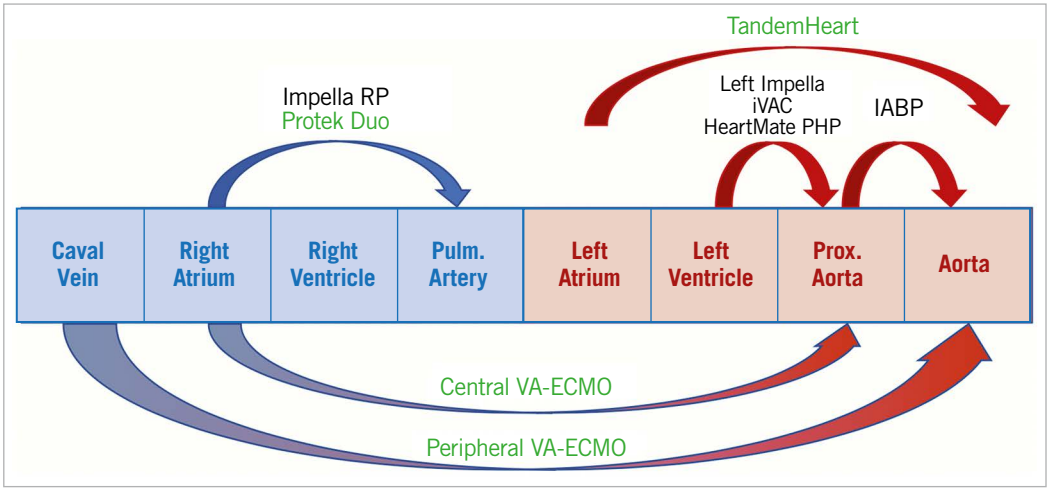

Figure 2. *Different options for pVAD. Arrows indicate which part of the circulation is supported by the pVAD-modality. Devices in green can add blood oxygenation next to mechanical support. IABP: intra-aortic balloon pump; VA-ECMO: veno-arterial extracorporeal membrane oxygenation*

Table 3. Indication for pVAD in HR-AMI without CS.

Device	Indication	Evidence
IABP	It is not suggested	CRISP-AMI and PAMI-II [17,18]
AFP	Impella CP use seems feasible as a preventive unloading strategy; currently, there are no data showing an advantage for this approach	Pre-clinical studies and pilot trial [19-22]
VA-ECMO	Should not be used; increasing afterload in the setting of acute coronary ischaemia might be harmful	No data available

AFP: microaxial flow pump; CS: cardiogenic shock; HR-AMI: high-risk acute myocardial infarction; IABP: intra-aortic balloon pump; VA-ECMO: veno-arterial extracorporeal membrane oxygenation

Table 4. Indication for pVAD in CS.

Device	Indication	Evidence
IABP	Routine use is not recommended [23]; may be used in patients with mechanical complications post-AMI or in non-AMI related shock	IABP-SHOCK II [24-26]
AFP	Impella CP may be used as a short-term therapy in CS,[a] stage C and D with potentially reversible underlying cause/transplant/VAD candidates	Small randomized study and cohort studies [4,27-29]
VA-ECMO	May be used as a short-term therapy in CS stage C, D, and E, particular in patients with combined respiratory insufficiency with potentially reversible underlying cause/transplant/VAD candidates May be used for selected patients in refractory cardiac arrest	Prospective and retrospective cohort studies [30-32]

AFP: microaxial flow pump; AMI: acute myocardial infarction; CS: cardiogenic shock; IABP: intra-aortic balloon pump; VAD: ventricular assist device; VA-ECMO: veno-arterial extracorporeal membrane oxygenation. [a]According to SCAI CS classification.[33]

pVADs primarily aim to restore CO in patients with CS or in case of refractory cardiac arrest. There are, however, no randomized clinical trials addressing optimal timing or selection of pVAD in CS. Outside the cardiac arrest setting, usual practice is to initiate pVAD in CS as soon as possible, and before the onset of multi-organ failure. In patients with CS complicating AMI, registry data (uncontrolled and with inherent selection bias) suggest higher survival rates with device placement before revascularization than after in patients with AMI and CS.[27] These findings have been supported by preclinical data.[20] Recent data in a larger cohort of CS patients have challenged the concept of pre-emptive device placement.[34] Until high-quality data are available, decisions regarding the timing of pVAD initiation (as with every pMCS), are therefore based on the risk/benefit assessment, including severity of shock and the burden of comorbidity, as evaluated by the multidisciplinary shock team.

Right-sided pVAD in cardiogenic shock

The rationale and indications **(Table 5)** for RV-pVAD in CS are described in the **Supplementary material online**. No clinical trials exist that address the optimal timing of RV-pVAD placement in patients with acute RV failure. Furthermore, there are no parameters that have been demonstrated to predict RV failure or requirement for RV-pVAD after initiation of LV-pVAD. The decision to initiate RV-pVAD should be based on decisions made by the multidisciplinary shock team.

Biventricular pVAD in cardiogenic shock

The rationale and indications **(Table 6)** for biventricular pVAD in CS are described in the **Supplementary material online**. Acute, primary biventricular support (vs. delayed, secondary) should be

Table 5. Indications for right pVAD in CS.

Device	Indication	Evidence
IABP	It is not suggested in isolated RV failure	None
Percutaneous right-sided support	Impella RP may be used in patients with CS predominantly due to RV failure Protek Duo may be used in those requiring isolated right heart support ± oxygenation	Small cohort studies [35-38]
VA-ECMO	May be used in case of severe haemodynamic compromise especially when combined LV failure and/or respiratory insufficiency, in CS stage C, D, and E in patients with potentially reversible underlying cause/ transplant/VAD candidates	Case series [39-41]

AFP: microaxial flow pump; CS: cardiogenic shock; IABP: intra-aortic balloon pump; LV: left ventricle; RV: right ventricle; VAD: ventricular assist device; VA-ECMO: veno-arterial extracorporeal membrane oxygenation

Table 6. Indications for percutaneous biventricular assist devices in CS.

Device	Indication	Evidence
VA-ECMO	May be used in case of: – Combined left and right ventricular failure – Combined left ventricular and ventilation/oxygenation failure – Combined ventilation/oxygenation and right ventricular failure – Refractory cardiac arrest	Registry data, case reports [42-44]
ECPella	VA-ECMO and left ventricular unloading	Registry data, case reports [45-47]
BiPella	May be used in right and left ventricular failure without pulmonary failure	Registry data, case reports [48,49]

CS: cardiogenic shock; VA-ECMO: veno-arterial extracorporeal membrane oxygenation.

implemented before the onset of multiorgan failure in selected patients as a strategy to buy time for recovery or bridge to other therapies.

Clinical monitoring and ongoing management of patients requiring pVAD

The monitoring of cardiac function and tissue perfusion is pivotal to optimize treatment and recognize potential complications of pVAD. This is described in **Table 7** and the **Supplementary material online**.

