Impella hemodynamic support for cardiogenic shock and high-risk percutaneous coronary intervention: Initial experiences at the University Hospital of Split

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LIST OF ABBREVIATIONS

ACT – *Activated clotting time*

AIC – *Automated Impella Controller*

AMI – *Acute myocardial infarction*

APTT – *Activated partial thromboplastin time*

BNP – *Brain natriuretic peptide*

CABG – *Coronary artery bypass graft*

CAD – *Coronary artery disease*

CHIP-PCI – *Complex high-risk indicated percutaneous coronary intervention*

CI – *Cardiac index*

CPO – *Cardiac power output*

CRRT – *Continuous renal replacement therapy*

CS – *Cardiogenic shock*

CTO – *Chronic total occlusion*

Cx – *Left circumflex artery*

DBP – Diastolic blood pressure

DCB – *Drug coated balloon*

DES – *Drug eluting stent*

ECG – *Electrocardiogram*

EDP – *End-diastolic pressure*

EDV– *End-diastolic volume*

eGFR - *Estimated glomerular filtration rate*

ESC – *European Society of Cardiology*

FFR – *Fractional flow reserve*

HR-PCI – *High-risk percutaneous coronary intervention*

IABP – *Intra-aortic balloon pumping*

iVAC – *Intra-aortic Ventricular Assist Catheter*

IVUS – *Intra-vascular ultrasound*

LAD – *Left anterior descending*

LM – *Left main*

LV – *Left ventricle*

LVEDP – *Left ventricular end-diastolic pressure*

LVEDV – *Left ventricular end-diastolic volume*

MCS – *Mechanic circulatory support*

MI – *Myocardial infarction*

MODS – *Multi organ dysfunction syndrome*

NSTEMI – *Non-ST-elevation myocardial infarction*

OCT – *Optical coherence tomography*

PAC – *Pulmonary artery catheter*

PAPi – *Pulmonary artery pulsatility index*

PCA – *Percutaneous coronary angiography*

PCI – *Percutaneous coronary intervention*

PCWP – *Pulmonary capillary wedge pressure*

pLVAD – *Percutaneous left ventricular assist device*

pMCS – *Percutaneous mechanical circulatory support*

POBA – *Percutaneous old balloon angioplasty*

RCA – *Right coronary artery*

RCA – *Right coronary artery*

RCT – *Randomized controlled trial*

RPM – *Revolutions per minute*

RRT – *Renal replacement therapy*

RV – *Right ventricle*

STEMI – *ST-elevation myocardial infarction*

VA-ECMO – *Veno-arterial extracorporeal membrane oxygenation*

1. INTRODUCTION

1.1.1 Cardiogenic Shock

1.1.2 Definition of cardiogenic shock

Cardiogenic shock (CS) could be defined as a clinical condition in which the heart is unable to pump sufficient amounts of blood, resulting in impaired end-organ perfusion that might lead to organ failure and death. CS is a common cause of mortality, and management remains challenging despite advances in therapeutic options. In clinical terms, this manifests as persistent low blood pressure despite attempts at volume restoration, accompanied by signs of inadequate blood flow to vital organs necessitating either pharmaceutical or mechanical intervention. Clinical criteria in studies and guidelines defining CS are not uniform. Contemporary trials recommendations (as depicted in **Table 1**) delineate the clinical parameters for defining CS (1).

Table 1. Contemporary trials recommendations.

Clinical Trial/Guideline	Cardiogenic shock criteria
SHOCK Trial (1999)	▪ SBP <90 mm Hg for >30 min or vasopressor support to maintain SBP >90 mm Hg ▪ Evidence of end-organ damage (UO <30 mL/h or cool extremities) ▪ Hemodynamic criteria: CI <2.2 and PCWP >15 mm Hg
IABP-SOAP II (2012)	▪ MAP <70 mm Hg or SBP <100 mm Hg despite adequate fluid resuscitation (at least 1 L of crystalloids or 500 mL of colloids) ▪ Evidence of end-organ damage (AMS, mottled skin, UO <0.5 mL/kg for 1 h, or serum lactate >2 mmol/L)
EHS-PCI (2012)	▪ SBP <90 mm Hg for 30 min or inotropes use to maintain SBP >90 mm Hg ▪ Evidence of end-organ damage and increased filling pressure
ESC-HF Guidelines (2016)	▪ SBP <90 mm Hg with appropriate fluid resuscitation with clinical and laboratory evidence of end-organ damage ▪ Clinical: cold extremities, oliguria, AMS, narrow pulse pressure. Laboratory: metabolic acidosis, elevated serum lactate, elevated serum creatinine
KAMIR-NIH (2018)	▪ SBP <90 mm Hg for >30 min or supportive intervention to maintain SBP >90 mm Hg ▪ Evidence of end-organ damage (AMS, UO <30 mL/h, or cool extremities)

AMS = altered mental status; CI = cardiac index; EHS PCI = Euro Heart Survey Percutaneous Coronary Intervention Registry; ESC HF = European Society of Cardiology Heart Failure; IABP-SOAP II = intra-aortic balloon pump in cardiogenic shock II; KAMIR-NIH = Korean Acute Myocardial Infarction Registry-National Institutes of Health; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure; UO, urine output.
SOURCE: Vahdatpour C, Collins D, Goldberg S. Cardiogenic Shock. J Am Heart Assoc. 2019;8.

Recently, a systolic blood pressure (SBP) of less than 90 mm Hg for ≥30 minutes or the need of vasopressor/mechanical support to sustain a SBP ≥90 mm Hg was used by the IABP-SCHOCK II trials to define CS (2). A "normotensive CS" can be the result of compensatory mechanisms which maintain the blood pressure via vasoconstriction with a lack of tissue and end-organ perfusion still being present (3,4). Additionally, to the previously mentioned parameters, the SCHOCK Trial included a cardiac index (CI) of ≤2.2 L/min per m^2, as well as a pulmonary capillary wedge pressure of ≥15 mm Hg (5). Signs of reduced blood flow to vital organs differed among the trials but commonly encompassed urine output below 30 mL/h, cold extremities, changes in mental status, and/or serum lactate levels exceeding 2.0 mmol/L. In 2019 Baran *et al.* proposed a newer classification with the aim to support and simplify communication at bedside and in the catheterization laboratory. The new schema includes five categories of shock (a) at risk, (b) beginning or pre-shock, (c) classical, (d) doom, and (e) extremis CS as shown in **Figure 1** (6).

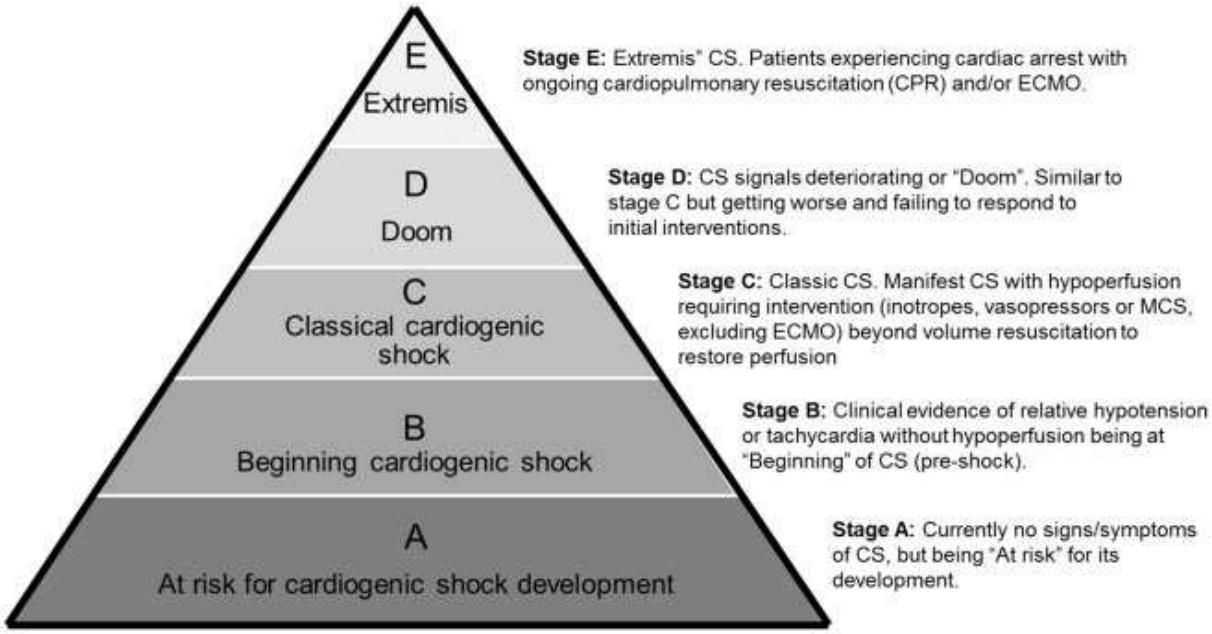


Figure 1: The pyramid of cardiogenic shock classification.

SOURCE: Thiele H, Ohman EM, de Waha-Thiele S, Zeymer U, Desch S. Management of cardiogenic shock complicating myocardial infarction: an update 2019. Eur Heart J. 2019;40:2671-83.

1.1.3 Epidemiology of Cardiogenic Shock

In Europe, each year 70.000-80.000 patients are admitted with CS, with their significant economic impact escalating when coupled with multi-organ failure, resulting in nearly 50% in-hospital mortality and prolonged hospital stay (7,8). An increase of incidence in the last years might be due to a better access to care and improved methods of diagnosis, but also to an aging population (9,10).

CS arises in 5% to 10% of cases of acute myocardial infarction (AMI) and stands as the primary cause of death subsequent to MI. ST-segment–elevation myocardial infarction (STEMI) carries a twofold higher likelihood of CS development compared to non–ST-segment–elevation myocardial infarction (NSTEMI). Patients with NSTEMI-related CS are less inclined to receive prompt cardiac catheterization, leading to delays in percutaneous coronary intervention (PCI) and/or coronary artery bypass graft procedures, thus elevating mortality risks in comparison to patients with STEMI-related CS (11).

Despite improvements in in-hospital mortality rates, the 6- to 12-month mortality for CS has remained steady at around 50% over the past two decades. Patients who survive MI-related CS face an 18.6% risk of readmission within 30 days post-discharge, typically occurring around 10 days after discharge. The likelihood of readmission tends to be slightly lower among patients with STEMI compared to those with NSTEMI. The primary reasons for readmission include congestive heart failure and new myocardial infarction. Predictors of readmission encompass female gender, lower socioeconomic status, placement of mechanical circulatory support (MCS) devices, atrial fibrillation, and ventricular tachycardia (12,13,14,15).

1.1.4 Etiology of Cardiogenic Shock

CS can be the result of anything leading to severe left or right ventricular dysfunction (16). The most typical causes and incidences of CS, stated in the shock trial are listed in **Table 2** (17).

Table 2. Causes and incidences of cardiogenic shock in the SHOCK trial registry and randomized SHOCK trial.

Category	N	Incidence (%)	Mortality (%)
LV failure	1116	78.5	59.2
VSD	55	3.9	87.3
Mitral regurgitation	98	6.9	55.1
RV failure	40	2.8	55.0
Tamponade	20	1.4	55.0
Other	95	6.7	65.3
Total	1,422	-	60.1

LV = left ventricle; VSD = ventricular septal defect; RV = right ventricle.

SOURCE: Thiele H. The PCR-EAPCI TEXTBOOK. Cardiogenic Shock. Toulouse. Europa Group.

Myocardial infarction followed by left ventricular dysfunction remains the predominant cause of CS. The occurrence of shock following NSTEMI appears to be less frequent compared to STEMI. In the (SHOCK) trial and the SHOCK registry, the median time from AMI onset to shock occurrence was 5.0 and 6.0 hours, respectively. Shock associated with unstable angina or NSTEMI tends to manifest at a later stage, with median times of 76.2 and 94.0 hours, respectively (18).

Typically, a loss of over 40% of functional myocardium is necessary to induce CS, as evidenced by autopsy studies. Nonetheless, structural complications like ventricular septal rupture, free wall rupture, and papillary muscle rupture or dysfunction also play a role in precipitating CS following AMI. Furthermore, any condition causing acute and severe dysfunction of the left ventricle (LV) or right ventricle (RV) can lead to CS. Acute perimyocarditis, the apical ballooning syndrome (Tako-Tsubo syndrome), and hypertrophic obstructive cardiomyopathy may all exhibit ST-segment changes, elevation of cardiac biomarkers, and shock despite minimal coronary artery disease. Tako-Tsubo syndrome, characterized by transient LV dysfunction following emotional or physical stress in the absence of significant coronary artery disease, can result in CS in approximately 4.2% of cases (19).

Acute valvular dysfunction, such as acute regurgitation typically due to endocarditis or chordal rupture from trauma or degenerative disease, can also lead to shock. Similarly, aortic dissection with acute, severe aortic insufficiency or infarction may precipitate CS. Cardiac

tamponade or massive pulmonary embolism can present as CS even without concurrent pulmonary congestion. The complete list of common etiologies of CS is shown in **Figure 2** (20).

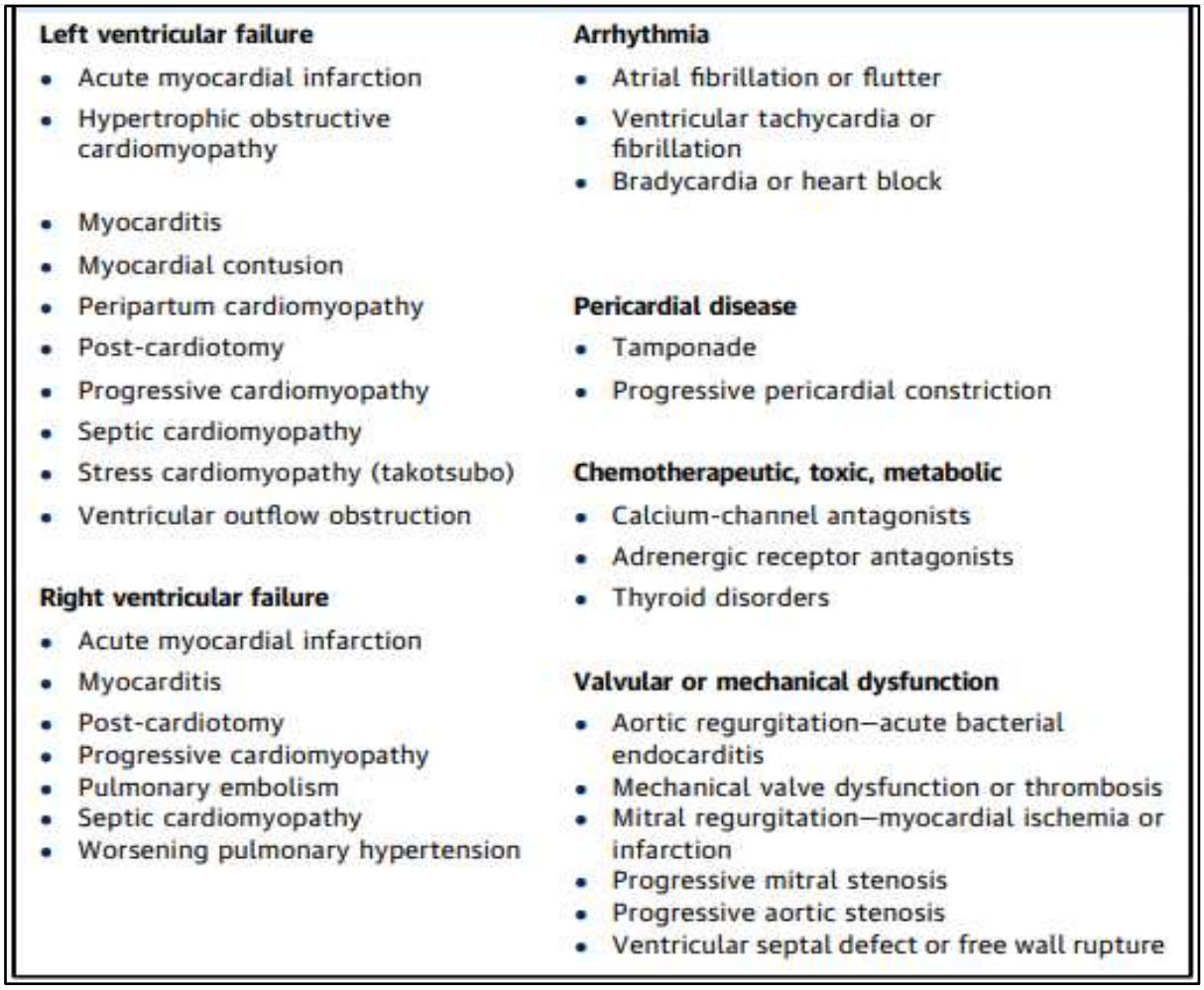


Figure 2. Common etiologies of cardiogenic shock.

