CLINICAL DOSSIER

Cardiogenic Shock

Therapy with Impella®
Executive Summary

Improving Outcomes in Cardiogenic Shock

Impella 2.5®, Impella CP®, Impella 5.0®, and Impella LD® heart pumps are now FDA indicated to provide treatment of ongoing cardiogenic shock. In this setting, the Impella heart pumps have the ability to stabilize the patient’s hemodynamics, unload the left ventricle, perfuse the end organs, and allow for recovery of the native heart. Impella devices have also been proven to be cost effective through reduction in length of hospital stay, readmissions, and overall costs compared with alternative treatment.66 The FDA has also approved Impella 2.5 and Impella CP for elective and urgent high risk percutaneous coronary intervention (PCI), or Protected PCI.

The Impella RP® heart pump has the ability to stabilize hemodynamics, unload the right ventricle and allow for native heart recovery in patients with right ventricular failure. Delivered through a minimally-invasive catheterization technique using the femoral vein as the access point, the Impella RP heart pump is designed to provide the flow and pressure needed to compensate for right heart failure. The device provides more than four liters of blood per minute for hemodynamic support.

Identify Cardiogenic Shock Early

- Systolic blood pressure (SBP) <90 mmHg or on inotropes/pressors
- Cold, clammy, tachycardia
- Lactate elevated >2 mmol/L

Cardiogenic Etiology Evaluation

- EKG (STEMI/NSTEMI)
- Echocardiography
- If available, PA catheter, assessment of cardiac output, CPO, CI, PCWP, SVO2

Hemodynamic Effects of Impella Support

- Early Stabilization Can Improve Outcomes in Cardiogenic Shock
  “Early initiation of hemodynamic support prior to PCI with Impella 2.5 is associated with more complete revascularization and improved survival in the setting of refractory CS complicating an AMI”.


Major society clinical guidelines now reference Impella devices, including ACC/AHA/SCAI/ISHLT/HFSA

*The catheter based VAD Registry is a worldwide, multicenter, IRB approved, monitored clinical registry of all patients at participating sites; registry data is used for FDA PMA submissions*
Epidemiology of Cardiogenic Shock

In cardiogenic shock, profound depression of myocardial contractility, results in the vicious spiral of reduced cardiac output (CO), low blood pressure, further coronary insufficiency, and further reduction in contractility and CO.\(^1\) Compensatory systemic vasoconstriction with high systemic vascular resistance (SVR) occurs in response to the depression of CO.\(^2\) Cotter, et al. categorized acute heart failure patients according to cardiac power and demonstrated its importance in risk stratification and selection of therapy.\(^3\) Cardiac power output (CPO) measured in watts, the product of cardiac output and mean arterial pressure, a \(\text{CPO} = (\text{CO} \times \text{MAP})/451\), is a useful prognostic indicator in chronic heart failure.\(^4\)

In the SHOCK trial, CPO was the hemodynamic variable most strongly associated with in-hospital mortality (See Figure 1).\(^4\) A subset of patients in the SHOCK registry were diagnosed with cardiogenic shock without hypotension based on systemic hypoperfusion, low CO, and elevated ventricular filling pressures. The patient in-hospital mortality rate (43%) was lower than the mortality rate of those with hypotensive shock (66%), despite similar baseline LVEF (34%), cardiac index (1.9 L/min per m\(^2\)), and pulmonary capillary wedge pressure (25 mmHg) between the two groups. Vasoconstriction of vascular beds that supply non-vital organs (e.g., skin) is an important compensatory response to a reduction in CO. Vasodilators (endogenous and exogenous) interfere with this critical response, which is needed to maintain flow to the cerebral and coronary circulations. CPO is also prognostically important because it reflects myocardial reserve adequate to generate flow, albeit reduced, in the face of high resistance.\(^4\)

Since publication of SHOCK-II, large RCT’s of PCI have been reported. IABP SHOCK-II shows no mortality difference in comparison.

Trends and Incidence of Cardiogenic Shock in Today’s Patient Population

Despite dramatic advancements in the last decade in interventional techniques, the overall incidence of cardiogenic shock has remained at 5-10% with an incremental increase in recent years.\(^5\) A similar trend is also observed in the Medicare patient population (See Figure 2), attributed to demographic changes in populations (e.g., increasing obesity, diabetes) being treated with primary PCI and possibly better documentation of shock in ST-segment elevation myocardial infarction (STEMI).\(^5\)
The in-hospital mortality rate for AMI cardiogenic shock has remained at 50% for more than a decade.9 Patients who survive AMI complicated by cardiogenic shock to hospital discharge are at risk of an additional 10% mortality in the first 60 days post discharge (See Figure 3).10 The combined effect of the in-hospital and early post discharge hazard approaches a mortality rate of 60%.

Despite the pressing clinical need for improved outcomes in cardiogenic shock, the improvements in systems of care in STEMI with primary PCI (e.g., national door to balloon time initiatives) have not made an impact on systems of care for shock complicating AMI, in general.11 As expected, with the proliferation of the number of primary PCI centers and the distribution of PCI volume and STEMI treatment to a greater number of centers, patients are more frequently presenting with AMI cardiogenic shock, often community hospitals and in catheterization laboratories with smaller procedural volumes.11 In 2005, two-thirds of AMI cardiogenic shock patients received PCI procedures in larger hospitals (>500 PCIs/year). In 2011, nearly half of AMI cardiogenic shock patients received PCI procedures in these larger hospitals, while the other half received PCI in smaller hospitals with lower PCI volumes (<500 PCIs/year; See Figure 4).11 This shift in treatment settings requires increased education in early identification, rapid treatment and a call to action for development of inter-hospital systems of care to optimize patient survival and outcomes. When appropriate, transfer for escalation of care for more advanced treatment is critical.
Challenges in Contemporary Therapies for Cardiogenic Shock

Prior to the availability of Impella devices, the traditional therapeutic options for the management of cardiogenic shock had been of limited benefit, and clinical outcomes remain poor. The current therapies used to treat cardiogenic shock are as follows:

1. **Intravenous Inotropic Drugs and/or Vasopressor Agents**—The use of intravenous inotropic drugs to treat cardiogenic shock remains a common practice. Commonly prescribed inotropes include dobutamine (Dobutrex) or milrinone (Primacor). Commonly prescribed vasopressor drugs include norepinephrine (Levophed), phenylephrine (Neo-Synephrine), or high-dose dopamine.

2. **Intra-aortic Balloon Pump (IABP)**—The IABP has been used to provide counterpulsation therapy, either with or without inotropes, in patients with cardiogenic shock. Results from large data sets including randomized clinical trials have not shown a hemodynamic or mortality benefit with IABP when compared with medical therapy. Guidelines from both the European Society of Cardiology (ESC) and the Japanese Circulation Society (JCS) consider IABP to be Class III, not recommended.

3. **Extracorporeal Membrane Oxygenation (ECMO)**—ECMO has been used to provide support in patients presenting with refractory cardiogenic shock. However, there are no ECMO systems approved or cleared by FDA to treat these patients.