Complications and their management

Complications associated with pVAD are potentially serious, life-threatening and may be related to the device itself, its insertion or from device-induced alteration of homeostasis or organ function, or anticoagulation **(Figure 3)**. The most frequent complication is bleeding (related to vascular cannulation, full anticoagulation, or device-induced alteration in the coagulation pathways).[50-54] Other complications include infection,[55,56] haemolysis,[57,58] limb ischaemia,[59] device failure, and central nervous system haemorrhage or infarction.[60,61] The incidence of heparin-induced thrombocytopenia is relatively low (0.36%, n=21/5797) in VA-ECMO and does not impact survival.[62]

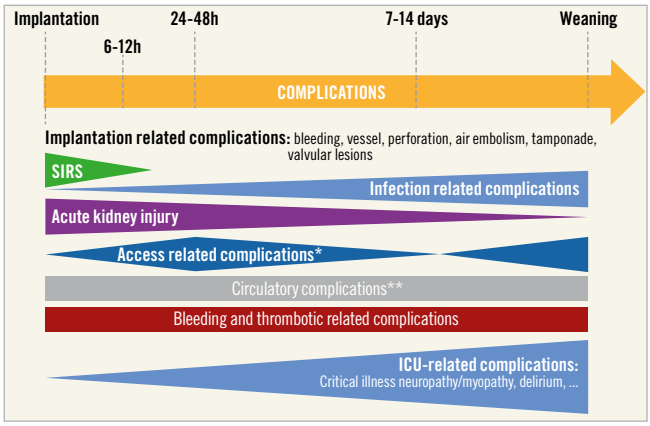

Figure 3. *Complications associated with pVAD. Most frequent complications associated with pVADs depending on timepoint of implantation and weaning. *Indicates problems like bleeding, leg ischaemia, dissection or pseudoaneurysm; **Indicates problems as Harlequin-syndrome, cannula dislocation, afterload and/or preload mismatch. ICU: intensive care unit; SIRS: systemic inflammatory response syndrome*

SPECIFIC, DEVICE-RELATED COMPLICATIONS AND THEIR MANAGEMENT

Impella devices are associated with the highest incidence of haemolysis among pVAD (5-10% in registry data).[57,58] Accurate placement, and reduction of pump speed may decrease haemolysis and associated acute kidney injury. In a retrospective analysis of patients with AMI-related CS, the use of Impella was associated with more frequent bleeding (10.4% vs 1.7%, P<0.01), sepsis (38.2% vs. 17.4%, P<0.01) and peripheral vascular complications (9.6% vs. 3.5%, P=0.05) compared with matched patients from the IABP-SHOCK II trial supported with intra-aortic balloon pump (IABP).[28] In a propensity-matched registry-based retrospective cohort study of patients with AMI complicated by CS, Impella was associated with more major bleeding (31.3% vs. 16.0%, P<0.001) compared with matched patients supported with IABP.[34] In another retrospective analysis of 48 306 patients, undergoing PCI with pVAD, when analysed by time-periods or at hospital/patient-level, Impella use was associated with: bleeding [odds ratio (OR)=1.10] and stroke (OR=1.34), although a similar, non-significant result was observed for acute kidney injury (OR=1.08).[63]

Specific complications of the TandemHeart include air embolism and cardiac perforation, tamponade, and atrial septal defect from transseptal cannulation.[64] Drainage cannula displacement in the right atrium may cause massive shunting of deoxygenated blood to the arterial circulation.

VA-ECMO provides retrograde blood flow in the aorta and increases LV afterload and left ventricular end-diastolic pressure, that may induce pulmonary oedema and potentially myocardial ischaemia.[65,66] Combining VA-ECMO and IABP (to unload the left ventricle) was associated with lower mortality in a meta-analysis based on observational data.[45] The addition of an Impella to VA-ECMO decompresses the left ventricle may also improve outcome.[45,67-69] Direct venting of left-cardiac chambers or percutaneous balloon atrial septostomy are other strategies used to offload the left ventricle in VA-ECMO. Since retrograde ECMO flow competes with the native heart ejection, in case of lung failure, deoxygenated blood may be directed to the upper part of the body resulting in heart and brain hypoxia. This situation is termed differential hypoxia, the North-South or Harlequin Syndrome.[70-72] Veno-arterial-venous ECMO (which splits the reinfused blood by a Y-connector into an arterial and a venous cannula, additionally returning oxygenated blood to the right atrium) can provide circulatory and adequate pulmonary support in this setting.[72] Veno-veno-arterial ECMO (VV-ECMO) configuration (completely offloading the right heart and reducing LV ejection) is another option. The incidence of major vascular complications with VA-ECMO can exceed 15% with significant impact on patient prognosis.[73] Insertion of a distal perfusion cannula into the superficial femoral artery, positioned using contrast-enhanced Doppler ultrasound or invasive angiography, may prevent limb ischaemia.[74] Ultrasound-guided percutaneous cannulation is the preferred option in VA-ECMO, and associated with less local infection (16.5% vs. 27.8%, P=0.001), similar rates of limb ischaemia (8.6% vs. 12.4%, P=0.3), sensory-motor complications (2.6% vs. 2.3%, P=0.8) and improved 30-day survival (63.8% vs. 56.3%, P=0.03) compared to surgical cannulation in a propensity-matched study including 532 patients receiving VA-ECMO.[75]

Antithrombotic pharmacology: anticoagulation and antiplatelet therapy

Up to 80% of patients on VA-ECMO suffer from major bleeding requiring transfusion and up to 16% develop intracranial

Table 7. pVAD monitoring.