SOURCE: Tehrani BN, Truesdell AG, Psotka MA, Rosner C, Singh R, Sinha SS, et al. A Standardized and Comprehensive Approach to the Management of Cardiogenic Shock. JACC Heart Fail. 2020;8:879-91.

1.1.5 Pathophysiology of Cardiogenic Shock

The main pathophysiologic pathway of CS is a diminished cardiac output (CO), hypotension, tissue hypoperfusion, peripheral vasoconstriction, increased afterload, cardiac ischemia, end-organ failure, and death (2). Myocardial infarction is the leading cause of CS although it may be caused by various other etiologies. The raised end-diastolic pressure resultant of the progressive diastolic dysfunction leads to a diminished coronary perfusion pressure, myocardial contractility, and stroke volume (2). **Figure 3** shows the vicious circle seen in CS, finally resulting in death (20).

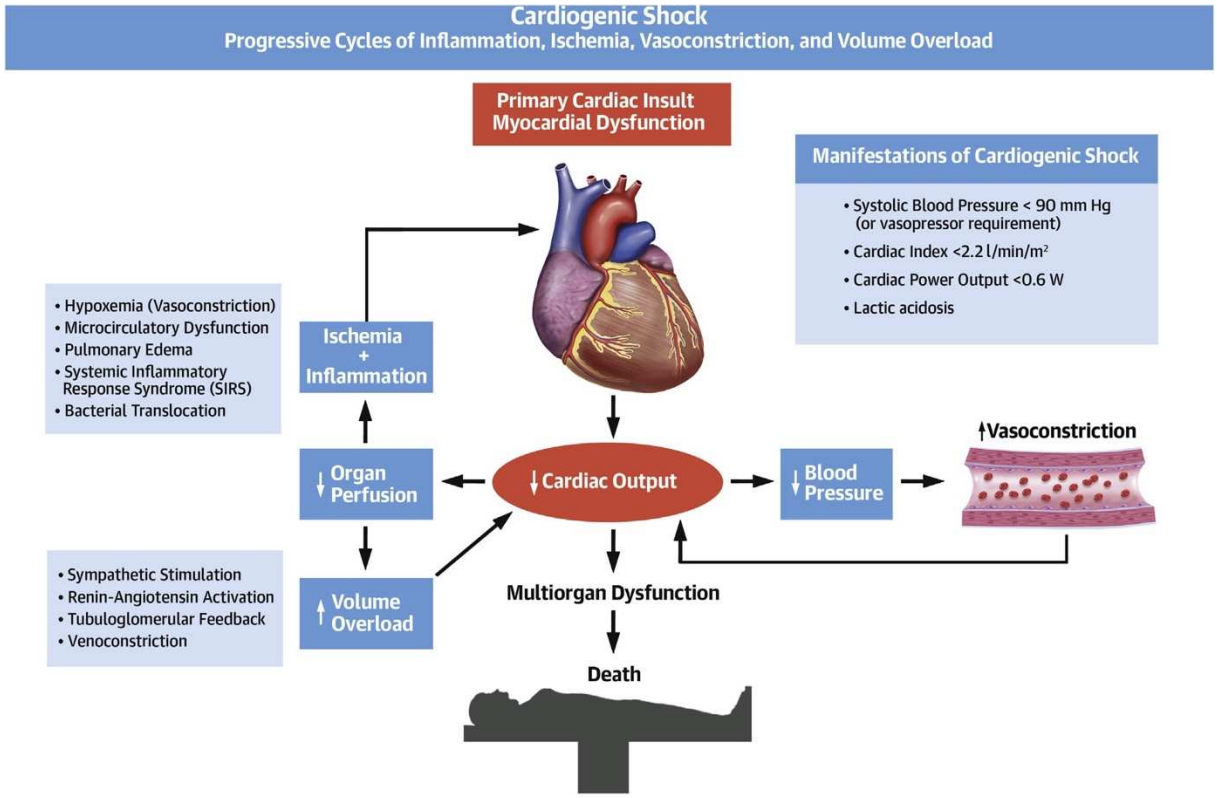


Figure 3. Cardiogenic shock, progressive cycles of inflammation, vasoconstriction, ischemia, and volume overload.

SOURCE: Tehrani BN, Truesdell AG, Psotka MA, Rosner C, Singh R, Sinha SS, et al. A Standardized and Comprehensive Approach to the Management of Cardiogenic Shock. JACC Heart Fail. 2020;8:879-91.

A sympathetic compensatory mechanism induces vasoconstriction, which together with fluid retention may initially maintain the blood pressure. This further increases the afterload, opposing ventricular contraction, exacerbating the heart's workloads and ischemia (2,21).

Tissue ischemia and necrosis induce a systemic inflammatory response further deteriorating tissue metabolism and stimulate the release of nitric oxide synthase and peroxynitrite, which catalyze the production of nitric oxide, leading to systemic vasodilation that exacerbates low blood pressure further, and have a cardiotoxic effect respectively, which all together reduces the contractility of the myocardium (22,2).

A lowered blood pressure leads to a diminished glomerular perfusion. Activation of the renin-angiotensin axis, and an increased tubular sodium reabsorption, lead to fluid retention and volume overload (23). The myocardial oxygen demand is further increased by pulmonary vasoconstriction as a result of hypoxia and pulmonary congestion, creating a higher right ventricular end diastolic pressure. Furthermore, as the left ventricular filling pressures rise, pulmonary capillary pressure rises too as the pressures are shifted retrogradely past the lungs. The right ventricle (RV) generally can compensate volume overload better than the left ventricle (LV) but lacks the ability to compensate for a severely elevated afterload. Therefore, an elevated pulmonary artery pressure is the reason for RV failure when the RV cannot provide a suitable stroke volume (24). The result is an elevated venous pressure (24). As the interventricular septum is displaced by the overfilled right ventricle, the left ventricular space becomes compromised. The result is a decreased left ventricular filling, leading to a further decreased ejection fraction and systemic hypoperfusion (24, 25). Typical hemodynamic characteristics in patients with CS are shown in **Figure 4** (17). Left untreated, a vicious cycle continues with the result of organ failure and death (2).

	CI (L/min/m²)	Systolic BP (mmHg)	CVP (mmHg)	PCWP (mmHg)	PAP (mmHg)	$scvO_2$ (%)	svO_2 (%)
LEFT HEART FAILURE	<1.8	<90	↑	>18	↑	↓	↓
VSD	<1.8	<90	↑↑	↑	↑↑	↓	>scv O_2
MITRAL REGURGITATION	<1.8	<90	↑	Tall v-wave	↑↑	↓	↓
RIGHT HEART FAILURE	<1.8	<90	>PCWP	<CVP	[↓]	↓	↓

VSD: ventricular septal defect; CI: cardiac index; BP: blood pressure; CVP: central venous pressure; PCWP: pulmonary capillary wedge pressure; PAP: pulmonary artery pressure; $scvO_2$: central venous oxygen saturation; svO_2: mixed venous oxygen saturation.

Figure 4. Hemodynamic characteristics of cardiogenic shock.

SOURCE: Thiele H. The PCR-EAPCI TEXTBOOK. Cardiogenic Shock. Toulouse. Europa Group.

1.1.6 Clinical Presentation of Cardiogenic Shock

Typical signs of CS are hypotension, cold and mottled skin, dyspnea, diminished pulses, peripheral edema, oliguria defined as a urine output less than 30 mL/h, and an altered mental status, suggesting that >40% of left myocardium is involved in the infarction (26,27,28,5).

In individuals suffering from CS secondary to AMI of the LV, the impaired ability to effectively eject blood leads to an elevation in left ventricular end-diastolic pressure (LVEDP). This increase in pressure correlates with raised pulmonary capillary wedge pressure. Patients with elevated LVEDP commonly exhibit an S3 gallop, an elevated breathing rate, and low oxygen levels resulting from pulmonary congestion, which may be detected by abnormal lung sounds (rales). When pulmonary edema develops rapidly due to dysfunction during both systole and diastole of the LV, patients may present with respiratory distress and failure. CS can either be evident upon hospital arrival following AMI or develop subsequently after the initial ischemic insult to the myocardium. According to a subsequent analysis of the SHOCK trial and registry, the average interval from the appearance of AMI symptoms to the development of CS was reported as 6.2 hours (with an interquartile range of 1.7 to 20.1 hours). The SHOCK registry further indicated a median time of 5.5 hours (with an interquartile range of 2.3 to 14.1 hours) from AMI symptom onset to CS onset. Very early CS (onset within <6 hours after AMI) was observed in 46.6% of SHOCK registry patients, early shock (onset within <24 hours) in 74.1%, and late shock (onset ≥24 hours) in 25.9%. Shock was diagnosed at presentation in 9% of registry patients and 14% of trial patients (29).

Patients experiencing CS after an acute LV infarction may present with low blood pressure, signs of insufficient end-organ perfusion (e.g., disorientation or cold/mottled extremities), signs of increased pressure within the heart (due to dysfunction during both ventricular contraction and relaxation), such as pulmonary edema, difficulty breathing while lying down (orthopnea), or elevated jugular venous pressure. Hypotension is typically defined as a SBP lower then 90 mm Hg or a significant drop in mean arterial pressure (MAP) >30 mm Hg from the patient's baseline. An arterial pulse pressure (the difference between SBP and diastolic blood pressure (DBP)) of < 25% of the SBP indicates a reduced CO.

Inadequate tissue perfusion may manifest as reduced or altered mental status, cold extremities with diminished intensity of distal pulses, or decreased urine output (less than 30 mL/hour). An elevated serum lactate level greater than 2.0 mmol/L upon presentation serves as a sensitive laboratory marker of inadequate tissue perfusion and is among the diagnostic criteria for CS following AMI. Additionally elevated BNP, troponin levels and metabolic acidosis can

give insight to the perfusion status and serve as diagnostic criteria and laboratory evidence of CS. Hemodynamic criteria are a decreased CI of less than 1.8 L/min/m^2 and an elevated capillary wedge pressure of >15mmHg, as well as a SBP of less than 90 mm Hg for ≥30 minutes as earlier mentioned (30).

In CS caused by AMI, a subgroup of individuals presents with an adequate SBP of >90 mm Hg but signs of end organ hypoperfusion when vasopressors are not used (5). This condition, which is connected to increased rates of negative effects is often termed non-hypotensive CS. In a re-evaluation of 1068 SHOCK registry patients, 943 (88.3%) presented with classic CS, 76 (7.1%) had low blood pressure, and 49 (4.6%) had non-hypotensive CS. Especially when normal blood pressures are measured, initial clinical signs of inadequate organ perfusion might be a better marker for undesirable events than a low blood pressure alone, as outlined by the previously mentioned results (5).

When RV infarction leads to CS, it usually is accompanied by signs of low blood pressure, a normal oxygen saturation and increased pressures of the jugular vein (5,27). As shown by the SHOCK registry, RV infarction leading to CS is relatively rare in comparison to LV infarction and only happened in 5.5% of SHOCK registry patients. These patients are usually younger with lower rates known morbidities. (5,27).

1.1.7 Differential diagnosis of CS

The diagnosis of CS could be broken down into two main aspects: distinguishing between pure CS and other factors contributing to shock, known as mixed shock, and discerning among the various causes of CS. Distinguishing between CS and other types of shock (such as hypovolemic, extracardiac obstructive, and distributive) primarily relies on a thorough assessment of medical history, physical examination findings, electrocardiogram (ECG) results, echocardiography, and laboratory tests. Echocardiography should be promptly conducted in all AMI patients presenting with CS to facilitate rapid diagnosis and exclusion of mechanical complications. CS is often indicated by left ventricular (LV) dysfunction, while a large right ventricle (RV) relative to a small LV may suggest pulmonary embolism, pericardial fluid may indicate cardiac tamponade, and small heart chambers with normal function may hint at hypovolemic shock. Additional imaging modalities like computed tomography (CT) scans or hemodynamic assessments using a pulmonary artery catheter (PAC) may be useful depending on the clinical context. **Table 3** outlines the causes of CS and the diagnostic approaches for the most significant ones (8).

Table 3. The most important differential diagnosis of acute myocardial infarct-related cardiogenic shock and diagnostic tools.

Diagnosis	Incidence	Diagnostic tool
Aortic dissection	Rare	CT, MRI, TEE
Pulmonary embolism	Common	CT, TTE
Tension pneumothorax	Rare	Chest X-ray, CT
Myocarditis	Intermediate	Coronary angiography, Cardiac MRI
Takotsubo syndrome	Intermediate	Coronary angiography, TTE
Valvular	Intermediate	TTE
Cardiomyopathy (ischaemic or non-ischaemic)	Common	TTE, history
Cardiac tamponade	Rare	TTE

CT = computed tomography; MRI = magnetic resonance imaging; TEE = trans-oesophageal echocardiography; TTE = transthoracic echocardiography.

SOURCE: Zeymer U, Bueno H, Granger CB, Hochman J, Huber K, Lettino M, et al. Acute Cardiovascular Care Association position statement for the diagnosis and treatment of patients with acute myocardial infarction complicated by cardiogenic shock: A document of the Acute Cardiovascular Care Association of the European Society of Cardiology. Eur Heart J Acute Cardiovasc Care. 2020;9:183-97.

1.1.8 Management and treatment of CS

1.1.8.1 Fluids, inotropes, vasopressors

Due to the intricate nature of most CS presentations, optimal management occurs within specialized intensive care units (ICUs), allowing for meticulous monitoring of volume status, vasopressor and inotropic support, and the prevention and treatment of multiorgan dysfunction syndrome (MODS). Early identification and treatment of the underlying cause, concomitant with hemodynamic stabilization and management of organ dysfunction, are key components of its management (**Figure 5**) (31).

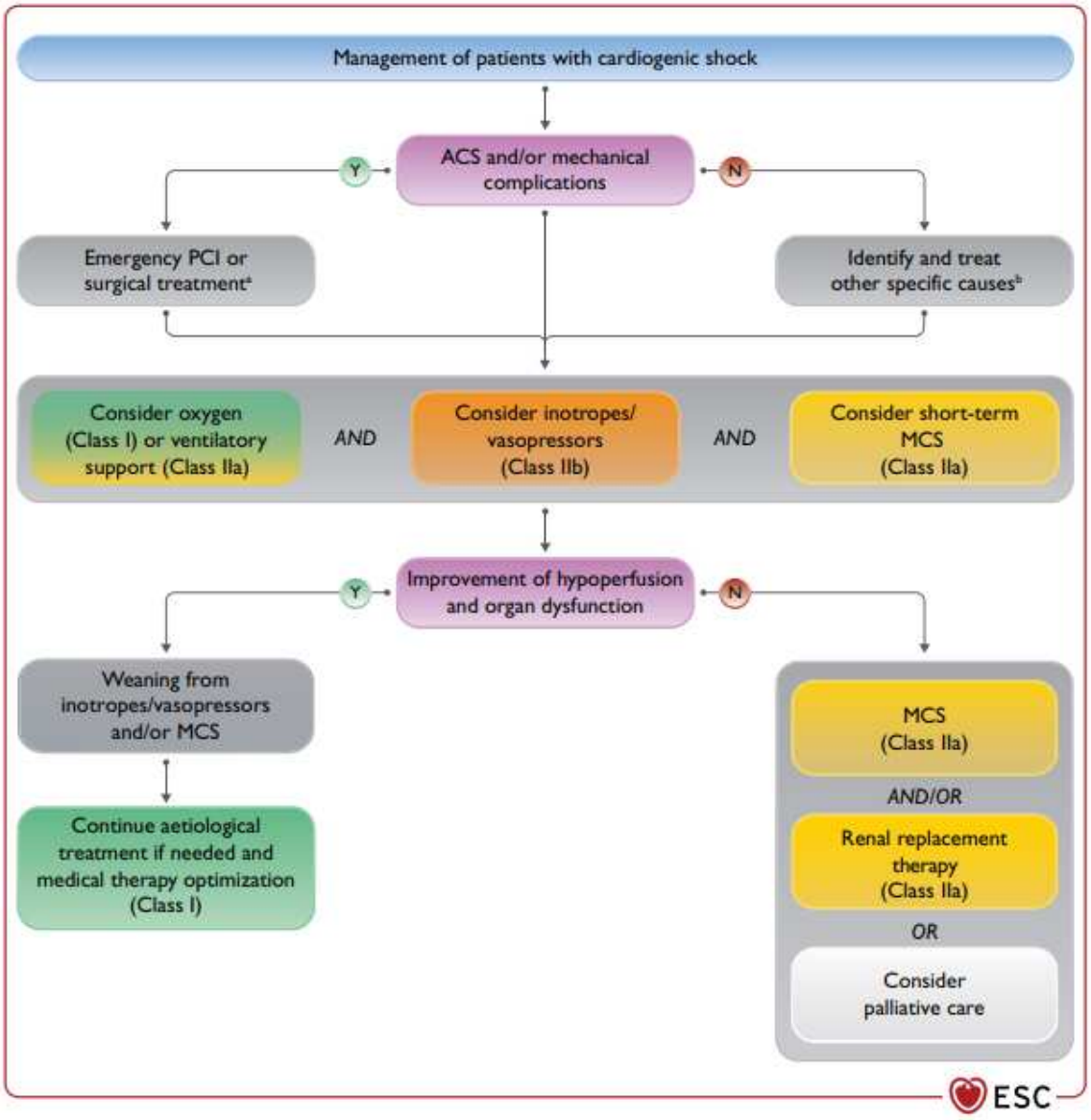


Figure 10 Management of cardiogenic shock. ACS = acute coronary syndrome; BTT = bridge to transplantation; MCS = mechanical circulatory support; PCI = percutaneous coronary intervention. [a]PCI in ACS, pericardiocentesis in tamponade, mitral valve surgery in papillary muscle rupture. In case of interventricular septum rupture, MCS as BTT should be considered. [b]Other causes include acute valve regurgitation, pulmonary embolism, infection, acute myocarditis, arrhythmia (see *Figure 12*).