**Intravenous Inotropic Drugs and/or Vasopressor Agents:**

Historically, inotropic and vasopressor agents have been used as the first-line therapies in cardiogenic shock patients to immediately increase systolic blood pressure through increased myocardial contractility (inotropes) or increased vascular tone (vasopressors). The use of these agents is largely confined to critically ill patients with profound hemodynamic impairment when tissue blood flow is not sufficient to meet metabolic requirements. A drawback associated with this therapy is the increased mortality associated with the administration of inotropes and the temporary improvement of hemodynamic parameters and cardiac output at the potential expense of increasing the myocardium oxygen demand and myocyte death, especially in the setting of AMI.

Intravenous inotropic drugs rapidly increase myocardial contractility, thereby increasing native cardiac output. Inotropes may also decrease systemic vascular resistance (SVR) through vasodilatory mechanisms. When a patient does not respond to the first drug, common practice has been to either increase the medication dose or add another vasoactive agent.

Samuels et al. demonstrated that the predicted hospital mortality correlates with the number and level of inotropic support. The study showed that a patient on one moderate dose inotrope or vasopressor had a mortality risk of 7.5%, which increased step-wise to 80% with three high-dose inotropes (Figure 5).
Inotropes and vasopressors increase the myocardial oxygen consumption (MVO₂). By increasing both contractility and afterload, they increase myocardial oxygen demand and mechanical work in an already compromised ventricle.

As noted by Dr. Samuels, vasopressors cause vasoconstriction and thereby elevate MAP. However, many drugs have both vasoconstrictive and inotropic effects. Although vasopressors have been used since the 1940s, few controlled clinical trials have directly compared these agents or documented improved outcomes. De Backer et al. found that dopamine was associated with an increased risk of patient mortality, when compared with norepinephrine in cardiogenic shock (See Figure 6).14

Vasopressors and inotropes are useful temporizing agents, but their use should be limited to the lowest dose and shortest time interval to limit cardiogenic and end-organ hazard.13 Addressing and treating the underlying etiology of shock and use of effective mechanical circulatory support (MCS) often allows reduction and termination of vasopressors and inotropes.

Intra-aortic Balloon Pumps:
In some cases of cardiogenic shock, the IABP is utilized in conjunction with an inotropic or vasopressor agent. The IABP is thought to decrease myocardial oxygen consumption (MVO₂) by decreasing afterload, thereby augmenting cardiac output (about 5-10% increase). IABP use requires timing to the patient’s EKG to provide benefit and is thought to be not optimal in patients with tachycardia or heart rate irregularity. In IABP-SHOCK-I15 there was no hemodynamic effect in AMI cardiogenic shock (See Figure 7) likely due to the low native cardiac output, which is normally experienced during cardiogenic shock.

IABP-SHOCK-II (n=600), concluded that there was no mortality benefit associated with the use of IABP compared with medical therapy in the setting of AMI complicated by cardiogenic shock treated with PCI.15 At 30 days, 39.7% of the patients in the IABP group and 41.3% of the patients in the control group had died (See Figure 7).15 At 12- month follow-up of these patients, there was no survival benefit observed between the IABP arm and control arm.16
Figure 7: IABP in AMI Cardiogenic Shock: No Hemodynamic or Survival Benefit

Additionally, a meta-analysis by Sjauw, et al. showed that the IABP was found to increase the risk of bleeding and stroke in AMI. Subsequently, both the European Society of Cardiology (ESC) and Japanese Circulation Society (JCS) downgraded the guidelines for the IABP to Class III, (may cause harm) advising that the IABP should not be used routinely in cardiogenic shock patients.

The U.S. population study by Stretch, et al. analyzed the contemporary use of MCS devices from 2004 to 2011 (data were collected from the Nationwide Inpatient Sample from the Healthcare Cost and Utilization Project) and determined that IABP use prior to MCS was a predictor of mortality and increased costs by 25.2% (p<0.001). This may be due to delayed care in AMI cardiogenic shock patients, according to the authors.

### Predictors of Mortality in AMI Cardiogenic Shock

Performed or administered up to 7 days before PVAD use.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPR Administration</td>
<td>3.50</td>
<td>2.20</td>
<td>5.57</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IABP Use</td>
<td>2.00</td>
<td>1.58</td>
<td>2.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intubation</td>
<td>1.71</td>
<td>1.27</td>
<td>2.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vasopressor Use</td>
<td>1.39</td>
<td>0.75</td>
<td>2.58</td>
<td>0.30</td>
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</tbody>
</table>

Figure 8: Predictors of Mortality in AMI Cardiogenic Shock
**Extracorporeal Membrane Oxygenation (ECMO):**
In the past decade, the use of ECMO has grown rapidly; however, publicly available data show no evidence of improved outcomes in the setting of cardiogenic shock.\textsuperscript{20} Patients with the greatest likelihood to benefit from ECMO are those with hypoxemia, newborn or infant patients with persistent fetal circulation and respiratory failure, or patients with acute cardiopulmonary arrest as an adjunct to cardiopulmonary resuscitation (CPR) or so-called ECPR.\textsuperscript{20}

A recent meta-analysis conducted by Cheng, et al. of 1,866 adult patients supported with ECMO for the treatment of cardiogenic shock and cardiac arrest reported significant morbidity with ECMO, including lower extremity amputation (4.7%), stroke (5.9%), neurological complications (13.3%), acute kidney injury (55.6%), major or significant bleeding (40.8%), bleeding or tamponade in post-cardiotomy patients (41.9%), and significant infection (30.4%).\textsuperscript{21} Outcomes with ECMO in the setting of cardiogenic shock include in-hospital mortality exceeding 70%.\textsuperscript{20,22}

ECMO systems (which consist of pumps, oxygenators, heater and cooler systems, and tubing) allow high blood flow, that supports vital non-cardiac organs but adds volume and pressure load to the failing heart. The retrograde flow provided from the ECMO outflow cannula in the descending aorta can lead to a dangerous rise in the left atrial and ventricular pressure.\textsuperscript{23,24} Result in extreme heart dilation and pulmonary edema and lowers the ischemic threshold of the heart and reduces the likelihood of left ventricular recovery.\textsuperscript{25-27} Systems to overcome ventricular dilatation have included the use of an IABP or ventricular sumps to drain the left heart, which may also increase complication rates.\textsuperscript{26}

In the context of Impella and cardiogenic shock, more recently, publications from Pappalardo et al.\textsuperscript{28} and Patel et al.\textsuperscript{29} demonstrated lower hospital mortality amongst cardiogenic shock patients when treated with Impella and concomitant VA-ECMO, compared to patients treated with only VA-ECMO. The papers showed survival increasing from 26% and 22%, to 52% and 43%, which while statistically significant still remains at or below the historical average of approximately 50% survival in cardiogenic shock.

Despite strategies to improve results and reduce complication rates, high morbidity and mortality rates persist with ECMO. Efforts to prevent distal limb ischemia, left ventricular distention, and central hypoxia, often involve additional devices, procedures, and expense and are often ineffective and detrimental to the long-term outcome of the patient.\textsuperscript{30}
Impella® Device Description and Hemodynamic Characteristics

The Impella heart pumps are the smallest, percutaneous ventricular support devices available. The left-sided Impella devices, 2.5 and CP are inserted percutaneously, whereas the Impella 5.0 is surgically implanted. The left sided devices are delivered across the aortic valve, generating forward blood flow in the ascending aorta and directly unloading pressure and volume the left ventricle. The Impella RP is delivered from the femoral vein over a wire through the right atrium ventricle to the pulmonary artery. Use of Impella left sided devices raises systemic aortic pressure (AOP), mean arterial pressure (MAP) and cardiac power output (CPO). Left ventricular unloading, during Impella support results from active removal of blood from the ventricular cavity thereby, reducing both volume and pressure (measured as left ventricular end-diastolic volume and pressure [LVEDV, LVEDP]) thereby augmenting peak coronary flow. These changes result in favorable alteration of the balance between myocardial oxygen supply and demand. These physiologic benefits provided by Impella technology optimize the conditions for native heart recovery.