Variable	Advantages	Limitations
Echocardiography		
Ventricular size	End-diastolic volume (EDV)	Difficult to assess for RV, may vary depending on the level of support
Ejection fraction	Global assessment of LV function	– Load and heart rate dependent – Less indicative in case of asynchrony
LV velocity time integral	– Estimation of LV stroke volume/CO	– Aortic stenosis
Pre ejection and total ejection time	– Integrated with LVEF allow the assessment of Ees	– Angle dependent – Not validated in cardiogenic shock
MAPSE/TAPSE	Early and sensitive for systolic function	Annular abnormalities
Tissue Doppler velocity; strain/strain rate	Early and sensitive for systolic and diastolic function	Require high skill and further validation
Valvular abnormalities	– Indirect evaluation of ventricular function (dP/dT; TAPSE/sPAP) – Ventricular offloading (MR) Dependent by alignment – Right side pressures (sPAP, dPAP)	– TOE is more sensitive – Dependent by alignment
Haemodynamic and respiratory		
Pulse-oximetry	Continuous monitoring of peripheral oxygen saturation	– To be placed on the right arm in ECMO patients – Dependent on skin conditions – Arterial flow pulsatility
Invasive blood pressure monitoring	– Systemic blood pressure – Oxygenation/metabolic profile (pH, paO_2, $paCO_2$, base excess, meta-haemoglobin) – Lactate – Haemoglobin	– Right radial artery is more representative of coronary and upper body oxygenation – To be taken before full regimen anticoagulation
Pulmonary artery catheter	– Pulmonary (sPAP, dPAP, mPAP) and right atrial pressures – SVR/PVR – Left ventricular capillary wedge pressure – CO/CI – PAPi – CPO – SvO_2 – Pa-vCO_2	– To be taken prior of full regimen anticoagulation – SvO_2 inaccurate in VA-ECMO and TandemHeart patients due to the venous component of the blood coming from the native pulmonary circulation
Conductance catheter	V-A coupling	Not validated in cardiogenic shock
Non-invasive monitoring		
Near-infrared spectroscopy (NIRS)	– Easy values to interpret – Regional oxyhaemoglobin saturation (rSO_2) – Perfusion of the distal limb	– No absolute numbers, but the trend of the values – Individual Hb level and variations in cerebral venous/arterial blood ratio – Needs confirmation with ultrasound
Optical nerve shear diameter	Indirect evaluation of intracranial pressure	Needs validation in this setting
Coagulation monitoring		
Activated clotting time	– Easy and bedside – Widely available and sensitive	High variability and non-specificity for heparin
aPTT	– Easy and bedside – Widely available and sensitive	High variability and non-specificity for heparin
Anti-Xa	Sensitive to heparin function	Not widely available
Cardiac-specific markers		
BNP, NT-pro-BNP	Ventricle overload	– No absolute numbers, but the trend of the values – No specific validation in this setting
hs-TnI	Rise/fall sensitive for myocardial ischaemia	– No absolute numbers, but the trend of the values – No specific validation in this setting

aPTT: activated partial thromboplastin time; BNP: B-type natriuretic peptide; CI: cardiac index; CO: cardiac output; CPO: cardiac power output; CRP: C-reactive protein; dPAP: diastolic pulmonary artery pressure; Ees: end-systolic elastance; hs-TnI: high-sensitivity troponin I; LV: left ventricle; LVEF: left ventricular ejection fraction; MAPSE: mitral annular plane systolic excursion; mPAP: mean pulmonary artery pressure; MR: mitral regurgitation; PAPi: pulmonary artery pulsatility index; PVR: pulmonary vascular resistance; RV: right ventricle; sPAP: systolic pulmonary artery pressure; SVR: systolic vascular resistance; TAPSE: tricuspid annular plane systolic excursion; TOE: transoesophageal echocardiography; V-A coupling: ventricular-arterial coupling; VA-ECMO: veno-arterial extracorporeal membrane oxygenation

haemorrhage.[76] The precarious balance between bleeding and thrombotic complications, is a significant challenge and strongly influences pVAD-induced morbidity and mortality.[51,77,78] A well-balanced antithrombotic strategy is mandatory.

Anticoagulation with unfractionated heparin (UFH) is the standard of care due to its short half-life, rapid on- and offset, low cost and ready availability.[79] Other anticoagulation strategies (bivalirudin, argatroban) have been reported, especially in the context of heparin-induced thrombocytopenia.[80,81] Due to their long half-life and renal excretion, the use of non-vitamin-K-oral-anticoagulants and low-molecular-weight heparins should be avoided.[82] Monitoring UFH in patients on pVAD is challenging. Although activated clotting time (ACT)-guided monitoring is common it should be avoided due to its high variability, the non-specificity for heparin and the lack of widespread availability of ACT monitoring outside the catheterization lab.[79,83] The activated-partial-thromboplastin-time (aPTT, most frequently used) and/or anti-Xa assays (the gold standard although not widely available) are preferred.[84] In patients with sepsis, disseminated intravascular coagulation, liver failure or unexplained aPTT-prolongation, anti-Xa-testing should be used. The use of thromboelastography-guided UFH-monitoring has been evaluated, aiming to take platelet interactions and fibrinolysis into account, but further validation is pending.[85] Antithrombin-monitoring should be considered when heparin-resistance is suspected.[86]

Randomized studies for specific heparin dose-regimens for anticoagulation are lacking. The Impella anticoagulation-guidelines favour therapeutic anticoagulation levels in all non-bleeding patients on pVAD.[87] Nevertheless, a more individualized approach, well-balanced with the risk of bleeding, is suggested.[88] **Supplementary material online, Table S3** describes various devices with recommended antithrombotic strategies. pVAD-patients with underlying atrial fibrillation, mechanical valves or fresh (venous or arterial) thrombi should additionally receive therapeutic anticoagulation in the absence of major bleeding. No anticoagulation in (left-sided) pVAD-supported patients can be considered in major, life-threatening bleeding but the high risk of acute circuit failure and/or systemic embolization/thrombosis must be taken into consideration. An important number of pVAD-supported patients will have an additional indication for dual antiplatelet therapy because of PCI with stent implantation. Here, UFH should be combined with low dose aspirin plus clopidogrel (triple antithrombotic therapy) or with clopidogrel alone (dual antithrombotic therapy) depending on the individual bleeding risk of the patient. Prasugrel and ticagrelor are not recommended in a triple therapy strategy due to their increased bleeding hazards when compared with clopidogrel.[89]

In addition to determining the optimal UFH-dose, optimizing the platelet count and fibrinogen levels, and any bleeding source control is mandatory (surgical control, topic tranexamic, and/or adrenaline application in the cannula or mucosal bleeds or circuit change in case of consumption coagulopathy).

Although bleeding and thrombotic complications are the most frequent cause of morbidity and mortality in pVAD-supported patients, evidence from randomized clinical trials is scarce. Large, prospective multicentre trials are urgently needed to investigate the optimal anticoagulation management strategies during pVAD support.

Pharmacological support

Catecholamines are a standard part of the armamentarium of pVAD-supported patients although few data on safety and outcome are available to recommend inotrope/vasopressor selection and use.[90] In CS, norepinephrine is the first-line vasopressor. Although vasopressin significantly increases mean arterial pressure (MAP), it has a lesser effect on cardiac index compared to norepinephrine.[91,92] Its theoretical advantage at low dose (pulmonary vasoconstriction) deserves further investigation. MAP should be titrated according to the clinical scenario—maintaining organ perfusion pressure, whilst avoiding excessive increases in after-load. Following pVAD initiation, pressor support should be reduced to the lowest dose possible, and relative hypotension may/may not be tolerated, depending on other organ involvement (e.g. cerebral perfusion pressure in the context of post-cardiac arrest management).

Inotropic support may be required to enhance ventricular contractility but may alter ventricular loading and precipitate arrhythmia. In the case of univentricular pVAD, inotropy may be required to maintain adequate function of the non-supported ventricle. In CS, dobutamine is the inotrope of choice in patients[93] as epinephrine has shown to be associated with a worse metabolic profile and patient outcomes.[94-96]

A randomized trial of norepinephrine versus epinephrine in patients with AMI-related CS demonstrated a higher incidence of lactateacidosis, tachycardia and refractory CS in the epinephrine-group, although many received concomitant dobutamine.[96] In case of RV failure, phosphodiesterase-type-3 inhibitors (i.e. milrinone) may be preferred for their inodilators effects, despite lacking randomized trials.[97] The long-acting calcium-sensitizer levosimendan (0.05-0.1 μg/kg/min) may be used given its inotropic and vasodilatory effect. However, hypotension and supraventricular arrhythmias may occur.[98] Although levosimendan has shown beneficial haemodynamic effects during pVAD-weaning, further validation is needed.