Figure 5. Management of patients with CS.

SOURCE: McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42:3599-726.

Fluid administration in CS primarily follows pathophysiological principles, and as per current guidelines, a fluid challenge is typically recommended as first-line therapy unless evident signs of fluid overload are present (class 1C recommendation). Despite the prevalent

use of vasopressors and inotropes in patients presenting with CS (approximately 90%), it's crucial to acknowledge that these medications elevate the hearts oxygen demand and induce vasoconstriction, potentially compromising microcirculation and increasing afterload. Consequently, they should generally be administered at the minimum effective dosage for the briefest time possible (32).

Vasopressors and inotropes are used in around 90% of CS patients but should be used with caution since they induce vasoconstriction and thereby increase vascular resistance, thus increasing afterload and the heart's oxygen consumption (28). Vasopressors can be used to achieve a generally accepted target pressure of >65 mm Hg with vasopressin mostly leading to a better lung perfusion and gas exchange than norepinephrine which leads to a more pronounced pulmonary vasoconstriction, making vasopressin the vasopressor of choice in the setting of CS with RVF (33).

In patients with severely reduced blood pressure, norepinephrine, acting as a peripheral arterial vasoconstrictor, can be used (20). To reduce the negative effect of norepinephrine, increasing the LV afterload, it can be given together with an inotropic agent (20). Using epinephrine as a vasoconstrictor in CS has no benefit over norepinephrine as a meta-analysis of 2583 patients by Leopold V *et al.* revealed a threefold increase in risk for mortality when epinephrine is used for hemodynamic control in patients with CS (20,34). De Backer *et al.* found that norepinephrine is more beneficial for patients with CS than dopamine, as dopamine tends to cause arrhythmias (35,36). Underlined by Levy *et al*., norepinephrine has proven to have less negative effect on CI and fewer changes in metabolism such as lactic acidosis and heart rate than epinephrine, as well as having a much lower incidence of development of refractory CS with 37% vs 7%; p=0.008 (36,37).

Inotropes are indicated in patients with organ hypoperfusion caused by LV systolic failure with a low CO and a SBP of <90 mmHg and should be used in the lowest dose possible (20,38,39), as they are known to cause various side effects such as sinus tachycardia, arrhythmias and myocardial ischemia leading to increased mortality, as stated by the recent ESC Guidelines on Acute and Chronic Heart Failure (20,38-42).

Dobutamine is the first-line treatment in CS with low CO (43,44) and can be given together with norepinephrine to increase blood pressure as dobutamine doesn't act as a vasopressive agent itself.

A good choice of treatment is calcium sensitizers, e.g., levosimendan, which has shown to be beneficial in AMI-CS since they do not increase the myocardial oxygen demand and are

not as arrhythmogenic as dobutamine (45). In patients using beta-blockers, levosimendan may be more beneficial than dobutamine, as it acts via a different mechanism of action, but major side effects such as peripheral vasodilation are known (44,46,47). **Figure 6** shows the action of the most common inotropic agents, used in the treatment of CS (17).

RECEPTOR AGENT	DOSE	β1	β1	β2	D	SPECIFIC CONSIDERATIONS
Dopamine	2.0-20 µg/kg/min (max. 50 µg/kg/min)	+++	++++	++	+++++	Dose-dependent effect: D< β1< α1 Inhibition of norepinephrine-uptake Norepinephrine-release ↑ O2-consumption ↑↑ →cardiac ischaemia Arrhythmias Tissue/peripheral ischaemia
Dobutamine	2.0-20 µg/kg/min (max. 40 µg/kg/min)	+	+++++	+++	-	Mild vasodilatation O2-consumption (↑) Tolerance Arrhythmias
Norepinephrine	0.01-3 µg/kg/min	+++++	+++	++	-	Coronary flow ↑ Antithrombotic effects Cardiotoxic Tissue/peripheral ischaemia
Epinephrine	0.01-0.10 µg/kg/min	+++++	++++	+++	-	Coronary flow ↑ Prothrombotic effects Cardiotoxic Tissue/peripheral ischaemia

D: dopamine receptor; + - ++++: effect size; ↑ increase.

Figure 6: action of the most common inotropic agents, used in the treatment of CS.
SOURCE: Thiele H. The PCR-EAPCI TEXTBOOK. Cardiogenic Shock. Toulouse. Europa Group.

1.1.8.2 Oxygenation and ventilation

Oxygen therapy should not be administered in individuals with normal oxygen saturations, suffering from acute heart failure, as oxygen can induce vasoconstriction, leading to a diminished CO (31,48). In the acute management of CS, an oxygen saturation of more than 90% is typically considered acceptable but higher values might be considered for patients with comorbidities (49,50). Patients with an oxygen saturation <90% or oxygen partial pressure <60 mmHg, are eligible for non-invasive oxygen therapy. In respiratory distress, this can facilitate diffusion and decrease the frequency of intubation (49,50). When invasive ventilation is necessary, patients benefit from low tidal volumes of 5-7 mL/kg of ideal body weight since this has shown to be lung protective and improves the circulation by decreasing vascular resistance in contrast to higher tidal volumes (31,51).

1.1.8.3 Continuous renal replacement therapy

Around 10%-30% of CS patients develop acute kidney injury with continuous renal replacement therapy (RRT) necessary in 20% of cases (2). When stage 2 kidney injury is present continuous renal replacement therapy (CRRT) should be induced. This is characterized by urination of less than 0.5 mL/kg per hour for at least 12 hours and elevated serum creatinine (≥2x baseline) or when critical changes in acid-base status, fluid, and electrolyte, necessitate dialysis (52).

1.1.8.4 Invasive hemodynamic monitoring.

The objectives of hemodynamic monitoring should prioritize adjusting hemodynamics to maintain stable vital signs and ensure sufficient tissue perfusion. Basic parameters for monitoring include continuous blood pressure measurement using an arterial line, temperature, continuous pulse oximetry, telemetry, urinary output and respiratory rate. (53-57).
Echocardiography is instrumental in verifying initial mechanical issues like free wall rupture, ventricular septal defect, and papillary muscle rupture, typically occurring within the first day after admission. Throughout treatment, echocardiography, and catheterization work in tandem to evaluate the hemodynamic response to intervention.

During cardiac catheterization, a PAC is commonly inserted to help identify patients in need of mechanical circulatory support. Subsequently, it is used for the observation of blood flow, offering accurate assessments of the volume status, the saturation of oxygen inside the central vein, the reaction to therapy, and the effectivity of mechanical support (24,56-59).

PACs provide benefits by continuously visualizing CO while titrating inotropic agents and pulmonary artery vasodilators. This intervention proves beneficial as patient responsiveness to MCS relies on various components, such as, RV contractility, volume status, the pulmonary and systemic vascular characteristics, and valvular abnormalities.

1.1.8.5 Revascularization in CS

Coronary angiography stands out as the pivotal investigation when used in individuals presenting with CS accompanied by AMI. It allows medical care personnel to pinpoint the injuries exact site that triggered the condition (5,27). In approximately 15% of cases, significant left main lesions are detected, and over 50% exhibit triple-vessel disease on coronary angiography. Mortality rates are linked to culprit lesions, with left anterior descending coronary artery, saphenous vein graft, right coronary artery, left main coronary artery and circumflex

coronary artery, being notable factors. Primary PCI is usually done after the assessment of the anatomy of the coronary arteries (5,27). Coronary artery bypass graft (CABG) surgery, combined CABG and PCI, or urgent cardiac transplantation can might be performed in some cases (1).

Multiple randomized controlled trials (RCT), the SHOCK trial being one of the best-known ones in this field, found a significant mortality reduction at six months and long term follow up, with an early revascularization strategy using PCI or CABG after CS (5,60,61). With an all-cause mortality at 6 months being significantly lower in the revascularization group than in the medical therapy group (50.3 vs. 63.1%, revascularization vs. medical therapy; relative risk 0.80, 95% confidence interval 0.65– 0.98, p 1⁄4 0.03) (5,61). Reviews of the SHOCK trial suggested that revascularization is the benchmark when managing CS although it failed to meet the studies primary endpoint in reducing the 30-day mortality, making it a class I indication (5).

As stated by the European Society of Cardiology (ESC) percutaneous coronary angiography (PCA) has a class 1 recommendation in patients with AMI CS. Almost 80% of patients with CS are presenting with underlying multivessel disease/left main disease which is associated with increased mortality rates compared to single vessel disease (62,63). Currently the ESC suggests that there is no benefit in multivessel revascularization in AMI CS giving it a class III recommendation (64). A significant decrease in 30-day mortality or RRT was shown by the Culprit Lesion Only PCI vs. Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial when using a culprit-lesion-only PCI approach compared with multivessel PCI (45.9% culprit-lesion-only PCI vs. 55.4% immediate multivessel PCI; relative risk 0.83; 95% CI 0.71-0.96; P = 0.01) the 30-day mortality was reduced by 8.2% (43.3% vs. 51.5%; relative risk 0.84; 95% CI 0.72-0.98, P = 0.03) (27). Therefore, a routine revascularization multivessel PCI is not indicated and revascularization reserved to culprit lesions with the possibility of staged revascularization for non-culprit on another occasion (65).

The ESC and other contemporary guidelines recommend a transradial access as a standard route in STEMI and NSTEMI patients without shock (66,67). In the retrospective meta-analysis of 8131 CS registry patients, Pancholy *et al.* illustrated a reduction in mortality that can be associated with a transradial approach (68). When PCI is not feasible, fibrinolytic therapy should be considered in CS and should be done in the first 6 hours after the onset of symptoms of MI (69). High-risk patients, such as patients of older age, are profiting the most from such treatment (69,70).

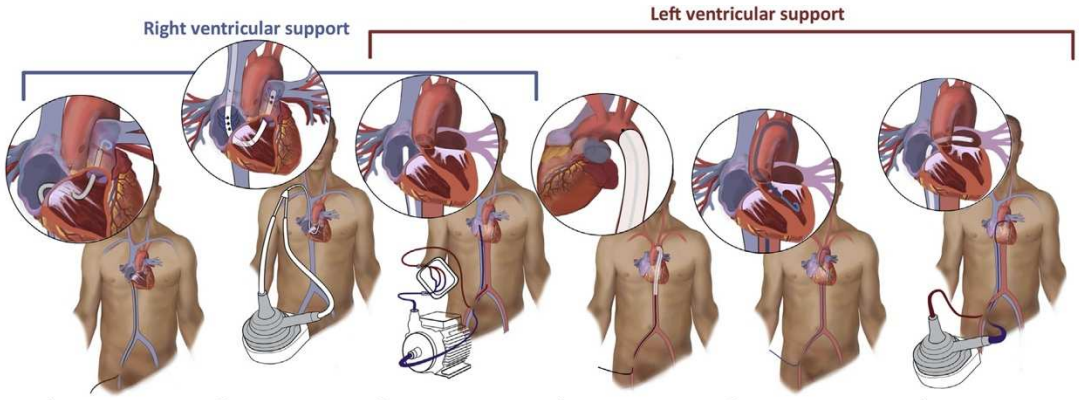
Today CABG is only performed in less than 5% of patients presenting with CS (28,71), with similar outcomes as PCI (72). According to contemporary guidelines, CABG and PCI are both indicated in AMI CS, with CABG being the choice when coronary artery anatomy or mechanical complications make PCI unfeasible (65,66,73).

1.2 Mechanical circulatory support devices

Mechanical circulatory support (MCS) devices help in sustaining adequate perfusion of tissues and cardiac muscle, when CO cannot meet the body tissues oxygen demand. The shortage of donor organs and the possibility of quick use of these devices have led to multiple inventions, of which the practicability and utility as well as the timeframe of introduction have still to be determined.

MCS devices are becoming more and more prevalent in the treatment of CS and substantially help in stabilizing circulation (74). Different possible advantages of percutaneous ventricular assistance are the reduction of the LV pressure and volume, a reduced tension of the heart's walls leading to increased endocardial perfusion, decreased cardiac metabolic needs, protection of end organ perfusion and better cellular repair (17).

Three common pathways of circulating the blood with these devices are from the right atrium (RA) to a central vein or systemic artery, the left atrium (LA) to a systemic artery, or the left ventricle to a systemic artery. Peak flow rates range from 2.5 to 7 liters/minute. The most common MCS devices used in the treatment of CS, their specifications and hemodynamic profiles are shown in **Figure 7** (1,20,17,75,76).



	Impella RP	TandemHeart RA-PA	VA-ECMO	IABP	Impella (2.5, CP, 5.0, 5.5)	TandemHeart LA-FA
Flow	max 4.0 l/min	max 4.0 l/min	max 7.0 l/min	0.5 l/min	2.5 - 5.5 l/min	max 4.0 l/min
Pump Speed	33000 rpm	max 7500 rpm	max 5000 rpm	NA	max 51,000 rpm	max 7500 rpm
Mechanism	Axial flow continuous pump (RA-to-PA)	Centrifugal flow continuous pump (RA-to-PA)	Centrifugal flow continuous pump (RA-to-AO)	Balloon inflation-deflation (AO)	Axial flow continuous pump (LV-to-AO)	Centrifugal flow continuous pump (LA-to-AO)
Cannula Size	22 F venous	29 F venous	14-19 F arterial 17-21 F venous	7-8 F arterial	13-21 F arterial	12-19 F arterial 21 F venous
Insertion/Placement	Femoral vein	Internal jugular vein	Femoral vein Femoral artery	Femoral artery Axillary artery	Femoral artery Axillary artery	Femoral artery Femoral vein
LV Unloading	-	-	-	+	+to+++	++
RV Unloading	+	+	++	-	-	-
Cardiac Power	-	-	↑↑	↑	↑↑	↑↑
Afterload	-	-	↑↑	↓	↓↓	↑
Coronary Perfusion	-	-	-	↑	↑	-
Considerations	• *RECOVER RIGHT: 73% survival-to-30 days in RVF post LVAD, AMI or cardiotomy* • *May 2019 - FDA post-approval study: 33% survival-to-30 days*	• *IJ access may facilitate early ambulation*	• *Bi-V + oxygenation support for CS following:* *- AMI, ADHF or cardiac arrest* *- Cardiotomy* *- Myocarditis* *- Allograft rejection*	• *Requires stable cardiac rhythm and native heart function* • *May consider in select cases of post-AMI mechanical complications*	• *June 2008 – FDA 510(k) approval for HR-PCI* • *April 2016: Expanded Indication for CS* • *Contraindicated with mechanical aortic valve, LV thrombus*	• *Requires transseptal access* • *Oxygenator may be added to the circuit*

Figure 7: The hemodynamic profiles of the various circulatory support devices available for treatment of CS.