Current Clinical Experience:
The Impella 2.5, Impella CP, and Impella 5.0 devices are used in clinical practice in a variety of clinical scenarios to support emergent patients with hemodynamic instability from cardiogenic shock. Worldwide, the technology has been used by over 3,000 physicians at over 1,200 hospitals to support more than 65,000 patients. The Impella platform, also includes the Impella RP (right percutaneous). The entire Impella platform is approved by the U.S. Food & Drug Administration (FDA) for use in patients with cardiogenic shock due to AMI, cardiomyopathy (including peripartum and myocarditis), or after cardiac surgery. A large body of evidence has been generated through prospective clinical trials, registries, as well as single and multi-center studies resulting in over 300 peer-reviewed publications, making Impella the most studied percutaneous circulatory support devices on the market. The devices are also approved in Europe (2004), Canada (2007), Latin and South Americas (2008-2012) China (2013), India (2017) and Japan (2017) for indications including high-risk Percutaneous Coronary Intervention (PCI) and cardiogenic shock.

Impella® Platform/FDA Approvals for Cardiogenic Shock:
In the United States, the Impella 2.5 device has been used since 2006. The first clinical trial investigation of Impella was the PROTECT I, FDA trial for high-risk PCI.32

In 2016, the Impella 2.5, Impella CP, Impella 5.0 and Impella LD devices received first of its kind FDA approval for the treatment of ongoing cardiogenic shock, immediate (<48 hours) post-acute myocardial infarction (AMI) or post-cardiomyotomy cardiogenic shock (PCCS). The FDA indication states that these Impella devices, in conjunction with the Automated Impella Controller®, are safe and effective, and intended for short-term use (≤4 days for the Impella 2.5 and Impella CP, and ≤6 days for Impella 5.0) for the treatment of ongoing cardiogenic shock that occurs immediately (<48 hours) following acute myocardial infarction (AMI) or open heart surgery as a result of isolated left ventricular failure that is not responsive to optimal medical management and conventional treatment measures with or without an intra-aortic balloon pump (IABP). The intent of Impella® System therapy in the cardiogenic shock setting is to reduce ventricular work and allow heart recovery and early assessment of residual myocardial function.

In 2017, the Impella RP received PMA approval from the FDA for circulatory assistance in patients with a body surface area ≥1.5 m² who develop acute right heart failure or decompensation following left ventricular assist device implantation, myocardial infarction, heart transplant, or open-heart surgery. The Impella RP is a percutaneous pump designed for right heart support that optimizes right heart hemodynamics, providing more than four liters per minute of blood flow.
The Impella left side heart pump propels blood forward from the left ventricle into the aorta increasing MAP. This increase in MAP and forward flow provides end-organ perfusion. The objective measure of pressure and flow is objectively characterized by their product (MAP x CO/451) is referred to as cardiac power output (CPO). Impella’s action, directly unloading the left ventricle, is unique among MCS devices.33

The active removal of blood from the LV cavity reduces end-diastolic volume and pressure (LVEDV, LVEDP) and augments peak coronary flow by increasing coronary perfusion gradient by simultaneous effect of increasing coronary perfusion pressure reduction in LVEDP. These hemodynamic effects are described in the literature in a variety of pre-clinical and clinical studies and validated in computational modeling (See Figure 9).4,39,52,62,67-80 Coronary flow increases in the setting of shock through a dual mechanism during Impella support. First, increased aortic pressure (the pressure head for coronary flow during diastole) increases the upstream pressure for myocardial perfusion. Secondly, through Impella’s unloading mechanism, with continuous removal of ventricular volume, LV wall tension falls (See Figure 10). LV wall tension (characterized by Laplace as Pressure x Diameter/wall thickness) falls leading to subsequent reduction in microvascular resistance. Myocardial perfusion gradient improves with a rise in MAP and drop in LVEDP. Nellis et al. demonstrated in an animal model that there is a minimum myocardial perfusion gradient of 40 mmHg between coronary arterioles and venules.34 Sustained hypotension with coronary perfusion gradients <40 mmHg can result in global myocardial ischemia, which quickly depresses an already impaired left ventricle and may lead to cardiovascular collapse and arrest.35

**Figure 9: Hemodynamic Stabilization with Impella**

**Figure 10: Principles of Impella® Design**

*The catheter based VAD Registry is a worldwide, multicenter, IRB approved, monitored clinical registry of all patients at participating sites; registry data is used for FDA PMA submissions*
The coronary perfusion effects of Impella have been assessed using the coronary flow velocity reserve (CFVR) demonstrating beneficial unloading effects of Impella during high-risk and primary PCI. Recently, the impact on coronary perfusion pressure was evaluated by Alqarqaz et. al demonstrating increased perfusion pressure distal to significant stenosis with increased flow provided by Impella devices. The myocardial perfusion effects of Impella was visualized on myocardial scintigraphy study by Aqel et al. In this case report, a patient enrolled in The Protect II Study underwent hemodynamically supported PCI of the last remaining vessel, the Left Anterior Descending (LAD) in the setting of the right coronary artery (RCA) and circumflex coronary chronic total occlusions (CTO). After LAD PCI, without revascularization of the RCA and circumflex, multiple differences can be noted. With Impella support, there is resolution of the inferolateral wall myocardial perfusion detected (circles), improved endocardial perfusion, and smaller ventricular volume (See Figure 11).

End-organ perfusion with Impella has also been demonstrated through advanced imaging of the sublingual mucosal vasculature. Lam et al. used side stream dark field (SDF) imaging to evaluate improvement of sublingual microcirculation as a surrogate for cerebral perfusion with the Impella device turned off (A) and turned on (B), in the setting of STEMI with shock (See Figure 12).
Clinical Evidence of Safety and Effectiveness for Impella® in Cardiogenic Shock

Clinical evidence from various primary sources and a comprehensive literature review supported the FDA’s determination of overall safety and effectiveness of the Impella devices in cardiogenic shock:

- USpella/cVAD Registry (data from all Impella devices at participating sites)
- Detroit Cardiogenic Shock Initiative (DCSI)
- Prospective randomized controlled data from the ISAR-SHOCK trial
- Clinical data from the RECOVER I trial
- Literature review of scientific publications

USpella/cVAD Registry Results (for All Impella Devices):
Data for US PMA approvals came from the USpella, which preceded the cVAD Registry. cVAD, a global registry, is in use today to continue data collection activity related to the use of Impella around the world. The Catheter based Ventricular Assist Device Registry or the cVAD Registry is an observational, multicenter, retrospective registry of patients supported with Impella 2.5, Impella CP, Impella 5.0, Impella LD or Impella RP. The cVAD Registry captures data reflecting “real-world” use of Impella devices in current clinical practice and provide insights to patient characteristics, comorbid conditions, outcomes, patterns of care, and performance metrics of participating institutions to guide improvement efforts (See Figure 13). The registry, started by Abiomed in 2009, enrolls patients at qualifying sites in the United States, Canada and Europe. The current sites include centers, academic (teaching) and non-academic hospitals, public and private institutions as well as for profit and not for profit centers, thus providing a broad representation of U.S. clinical practice.