Weaning from pVAD

The potential for weaning from pVAD should be evaluated daily from 24 to 48 h after the initiation of support. Several clinical features may predict the likely duration of pVAD support and likelihood of cardiac recovery including age, underlying pathology and presence/absence of pulmonary hypertension. Although the patient's condition/pVAD complications may demand accelerated weaning/device explantation, the cornerstones guiding elective weaning include clinical, biochemical, echocardiographic parameters and right heart catheterization, depending on the clinical context, and all indicating resolution of cardiac/non-cardiac pathophysiological derangement.

Measures of 'off-pump' LVEF, end-diastolic diameter, pulmonary capillary wedge pressure (PCWP), together with tissue Doppler and strain imaging on echocardiography are widely used to predict successful long-term pVAD explantation.[99] Similar parameters have been proposed to predict weaning from VA-ECMO. Here, in stable patients (low dose vasopressor ± inotropic support without pulmonary congestion/hypoxemia or other significant uncontrolled medical conditions) echocardiographic signs of improved LV function (LVEF >20-25%, velocity-time integral >10 cm and lateral mitral annulus peak systolic velocity >6 cm/s) during reduced flow (1-2 L/min) with no significant fall in MAP predict weaning success.[100,101] There are many proposed VA-ECMO weaning algorithms, but none has been shown to be superior in randomized studies. In case of cardiorespiratory failure, where cardiac function has recovered, but the lungs remain severely impaired, downgrading to VV-ECMO may be an option. If the right ventricle is also significantly compromised, but the left ventricle has recovered, an oxy-right ventricular assist device may be an option.

The literature on weaning from other pVAD is limited, with recommendations/weaning algorithms based on expert consensus **(Figure 4)**. Principles are, however, similar to VA-ECMO; the patient must be stable with a pulsatile arterial waveform (MAP >60-65 mmHg) on low-dose vasopressor ± inotropic support without pulmonary congestion/other conditions that may preclude successful weaning including arrhythmia, acid-base/metabolic disturbance, and mechanical complications. In left-sided support, PCWP should be near normal (preferably <15 mmHg) in a patient without former heart failure, before weaning is considered. There are no validated echocardiographic cut-off values that predict successful weaning in either left- or right-sided pVAD.

Where a weaning trial is unsuccessful, it is vital to identify and address the cause of weaning failure. When the patient continues to fail to wean, consideration should be made regarding the potential options, including a longer run on the existing device/modification of support to the least injurious to the patient (if cardiac recovery is anticipated), upgrade to more durable circulatory support, or withdrawal of support.[59,102-117]

Futility

Ceilings of care, and determining futility are important, but challenging to set in the context of patients referred for pVAD, especially with the absence strong predictors of outcome at the time of onset of CS, and the need to proceed quickly to pVAD initiation. These challenges are discussed in the **Supplementary material online**.

Future directions and conclusions

The rapid expansion of pVAD use in the settings of CS and HR-PCI without sufficient evidence from large-scale randomized trials is problematic. Currently, this widespread adoption is based on small series and registries, including industry-sponsored studies alone. Importantly, in particular in CS, the rates of device-related complications remain high. Consequently, there is an urgent need for adequately powered randomized clinical trials and large national/multinational registries to better define those patients who may benefit from pVAD, and how best to evaluate, monitor and manage every aspect of their care, especially in the setting of CS.

GAPS IN KNOWLEDGE AND FUTURE STUDIES

(1) Pathophysiological studies evaluating ventricular unloading in high-risk myocardial infarction and CS.

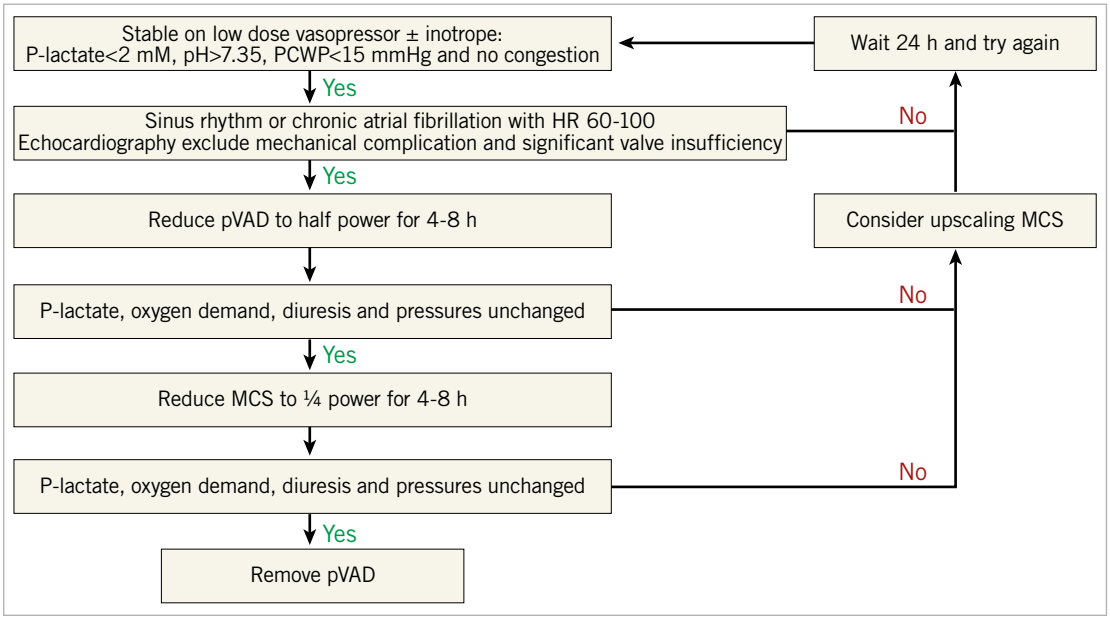

Figure 4. *Algorithm for pVAD weaning in cardiogenic shock. MCS: mechanical circulatory support; PCWP: pulmonary capillary wedge pressure*

(2) Randomized clinical trials demonstrating the benefit of pVAD over standard of care in high-risk PCI and CS.
(3) Randomized clinical trials demonstrating the benefit paradigm shift from door to balloon to door to unload.
(4) Large prospective national and international registries evaluating the outcomes of pVAD in a real-world population.
(5) Algorithms and protocols to better define patients population and timing for pVAD.
(6) Protocols and proper education of physicians and healthcare providers to reduce device-related complications.