ADHF = acute decompensated heart failure; AMI = acute myocardial infarction; AO = aorta; Bi-V = biventricular; CS = cardiogenic shock; FA = femoral artery; FDA = Food and Drug Administration; HR-PCI = high risk percutaneous coronary intervention; IABP = intra-aortic balloon pump; IJ = internal jugular; LA = left atrium; LV = left ventricular; LVAD = left ventricular assist device; PA = pulmonary artery; RA = right atrium; RPM = revolutions per minute; RV = right ventricular; RVF = right ventricular failure; VA-ECMO = venoarterial extracorporeal membrane oxygenation.

SOURCE: Tehrani BN, Truesdell AG, Psotka MA, Rosner C, Singh R, Sinha SS, et al. A Standardized and Comprehensive Approach to the Management of Cardiogenic Shock. JACC Heart Fail. 2020;8:879-91.

All MCS devices share the need for anticoagulation with the aim of preventing thrombus formation and, as a result, an increased risk of bleeding complications. Other common complications are hematoma formation, vascular injury, and hemolysis.

1.2.1 Intra-aortic balloon pumping

Introduced in the 1960s, IABP is used as a supportive measure in the treatment of CS. The effect of using this device is a reduction in cardiac afterload, an increase in myocardial perfusion and a reduction in oxygen consumption (25,1).

It is placed with a 7-8 Fr cannula commonly through a large artery such as the axillary or femoral artery and its polyethylene balloon can be inflated and deflated in diastole and systole respectively, dictated by the heart rhythm in synchronization with the ECG, a mechanism known as counter pulsation. It thereby achieves a systolic LV unloading and increases stroke volume (1,77-80). The inflation of the balloon in diastole increases the pressure upstream of the balloon and pushes the blood backwards and into the coronary arteries, which helps in myocardial perfusion. The rapid deflation during systole creates a pressure gradient, effectively reducing the resistance against which the myocardium must pump. The IABP is a crucial instrument, beneficial when used in critically ill patients, helping in stabilizing the patient's hemodynamics, relieving symptoms of heart failure, and serving as a temporary support during coronary intervention.

Despite its prevalent clinical usage IABP-Shock II study published in 2013, failed to provide definitive evidence supporting the efficacy of intra-aortic balloon pump (IABP) insertion in patients experiencing CS resulting from acute coronary syndrome (ACS), as it did not result in reduced 30-day mortality rates or improvements in outcomes over a six-year period (80,81). These findings might be due to the circumstance that the IABP isn't effective in saving heart muscle, indicating its minimal influence on cardiac function in this regard (1,82,83). According to these results, the 2014 guidelines from the European Society of Cardiology (ESC) revised their stance on the usage of IABP in individuals experiencing CS connected to ACS, changing it from the previous status of "recommended" (Class I) to "not recommended" (Class III) (80,84).

1.2.2 iVAC 2L®

The iVAC® (Intra-aortic Ventricular Assist Catheter) is an advanced type of pMCS whose core principle is based on LV unloading. It consists of a bi-directional flow catheter that

can be inserted through the common femoral artery via a 17 F cannula, navigated through the aortic valve and reaching into the LV. A catheter integrated membrane pump which itself is controlled by an IABP console, lies outside of the body and actively removes the blood from the LV and expels it into the aorta (85). With its pulsatile support of additional 1.5 L/min delivered by the extracorporeal membrane pump, it aids in stabilizing patients with CS or undergoing high-risk PCI and exceeds the capabilities of the IABP. During systole, blood is drawn from the left chamber into the device, and then expelled during diastole, opening a patented rotating two-way valve directing the blood to the ascending aorta *via* its side outflow port, effectively simulating an additional heartbeat. The pumping velocity can be adjusted according to the physiological needs and important parameters such as flow rate, pumping speed, MAP and differential pressure between inlet and outlet can be read from the controller, giving insight into proper functioning of the device. The data available unfortunately is limited to small case studies, and further research is needed to thoroughly assess the clinical significance of this device (85).

1.2.3 VA-ECMO

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is a potent MCS device with the application as critical support in individuals suffering from cardiac or respiratory failure. The device consists of inflow and outflow cannulas, a centrifugal pump, and a membrane oxygenator. With its centrifugal pump, deoxygenated venous blood is removed from the circulation, commonly through a 17-21 French cannula and is then passed through the membrane oxygenator. After being oxygenated, blood flows back to the circulation mostly through an arterial cannula of 14-19 French. This creates a temporary bypass of the heart and lungs and at the same time reduces venous return, significantly increasing tissue oxygenation. With its high flow rates of max. 7 L/min it outperforms the other MCS devices in in terms of flow capacity, making it suitable for even the most critical patients, by taking over the functions of the heart and lung together. By its nature of primarily supporting the systemic circulation it bears the disadvantage of loading the LV which can further exacerbate heart failure (86,87). According to the ESC guidelines, the use of ECMO in CS and for in-hospital and out-of-hospital cardiac arrest has a Class IIb recommendation (84). Tsutsui *et al.* stated that VA-ECMO should be considered in CS refractory to drug therapy or in circulatory failure due to mechanical complications with Class IIa and IIb recommendation respectively (88,89). Altogether it remains one of the most potent MCS devices to date.

1.2.4 ECPELLA

ECPELLA is a portmanteau of the words “ECMO” and “Impella”. This refers to the hybrid approach of combining both MCS systems to annihilate potential drawbacks. As earlier mentioned, the use of VA-ECMO alone tends to increase LV afterload, thereby increasing the cardiac workload. To counteract this right shift of the pressure-volume loop, a combined use of Impella® and ECMO leads to the synergistic effects of a remarkable hemodynamic stability, achieved by combination of the strong circulatory support of ECMO with the LV unloading capabilities of Impella®, leading to a significant reduction in myocardial oxygen demand, and improved end organ perfusion.

Challenges of this approach are the increased complexity of operating two different systems in one patient at the same time, requiring a high level of expertise in device management, as well as a potential higher risk of device related complications such as hemolysis, bleeding, and vascular complications, which are associated with both devices (90).

Examining the efficacy of ECPELLA in patients with CS, Schrage *et al*. compared the outcomes of 255 patients treated with VA-ECMO and 255 patients with ECPELLA, revealing a significant improvement in 30-day mortality rates in the ECPELLA group in comparison to the VA-ECMO group (HR 0.79, 95% CI 0.63–0.98, p=0.03) (91). Although there was a reduction in short-term mortality, individuals undergoing ECPELLA therapy were found to have a significantly elevated risk of bleeding (risk ratio [RR] 1.45, 95% CI 1.20–1.75), limb ischemia (RR 1.43, 95% CI 1.17–1.75), hemolysis (RR 1.71, 95% CI 1.41–2.07), and requirement for RRT (RR 1.54, 95% CI 1.19–1.99) in comparison to the patients only treated with VA-ECMO (90).

1.2.5 TandemHeart®

TandemHeart® is a “left atrial-to-femoral bypass system” used in the treatment of CS and high-risk percutaneous coronary intervention (HR-PCI), which consists of a centrifugal pump that withdraws oxygenated blood from the left atrium via a 21F inflow cannula (92). Its pump lies outside the body and feeds the blood to the femoral artery via a 17F or 19F arterial cannula, providing a 4L/min flow during a timeframe of maximum 14 days (92,93). It efficiently unloads the LV by bypassing it and increases CO and cardiac power, thereby accomplishing high quality percutaneous support and a decreased myocardial oxygen consumption. Compared to the IABP, TandemHeart provides better hemodynamics in patients

with CS but lacks a significant survival benefit (94,95). Pump speed, flow rates and pressures can be accessed and adjusted in real time with a control console.

Limitations of the TandemHeart® LV assist device are the required transseptal puncture, which is needed for inflow cannula placement. This is connected to higher rates of complications such as acquired atrial septal defect or cardiac tamponade and the need for intracardiac or transesophageal echocardiography, which itself bears its own risks for complications, as well as a higher risk for limb ischemia, hemolysis, and infection (96).

1.2.6 Impella® MCS devices

The Impella® (Abiomed®, Inc., Danvers, Massachusetts) micro-axial flow pump is a percutaneous left ventricular assist device (pLVAD) and one of the most innovative technologies used to provide MCS for CS or elected for HR-PCI, providing crucial hemodynamic support, and allowing for myocardial recovery and stabilization of the condition. Its indication is to maintain hemodynamic stability during complex procedures. This device is a true alternative to many traditional forms of circulatory support. Impella® was introduced to the market in 2003 and is now available in various versions, some of which are the Impella 2.5®, Impella CP®, Impella 5.5® and the Impella RP®. The different specifications of the devices are listed in **Table 4** (97).

1.2.6.1 Mechanism of action

The use of an Impella pump to support the LV leads to several positive physiological effects. These devices decrease both end-diastolic volume (EDV) and end-diastolic pressure (EDP) in the left ventricle, thereby decreasing cardiac workload, resulting in a reduced oxygen consumption (98). MAP is increased at the same time, enhancing blood flow to the coronary vessels. Hence, in addition to hemodynamic stabilization the use of the Impella® pump is thought to provide myocardial protection, by reducing the heart's oxygen requirements while simultaneously improving its oxygen supply (99).

The Impella CP® device, which was also used in our study, is percutaneously inserted, most commonly by a transfemoral approach. It is guided through the aortic valve, reaching inside the LV, where it withdraws the blood through an inlet cage and pumps it directly into the ascending aorta with its motor driven impeller, thereby effectively unloading the LV and increasing CO (100). The flow rates of these devices in general ranges from 2.5-5.5 l/min with a maximum impeller speed of 51.000 revolutions per minute (RPM), depending on the pump

diameter and specifications (101). The RPM can be adjusted to meet the needed flow rate, which allows tailoring cardiac support to the patient's hemodynamic needs, with an increased RPM being beneficial in patients suffering from severe left ventricular dysfunction needing a higher CO to sufficiently perfuse the coronary vessels (102,103). RPM must be chosen correctly in order to balance an effective cardiac support with the safety of the patient, in e.g., avoiding excessive speeds that might lead to complications like hemolysis. The technical specifications of different Impella® devices are shown in **Table 4** (97).

Table 4: Technical specifications of Impella devices.

Impella device	**2.5**	**CP**	**5.0**	**LD**	**5.5**	**RP**
Indication	HRPCI and CS	HRPCI and CS	CS	CS	CS	RHF or decompensation
Introducer diameter	13 Fr	14 Fr	23 Fr	--	23 Fr	23 Fr
Pump motor Access	12 Fr Percutaneous femoral or axillary	14 Fr Percutaneous femoral or axillary	21 Fr Femoral cutdown or axillary	21 Fr Direct insertion into AA	19 Fr Axillary cutdown or direct insertion into AA	22 Fr Percutaneous femoral vein (to PA)
Maximum average flow (l/min)	2.5	3.7	5.0	5.3	5.5	4.4
Maximum duration of support	HRPCI: ≤6 hours, CS: ≤4 days	HRPCI: ≤6 hours, CS: ≤4 days	14 days	14 days	14 days	14 days
SmartAssist?	No	Yes	No	No	Yes	No

AA = ascending aorta; CS = cardiogenic shock; HRPCI = high-risk percutaneous coronary intervention; PA = pulmonary artery; RHF = right heart failure.

SOURCE: Zein R, Patel C, Mercado-Alamo A, Schreiber T, Kaki A. A Review of the Impella Devices. Interv Cardiol. 2022;17:5.

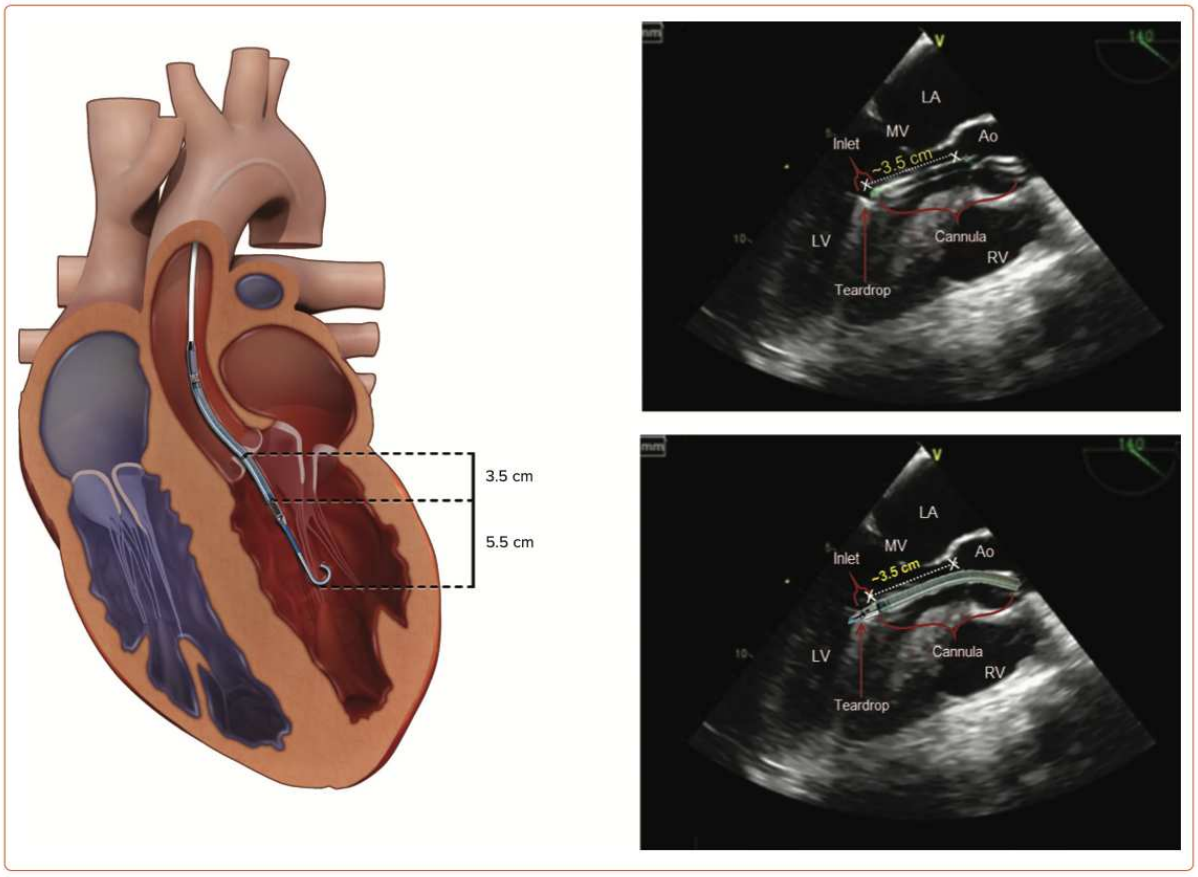
1.2.6.2 Impella® Controls

In contrast to some of the other devices the Impella® is dependent rather on loads and pressure than rate and rhythm. The device is controlled with the „Automated Impella Controller™ "(AIC) (97). The CP and 5.0 models feature the Impella SmartAssist® technology, allowing for close monitoring of pump settings and giving insight into device positioning. With these devices aortic pressure can be measured *via* sensors on the output opening of the device as well as the pressure gradients of the inlet (LV) and outlet (the ascending aorta) of the Impella® device by utilizing pump speed. Other data provided to the AIC include LV pressure

EDP, CO, and cardiac power output (CPO). This monitoring is critical for ensuring that the device operates within the safe and effective range specific to each patient's condition. During a procedure or throughout the treatment period, adjustments to the RPM may be necessary based on the patient's response and changing condition (97).

1.2.6.3 Access and positioning of the Impella® device

The Impella 2.5® and Impella CP® are typically percutaneously placed through the femoral artery using 13 Fr or 14 Fr sheaths depending on the device. Placement is done with a so-called retrograde approach. The catheter is advanced inside the blood vessel until it reaches the ascending aorta, then through the aortic valve into the left ventricle, guided by fluoroscopic or echocardiographic imaging. Depending on the patient’s anatomy an axillary access might be more beneficial. For larger catheter size, being the case in the Impella 5.0® and Impella 5.5® devices, a surgical cutdown of the accessed artery is necessary. In RV support, Impella RP® is inserted through the femoral vein, and its pump housing is placed into the vena cava with the catheter tip extending through the tricuspid and pulmonary valve into the pulmonary artery (97). The positioning of the device can be controlled with transthoracic echocardiography as seen in **Figure 8** (97).