*USpella/cVAD Registry data of patients undergoing PCI for AMI complicated by cardiogenic shock as of September 2015.

Figure 13: USpella/cVAD Registry
The PMA approval of the left side Impella devices for the cardiogenic shock indication was supported by the cVAD Registry data. The data included: patient demographics and baseline characteristics (risk factors, medical history and history of previous cardiac interventions), clinical presentation for the index hospitalization, index cardiac procedure information, Impella device information, hemodynamic parameters (before, during, and after Impella support), cardiovascular medications, laboratory results, patient outcome information at discharge and 30-day follow-up as well as site-reported adverse events. Both site-reported safety data and clinical event committee (CEC) adjudicated data were submitted.

The data submitted included 324 patients who underwent a PCI and were supported with a left side Impella device for cardiogenic shock complications and AMI. The average age was 65 years and the majority were male (75%). They presented with significant risk factors and comorbidities including diabetes (42%), hypertension (71%), renal insufficiency (24%) and a Society of Thoracic Surgery (STS) score for mortality and morbidity of 21% and 60%, respectively. Prior to Impella support initiation, the patients were in cardiogenic shock with poor hemodynamics, overt signs of tissue hypoperfusion, and end-organ dysfunction, despite catecholamine therapy and/or IABP support.

The median duration of Impella support for the entire cohort was 26 hours, and it was approximately twice as long for the survivors. During support, the mean pump flow was 2.2 L/min for Impella 2.5, 2.9 L/min for Impella CP and 4.3 L/min for Impella 5.0/LD. The median stay in the intensive care unit (ICU) was 6, 5, and 19 days for Impella 2.5, Impella CP, and Impella 5.0/LD, respectively. The median duration of hospitalization was 7, 5.5, and 23 days for Impella 2.5, Impella CP, and Impella 5.0/LD, respectively.

**Analysis of the USpella/cVAD Registry Data:**
A subset analysis was completed to evaluate patients similar to those in prior randomized cardiogenic shock trials of AMI cardiogenic shock. This was accomplished by dividing the cVAD Registry into two groups, a “DEFINE (RCT) group” (a group who may have qualified for the SHOCK trial) and a group of “salvage” patients, who would had exclusion criteria from prior trials. The “salvage patient population” included patients who presented with anoxic brain injury prior to implant, out of hospital cardiac arrest, and those who were transferred from another hospital. The overall 30-day survival results (Kaplan-Meier curve estimates) for the two subgroups described above (See Figure 14). As expected, the “salvage” group of patients had higher mortality outcomes than the RCT group, which is more representative of patients chosen for cardiogenic shock RCTs. Outcomes data for both 30-day survival and survival to discharge are provided respectively, for each Impella device (See Figures 15 and 16).

![Outcomes between Impella Registry subgroups: Patients likely to be eligible for RCTs vs. patients likely to be excluded from RCTs ("salvage" patients)](image)

*Figure 14: Outcomes Between Impella Registry Subgroups*

Since publication of SHOCK-II, large RCT’s of PCI have been reported. IABP SHOCK-II shows no mortality difference in comparison.
30-day outcomes (by device) between Impella Registry subgroups: Patients likely to be eligible for RCTs vs. patients likely to be excluded from RCTs (“salvage” patients)

<table>
<thead>
<tr>
<th>Device</th>
<th>AMI CS Likely to be excluded</th>
<th>AMI CS Likely to be included</th>
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</thead>
<tbody>
<tr>
<td>Impella 2.5</td>
<td>31.0%</td>
<td>50.0%</td>
</tr>
<tr>
<td>Impella CP</td>
<td>24.1%</td>
<td>51.4%</td>
</tr>
<tr>
<td>Impella 5.0/LD</td>
<td>47.4%</td>
<td>75.0%</td>
</tr>
<tr>
<td>n=116</td>
<td>n=54</td>
<td>n=37</td>
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<tr>
<td>n=58</td>
<td>n=37</td>
<td>n=4</td>
</tr>
</tbody>
</table>

Survival to discharge outcomes (by device) between Impella Registry subgroups: Patients likely to be eligible for RCTs vs. patients likely to be excluded from RCTs (“salvage” patients)

<table>
<thead>
<tr>
<th>Device</th>
<th>AMI CS Likely to be excluded</th>
<th>AMI CS Likely to be included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impella 2.5</td>
<td>40.2%</td>
<td>54.8%</td>
</tr>
<tr>
<td>Impella CP</td>
<td>31.8%</td>
<td>64.6%</td>
</tr>
<tr>
<td>Impella 5.0/LD</td>
<td>42.1%</td>
<td>80.0%</td>
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<td>n=127</td>
<td>n=62</td>
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<tr>
<td>n=5</td>
<td>n=5</td>
<td>n=4</td>
</tr>
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</table>

Detroit Cardiogenic Shock Initiative (DCSI)

Based on the consistent finding of good survival outcomes with early hemodynamic support with Impella, collaborators of DCSI established a best practices algorithm for the treatment of patients with AMICS. They assessed the feasibility and effects of the best practices algorithm in achieving rapid door to support times in 41 patients with AMICS. Before initiation of Impella support, 93% of patients received vasopressors or inotropes, 15% had out of hospital cardiac arrest, 27% had in-hospital cardiac arrest, and 17% were under active cardiopulmonary resuscitation during Impella implantation. In accordance with the adoption of a uniform shock protocol, 66% of patients had Impella inserted pre-PCI, 83% of patients had right heart catheterization and hemodynamic monitoring. The study reported average door to support times of 83 minutes and reduction in doses of inotropes and vasopressors within the first 24-hours in 71% of patients. A 66% increase in cardiac power output was observed (See Figure 17). Survival to explant for the entire cohort was 85% compared to 51% with institutional historical controls (p < 0.001). The study also reported a survival to discharge of 76% with native heart recovery in 100% of patients who survived (Figure 20) and achievement of TIMI III flow after PCI in 87%. In conclusion, this pilot study conducted in 4 metro Detroit hospital sites demonstrated that systematic use of a shock protocol emphasizing early initiation of Impella with invasive hemodynamic monitoring is feasible and may improve survival in AMICS. Based on the encouraging findings of this study, a national, multicenter, quality initiative titled the National Cardiogenic Shock Initiative (NCSI) has been launched.