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Conflict of interest statement

A. Chieffo received consulting fees/honoraria from Abiomed, Abbott Vascular, Cardinal Health, Biosensor, Magenta Medical. D. Dudek has served on the Scientific Advisory Board of Impella CP. A. Combes received grants and personal fees from Getinge. J. E. Møller received grants and personal fees from Abiomed and personal fees from Orion Pharma and Novartis. F. Pappalardo received personal fees from Abiomed. G. Tarantini received personal fees from Abiomed and GADA. G. Tavazzi received personal fees from GE Healthcare. N. van Mieghem received grants and personal fees from Abbott Vascular, Medtronic, Boston Scientific, PulseCath BV. N. Werner received personal fees and non-financial support from Abiomed. None of the other authors has relevant conflicts of interest to disclose.

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Supplementary material

Supplementary File.

Supplementary Table 1. Comparison among different devices.

Supplementary Table 2. Randomized Clinical Trials on pVAD.

Supplementary Table 3. Proposed Antithrombotic Strategy in pVAD.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJY21M05_01

2. HEMODYNAMIC RESPONSES TO DIFFERENT PVADS

Veno-arterial Extracorporeal Membrane Oxygenation, VA-ECMO

Percutaneous VA-ECMO, especially at higher flow rates or in the presence of even minor degrees of aortic regurgitation may cause left ventricle (LV) distension, significantly increases left atrium (LA)-pressure and the risk of pulmonary congestion/edema.[1, 2] High ECMO flow increases LV-afterload pressure and effective Ea, further resulting in increased LV end-diastolic pressures (LVEDP), LA pressure, and pulmonary capillary wedge pressure (PCWP). The pressure-volume (PV) loop becomes narrower, taller and shifts right and upward along the end-diastolic PV relationship (EDPVR) (Figure 1B).[3] In extreme LV dysfunction, this can be manifest specific echo features (e.g. persistently closed aortic valve, retrograde diastolic transmitral flow, retrograde pulmonary venous systolic flow). Numerous methods can reduce the LVEDP including non-surgical venting by atrial septostomy, a 7-Fr pigtail catheter in the LV connected to the venous limb of the ECMO circuit or by insertion of an additional pVAD or intra-aortic balloon pump (IABP) (Section 6).

Isolated left-sided support

A major consideration for the overall cardiac output (CO) achieved in left-sided devices is residual RV function/dysfunction, which may only be assessed accurately on institution of left-sided support.[4] With an LA-aorta configuration, PCWP and LVEDP will decrease dependent on flows achieved and residual LV function (Ees, contractility) and afterload.[3] Use of a microaxial flow pump (LV-to-aorta configuration) results in a loss of normal isovolumetric periods, and the standard pressure-volume-loop is converted from its traditional trapezoidal to a triangular shape (Figure 1C).[3] Blood flow is independent of LV ejection, and with increased pump flow (depending on configuration and speed), the LV becomes increasingly unloaded, resulting in decreased PCWP and LVEDP.

Isolated right-sided support

In isolated right ventricle (RV) failure, support will directly reduce RV stroke volume, RV and pulmonary artery (PA) peak systolic pressure, narrow PA pulse pressure and decrease right atrial pressure (RAP). When LV function is preserved, LV stroke volume increases, and LV filling pressures increase/remain unchanged. Pulmonary artery pulsatility index (PAPi, defined as [systolic pulmonary artery pressure (PAP) - diastolic PAP]/ central venous pressure (CVP)) has gained wide application for identifying RV dysfunction with a low pulmonary artery pressure and elevated CVP. Similar to isolated left-sided support, a major factor determining the CO achieved in right-sided devices is the severity of LV dysfunction, which is often unmasked when the LV is subject to adequate preload. The normal isovolumetric periods in the right heart have only recently been defined, and the effects of pVAD in RV are not yet known, but the PV loop of the RV shifts up and to the right.[5] The effects on left-sided hemodynamics depend on intrinsic left-sided function as well as right-sided flow.

3. RATIONALE AND INDICATIONS FOR DIFFERENT pVADS IN HIGH-RISK PCI

With an ageing population and increasing numbers of patients considered too high-risk for surgical revascularization, indications for PCI are increasing and now include high-risk PCI (HR-PCI) (Table 2). Despite the lack of randomized trials, the concept of pVAD in HR-PCI has become more widely promoted (Supplementary Table 2).[6, 7] The American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions acknowledged in 2011 the use of pVAD in HR-PCI with a Class IIb recommendation.[8, 9] Additional recommendations came from the European Society of Cardiology (ESC)[10] and working groups of national cardiac societies.[11] The available CE-marked pVAD systems and their indications in HR-PCI are shown in Table 2.

Intra-aortic balloon counterpulsation

The IABP has been used for decades to provide hemodynamic support during HR-PCI. However, the only adequately powered randomized trial did not show a benefit of routine IABP use[12] and therefore current European guidelines do not recommend IABP support in HR-PCI.[10]

Left-sided devices

There is no randomized trial studying TandemHeart supported HR-PCI, and the lack of demonstration of survival benefit, as well as risks of severe bleeding and limb ischemia and its complexity of insertion, have limited its use.[6]

Impella is the most frequently used pVAD for HR-PCI. A randomized trial has investigated its efficacy compared to IABP in HR-PCI [13] (Table 2) and was prematurely stopped for futility, showing no benefit at the primary endpoint of 30 days major adverse events, but at 90 days a secondary per-protocol analysis did show fewer major adverse events, mostly driven by repeat revascularization. Additional data is available from national registries and single/multicenter

series[14-16]. Impella is increasingly applied in patients at higher risk, i.e., severe CAD, complex anatomy, and extensive comorbidities, mostly in combination with a depressed left ventricle ejection fraction (LVEF) (Table 2).[17] High-quality data supporting their widespread use are lacking. A retrospective analysis was published using paying codes from Premier Healthcare Database of 48,306 patients, undergoing PCI with pVAD for a variety of indications from 2004 to 2016.[18] When analyzed by time-periods or at hospital/patient-level, the use of Impella was associated with higher mortality, more adverse events (including bleeding and limb ischemia) despite a lower risk profile in the Impella-treated group. Further, the costs were significantly higher. However, the global analysis of these very different patient cohorts (about 50% of patients with cardiogenic shock as well as bail-out use of Impella following severe complications together with planned HR-PCI) makes accurate conclusions difficult.

VA-ECMO

There are no randomized trials studying VA-ECMO-supported HR-PCI. The use of VA-ECMO during protected PCI is uncommon, mostly due to lack of familiarity/availability within the interventional cardiology arena, the complexity of management, and high incidence of vascular and bleeding complications.[6]

4. RATIONALE AND INDICATIONS FOR DIFFERENT PVADS IN HIGH-RISK MYOCARDIAL INFARCTION WITHOUT CS

Heart failure after myocardial infarction is the primary driver of early and late cardiovascular morbidity and mortality,[19] with infarct size as the major determinant of LV adverse remodeling and poor prognosis. Current ESC guidelines focus on early revascularization strategies, recommending reperfusion time as short as possible.[20] In patients at risk for extensive acute myocardial infarction (AMI), pre-PCI risk stratification, and different therapeutic strategies are suggested to improve myocardial perfusion beyond the immediate restoration of epicardial flow, aiming to reduce infarct size and reduce the risk of no-reflow. Here, a new management paradigm with primary LV unloading strategies using pVAD has been proposed.[21, 22]

Intra-aortic balloon counterpulsation

The Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction (CRISP-AMI) trial analyzed the impact of pre-PCI IABP on infarct size in high-risk AMI patients without CS.[23] The study failed to demonstrate a significant reduction in infarct size at follow-up using magnetic resonance imaging.