Correct positioning of the Impella CP, Impella 2.5 and Impella 5.0 across the aortic valve and into the left ventricle. The radiopaque marker should be positioned across the aortic valve annulus, allowing an approximate distance of 3.5 cm from the aortic valve annulus to mid-inlet for the Impella CP, 2.5 and 5.0 devices (left). The device extends a further 5.5 cm from mid-inlet to the tip of the pigtail catheter. On transthoracic echocardiography (TTE), two echogenic double lines of the cannula indicate either end of the Impella inlet. Reverberation artefacts on TTE posterior to the cannula may also assist in identification of the inlet. Correct placement of the Impella 5.5 catheter is 5.5 cm from the aortic valve annulus to mid-inlet of the inflow cage. This is deeper due to the lack of pigtail on the Impella 5.5 catheter. Ao = aorta: LV = left ventricule: MV = mitral valve: RV = right ventricle.

Figure 8. Positioning of the Impella® device.

SOURCE: Zein R, Patel C, Mercado-Alamo A, Schreiber T, Kaki A. A Review of the Impella Devices. Interv Cardiol. 2022;17:5.

1.2.6.4 The use of Impella® devices in the setting of CS

CS is the most severe complication of AMI, with immediate revascularization and inotropes being key to myocardial salvage (5). When inotropic agents are not sufficient in increasing CO during treatment, MCS can help improve hemodynamic parameters such as CI, CO, and MAP (35,97). Although there are different opinions about optimal timing for the initiation of MCS support in CS patients needing PCI, a meta-analysis by Flaherty *et al.* suggests that Impella® implantation before undergoing PCI leads to higher survival rates, in the context of better coronary artery perfusion and LV unloading, enhancing myocardial protection and hemodynamic stabilization, as mentioned earlier (99,104). After the initiation of Impella® pump support, three key points must be evaluated: the Impella® pump catheter must be placed correctly; possible bleeding at the insertion site has to be excluded; end organ function and pulmonary congestion have to be monitored (105). The target range for MAP is aimed to be between 70 and 90 mmHg (105). When inserting the Impella® device, it is advised that activated clotting time (ACT) be above 250 seconds. The systemic anticoagulation is then adjusted to ensure an ACT of between 160 and 180 seconds and an activated partial thromboplastin time (APTT) of between 50 and 70 seconds as soon as hemostasis at the insertion site is assured. ACT values of over 200 s should be avoided in order to prevent severe bleeding (105,106). The positioning of the device should be checked by echocardiography. A suction alarm can be set off due to the catheter coming into contact with the left ventricular wall and thereby increasing the pump's inflow resistance. Pulmonary artery pulsatility index (PAPi) can be helpful in evaluating whether the alarm was set off by right-sided heart failure or volume insufficiency (107).

1.2.6.5 Weaning of the Impella® device

For weaning off the Impella® device, it is important that the patient's hemodynamics is stable, and only require a minimal amount of pharmacological inotropic support (107). Echocardiographic supervision during short periods of weaning is useful to assess whether myocardial function is sufficient, while the device's output is gradually decreased over a period of 4 to 6 hours until it reaches a level of about 1 to 1.5 liters per minute. After hemodynamic stability is achieved, the device can be withdrawn into the descending aorta where it is checked for the next 30 minutes while the administration of systemic anticoagulation is ceased. After the device is turned off and removed, hemostasis at the insertion site is achieved using a suture-based closure device or collagen-based vascular closure device (107).

1.2.6.6 Clinical data associated with the use of Impella®

The growing utilization of the different Impella® devices in the scenario of CS and HR-PCI and their scientific refinements in different settings of care is a significant step in the development of MCS devices, offering a new approach to a patient group with a high rate of morbidities and mortality.

Different clinical outcomes connected with the use of Impella®, particularly regarding CS and HR-PCI, have been studied to some extent. Yet, a universal approach has not been found underlining the need for further research in this field of medicine. In the following section, some of the most current findings will be broached.

In a comprehensive meta-analysis published in 2022 incorporating data from over 5204 patients and 33 studies, Panuccio *et al.* showed a short-term mortality rate of 47% among those treated with Impella® device (108). Secondary endpoints were vascular access complications, which appeared in 6.4% of cases, and major bleeding appearing in 16.4% of cases. The meta-analysis of a subgroup of studies in which IABP and Impella® were compared, indicated that the use of Impella® was connected to significantly higher rates of bleeding and vascular complications, while short term mortality was comparable (108).

The comparison of Impella CP® with IABP in patients with CS has been the subject of a randomized, prospective, multicenter trial involving 48 patients with the need for mechanical ventilation and severe AMICS conducted by Ouweneel DM *et al.* where no significant difference in 30-day mortality between the two groups was found, with mortality rates being 46% for Impella CP® and 50% for IABP (HR: 0.96; 95% CI: 0.42 to 2.18; p = 0.92) (109). It was stated that both devices can provide essential hemodynamic support, but the choice of the device mostly depends on the specific clinical context such as the “selection based on age, ROSC times, and pre-procedural traumatic injuries” (109). In this study the use of Impella® was connected with increased vascular complications and major bleeding events, which might be linked to the administration of the standard dual antiplatelet therapy and heparin prior to PCI (109).

In a European expert user group review Burzotta *et al.* summarized a stepwise approach to the clinical application of Impella® for the use as ventricular support by critically comparing different experiences with the device (106).

In their randomized controlled trial including 15 patients, Bochaton *et al.* found that the Impella 5.0® pump for mechanical circulatory support in severe CS already managed by IABP

and inotropes did not provide additional hemodynamic support and cardiac function recovery, highlighting that the additional use of the device might be harmful (100).

In a study including 276 men and 82 women (a total of 358 patients) Shah *et al.* outlined the differences in sex regarding presentation, treatment, and outcome in patients with AMI-CS undergoing treatment with pLVADs, especially through Impella devices, with evidence pointing towards slightly improved support and potential impacts on survival and recovery rates in women (111).

In a review and meta-analysis of 17 observational studies including 3933 patients, Iannaccone *et al.* concluded the safety and efficacy of the Impella® devices in providing circulatory support during complex and high-risk cardiac procedures, stating that, based on a meta-regression analysis that the use of Impella CP®) and Impella 5.0® in treatment of CS mainly due to ACS was associated with higher survival rates than the Impella 2.5®. Additionally, patients with CS not complicated by cardiac arrest who received Impella® initiation prior to PCI, showed a lower mortality ($p < 0.001$) (112). Generally, the use of Impella CP® and Impella 2.5® was connected to fewer complications, which were mainly due to comorbidities and advanced age, with a vascular complication rate of the Impella 5.0® being 7.4% (95% CI 5.6–9.6%) and major bleeding rate being 15.2% (95% CI 10.7–21%) (112).

A systematic literature review and meta-analysis collecting data from a total of 2827 patients conducted by Hill *et al.* found promising survival outcomes in patients with CS and in patients undergoing elective high-risk PCI (40.5% and 59.5% respectively) (113).

The “DanGer Shock study”, officially known as "Danish-German cardiogenic shock trial", is a clinical trial that investigates the “efficacy and safety of mechanical circulatory support in patients with cardiogenic shock” (114). The primary objective of the study is to compare the outcomes of patients treated with an Impella® device versus those receiving standard medical therapy alone. The study indicated that the utilization of Impella® resulted in improved hemodynamic parameters compared to standard therapy. Long-term survival rates were significantly higher in the Impella® group compared to those receiving standard therapy. The primary endpoint of all-cause mortality at 6 months for Impella CP + standard care vs. standard care alone was: 45.8% vs. 58.5% (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.55-0.99, $p = 0.04$). Overall, the DanGer Shock study suggests that the Impella® device is an effective intervention for improving survival and clinical outcomes in patients presenting with CS (114).

1.3. High Risk PCI

HR-PCI is a cornerstone in the field of contemporary interventional cardiology and an important therapeutic procedure for patients with severe acute or chronic CAD (65). These patients are often in a critical situation suffering from poor LV function with HR-PCI being their last resort. Due to the complex nature of HR-PCI it is necessary to consider various factors, such as hemodynamic status, LV ejection fraction, clinical features, comorbidities and the complexity of coronary anatomy and lesions prior to the treatment (65). PCI is a minimally invasive catheter-based procedure also known as coronary angioplasty, which allows the reopening of significantly stenosed or occluded coronary artery segments, resulting in a restored myocardial perfusion after episodes of ischemia.

Typical percutaneous access points for catheterization are the femoral or radial artery (115). After being placed and coronary angiography is performed to visualize the extent of the disease, a guide wire is advanced through the catheter and passed through the affected part of the vessel. A catheter of smaller diameter with a balloon tip is then placed, using the guide wire for proper positioning. The inflation of the balloon tip re-opens the stenosed segment of the coronary artery. At the same time, stent placement is possible, and is usually performed. The stent consists of a flexible metal mesh that holds the lumen of the vessel open, and is left in place, to prevent the vessel from re-stenosing. The achieved blood flow is usually documented with coronary angiography. After the procedure, both catheters and the guide wire are removed.

Advancements in percutaneous mechanical circulatory support (pMCS), potentially provided by Impella, have significantly improved the success and safety of HR-PCI. Careful selection of patients by a professional in this field, considering the risk-benefit ratio, is essential to achieve good results (115).

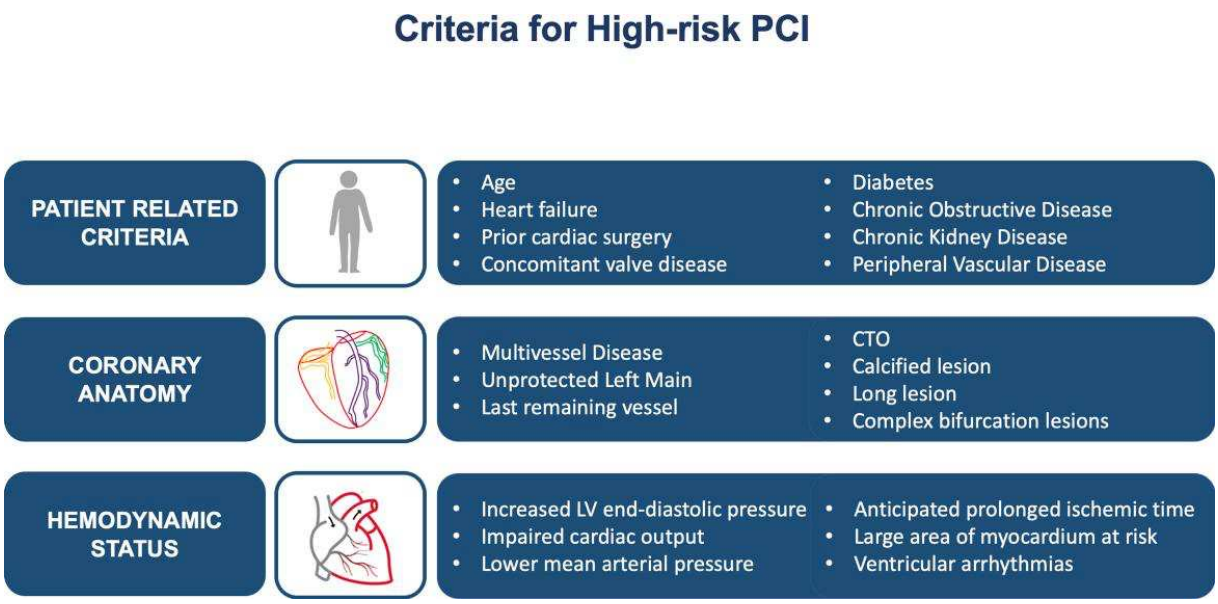


Figure 9. Criteria for high-risk percutaneous coronary intervention patients.
CT = chronic total occlusion; PCI = Percutaneous coronary intervention
SOURCE: Leick J, Werner N, Mangner N, Panoulas V, Aurigemma C. Optimized patient selection in high-risk protected percutaneous coronary intervention. Eur Heart J Suppl. 2022;24:4-10.

A variety of criteria must be assessed, to determine which patients are suitable for HR-PCI which are shown in **Figure 9** (65,115-117). Given the diversity of these parameters, patients elected for HR-PCI represent a highly vulnerable group, in which the correct use of mechanical support has yet to be researched (115,116).

There is no generally recognized definition of when PCI is connected to higher risk, but rather various different scores suggested by different guidelines, to assess interventional mortality risk for coronary artery disease (CAD) (65,118,119).

These scores are mostly composed of a combination of factors, including hemodynamic status, LVEF, and the nature of coronary anatomy (65,118,119). Additional parameters such as left ventricular end-diastolic volume (LVEDV) and pressure (LVEDP) can be utilized for the assessment of the patient's risk. Assessed by "the British Cardiovascular Intervention Society myocardial jeopardy score" (BCIS-JS) the presence of a significant quantity of "jeopardized myocardium" also influences the decision-making process for HR-PCI (120). Generally, PCI can be considered as being "high-risk" when serious underlying conditions are present, especially underlying CAD.

As mentioned in the sections before, the Impella® system has many beneficial effects on the myocardium when used during PCI. Even though the PROTECT-II randomized clinical trial, illustrating the use of MCS devices in patients undergoing high risk PCI, did not meet its primary endpoint, a significant reduction in adverse events was observed when using the Impella® device (121). Today, the use of pVLAD is only recommended for patients with CS, however the ability of Impella to prevent hypotension and a low CO is of great use in elective PCI (116,122,123).

Since CS and HR-PCI are both connected to hemodynamic instability, increasing the already high risk of mortality in these settings, assist devices used to create hemodynamic stability, could be a great advantage in the care and treatment of these patients. This MD thesis aims to explore a retrospective cohort of patients with CS or undergoing HRPCI, treated with the use of the Impella® device as MCS at the university Hospital of Split. In the context of the fatal nature of CS and the complexity of HR-PCI itself, the use of the Impella® device has been a central part in the management of our patients. As this special pLVAD was recently introduced at the University Hospital of Split, it is of our interest to collect and evaluate our initial clinical experiences with the Impella® device with the aim of this thesis to provide information about the effectiveness and safety of Impella® used in the setting of CS and HR-PCI.

2. OBJECTIVES

The main goal of the present study was to examine and describe initial clinical experiences with the use of the Impella CP® device used in the setting of CS and HR-PCI.

The specific goals of the present study were the following:

a) To identify the baseline characteristics and comorbidities of patients treated with the Impella CP® device.
b) To evaluate laboratory markers including hemoglobin, platelet count, creatinine levels, estimated glomerular filtration rate (eGFR), hs-troponin T, N-terminal pro brain natriuretic peptide (NT-proBNP), LDH, CRP, D-dimer, pH and lactate levels.
c) To describe the basic echocardiographic features of the patients.
d) To assess the effectiveness of mechanical circulatory support (MCS) using the Impella CP® device.
e) To evaluate the safety and feasibility of the Impella CP® device in these patients, particularly regarding bleeding complications and procedure-related mortality.

3. MATERIALS AND METHODS

3.1. Study design

The design of this study was that of a retrospective analysis (cross-sectional study). Procedural data and electronic medical records of patients treated for AMI complicated by CS or with the indication for elective HR-PCI with the support of the Impella CP® device at the Department for Cardiovascular Diseases, University Hospital of Split during the period from October 2022 to April 2024 were analyzed. Only patients undergoing treatment with the use of Impella CP® MCS were included in this study. All patients included in this study had the clinical indication for PCI with Impella® support in accordance with the current ESC guidelines and the ESC/EAPCI approaches for the management and diagnosis of AMI-CS as well as elective treatment of chronic coronary artery disease (31,124). The treatment of all participants of the current study was according to the current health care standards appropriate for their underlying condition. The data used in this study was anonymized in context of collection, analysis, and storage. This study was approved by the Ethics Committee of the University Hospital of Split (filed under No. 2181-147/01-06/LJ.Z.-24-02) and was performed in accordance with the declaration of Helsinki.

3.2. Data collection

The data of enrolled patients were primarily gathered using the electronic "Integrated Hospital Information System" (*IBIS – Integrirani Bolnički Informacijski Sustav*) by the IN2 group d.o.o. Data connected to the procedure were verified and evaluated against measurement data given by the manufacturer's representative. All patients undergoing treatment with the support of the Impella CP® device were examined.

3.3. Variables of interest

Variables of interest consisted of basic information regarding the patients included in the study. These are general health characteristics and habits suspected to be related to the outcome of the procedures. These variables included: sex, age in years, underlying clinical conditions and comorbidities (arterial hypertension, dyslipidemia, diabetes mellitus, smoking, atrial fibrillation, chronic kidney disease, chronic coronary syndrome, peripheral artery disease, chronic obstructive pulmonary disease, cerebrovascular insult). Laboratory parameters included in the study were provided by the hospital's central laboratory and included: hemoglobin (g/L), thrombocytes, creatinine, estimated glomerular filtration rate (eGFR,

mL/min./1,73 m^2), troponin T (ng/L), N-terminal pro brain natriuretic peptide (NT-proBNP, pg/mL), lactates (mmol/L).