Cardiac Power Output \( (CPO = MAP \times CO) \)

<table>
<thead>
<tr>
<th></th>
<th>Pre MCS</th>
<th>Post MCS</th>
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<tbody>
<tr>
<td>0.57 Watts</td>
<td>N=19</td>
<td>0.95 Watts</td>
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<tr>
<td>66% increase ( p&lt;0.001 )</td>
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Survival Before & After The Detroit CSI

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<th>Event</th>
<th>Pre MCS</th>
<th>Post MCS</th>
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<tbody>
<tr>
<td>Survival to Expant Metro Detroit Before Study</td>
<td>51%</td>
<td></td>
</tr>
<tr>
<td>Survival to Expant Detroit CSI</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td>Survival to Discharge Detroit CSI</td>
<td>75%</td>
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</tr>
</tbody>
</table>

Figure 15: 30-Day Outcomes (by device) Between Impella® Registry Subgroups

Figure 16: Survival to Discharge Outcomes (by device) Between Impella Registry Subgroups

Figure 17: Improvement in Hemodynamics and Survival in AMICS

1. Abiomed Impella Quality (IQ) Database, Jan 2015 to July 2016 for Aggregate DTW Metro Hospitals, all-comers who presented with AMICS, Survival to Explant
The Need for Early Identification of Cardiogenic Shock Patients

Ineffective or detrimental treatments continue to result in poor outcomes. A key to making an impact on these outcomes is early identification and rapid intervention of cardiogenic shock. While the scientific definition of cardiogenic shock in trials generally involves hemodynamic assessment with right heart catheterization, the identifiers used in clinical practice are more universally adopted due to the inherent urgency of treatment. It is critical to raise awareness of the “downward spiral” accompanying cardiogenic shock.

In the medical literature, cardiogenic shock is defined by decreased cardiac output and evidence of tissue hypoxia in the presence of adequate intravascular volume. The decreased cardiac output leads to a persistent systemic hypotension with systolic blood pressure below 90 mmHg (or the requirement of vasopressors and/or inotropes to maintain a blood pressure above 90 mmHg) with reduction in cardiac index below 2.2 L/min/m² and normal or elevated filling pressure with a pulmonary capillary pressure above 15 mmHg.43

In the clinical setting (emergency room, ICU, CCU) when a right heart catheterization is not immediately available, cardiac and end-organ identifiers are used to recognize cardiogenic shock. Signs of end-organ hypoperfusion may be manifested clinically by SBP of <90 mmHg, altered sensorium, cool extremities, decreased urine output and elevated lactate level of >2 mmol/L. In practice, blood lactate levels have been shown to be a surrogate for tissue oxygenation and can be helpful in the identification of end-organ hypoperfusion in the setting of shock.44

Early shock identification and determining the etiology as cardiogenic are critical for initiation of appropriate therapy. Recognition of end-organ hypoperfusion in a patient with cardiac failure, through clinical assessment, laboratory testing (lactate, acidemia), and invasive testing with right heart catheterization enables diagnosis and tailored treatment planning.

Evidence Supporting Impella Utilization Pre-Revascularization

Flaherty, et.al.45 published a Meta-Analysis combining three individual studies analyzing the use of Impella pre-revascularization in cardiogenic shock. The three articles are summarized and discussed individually below (See Figure 18). This meta-analysis suggests that early initiation of Impella in AMI/CS decreased in-hospital or 30-day mortality by 48% compared with post-revascularization initiation of Impella.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Log [Risk Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Risk Ratio IV, Fixed, 95% CI</th>
<th>Risk Ratio IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ouweneel et al, 2017</td>
<td>-1.4697</td>
<td>1.2461</td>
<td>4.7%</td>
<td>0.23 [0.02, 2.64]</td>
<td>0.23 [0.02, 2.64]</td>
</tr>
<tr>
<td>Basir et al, 2016</td>
<td>-0.7236</td>
<td>0.3589</td>
<td>56.4%</td>
<td>0.49 [0.24, 0.98]</td>
<td>0.49 [0.24, 0.98]</td>
</tr>
<tr>
<td>Schroeter et al, 2016</td>
<td>-0.462</td>
<td>0.4323</td>
<td>38.9%</td>
<td>0.63 [0.27, 1.47]</td>
<td>0.63 [0.27, 1.47]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.52 [0.31, 0.88]</strong></td>
<td><strong>0.52 [0.31, 0.88]</strong></td>
</tr>
</tbody>
</table>

CI = confidence interval.

Figure 18: Forest Plot Comparing In-Hospital/30-Day Mortality in “Early” vs. “Late” Impella46
O’Neill, et.al.\textsuperscript{46} performed a retrospective analysis of 154 consecutive, unselected patients who were reported in the Global CVAD Registry having undergone a PCI and Impella 2.5 heart pump hemodynamic support for a confirmed AMI with CS. The primary endpoint evaluated the survival to discharge of patients supported with Impella 2.5 heart pump prior to percutaneous coronary intervention (Pre-PCI) versus those who received IABP and, or inotropes prior to PCI (Impella Post PCI). Survival to 30 days was also reported. Figure 19 shows a statistically significant survival advantage in patients receiving the Impella device Pre-PCI.

Patient subset analysis demonstrated a consistent benefit for Pre-PCI implantation in all subgroups analyzed.

\textit{Figure 19: 30-Day Survival in Global CVAD Registry\textsuperscript{46}}
When comparing the various hemodynamic support strategies, the Impella Pre-PCI strategy demonstrates a survival to discharge of 65%.

![Support Strategy](image)

**Figure 21: Support Strategy**

Basir et al. evaluated patient characteristics and predictors of outcomes in patients presenting with AMI/CS supported with an Impella device. The authors studied 287 consecutive unselected patients enrolled in the Global cVAD registry. Patients were supported with either the Impella 2.5 or the Impella CP device. Before receiving Impella support, 80% of patients required inotropes or vasopressors and 40% were supported with intra-aortic balloon pump; 9% of patients were under active cardiopulmonary resuscitation at the time of MCS implantation. Survival was found to be significantly improved if Impella implantation was initiated before PCI.

This contemporary analysis also mirrors earlier data (Samuels et al. 1999) demonstrating predicted in-hospital mortality can be linked to the number of high-dose inotrope / vasopressor drugs the patient is receiving.

![Impact of Inotrope Number on In-Hospital Mortality](image)

**Figure 22: Impact of Inotrope Number on In-Hospital Mortality**

A single-center review of ACS patients receiving Impella support during cardiogenic shock was performed by Schroeter et al. The authors utilized their database of Impella patients and found 68 consecutive patients who underwent Impella implantation due to acute coronary syndrome (ACS) complicated by cardiogenic shock.

Most patients (74%) suffered from an ST-elevation myocardial infarction, and 59% of patients received the Impella device during the initial coronary angiography. In the remaining cases, Impella implantation was performed later, most commonly after IABP implantation. The predominantly implanted device was an Impella 2.5.

Interestingly, delayed initiation of Impella support was an independent predictor of higher long-term mortality (hazard ratio, 2.157; P=.04) within the Impella patient cohort. Early (compared with delayed) initiation of Impella support was a predictor of improved survival in this population of patients.
Ouweneel et al. published the IMPRESS trial, an exploratory safety study comparing mortality outcomes cardiac arrest patients with Impella CP versus IABP. The trial was terminated prior to full patient enrollment (n=48), with a high rate of patient crossover between groups. While most support devices were placed post-revascularization, a trend toward lower 30-day mortality was observed if therapy with the support device was initiated before the primary PCI.