Left-sided devices

The Impella device can improve distal coronary pressure and coronary perfusion pressure in the presence of critical coronary stenosis due to a combination of increased mean and diastolic blood pressures, and a reduction in LVEDP.[24] In an animal model of AMI, mechanical unloading of the LV with Impella (but not VA-ECMO) before coronary reperfusion significantly reduces infarct size and thus simultaneously activates a cardio-protective pathway.[22, 25] Subsequently, the Door-To-Unload (DTU) pilot study suggested that primary LV unloading strategy using Impella CP with a 30-minute delay before reperfusion was feasible and safe in anterior ST-elevation-myocardial

infarction (STEMI) patients.[21] Of note, the control group was Impella CP without delay in reperfusion. A randomized clinical trial has been designed to evaluate infarct size using an early left ventricular unloading strategy in anterior STEMI without CS in comparison to the standard of care without Impella (The STEMI-DTU Trial, NCT03947619) (Supplementary Table 2).

5. RATIONALE AND INDICATIONS FOR DIFFERENT LEFT PVADS IN CARDIOGENIC SHOCK

CS is a potentially lethal syndrome, and disappointing results from standard medical therapy to support the circulation has led to increasing interest in mechanical circulatory support (MCS) as a potential management option. Multi-disciplinary CS teams with an established pathways and protocols for therapy escalation are necessary in the management of CS.[26] IABP has been used in patients with CS for decades, despite limited/nonexistent data regarding hemodynamic effects and outcomes. Other pVADs improve hemodynamics in CS, however, despite extensive registry data (in particular for ECMO and Impella) high-quality data are limited to 4 randomized trials, enrolling only 148 patients in total [27]. Further, the current indications, optimal management, and timing of initiation and weaning of these devices in CS require further research.[28]

Intra-aortic balloon counterpulsation

The Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial randomized 600 patients with CS complicating AMI to IABP or standard of care treatment.[29] Both this study and meta-analyses evaluating the effect of IABP among patients with CS in AMI found no survival benefit for IABP.[29-31] Therefore, the routine use of IABP in CS is not recommended in STEMI complicated with CS. However, IABP is recommended in STEMI with mechanical complications and CS-based on theoretical assumptions and expert opinion. In addition, the benefit to support transportation of the critically ill CS patient to a shock center for initiation of more advanced circulatory support and intervention remains to be evaluated.

Left-sided devices

No difference was found in a retrospective matched-pair analysis using patients from the IABP-Shock trial with AMI complicated by CS in all-cause 30-day mortality between patients treated with Impella and patients receiving IABP and medical therapy (48.5% vs 46.4%, p=0.64). Severe or

life-threatening bleeding and peripheral vascular complications were recorded significantly more often in the Impella group.[32] In the IMPella versus IABP Reduces mortality in STEMI patients treated with primary PCI in Severe cardiogenic SHOCK (IMPRESS-in-Severe-SHOCK) trial, 48 patients with severe CS requiring mechanical ventilation were randomized to Impella CP vs. IABP.[33] Neither this trial nor a meta-analysis of 148 patients randomized to Impella or TandemHeart vs IABP showed any difference in all-cause mortality after 30 days.[27, 33]

In a retrospective analysis, half of 48,306 patients undergoing PCI with pVAD suffered CS.[18] When analyzed by time-periods or at hospital/patient-level, the use of Impella was associated with a higher occurrence of mortality, more adverse events including bleeding and limb ischemia. Recently, a propensity-matched registry-based retrospective cohort study of patients with AMI complicated by CS undergoing PCI was published. Among 1680 propensity-matched pairs, it was reported a significantly higher risk of in-hospital mortality associated with the use of an Impella (45.0%) vs with an IABP (34.1%, P<0.001) and also higher risk of in-hospital major bleeding (31% vs 16%, P<0.001). These associations were consistent regardless of whether patients received a device before or after initiation of PCI.[34] However, in this analysis refractory CS and escalated patients were excluded and anticoagulation data were not reported. In addition, the rate of in-hospital mortality with IABP was the lowest reported in the literature being lower than randomized controlled trials. In all these retrospective analyses, there are inherent selection biases that cannot be adequately controlled and cannot allow us to make any final assumption. The DanGer Shock (Danish-German cardiogenic shock) Trial (NCT01633502) is currently randomizing 360 patients with AMI and CS to Impella CP or conventional guideline-driven treatment.[35]

VA-ECMO

Data from randomized trials on VA-ECMO in CS are currently not available apart from a small randomized controlled trial. In this study, 42 patients with CS complicating AMI were randomly assigned to extracorporeal life support (ECLS) or no MCS. The study failed to demonstrate an

impact on LVEF at 30 days, including 30-day all-cause mortality and safety outcomes.[36] Most data are from national/international registries and observational studies. A meta-analysis of retrospective and prospective cohort studies showed a significant mortality benefit in CS with VA-ECMO but outcomes varied widely depending upon the underlying etiology, including the presence/absence of cardiac arrest.[37] In patients with CS complicating acute coronary syndromes undergoing VA-ECMO, a meta-analysis demonstrated high mortality and complication rates, with little standardization of care, including the time of initiation of support.[38] Patients with CS have different pathophysiological features with several factors influencing the prognosis. For this reason, futility and efficacy of MCS in this setting varies significantly.[39] Further studies are needed to determine the benefit of ECMO support in CS. Randomized trials are currently ongoing (e.g. ECLS-SHOCK, NCT03637205; ECMO-CS, NCT023018; EURO-SHOCK, NCT03813134) (Supplementary Table 2).

6. RATIONALE AND INDICATIONS FOR RIGHT-SIDED PVADS IN CARDIOGENIC SHOCK

RV failure confers a poor prognosis in CS. RV failure frequently occurs after AMI, after cardiac surgery (in particular after LVAD implantation and heart transplantation) and in conditions with high afterload, such as pulmonary embolism and acute or decompensated pulmonary hypertension. In addition to standard therapies, RV failure may require escalation to RV-pVAD.[4] The underlying pathophysiological mechanism of RV failure determines the effectiveness of RV-pVAD. [40] The indication for a RV-pVAD is based on clinical assessment, echocardiography and right heart catheterization . RV-pVAD is suggested in patients with continued low and insufficient CO despite inotropic/vasopressor drugs and/or LV-pVAD in combination with high central venous pressure (>15 mmHg) and a dilated hypo/akinetic RV.[40] Thirty-day survival after RV pVAD treatment (median 4 days) in a mixed population with CS (mainly post LVAD, cardiotomy and heart transplant) was 72%.[40] Weaning from a RV-pVAD should be performed slowly over hours monitored mainly by echocardiography and if needed right heart catheterization.