Additionally, CS and HR-PCI-related variables were collected with special attention to whether the nature of the underlying indication for PCI with Impella® support was AMI CS or treatment of chronic coronary disease. These variables included cardiac arrest on admission, STEMI or NSTEMI as part of acute coronary syndrome, underlying multi-vessel disease, left-main disease, and chronic total occlusion (CTO) as well as underlying calcifying coronary disease. Hemodynamic parameters were registered on admission and included systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg) and the need for vasopressors as well as mechanical ventilation as a part of life support during the course of hospital stay. For each patient transthoracic echocardiographic parameters were measured assessing left ventricular ejection fraction (LVEF, %) and tricuspid annular plane of systolic excursion (TAPSE, mm). Variables connected to the severity of condition such as the need for mechanical ventilation or hemodialysis and the use of ECMO were included. Variables correlating to coronary angiography findings included the presence of multivessel disease, left main disease, CTO and calcifying coronary disease. Parameters of PCI were registered consisting of the treated vessels, with variables being PCI left main (LM), PCI left anterior descending artery (LAD), PCI left circumflex artery (Cx), PCI right coronary artery (RCA), as well as PCI on the last remaining vessel and the number of implanted stents. Variables of interest connected to the use of the Impella® device included time on Impella® support (hours) and procedure related complications including critical limb ischemia, bleeding complications, and vascular complications. The use of rotational atherectomy, intra-vascular ultrasound (IVUS), optical coherence tomography (OCT) and fractional flow reserve (FFR) was noted. Additional outcomes of interest were in-hospital death due to any cause, as well as the length of stay in days.

3.4. Statistical analysis

The statistical analysis was performed by the SPSS Statistics version 23 (IBM, Armonk, NY, USA). Due to a relatively small sample size, no inferential statistical analyses were performed. Standard descriptive methods were used with outcome measures reported as frequency (percentage, %), mean (± standard deviation, SD) or median (interquartile range, IQR).

4. RESULTS

4.1. Baseline characteristics and laboratory parameters of the patients treated with the Impella device

4.1.1 Baseline characteristics of the patients treated with the Impella device

A total of 16 patients were observed in this analysis. It was composed of two groups, categorized based on the indication for MCS with the Impella CP® device. These groups consisted of patients presenting with CS (N=6) and patients elected for complex HR-PCI (N=10) (**Figure 10)**. The mean age of the participants included in this analysis was 64±8.8 years as seen in **Figure 11** with the mean age in the complex HR-PCI being slightly higher than in the CS group (65.7±8.4 and 62.1±10.2 respectively). Approximately 70% percent of patients treated with Impella were male, with 11 male patients (68.8%) and 5 female patients (31,3%) in total (**Figure 12**). The gender distribution was similar throughout both groups.

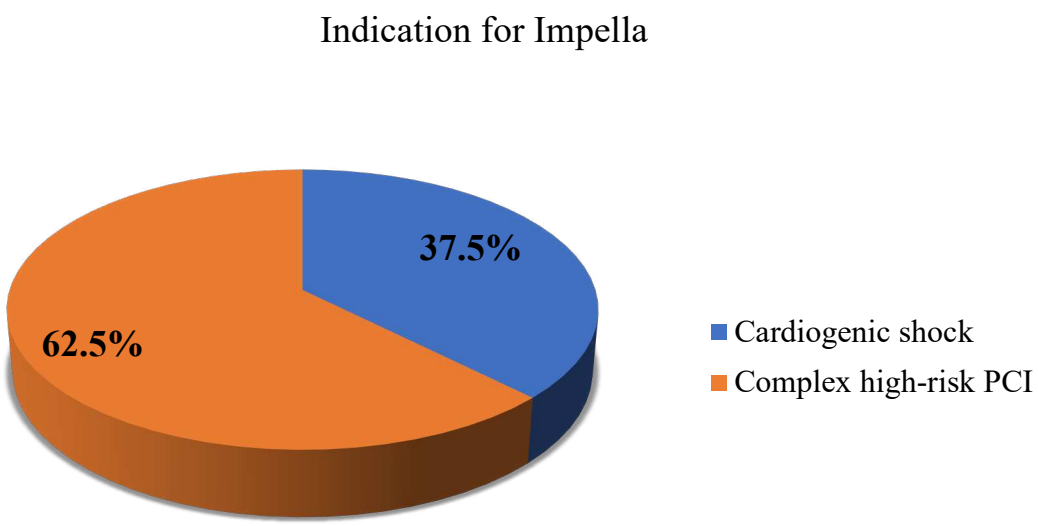


Figure 10. Ratio of patients between the groups CS and HR-PCI.

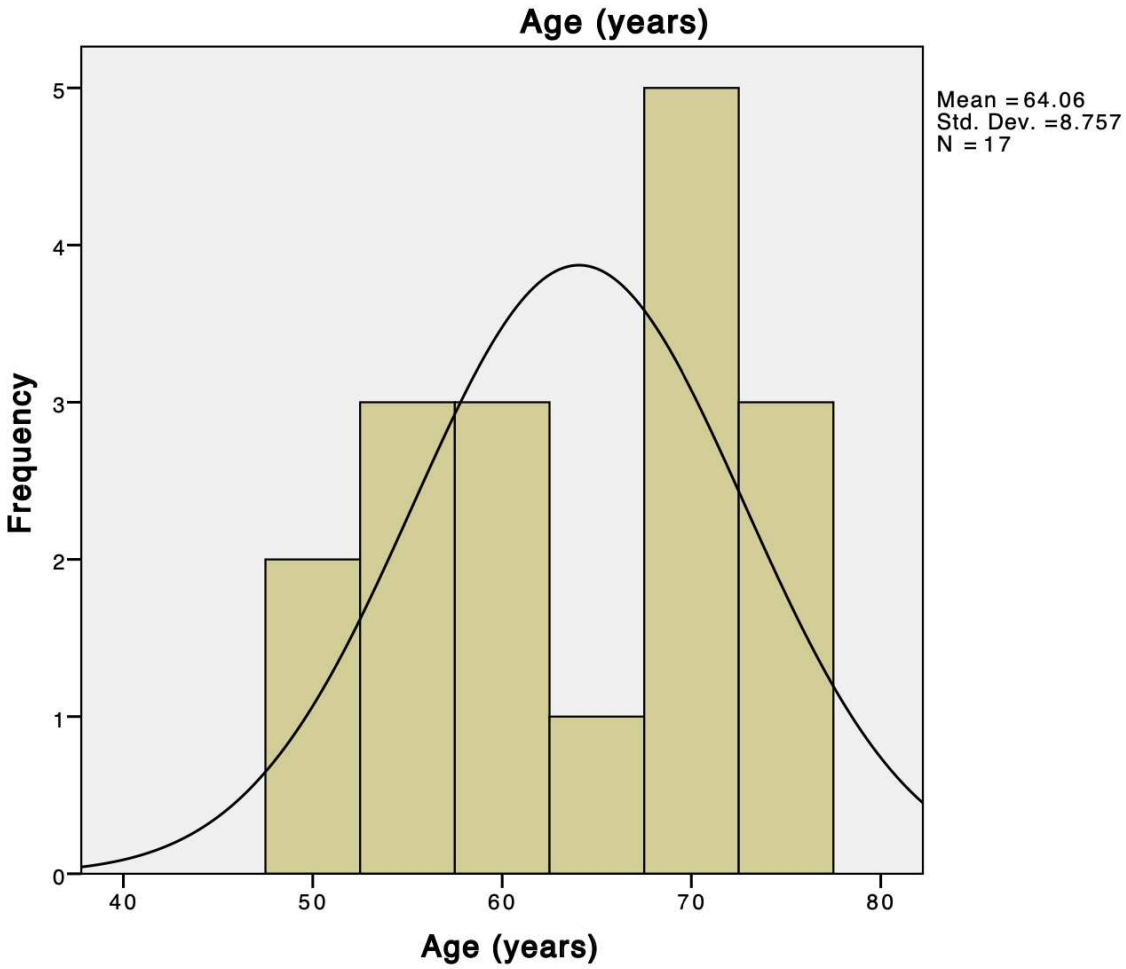


Figure 11. Age distribution of patients enrolled in the study.

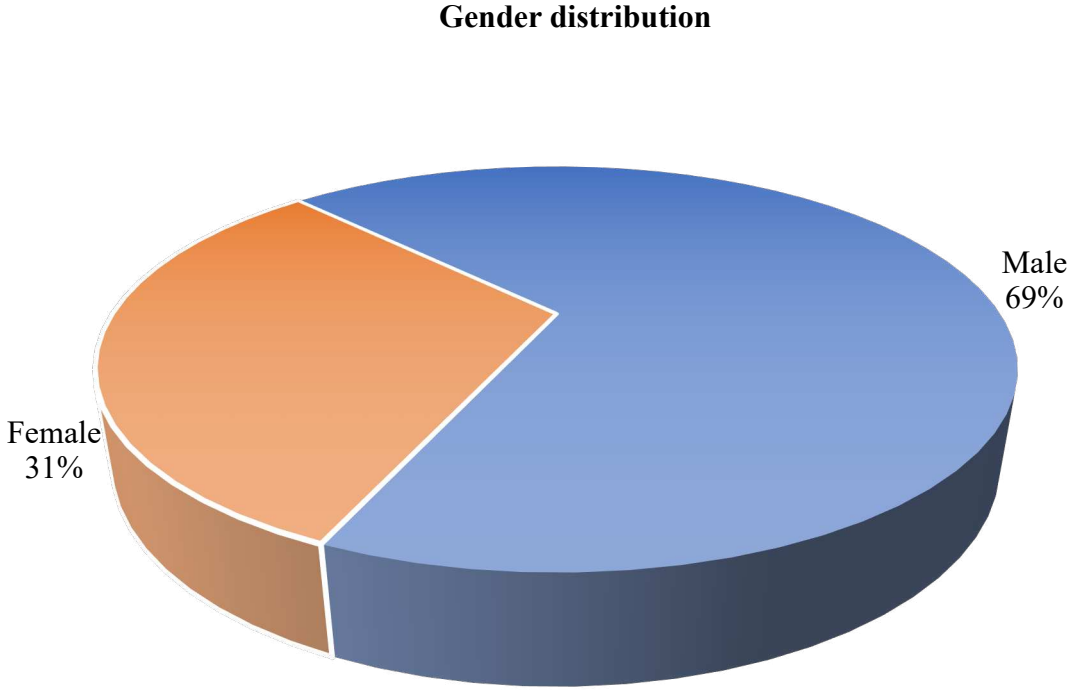


Figure 12. Gender distribution of patients enrolled in the study.

The majority of patients had previously diagnosed arterial hypertension with a higher prevalence in the complex high-risk PCI group (N=8, 80%,) compared to the CS group (N=4, 66.7%,). Over two thirds of patients with the indication of complex HR-PCI had a history of diabetes mellitus (N=7, 70%,), whereas the disease was only being present in 1/3 of patients in, the CS group (N=2, 33.3%). Dyslipidemia was previously diagnosed in almost all patients (N=15, 93.8%). Smoking was more prevalent in the complex HR-PCI group with 50% of patients having a history of smoking. 1/3 of patients in the CS group (N=2, 33.3%) presented with cardiac arrest at admission. STEMI was significantly more common in the CS group with ECG readings showing STEMI in over 80% of CS patients (N=5, 83.3%) compared to 10% (N=1, 10%) of complex HR-PCI patients. NSTEMI was present in over half of the participants in the complex HR-PCI group (N=6, 60%) but rare in the CS group (N=1, 16.7%). Chronic coronary syndrome was seen in 30% of patients in the HR-PCI group (**Figure 13**). Baseline characteristics of the enrolled patients are presented in **Table 5.**

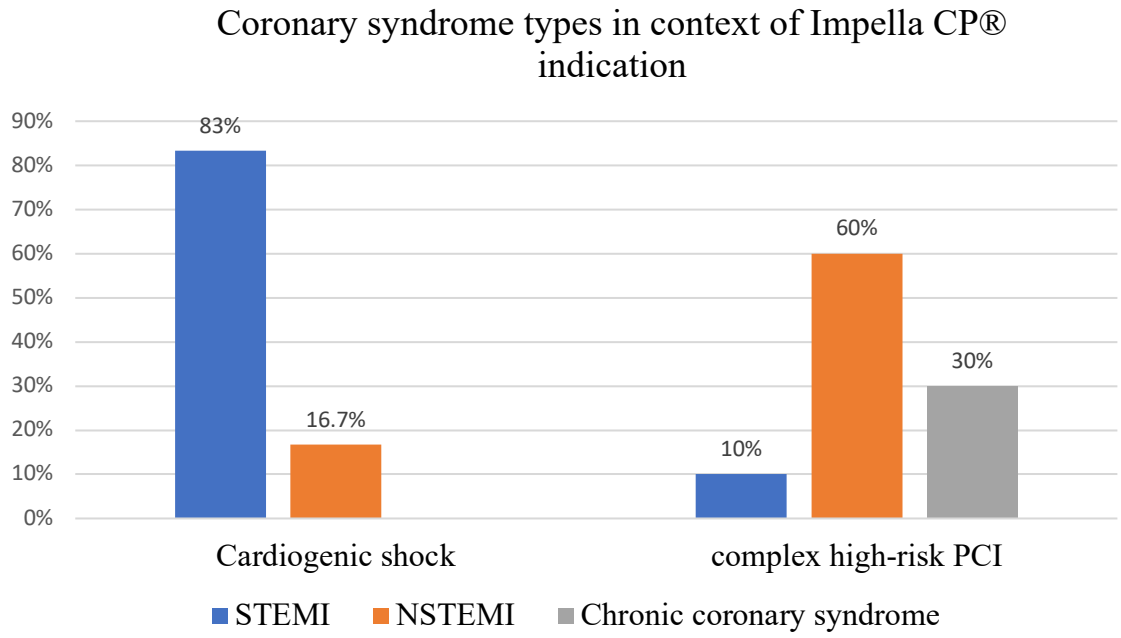


Figure 13. Coronary syndrome types in context of Impella CP® insertion indication.

NSTEMI = non-ST-elevation myocardial infarction; PCI = Percutaneous coronary intervention

STEMI = ST-elevation myocardial infarction

Table 5. Baseline characteristics of patients treated with Impella CP® device with indications of CS and those undergoing complex high-risk PCI.

Clinical characteristics	Total (N=16)	Cardiogenic shock (N=6)	Complex high-risk PCI (N=10)
Arterial hypertension	12 (75%)	4 (66.7%)	8 (80.0%)
Diabetes mellitus	9 (56.3%)	2 (33.3%)	7 (70%)
Dyslipidemia	15 (93.8%)	6 (100%)	9 (90%)
Smoking	6 (37.5%)	1 (16.7%)	5 (50%)
Atrial fibrillation	8 (50%)	3 (50%)	5 (50%)
Chronic kidney disease	3 (18.8%)	1 (16.7%)	2 (20%)
Previous MI	1 (6.3%)	0 (0%)	1 (10%)
Previous stroke	1 (6.3%)	1 (16.7%)	0 (0%)
COPD	1 (6.3%)	0 (0%)	1 (10%)
Peripheral artery disease	1 (6.3%)	1 (0%)	1 (10%)
Cardiac arrest at admission	2 (12.5%)	2 (33.3%)	0 (0%)
LVEDd (mm)	57.4±8.1	57.8±8.8	57±8.1
Left ventricular ejection fraction (%)	29.3±12.4	28.2±9.3	29.9±14.4
TAPSE (mm)	17.4±3	19.7±2.3	16±4.1

COPD = Chronic Obstructive Pulmonary Disease; LVEDd = Left Ventricular End-Diastolic Dimension; MI = Myocardial Infarctiom; N = Number; PCI = Percutaneous Coronary Intervention; TAPSE = Tricuspid Annular Plane Systolic Excursion.

4.1.2. Laboratory parameters of the patients treated with the Impella CP® device

Laboratory diagnostic values of the patient groups "CS" and "complex HR-PCI" are shown in **Table 6.** MAP, as well as the estimated glomerular filtration rate (eGFR), were lower in the shock group, calculated as 69.5±12.2 mmHg vs. 97.1±19.4 mmHg (CS vs. complex HR-PCI) and 44.3±13.3 mL/min./1.73 m^2 vs. 64.1±24.7 mL/min./1.73 m^2 (CS vs. complex HR-PCI). Peak hs-Troponin was significantly higher in the CS group measuring 22903.7±20571.4 ng/L, although values fluctuated greatly between patients. CRP levels were elevated in the complex HR-PCI group with a mean of 10.9 mg/L in the HR-PCI group compared to a mean of 2.2 mg/L in the CS group. Lactate levels were elevated in the CS group with 4.6±5.1 mmol/L, while lactate levels in the complex HR-PCI group were mostly normal. LDH levels were high in both groups, with 342.8±219.8 U/L in the CS group and 226.4±65.3 U/L in the complex HR-PCI group. Arterial oxygen saturation at admission varied among patients and was generally lower in the CS group with an Sp02 of 84.5±15.8%.