**Figure 23: Impact of Impella Early vs Late on Survival Proportion**

AMI, SCAD, Cardiomyopathy, (Peripartum, Myocarditis), Post-cardiotomy

**Cardiogenic Shock Therapy**

AMI, SCAD, Cardiomyopathy, (Peripartum, Myocarditis), Post-cardiotomy

**Figure 24: Reverse the Cardiogenic Shock Spiral**
Prospective Randomized Trial: ISAR-SHOCK (for the Impella 2.5):
Seyfarth, et al. published the results from ISAR-SHOCK (n=26) in the Journal of the American College of Cardiology, which compared the hemodynamic effects of the Impella 2.5 with the IABP. This prospective randomized study demonstrated that the Impella 2.5 provided superior hemodynamic improvement compared with IABP for cardiogenic shock patients (See Figure 25). The Impella 2.5 device was found to significantly increase cardiac index compared to IABP, while simultaneously unloading the left ventricle.

**Figure 25: Hemodynamic Stability and LV Unloading with Impella**

**Literature Review:**
The Impella literature review encompasses a large body of scientific evidence from over 315 publications. The literature review provides further insight into the use of the Impella devices in routine clinical practice.

The literature analysis shows that cardiogenic shock patients, who were treated with emergent hemodynamic support, are, in general, older and present with high-risk comorbidities, poor functional status, and depressed cardiac function. Overall, the survival rates and morbidities also appear to be favorable for use of the Impella devices as compared with the surgical VAD. This comprehensive set of data that was collected over the course of more than 12 years, from real-world registry results, clinical trials, and published literature on the Impella 2.5, Impella CP, and Impella 5.0, were presented to the U.S. FDA and resulted in the FDA’s designation that Impella is safe and effective in the post-surgery and post-AMI cardiogenic shock setting.

**Figure 26: Clinical Society Guidelines for Impella Therapy**

<table>
<thead>
<tr>
<th>Clinical Society Guideline Populations (SCAI, ACCF, HFSA, STS, ISHLT, HRS)</th>
<th>Class</th>
<th>Latest Update</th>
<th>Impella FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI in Cardiogenic Shock</td>
<td>I</td>
<td>2013</td>
<td>2016</td>
</tr>
<tr>
<td>Multi-organ Failure, Cardiogenic Shock</td>
<td>I</td>
<td>2013</td>
<td>2016</td>
</tr>
<tr>
<td>PCI in Low Ejection Fraction, Complex CAD</td>
<td>IIIb</td>
<td>2011*</td>
<td>2015</td>
</tr>
<tr>
<td>Bridge to Recovery or Decision, Cardiogenic Shock</td>
<td>IIa</td>
<td>2013</td>
<td>2016</td>
</tr>
<tr>
<td>STEMI and Cardiogenic Shock</td>
<td>IIIb</td>
<td>2013</td>
<td>2016</td>
</tr>
<tr>
<td>STEMI and Urgent CABG</td>
<td>IIIa</td>
<td>2013</td>
<td>2016</td>
</tr>
<tr>
<td>Acutely Decompensated Heart Failure</td>
<td>IIa</td>
<td>2012</td>
<td>TBD</td>
</tr>
<tr>
<td>Consensus Document on Hemodynamic Support</td>
<td>N/A</td>
<td>2015</td>
<td>2015-2016</td>
</tr>
</tbody>
</table>

**Categories referencing Impella include Percutaneous LVAD, PVAD, Non-durable MCS, TCS and percutaneous MCS**

* Excludes Protect II Randomized Controlled Trial, and FDA PMA approval studies due to timing of available data in 2011
Challenges in Data Capture in Cardiogenic Shock

Randomized trials play a key role in assessment of cardiovascular and medical device innovations. Trials in cardiogenic shock pose many logistic and methodological challenges. Consequently, evidence on the impact of MCS in CS based on randomized controlled trials is limited. So far, eight randomized control trials have been initiated with Impella in CS (Figure 27). Of these, five trials were terminated due to markedly lower enrollment rates than the target numbers needed to assess primary outcome of the trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial ID</th>
<th>Condition</th>
<th>Patients Required (n)</th>
<th>Patients Enrolled (n)</th>
<th>Duration (months)</th>
<th>Status</th>
<th>Discontinuation Reason &amp; Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRENCH TRIAL (2006)</td>
<td>NCT00314847</td>
<td>AMI CS</td>
<td>200</td>
<td>19</td>
<td>52</td>
<td>Discontinued</td>
<td>Low enrollment, not published</td>
</tr>
<tr>
<td>ISAR-SHOCK (2006)</td>
<td>NCT00417378</td>
<td>AMI CS</td>
<td>26</td>
<td>26</td>
<td>19</td>
<td>Completed</td>
<td>Hemodynamic assessment, not randomized</td>
</tr>
<tr>
<td>IMPRESS in STEMI (2007)</td>
<td>NTR1079 Trialregister.nl</td>
<td>STEMI Pre-CS</td>
<td>130</td>
<td>18</td>
<td>22</td>
<td>Discontinued</td>
<td>Low enrollment</td>
</tr>
<tr>
<td>RECOVER I FDA (2008)</td>
<td>NCT00596726</td>
<td>PCCS</td>
<td>Up to 20</td>
<td>17</td>
<td>28</td>
<td>Completed</td>
<td>Feasibility study</td>
</tr>
<tr>
<td>RECOVER II FDA (2009)</td>
<td>NCT00972270</td>
<td>AMI CS</td>
<td>384</td>
<td>1</td>
<td>18</td>
<td>Discontinued</td>
<td>Low enrollment; 11 active sites 50 IRB approved</td>
</tr>
<tr>
<td>RELIEF I (2010)</td>
<td>NCT011185691</td>
<td>ADHF</td>
<td>20</td>
<td>1</td>
<td>33</td>
<td>Discontinued</td>
<td>Low enrollment</td>
</tr>
<tr>
<td>DANSHOCK (2012)</td>
<td>NCT01633502</td>
<td>AMI CS</td>
<td>360</td>
<td>~100</td>
<td>64 (Dec 2012)</td>
<td>Enrolling</td>
<td>Ongoing</td>
</tr>
<tr>
<td>IMPRESS Cardiac Arrest (2016)</td>
<td>NTR3450</td>
<td>Cardiac Arrest Mechanical Ventilation</td>
<td>&gt;100</td>
<td>48</td>
<td>52</td>
<td>Discontinued*</td>
<td>Low enrollment</td>
</tr>
</tbody>
</table>

*Decided to complete the study with 48 patients as an exploratory safety study.

Figure 27: Randomized Control Trials with Impella
Impella RP for Right Heart Support in Cardiogenic Shock

The presence of right ventricular (RV) dysfunction increases the risk of cardiogenic shock (CGS), high-grade atrioventricular-conduction block, and in-hospital mortality. Additionally, failure of the RV can lead to longer ICU stays, higher short-term mortality, and worsening end-organ dysfunction. Typically, RV failure (RVF) can occur after an acute myocardial infarction (AMI), after durable LV implantation, post-cardiotomy, or post-transplant. The occurrence of RVF in any of these patient populations is associated with worse outcomes. A major cause of morbidity and mortality in acute inferior wall myocardial infarction (IAMI) can be attributed to RV dysfunction. Kapur et al. illustrated the prevalence of RVF in AMI by analyzing the Shock Trial Data where RV dysfunction was present in 37% of the patients when using a contemporary definition of RVF.