7. Rationale and indications for Percutaneous Biventricular Assist Devices in Cardiogenic shock

Acute biventricular failure occurs in multiple settings.[41-46] VA-ECMO can provide near-full support including extracorporeal gas exchange, and is the first choice in patients requiring biventricular support, with/without oxygenation, including cardiopulmonary resuscitation (eCPR).[47] Several complications are recognized (Section 9), and there is some evidence that unloading the LV with Impella (ECPella) may improve survival and myocardial recovery but at the cost of increased morbidity.[2, 48, 49] Recent metanalyses showed that an IABP offloading strategy may have significant value as compared to VA-ECMO alone with respect to outcomes.[50] Biventricular support can be obtained via two percutaneous devices (left and right-sided ie Bipella or Protek duo + Left-sided Impella), which allow for progressive and stepwise weaning of each pump.[51, 52] Current recommendations are that in patients with CS, short-term ECMO may be used to support patients with biventricular failure until cardiac and other organ function have recovered and that the SAVE score can help predict survival (online calculator at http://www.save-score.com[53, 54]). LV unloading in ECMO patients may be beneficial from a pathophysiological standpoint but only limited clinical data is available.

8. CLINICAL MONITORING AND ONGOING MANAGEMENT OF PATIENTS IN NEED OF PVAD

Besides the monitoring of organ-specific biomarkers, echocardiography (transthoracic or transesophageal) assesses cardiac function and its response to pVAD placement by monitoring ventricular dimensions, contractility, valvular function and hemodynamics.[55, 56] Echocardiography should be performed daily and when hemodynamic changes occur.[57] Peripheral saturations and invasive systemic pressure monitoring are pivotal for the assessment of the metabolic/oxygenation status and arterial waveform analysis aiming at a mean arterial pressure of 65mmHg (or lower in specific circumstances) for the maintenance of adequate end-organ perfusion.[58] A decrease in saturation/paO_2 should advocate a prompt evaluation of cardiac and lung function, with chest imaging/ultrasound, to rule out interstitial edema or new ongoing primary infective process.[57] In VA-ECMO, oxygenation should be measured from the right radial artery, and cerebral saturation monitoring is suggested. Pulmonary artery catheterization is indicated in case of refractory circulatory shock and for weaning.[59] In case of Impella support, if the failing left ventricle is no longer able to overcome afterload in the new equilibrium of increased mean arterial pressure and reduced preload created by the continuous flow of the pVAD device, the arterial trace will flatten. This process is called ventriculo-arterial uncoupling.[60, 61]

Lactate and SvO_2 are indicators of global tissue perfusion, representing the balance between oxygen consumption (VO_2) and delivery (DO_2). In very low CO state, increase in total CO by the rotation flow rate manipulation or optimizing hemoglobin (acting on DO_2) as well as reducing VO_2 by antipyretics, cooling, or increasing sedation might help to increase the SvO_2.[62] SvO_2 may be inaccurate in VA-ECMO and TandemHeart patients due to the venous component of the blood coming from the native pulmonary circulation. Cerebral and distal limb perfusion be monitored using near-infrared spectroscopy (NIRS) to measure regional oxyhemoglobin saturation or tissue oxygenation index although formal validation is still needed.[63]

13. FUTILITY

Relatives/next of kin must be informed of the high mortality rates, that pVAD is not a treatment, but rather a temporary form of support, and that if it becomes apparent that treatment is futile, then it will be necessary to consider withdrawal. It must be clearly explained that pVAD does not compromise long term VAD/transplantation.

PVAD might be futile in patients who suffer from the chronic disease with life expectancy less than 6 months and in those who suffer irreversible cardiogenic shock as a terminal epiphenomenon of a different primary disorder, in which case it should not be initiated. Where pVAD has been instituted and there is no possibility for recovery/long-term device/transplantation, then withdrawal of support is required. Consideration for organ donation, either with donor after cardiac death (DCD) or donor after brain death (DBD) criteria, should be taken into account in centers using a structured protocol. Patient management throughout their intensive care admission should be in collaboration with multidisciplinary experts, including those from psychology and palliative care.

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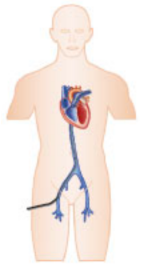
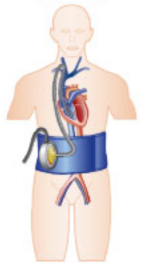
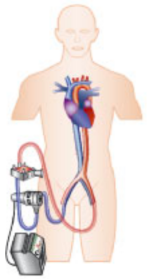
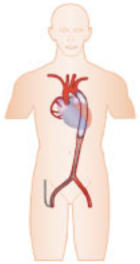
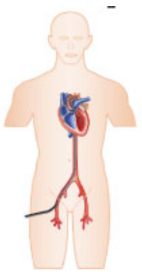
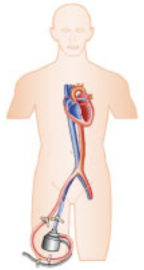
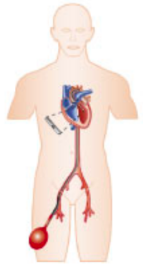
Supplementary Table 1. Comparison among different devices

	RV Support		BiV Support	LV Support			
							
	Impella RP	**TandemHeart RV /ProtekDuo**	**VA-ECMO**	**IABP**	**Impella (2.5/CP/5.0/5.5)**	**TandemHeart**	**iVAC 2L**
Type Flow	Continuous Axial	Continuous Centrifugal	Continuous Centrifugal	Pulsatile	Continuous Axial	Continuous Centrifugal	Pulsatile
Flow	Max 4.0 L	Max 4.0 L	Max 7.0 L	0.5 L	2.5-5.5 L	Max 4.0 L	40 ml/beat
Insertion	Femoral Vein	Femoral Vein/Internal Jugular Vein	Femoral Vein/Femoral Artery	Femoral Artery	Femoral Artery	Femoral Vein/Femoral Artery	Femoral Artery
Cannula Size	22F	21/29F	14-19F arterial 17-21F venous	7-8F	12-21F	12-19F arterial 21F venous	17F
Inflow	RA	RA	RA		LV	LA	LV
Outflow	PA	PA	FA		AO	FA	AO
LV unloading	-	-	-	+	+++	++	+
RV unloading	++	++	+	-	-	-	-
Implantation Time	++	++	+	+	++	++	++
Bedside Positioning	-	-	+	+	+	-	-
Oxygenator	-	+ (optional)	+	-	-	+ (optional)	-
Mobilization	-	+ (ProtekDuo)	-	-	+ (5.0/5.5)	-	-
Haemolysis	++	+	+	-	++	+	+
Anticoagulation	+	++	++	-	+	++	++

Bleeding	+	++	++	+	+	++	+
Limb Ischemia	+	+	++	+	++	++	++

AO: aorta; BiV: biventricular; FA: femoral artery; LA: left atrium; LV: left ventricle; PA: pulmonary artery; RA: right atrium; RV: right ventricle; VA-ECMO: venous-arterial extracorporeal membrane oxygenator.
Adapted from Thiele H, et al. Eur Heart J. 2019;40(32):2671-2683.