Table 6. Laboratory diagnostic values in patients of the groups "CS" and "complex HR-PCI"

Laboratory values	**Cardiogenic shock (N=6)**	**Complex high-risk PCI (N=10)**
Mean arterial pressure (MAP) (mmHg)	69.5±12.2	97.1±19.4
Index hospitalization systolic BP (mmHg)	112.7±35.8	131.3±26.1
Index hospitalization diastolic BP (mmHg)	60.5±19	80.4±15.8
Hemoglobin at admission (g/L)	141.2±25.7	131.2±15.4
Platelets at admission (1x109)	289±60.6	239.8±58.5
Creatinine at admission (micromoles/L)	138.8±28.7	108.4±38.7
eGFR (mL/min./1.73 m^2)	44.3±13.3	64.1±24.7
Peak hs-Troponin T (ng/L)	22903.7±20571.4	932.3±1236.9
Peak NT-proBNP (pg/mL)	4134.3±3723.3	6179.4±6650.3
CRP (mg/L)	2.2±1.4	10.9±11.6
D-dimer (mg/L)	5 ±3.9	8.7±10.9
pH	7.4±0.2	7.3±0.2
Lactate (mmol/L)	4.6±5	1.9±0.8
LDH (U/L)	342.8±219.9	226.4±65.3
SpO2 at admission (%)	84.5±15.8	92.46±6.5

BP = Blood pressure; CRP = C-reactive protein; eGFR = estimated Glomerular Filtration Rate; hs-Troponin T = high-sensitivity Troponin T; LDH = Lactate Dehydrogenase; MAP = Mean arterial pressure; NT-proBNP = N-terminal pro b-type Natriuretic Peptide; pH = Potential of Hydrogen; SpO2 = Peripheral capillary oxygen saturation.

4.2. Angiographic characteristics of patients treated with Impella MCS

Angiographic characteristics of patients with the indication of CS and complex HR-PCI are depicted in **Table 7**. It was found that all patients (N=10, 100%) of the group "complex HR-PCI" and two thirds (N=4, 66.7) in the group "CS" had multivessel disease. The left main (LM) was affected in 1/3 (N=2, 33.3%) of patients with CS and almost 2/3 (N=6, 60%) of patients elected for complex HR-PCI. Chronic total occlusion (CTO) was equally prevalent in both groups with 50% of patients and significant coronary calcification was present in over 1/3 of the patients.

Table 7. Angiographic characteristics of patients treated with Impella CP® MCS

Angiographic characteristics	Total (N=16)	Cardiogenic shock (N=6)	Complex high-risk PCI (N=10)
Multivessel disease	14 (87.5%)	4 (66.7%)	10 (100%)
Last remaining vessel	2 (12.5%)	1 (16.7%)	1 (10%)
Left main disease (50% or more)	8 (50%)	2 (33.3%)	6 (60%)
Chronic total occlusion (CTO)	8 (50%)	3 (50%)	5 (50%)
Significant coronary calcification	6 (37.5%)	2 (33.3%)	4 (40%)

PCI = Percutaneous coronary intervention

4.3. Procedural characteristics of the patients treated with the Impella CP® device

Most of the patients presenting with CS required mechanical ventilation (N=83.3%) and the use of inotropes or vasopressors to maintain adequate blood pressure (N=83.3%). This is in contrast with the complex HR-PCI group in which neither inotropes and vasopressors nor mechanical ventilation were necessary. PCI of LM was performed in half of the patients enrolled but more often in the complex HR-PCI group with PCI LM performed in 70% (N=7) of these patients.

Half of patients in the complex HR-PCI group (N=5, 50%) and 1/3 of patients in the CS group (N=2, 33.3%) underwent PCI of the left circumflex artery (Cx). PCI of the right coronary artery (RCA) was performed in half of the patients in the complex high-risk PCI group (N=5, 50%). 3- vessel PCI was only performed in one CS patient (16.7%) but in 60% of complex HR-PCI patients (N=6).

The total mean time on Impella CP® support was significantly lower in the complex HR-PCI group (4.3±6.9 hours) and is shown in **Figure 14**. Patients in the CS group required a

mean of 33±38.2 hours of Impella CP® support. The total length of hospital stay was longer in the complex HR-PCI group with a mean stay of 14±9.1 days. CS patients had a length of hospital stay of approximately half that time (8.2±7.6 days). The difference in length of hospital stay is depicted in **Figure 15**. A drug coated balloon (DCB) was used in 3 patients (N=3, 30%) undergoing complex HR-PCI. Procedural characteristics are depicted in **Table 8**.

Table 8. Procedural characteristics of patients treated with the Impella CP® device.

Procedural characteristics	Total (N=16)	Cardiogenic shock (N=6)	Complex high-risk PCI (N=10)
Mechanical ventilation	5 (31.3%)	5 (83.3%)	0 (0%)
ECMO use	1 (6.3%)	1 (16.7%)	0 (0%)
Use of inotropes or vasopressors	5 (31.3%)	5 (83.3%)	0 (0%)
PCI of left main (LM)	9 (56.3%)	2 (33.3%)	7 (70%)
PCI of LAD	15 (93.8%)	6 (100%)	9 (90%)
PCI of ramus intermedius	1 (6.3%)	1 (16.7%)	0 (0%)
PCI of Cx	7 (43.8%)	2 (33.3%)	5 (50%)
PCI of RCA	5 (31.3%)	0 (0%)	5 (50%)
3-vessel PCI	7 (43.8%)	1 (16.7%)	6 (60%)
Number of implanted DES (N)	1.8±1.1	0.7±0.8	2.5±1.3
Total stent length (mm)	60±36.7	39.3±19.7	72.5±43.4
Drug-coated balloon (DCB)	3 (18.8%)	0 (0%)	3 (30%)
POBA only	3 (18.8%)	3 (50%)	0 (0%)
Rotational atherectomy use	1 (6.3%)	0 (0%)	1 (10%)
Cutting balloon use	2 (12.5%)	0 (0%)	2 (20%)
Intravascular lithotripsy use	1 (6.3%)	0 (0%)	1 (10%)

Cx = Circumflex artery; DCB = Drug-coated balloon; DES = Drug-eluting stent; ECMO = Extracorporeal membrane oxygenation; LAD = Left anterior descending artery; LM = Left main artery; N = Number; PCI = Percutaneous coronary intervention; POBA = Plain old balloon angioplasty; RCA = Right coronary artery.

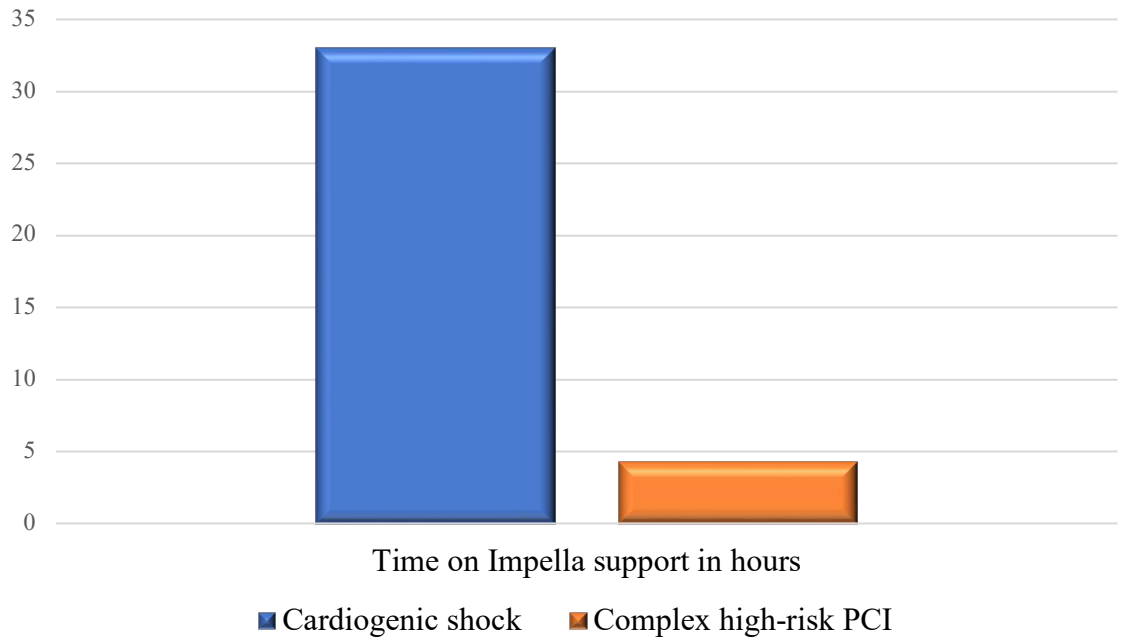


Figure 14. Mean time on Impella CP® support in the two groups.

PCI = Percutaneous coronary intervention

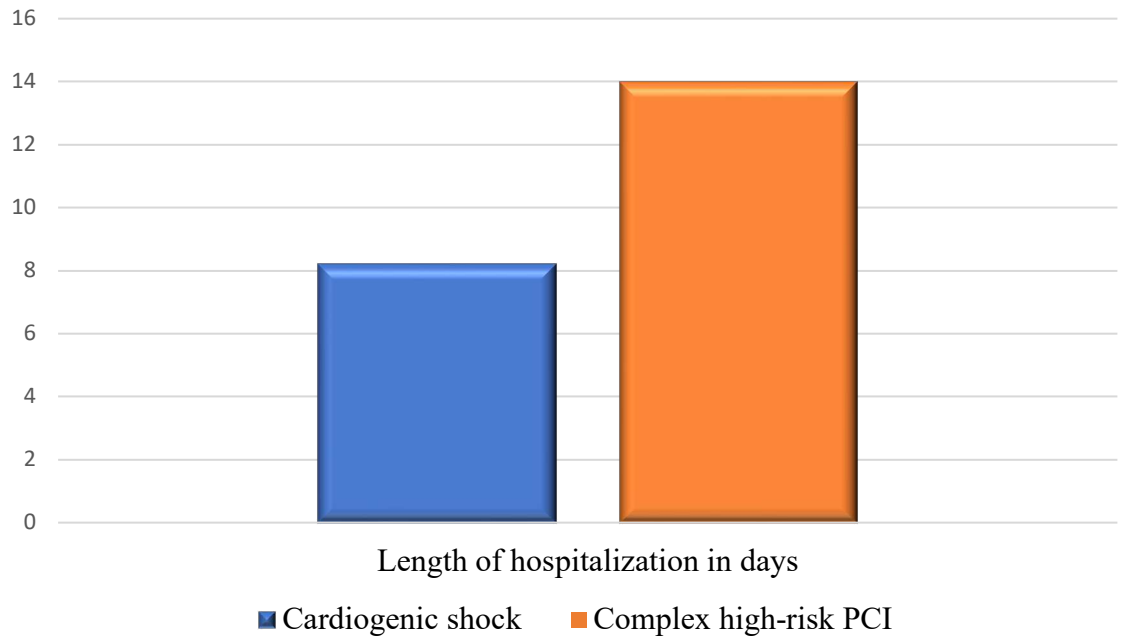


Figure 15. Mean total length of hospitalization.

PCI = Percutaneous coronary intervention

4.4. In-hospital outcomes and complications in the groups "Cardiogenic shock" and "complex high-risk PCI"

Complications in the CS group were generally more common than in the complex HR-PCI group. In the CS group complications included vascular complications in one patient (16.7%), as well as critical limb ischemia (N=1, 16.7%) and the need for RRT in 50% of patients (N=3, 50%) due to kidney failure resulting from decompensated shock. In the complex HR-PCI group complications were rare and included only one vascular complication (N=1, 10%) and one bleeding complication (N=1, 10%) both of which were due to difficulties in the closing of the catheterization site (**Table 9**). Death occurred in half of CS patients (N=3, 50%), but in none of the complex HR-PCI patients (**Figure 16**).

Table 9. Complications and in-hospital outcomes of patients treated with the Impella CP® device.

Complications and in-hospital outcomes	Total (N=16)	Cardiogenic shock (N=6)	Complex high-risk PCI (N=10)
Critical limb ischemia	1 (6.7%)	1 (16.7%)	0 (0%)
Bleeding complication	1 (6.3%)	0 (0%)	1 (10%)
Vascular complication	2 (12.5%)	1 (16.7%)	1 (10%)
Need for RRT	3 (18.8%)	3 (50%)	0 (0%)

PCI = Percutaneous coronary intervention; RRT = Renal replacement therapy

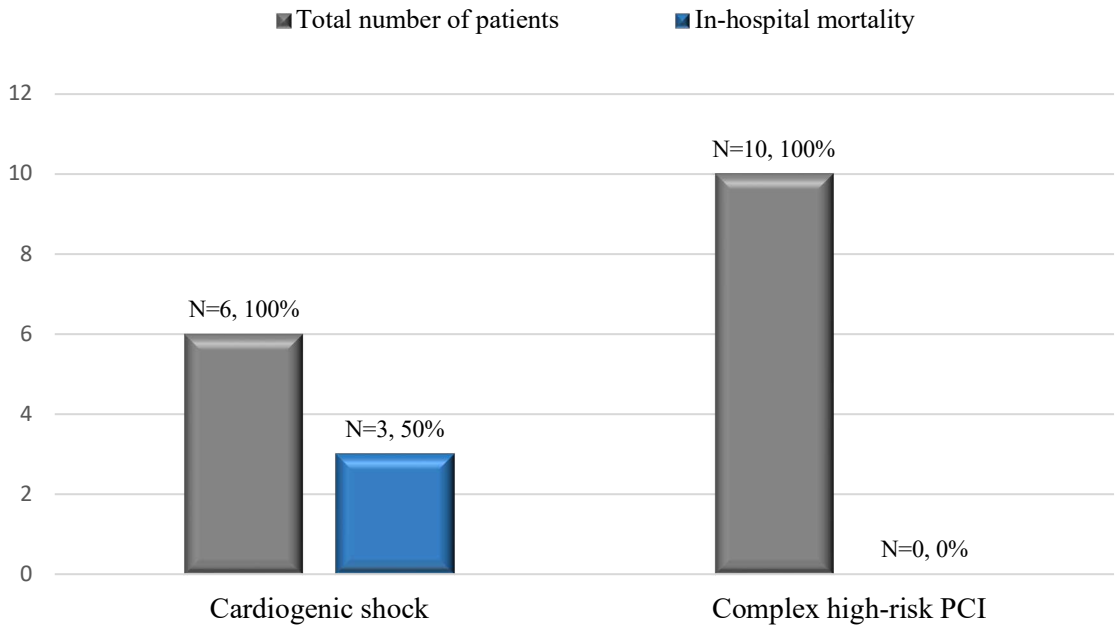


Figure 16. In-hospital mortality of patients treated with Impella CP® device.

PCI = Percutaneous coronary intervention

5. DISCUSSION

This study had the aim to collect, examine and describe our initial clinical experiences with the use of Impella CP® as hemodynamic support for patients with the indication of CS and high-risk PCI at the University Hospital of Split. In this section we will reflect our results consisting of baseline characteristics, laboratory parameters, angiographic and procedural characteristics as well as clinical in-hospital outcomes and complications and highlight the significant differences between the two groups treated with the Impella CP® device. We will compare them to recent studies in this field in context of efficacy, safety, and feasibility of this device.

In our study Impella CP® proved to be a generally safe, effective, and feasible option even when used in multimorbid patients, which is shown by the relatively low rates of complications and periprocedural mortality in our studied population, where it succeeded to improve the outcome of high-risk and emergency procedures in our study population.

Our study population was composed of 16 individuals divided into two groups, the CS group (N=6) and the complex HR-PCI group (N=10). Mean age of this cohort was 64 years, which is comparable to most other studies with the observing the use of Impella in CS and HR-PCI. A higher prevalence of male patients (68.8%) can be found in our sample. The demographic distribution, with a higher prevalence of male patients, reflects the general population trends in the incidence of conditions necessitating Impella® support. Most patients undergoing treatment had underlying pre-existing conditions, with high prevalence of arterial hypertension (N=12, 75%), dyslipidemia (N=15, 93.8%) and diabetes mellitus (N=9, 56.3%), diseases likely contributing to the formation of ACS and to the high-risk nature of patients' conditions.