Hemodynamic variables may help determine patient risk in this setting. The pulmonary artery pulsatility index (PAPi) is one such tool calculated as the [(systolic pulmonary artery pressure – diastolic pulmonary artery pressure)/central venous pressure]. This hemodynamic measurement index helps predict severe RV dysfunction during AMI/CGS and in post-LVAD patients and aims to identify subjects requiring a percutaneous RV assist device (RVAD).

RECOVER-RIGHT HDE Trial

The RECOVER-RIGHT Trial, a multi-center, prospective, open-label study by Anderson et al., reported on the safety and efficacy outcomes associated with Impella RP support in 30 patients with right-sided failure. Two cohorts comprised this non-randomized study’s patient population: patients with RVF 48 hours after LVAD implantation (n = 18; Cohort A) and patients with RVF 48 hours after myocardial infarction or cardiotomy (n = 12; Cohort B). The majority of the patients had congestive heart failure history at baseline (88.5%).

Primary endpoint was survival to hospital discharge or 30 days, and major secondary endpoints were indices of efficacy and safety. Initiation of device weaning occurred in a stepwise manner every 2 to 3 hours, with a decreasing flow rate of 0.5 to 1 liters/min each time. Patients developing RVF following implantation of an LVAD had lower LVEF and were more likely to be symptomatic (NYHA class III and IV) and present with end-stage heart failure than Cohort B.

Following support with Impella RP, there was a significant increase in cardiac index (1.8 ± 0.2 to 3.3 ± 0.23 liters/min/m²; p <0.001). Additionally, there was an observed reduction in central venous pressure (19.2 ± 4 to 12.6 ± 1 mm Hg; p <0.001). The increase in cardiac index, along with the decrease in central venous pressure were immediate after pump implementation and sustained after pump explant.

RV Failure as defined by Recover Right:

- CI <2.2 L/min/m² (despite continuous infusion of ≥ 1 high does inotrope, i.e., da/dobutamine ≥ 10 µg/kg/min or equivalent) and any of the following:
  - 1. CVP > 15 mmHg, or
  - 2. CVP/PCWP or LAP ratio >0.63, or
  - 3. RV dysfunction on TTE (TAPSE score ≤ 14mm)

Figure 28: RV Failure Definition
The need for concomitant inotropic drug support also decreased over time.

**Figure 30: Use of Inotropes/Pressors After Initiation of Support with Impella RP**

Overall survival was 73.3%, and all discharged patients were alive at 180 days. The investigators concluded that the Impella RP was safe and reliable for providing hemodynamic improvement in patients with life-threatening RV failure.
Utility of the PAPi for Risk Stratification in the Setting of Acute Inferior Wall Myocardial Infarction

Pulmonary Artery Pulsatility Index (PAPi) is a hemodynamic index that has been shown to predict right ventricular failure. It is measured by taking the Systolic Pulmonary Artery Pressure and subtracting the Diastolic Pulmonary Artery Pressure and dividing by the Central Venous Pressure: 

\[
\frac{(\text{Systolic PaP} - \text{Diastolic PaP})}{\text{RAP}} = \text{PAPi}.
\]

A PAPi score of <1 is an indicator of right ventricular failure. Worsening right ventricular failure may be indicated by worsening PAPi scores.

A retrospective study by Korabathina et al., examined three cohorts of patients, those with suspected RVD (n=20 patients with nonobstructive coronary artery disease ([non-CAD], n = 50), and 2) patients presenting with acute coronary syndrome requiring left coronary stenting ([ACS], n = 14). Compared to the non-CAD and ACS control groups, the PAPi was lower in suspected RV dysfunction (5.52 ± 4.40 vs 4.32 ± 3.04 vs 1.11 ± 0.57, respectively, P <0.01). RV stroke work was lower in participants with suspected RV dysfunction compared with controls (9.50 ± 8.01 vs 17.71 ± 12.24 vs 17.53 ± 10.32, respectively, P <0.05). The PAPi showed the strongest association with estimates of RV systolic function compared with the other hemodynamic variables studied (r = -0.731, P <0.001) and a decreased PAPi was consistently found among subjects with the combined outcome of in-hospital death and/or need for a pRVSD. According to the authors, the PAPi demonstrated specificity and sensitivity for predicting the need of a pRVSD with a diagnostic accuracy of 97.1%.

The use of invasive hemodynamic measurements with the PAPi may identify patients with severe RV dysfunction while acting as a risk stratification and prediction tool for in-hospital mortality and the need for mechanical circulatory support.

Right Ventricular Failure Increases Risk of Mortality

Patients experiencing RV failure have a high risk for short-term mortality, an effect that has been consistently observed in the setting of cardiogenic shock, pulmonary hypertension, and acute myocardial infarction and post LVAD and Cardiac Transplant.

Management of RV failure with RV support devices may facilitate the rapid stabilization of patients with CS involving the RV. Using a PA catheter, hemodynamic measures predictive of RV failure can be obtained. The measurement of the right atrial to pulmonary capillary wedge pressure ratio is perhaps the simplest method for quantifying RV dysfunction.

Mechanical circulatory support (MCS) devices, represent a useful therapy in the setting of RV failure. While several options exist for percutaneous MCS, Impella RP is the only percutaneous MCS option proven safe and effective by the FDA for support of the RV for up to 14 days. Other devices such as CentriMag® TandemHeart™ and VA-ECMO are used to support the RV. Although CentriMag received FDA HDE approval for CentriMag for use in RVF after LVAD, Impella RP has a broad approval under the PMA and has the longest approved duration.

Utilization of the Impella RP device in isolated RV failure results in the reduction of RA pressure as well as an increase in LV preload and PA pressure. In the setting of biventricular failure, an Impella RP reduces RA pressure while also increasing PA pressure and LV preload.

Early identification of RV failure coupled with utilization of Impella RP may improve outcomes in patients suffering from cardiogenic shock and RV failure.
Best Practices in Cardiogenic Shock

Early diagnosis, stabilization, revascularization, and assessment of heart recovery in patients with cardiogenic shock is needed. Protocol development is increasing at institutions in the United States, and some hospitals have developed a coordinated strategy including shock teams. These structures are being developed to mimic best practices in trauma, STEMI, and acute pulmonary embolism care. Shock teams should be multidisciplinary and have a full understanding of the resources that the hospital can provide. If the hospital cannot provide early revascularization for the cardiogenic shock patient, rapid transfer to a facility that can provide early revascularization is recommended. A multistep strategy to identification and treatment of cardiogenic shock is provided (See Figure 32).