Supplementary Table 2. Randomized Clinical Trials on pVAD

Trial	Year	Cohort	Treatment arms	Primary outcome
Cardiogenic Shock				
Thiele et al.	2005	41 AMICS patients with intent for primary PCI at 1 German center	IABP (n= 20) or TandemHeart (n= 21).	Cardiac power index within 2h after device implantation
ISAR-SHOCK	2006	26 AMICS patients with MCS placed after revascularization in 2 German centers	Impella 2.5 (n= 12) vs. IABP (n= 13)	Cardiac index at 30 min
Burkhoff et al.	2006	42 CS patients across 12 US centers	Initial roll-in phase (n = 9) or IABP (n = 14) or TandemHeart pVAD (n = 19)	Hemodynamic benefits during support
IABP- SHOCK II	2012	600 AMICS patients with intent for primary PCI across 37 German centers	IABP (n= 301) vs. no IABP (n= 299)	30-day, 12-month, and 6-year mortality
IMPRESS-in-SEVERE-SHOCK	2017	48 mechanically ventilated AMICS patients with cardiac arrest at 2 European centers	Impella CP (n= 24) vs. IABP (n= 24)	30-day and 6-month mortality

ECLS-SHOCK I	2019	42 Postcardiac arrest AMICS patients at a single center in Germany	VA-ECMO (n= 21) vs. no MCS (n= 21)	LVEF at 30 days
AMI without shock				
PAMI-II	1997	437 high-risk AMI patients with MCS placed after revascularization across 34 international sites	IABP (n= 211) or no IABP (n= 226)	In-hospital Major Adverse Cardiovascular Events
CRISP AMI	2011	337 patients with anterior STEMI without CS across 9 international sites	IABP (n= 162) vs. no IABP (n= 176)	Infarct size measured by cardiac MRI
High-Risk PCI				
PROTECT-II	2012	452 Symptomatic patients with complex 3 vessels or unprotected left main CAD and severely	IABP (n= 226) vs. Impella 2.5 (n= 226)	Major Adverse Event incidence at 30 days

		depressed left ventricular function across 112 international sites		
BCIS-1	2013	301 patients with LVEF <30% and BCIS-1 jeopardy score ≥8 across 17 centers in the UK	PCI with elective IABP (n= 151) vs. PCI without planned IABP (n= 150)	Major Adverse Cardiac and Cerebrovascular events at hospital discharge
Ongoing Trials				
DanGer Shock NCT01633502	2012-2023	360 AMICS patients across 5 Danish and German centers	Impella CP vs. Guideline directed therapy	6-month mortality
STEMI-DTU NCT03947619	2019-2023	688 Anterior STEMI patients across 25 US centers	30 min on Impella CP prior to PCI vs. Standard treatment	Infarct size at 3-5 days measured by cardiac MRI
EURO SHOCK NCT03813134	2019-2024	428 AMICS patients across 44 European centers	ECMO vs. Medical Therapy	30-day mortality
ECMO-CS NCT02301819	2014-2020	120 severe CS patients across 3 Czech centers	ECMO vs. conservative standard therapy	Incidence of death, resuscitated circulatory arrest or implantation of additional MCS at 6 months

ANCHOR NCT04184635	2019-2023	400 AMICS patients at 1 French center	ECMO + IABP vs. Standard treatment	Treatment failure at Day 30
ECLS-SHOCK NCT03637205	2019-2023	420 AMICS patients with planned PCI or CABG across 3 German centers	ECMO + medical therapy vs. Medical Therapy alone	30-day mortality
IABP pre Revasc NCT03635840	2018-2019	92 AMICS patients with planned PCI at a single Indonesian center	Pre-PCI IABP vs. No IABP	30-day mortality
REVERSE NCT03431467	2018-2022	92 CS patients at a single US center	ECMO alone vs. ECMO + Impella CP	Survival free from mechanical circulatory support, heart transplantation or inotropic support at 30 days
PULSE NCT03200990	2016-2019	33 non-CS HR-PCI patients at a single Dutch center	Pulsecath iVAC2L vs. Impella CP	Change in pressure-volume area from the beginning of PCI until its conclusion

AMI: acute myocardial infarction; AMICS: acute myocardial infarction cardiogenic shock; CAD: coronary artery disease; CS: cardiogenic shock; HR-PCI: high risk percutaneous coronary intervention; IABP: intra-aortic balloon pump; LVEF: left ventricle ejection fraction; MCS: mechanical circulatory support; MRI: magnetic resonance imaging; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; VA-ECMO: venous-arterial extracorporeal membrane oxygenator.

Supplementary Table 3. Proposed Antithrombotic Strategy in pVAD

Patient group	**Device**	**Suggested antithrombotic strategy**
Elective pVAD supported procedures (e.g. protected PCI)	AFP IABP*	UFH-bolus +/- DAPT or single APT Keep pVAD-support as short as possible
Acute, ischemic cardiogenic shock	AFP VA-ECMO (IABP)*	Therapeutic UFH-anticoagulation +/- DAPT or single APT Keep pVAD-support as short as possible; Prophylactic UFH-dose in case of non-controlled bleeding
Acute, non-ischemic cardiogenic shock	AFP VA-ECMO, (IABP)*	Therapeutic UFH-anticoagulation Prophylactic UFH-dose in case of non-controlled bleeding
ECMO-patients with LV unloading	ECMO plus AFP (ECMO + IABP)*	Therapeutic UFH-anticoagulation +/- DAPT (indication-related) Prophylactic UFH-dose in case of non-controlled bleeding
pVAD-patients with fresh clots, AF or mechanical valves	All pVAD-devices	Therapeutic UFH-anticoagulation +/- DAPT (indication-related) Prophylactic UFH-dose in case of non-controlled bleeding
Right-sided support devices	Protek, right-sided AFP	Therapeutic UFH anticoagulation Therapeutic anticoagulation levels are strongly advised (high thrombotic risk)

Proven heparin induced thrombocytopenia (HIT)	All pVAD-devices	Therapeutic Argatroban or Bivalirudin

AF: atrial fibrillation; AFP: micro-axial flow pump; APT: antiplatelet therapy; DAPT: dual antiplatelet therapy; IABP: intra-aortic balloon pump; LV: left ventricle; PCI: percutaneous coronary intervention; UFH: unfractioned heparin; VA-ECMO: veno-arterial extracorporeal membrane oxygenation. * IABP still widely available although no longer recommended by international guidelines. [25]