One of our key findings was the significantly high prevalence of STEMI in the CS group, which accounted for 83.3% of patients (N=5, 83.3%). This stands in contrast to the complex HR-PCI group where STEMI prevalence was only 10% (N=1, 10%). The presence of STEMI directly contributes to the severity of the condition as the extent of jeopardized tissue directly influences the rate of hemodynamic deterioration necessitating pMCS. Therefore, it is not surprising that STEMI was diagnosed in higher rates in the CS group. Similar findings were reported in a multicenter registry analysis of 308 patients called the IMPELLA-PL study in Poland by Pietrasik *et al.* where a STEMI incidence of 72.7% in the CS group was found (125). In a study conducted by Shah *et al.* STEMI was documented in 72.4% of patients (111). Somewhat lower incidences of STEMI in patients with CS were reported by Chieffo *et al.* with 55% of patients presenting with STEMI CS (119).

Laboratory parameters in our two groups showed significant differences. MAP and eGFR were significantly lower in the CS group compared to the complex HR-PCI group (69.5 mmHg and 44.3 mL/min/1.73 m² in the CS group vs. 97.1 mmHg and 64.1 mL/min/1.73 m² in the complex HR-PCI group), indicating the more severe hemodynamic compromise with renal injury in patients with CS. Peak hs-Troponin levels were significantly higher in the CS group as well (22903.7 ng/L vs. 932.3 ng/L), which is consistent with the severity of myocardial injury and therefore correlates with the pathophysiological hallmark of systemic hypoperfusion, multi-organ failure and myocardial injury in CS. Similar MAP were reported by Bochaton *et al.* and Ouweneel *et al*. counting 67.7 mmHg and 66 mmHg respectively in patients with CS (100, 109).

The need for mechanical ventilation and use of vasopressors or inotropic therapy to maintain adequate blood pressure in 83.3% patients in the CS group reflects the severity of their condition and high risk of this group. In contrast neither mechanical ventilation nor inotropic therapy or vasopressors were needed in the complex HR-PCI group indicating a relatively stable hemodynamic status. Similar rates of mechanical ventilation were reported by Chieffo *et al.* with 75.7% of patients needing ventilation in the CS group and only 17.2% in the HR-PCI group (119). Even higher numbers were reported by Brandão *et al.* who stated that vasopressors or inotropes were used in all patients with CS and 91.7% needed mechanical ventilation (126). Cardiorespiratory arrest in that study occurred in 83.3% of CS patients correlating highly with the progression of the condition (126). Pietrasik *et al*. reported the use of mechanical ventilation in 80% of CS patients (125).

Mean length of hospital stay in the HR-PCI was 14 days which is likely due to the complexity of interventions and recovery process as well as the time intensity of comprehensive post-procedural care, including monitoring for complications and managing comorbid conditions.

The duration of Impella CP® support in the CS group was significantly longer than in the complex HR-PCI group (33 hours vs. 4.3 hours), reflecting the need for prolonged hemodynamic support in patients with severely altered hemodynamic status. Impella CP® devices in the HR-PCI group were inserted before the PCI in all patients and were explanted immediately after the procedure. In the CS group Impella CP® was implanted before the PCI procedure in four of the patients. In these patients, Impella CP® was implanted due to signs of CS as the initial presentation or cardiac arrest at admission. In one patient presenting with STEMI and occlusion of the LM, PCI was started first and due to the circulatory collapse and

resulting CS. Impella CP® was implanted during the same procedure which was finished with PCI-LM/LAD including placement of two drug eluting stents. Another patient had the Impella CP® device implanted after the initial PCI procedure with an indication for MCS due to the deterioration of the clinical status four days after PCI. Similar as in our findings, Pietrasik *et al.* reported a duration of Impella support of 45 hours in the CS group vs. 3 hours in the HR-PCI group (125). A duration on Impella support of 72 hours vs. 1.5 hours (CS vs. HR-PCI) was stated by Chieffo *et al.* (119). The length of hospital stay on the other hand was shorter in the CS group (8.2 days) which can partially be explained by the fact of high in- hospital mortality rate in this group.

In the CS group the incidence of complications was generally higher than in the complex HR-PCI group. We documented vascular complications in one CS patient (16.7%) who also developed critical limb ischemia, and the need for RRT which accounted for 50% of CS patients. The aforementioned patient was admitted with NSTEMI and developed CS indicating the use of Impella CP® as MCS. An occlusion of the IM was opened and a CTO of the LAD was opened with partial success. Impella CP® was installed in the same act due to signs of CS. After removal of the device ischemic changes of the left leg appeared and urgent thrombectomy was done. The patient continued to be highly febrile and initial gangrene in the left leg developed. Signs and symptoms of multi organ dysfunction and failure were monitored despite the permanent use of intravenous and vasoactive support. Unfortunately, this patient died from cardiorespiratory arrest soon after. The higher rates of need for RRT can be attributed to the severe hemodynamic impairment in CS causing acute kidney injury. Similarly, one of patients from the complex HR-PCI group was not treated with Impella CP® in the initial procedure. Hospitalization was due to chest pain which was caused by NSTEMI. Severe multivessel disease was revealed by coronary angiography and was successfully treated by PCI of the LAD and LM the following day with the support of Impella CP®. Attempts to close the right femoral access site (14F) percutaneously with Proglide and Angioseal 8F devices were unsuccessful and hemostasis was not achieved, after which the patient was treated in the department of vascular surgery. This vascular and bleeding complication was the only case in the complex HR-PCI group where complications were documented (N=1,10%), underlining the safe nature of protected complex HR-PCI.

In-hospital mortality in our CS group was high at 50% (N=3, 50%), similar to findings by other investigators. One of our female patients which was part of the CS group was initially treated for STEMI with PCI of the LAD without the MCS of Impella CP®. After placement of

one stent in an uneventful procedure, echocardiography showed a significantly reduced left ventricular ejection fraction of 30%. After initial stabilization this patient was transferred to the ward with a plan for discharge to home-care. However, four days after the procedure, the patient was re-admitted to the coronary-unit due to hemodynamically unstable ventricular tachycardia. After successful defibrillation she was endotracheally intubated and despite maximum doses of vasopressors and inotropic agents, refractory hypotension with signs of end organ damage persisted, necessitating pMCS with Impella CP® and RRT. Despite these measures, the patient's condition continued to deteriorate, ultimately leading to her death. The second fatality is the previously described case of a patient with a vascular complication. The third fatality occurred in a patient presenting with cardiac arrest at admission due to CS caused by STEMI. Impella CP® was placed as MCS and PCI Cx and LAD and POBA LM were performed unsuccessfully. After the procedure the patient was transferred to emergency CABG with central VA-ECMO. During the procedure, a massive, spontaneous bleeding evident on the endotracheal tube and then a large amount of bubbly effusion in terms of pulmonary edema were noted. A loss of circulatory volume with a subsequent drop in arterial blood pressure were noted but the location of the loss of circulating volume could not be verified. This patient died due to profuse internal bleedings.

Panuccio *et al.* showed a short-term mortality rate of 47% for patients treated with Impella® (108). Similarly, Ouweneel *et al.* reported a 46% mortality in a study involving 48 ventilated patients treated with Impella CP® for severe AMICS (109). Hill *et al.* reported a 6-month survival of 58.8% in the AMICS subgroup of their meta-analysis, and the DanGer shock trial revealed an all-cause mortality of 45.8% in CS patients treated with an Impella® device (114). Chieffo *et al.* reported an in-hospital mortality of 46.9% in patients with CS treated with an Impella® device (119). Pietrasik *et al.* revealed a 76.4% in-hospital mortality in CS patients treated with Impella®, attributing the higher mortality to a higher baseline risk profile, including 50% presenting with cardiac arrest at admission, which was somewhat higher than in our study, where one-third presented with cardiac arrest at admission (125). The need for mechanical ventilation was with around 80% similarly high as in our study as well as the percentage of underlying multi-vessel disease in around 70% of cases (125). Factors such as early intervention, patient selection, and effective management of complications are essential in improving survival rates. On the contrary, in-hospital mortality rate in the HR-PCI group in our study was 0%. A low in-hospital mortality of 8.3% in HR-PCI group was revealed by Pietrasik *et al.* in the IMPELLA-PL study (125). Chieffo *et al.* reported a very low in-hospital

mortality rate of 5.7% (119), as well as Brandão *et al* reporting a 10% in-hospital mortality rate in the HR-PCI group (126). The low incidences in mortality in these groups can be attributed to the high safety profile of the Impella® device especially in elective procedures.

The extreme difference in mortality between the CS and complex HR-PCI groups underlines the critical nature of CS and its associated challenges in the care and management of these patients. The high mortality rates seen in the CS group highlight the need for an early introduction of MCS possibly with Impella CP® as it was used in our study.

Despite the generally promising outcomes, our study bears some limitations. The small sample size of only 16 patients, which reduces the statistical power of our findings, which may not be projectable to a larger population. This study was conducted at a single medical center, and our results might not be generalizable to other centers with different patient demographics or healthcare practices. Still in comparison to other studies, our results have shown to be similar and comparable to them and we gained external validation through larger, multicenter studies. As we conducted this study with the aim to collect and evaluate our initial experiences with the use of the Impella CP® MCS device, we focused on the two groups of patients in which this device was primarily used and therefore lack a control group. As we did not compare our outcomes to those who did not receive the device or received alternative MCS it was impossible for us to conclude if the device was more effective and safer than alternative therapeutic approaches. At this point it would be necessary to conduct further research on a larger scale, with the possibility to involve a control group. This study also focused on in-hospital outcomes and complications and long-term follow-up would be necessary to fully understand the impact of Impella CP® on patient survival or quality of life.

6. CONCLUSIONS

This diploma thesis had the main goal to examine and describe the initial clinical experiences with the Impella CP® device in the management of CS and HR-PCI. The following was observed based on the results from our retrospective analysis of patients treated at our hospital:

- The Impella CP® device proved to be effective in providing MCS in patients with CS and especially those undergoing HR-PCI.
- The procedural success rate was high, with minimal procedure-related complications observed.
- The Impella CP® device was associated with a low incidence of bleeding complications and no procedure-related mortality.
- Despite the still high mortality rate in cardiogenic shock, the Impella CP® device is an excellent choice for MCS, especially in patients undergoing HR-PCI.

In summary, we can conclude that the Impella CP® device is a feasible, safe, and effective option in the management of CS and protected HR-PCI. However, further studies, especially randomized controlled trials, are needed to validate these findings and compare the device's efficacy against other options such as medical therapies or other MCS devices.

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8. SUMMARY

Objectives: This study sought to describe the initial experiences, clinical features, safety, and effectiveness of Impella CP® hemodynamic support for cardiogenic shock (CS) and high risk percutaneous coronary intervention (HR-PCI). Specific goals were to evaluate baseline characteristics, comorbidities, laboratory markers, echocardiographic findings, complications, in-hospital, and procedure-related mortality.

Materials and methods: This retrospective study was conducted at the Clinic for Cardiovascular Diseases, University Hospital of Split from October 2022 to April 2024 and involved patients treated with Impella CP®. Data were collected from the hospital information system. Variables included laboratory, echocardiographic and angiographic findings, clinical and procedural characteristics, and in-hospital outcomes and mortality. Standard descriptive methods were used, and inferential analyses avoided due to the small sample size.

Results: The study involved 16 patients in two groups: CS group (N=6) and HR-PCI group (N=10). Most patients had previously diagnosed arterial hypertension (75%). ST elevation myocardial infarction (STEMI) was more common in the CS (83.3%) compared to the HR-PCI group (10%). Non-ST elevation myocardial infarction (NSTEMI) was present in 60% of HR-PCI patients but rare in the CS group (16.7%). All HR-PCI patients and 66.7% of CS patients had multivessel disease. Most CS patients required mechanical ventilation (83.3%) and inotropes or vasopressors (83.3%). PCI of LM was performed in 70% of patients in the complex HR-PCI group. Half of patients in the complex HR-PCI group (50%) and 1/3 of patients in the CS group (33.3%) underwent PCI of the left circumflex artery (Cx). PCI of the right coronary artery (RCA) was performed in half of the patients in the HR-PCI group (50%). 3- vessel PCI was only performed in one CS patient (16.7%) but in 60% of complex HR-PCI patients. The mean time on Impella CP® support in the complex HR-PCI group was 4.3±6.9 hours and 33±38.2 hours in the CS group. The mean length of hospital stay was 14 days in the HR-PCI group and 8.2 days in the CS group. In the CS group complications included vascular complications in one patient (16.7%), critical limb ischemia in 16.7% of patients and the need for RRT in 50% of patients. In the complex HR-PCI group complications were rare. Death occurred in half of CS patients (50%), but in none of the complex HR-PCI patients.

Conclusions: Impella CP® device is a feasible, safe, and effective option in the management of CS and protected HR-PCI. The procedural success rate was high, with minimal procedure-related complications observed and no procedure-related mortality.

9. CROATIAN SUMMARY

Naslov: Hemodinamska potpora uporabom Impella uređaja za kardiogeni šok i visokorizičnu perkutanu koronarnu intervenciju: Početna iskustva u Kliničkom bolničkom centru Split.

Ciljevi: Ova studija je imala za cilj opisati početna iskustva, kliničke značajke, sigurnost i učinkovitost hemodinamske potpore Impella CP® kod kardiogenog šoka (CS) i visokorizične perkutane koronarne intervencije (HR-PCI). Specifični ciljevi bili su procijeniti osnovne karakteristike, komorbiditete, laboratorijske markere, ehokardiografske nalaze, komplikacije, bolničku smrtnost i smrtnost povezanu s postupkom.

Materijali i metode: Ova retrospektivna studija provedena je na Klinici za kardiovaskularne bolesti, Klinički bolnički centar Split od listopada 2022. do travnja 2024. godine i uključivala je pacijente liječene Impella CP® uređajem. Podaci su prikupljeni iz bolničkog informacijskog sustava. Varijable su uključivale laboratorijske, ehokardiografske i angiografske nalaze, kliničke i proceduralne karakteristike te bolničke ishode i smrtnost. Korištene su standardne deskriptivne metode, a inferencijalne analize su izbjegnute zbog malog uzorka.

Rezultati: Studija je uključivala 16 pacijenata u dvije skupine: CS skupina (N=6) i HR-PCI skupina (N=10). Većina pacijenata imala je prethodno dijagnosticiranu arterijsku hipertenziju (75%). ST elevacijski infarkt miokarda bio je češći u CS skupini (83,3%) u usporedbi s HR-PCI skupinom (10%). Non-ST elevacijski infarkt miokarda bio je prisutan kod 60% pacijenata u HR-PCI skupini, ali rijedak u CS skupini (16,7%). Svi HR-PCI pacijenti i 66,7% CS pacijenata imali su višežilna koronarna bolest. Većina CS pacijenata zahtijevala je mehaničku ventilaciju (83,3%) i inotrope ili vazopresore (83,3%). PCI debla izveden je kod 70% pacijenata u HR-PCI skupini. Polovica pacijenata u HR-PCI skupini (50%) i 1/3 pacijenata u CS skupini (33,3%) podvrgnuta je PCI lijeve cirkumfleksne arterije (Cx). PCI desne koronarne arterije (RCA) izveden je kod polovice pacijenata u HR-PCI skupini (50%). PCI na tri krvne žile izveden je samo kod jednog CS pacijenta (16,7%), ali kod 60% pacijenata u HR-PCI skupini. Prosječno vrijeme podrške Impella CP® uređajem u HR-PCI skupini bilo je 4,3±6,9 sati, a u CS skupini 33±38,2 sati. Prosječna duljina boravka u bolnici bila je 14 dana u HR-PCI skupini i 8,2 dana u CS skupini. Komplikacije u CS skupini uključivale su vaskularne komplikacije kod jednog pacijenta (16,7%), kritičnu ishemiju uda kod 16,7% pacijenata i potrebu za hemodijalizom kod 50% pacijenata. Komplikacije su bile rijetke u HR-PCI skupini. Smrt se dogodila kod polovice CS pacijenata (50%), ali kod nijednog pacijenta u HR-PCI skupini.

Zaključci: Impella CP® uređaj je izvediva, sigurna i učinkovita opcija u upravljanju kardiogenim šokom i zaštićenim HR-PCI. Stopa uspješnosti postupka bila je visoka, s minimalnim komplikacijama povezanim s postupkom i bez smrtnosti povezane s postupkom.