**Impella® Devices Best Practices in AMI Cardiogenic Shock**

- **Identify**
  - SBP < 90 mmHg or on inotropes/pressors
  - Cold, clammy, tachycardia
  - Lactate elevated > 2 mmol/L

- **Stabilize Early**
  - Reduce Door to Unloading Time (DTU)
  - Impella support pre-PCI
  - Reduce inotropes/pressors

- **Complete Revascularization**
  - Per guidelines

- **Assess for Myocardial Recovery**
  - Cardiac Output
  - Cardiac Power Output
  - Urine Output
  - Lactate
  - Inotropes

- **Myocardial Recovery**
  - Ongoing Left Heart Failure
  - Assess for Right Heart Failure

**Figure 32: Impella Devices Best Practices in AMI Cardiogenic Shock**

**The Key to a Good Outcome**

An editorial by Hollenberg et al. identified the key to a good outcome in cardiogenic shock as “an organized approach” which starts with the early diagnosis and prompt treatment. There are multiple steps in the aggressive treatment of cardiogenic shock, including: rapid diagnosis (identification) and prompt initiation of pharmacological treatment (stabilization) and reversal of the underlying cause (revascularization). The most important intervention (in cardiogenic shock due to AMI) required to improve survival is “early and definitive restoration of coronary blood flow.” In addition, the 2015 SCAI/ACC/HFSA/STS Clinical Expert Consensus Statement on the Use of Percutaneous Mechanical Circulatory Support Devices in Cardiovascular Care, supports the “insertion of mechanical support devices as soon as possible in the cardiogenic shock patient, if initial attempts with fluid resuscitation and pharmacologic support fail to show any significant hemodynamic benefit, and before PCI.” Therefore, the development and implementation of rapid cardiogenic shock identification and stabilization, including the early use of mechanical support devices and revascularization protocols, is imperative to achieving improved outcomes in the cardiogenic shock patient population.
Stabilize Early (STEMI and NSTEMI):
Once the patient is diagnosed with cardiogenic shock, the immediate stabilization of the patient becomes priority and locally developed protocols must provide guidance for early and aggressive treatment. As demonstrated by Wayangankar et al., the risk of poor outcomes in the AMI cardiogenic shock patient is higher, when therapeutic intervention is delayed; therefore, the basis for the protocol must focus on the early identification of the patient in cardiogenic shock, rapid stabilization, and revascularization.11

Protocols and processes must allow for stabilization to be immediate. Hospitals should consider this immediate stabilization in both the ST elevation MI (STEMI) and non-STEMI patient populations experiencing cardiogenic shock. As per existing protocols for diagnosis of STEMI, an immediate EKG should be performed to determine if the shock is linked to STEMI. If STEMI is diagnosed, the hospital should follow the existing STEMI algorithm for expediting the revascularization of the patient. However, as indicated in the 2015 SCAI/ACC/HFSA/STS consensus statement, the use of a percutaneous support device should be utilized in the cardiogenic shock patient before revascularization is attempted.65 Therefore, hospitals should adapt their existing STEMI protocols to follow this guidance when the patient develops cardiogenic shock.

Traditionally, in both the STEMI and non-STEMI cardiogenic shock patient population, inotropes and vasopressors have been the first-line therapy to stabilize the hemodynamics. Due to the potential harm from utilizing multiple high-dose inotropes and vasopressors, clinicians should continuously evaluate opportunities to wean patients from inotropes/vasopressors.11 Therapy escalation to MCS should be considered as patients are continually reassessed in the intensive care setting for failure of improvement in cardiogenic shock signs (such as increased cardiac output, increased urine output, increased blood pressure and decreased serum lactate levels). The timeframe for this decision should be determined by the clinical team; however, the key to a successful outcome in this patient population is based upon early stabilization and revascularization, making it an imperative decision for rapid escalation to the use of MCS such as Impella. In the algorithm (See Figure 32), the successful identification of cardiogenic shock is followed by the establishment of hemodynamic stability and revascularization. Once the patient has been revascularized, clinicians should continuously monitor the patient for hemodynamic stability.

Complete Revascularization:
Historically, clinical practice guidelines have recommended against PCI Class III, (may cause harm) of non-culprit artery stenoses at the time of primary PCI in hemodynamically stable patients with STEMI, based primarily on the results of nonrandomized studies, meta-analyses and safety concerns (2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction). However, four randomized controlled trials (PRAMI, CvLPRIT, DANAMI 3 PRIMULTI, PRAGUE-13) have since suggested that a strategy of multi-vessel PCI, either at the time of primary PCI or as a planned, staged procedure, may be safe and beneficial in selected patients with STEMI.81

On the basis of these findings, the guidelines have recently updated (2015 ACC/AHA/SCAI Focused Update on Primary PCI for Patients with STEMI: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention) the recommendation for multi-vessel primary PCI in hemodynamically stable patients with STEMI to a Class IIb recommendation to include consideration of multi-vessel PCI, either at the time of primary PCI or as a planned, staged procedure. (Class IIb, Level of Evidence B-R)

Assess for Myocardial Recovery:
As soon as hemodynamic stability is achieved, and the patient is revascularized (as indicated), protocols should include a pathway for weaning the patient from any inotropes/vasopressors, followed by weaning from Impella support. Weaning protocols are important to ensure that patients can recover the function of their heart before increasing the workload of the heart.

Hospitals with successful programs focused on heart recovery, dedicate training time for the ICU nursing staff to learn the benefits of early weaning from inotropes/vasopressors. Protocols should also address the patient’s need to return to their activities of daily living and quality of life. Therefore, as soon as it is achievable, plans should be made to ambulate the patient.
Protocols should provide further guidance on how to respond when patients do not improve while on hemodynamic support despite successful revascularization. Protocols provide common parameters for patient presentations in cardiogenic shock and right heart failure. If the patient fails to improve or demonstrates right heart failure, hospital protocols are needed to identify refractory shock and clarify a pathway to escalate the level of support needed to allow for heart muscle recovery. Clinicians should also consider the patient’s neurological and end-organ status. Protocols should also include steps to determine if further treatment for the patient will be futile. If futility is determined, the clinicians should discuss weaning and end-of-life decisions with patients and their family.

**Escalate and/or Ambulate:**

If the patient’s stages (Clinical and Hemodynamics) fail to improve, escalation of therapy should be immediate and based upon the individual needs of the patient. Two important questions must be evaluated prior to instituting and escalating support. One is the physiologic requirements of the patient based on the patient’s size, or body surface area (BSA). The other factor is the degree of compromise that a patient has experienced. A qualitative judgment about the extent of reduction in cardiac output and the duration of the defect is valuable to assess the magnitude of MCS needed.

Just as earlier intervention with mechanical support improves outcomes, prompt escalation of support is a time-sensitive decision. When patients fail to exhibit signs of cardiogenic shock resolution and exhibit continued signs of deterioration while on inotropes/vasopressors or first-line Impella support, clinicians must evaluate the need of the patient for escalation to an Impella device with greater level of support. Invasive hemodynamic monitoring, as well as clinical status, will help the physician to determine whether the current hemodynamic support is adequate. Signs of improving native contractility include increased arterial pulsatility improving cardiac index and evaluation of ventricular performance on echocardiography. Decreased inotropic requirement, improving lactate levels, and well perfused end organs are signs of myocardial recovery.

**Left and Right Heart Support:**

Patients who fail to improve despite univentricular Impella support should be evaluated for contralateral ventricular failure, as well as for escalation of the support for the supported side. The Impella RP system is FDA approved for patients who develop acute right heart failure or decompensation following LVAD implantation, myocardial infarction, heart transplant, or open-heart surgery. The Impella RP system is the only FDA-approved percutaneous right ventricular support device. It provides over four liters per minute of hemodynamic support by aspirating blood from the RA/IVC junction and delivering the blood into the pulmonary artery. Identification of right heart failure in a patient already on left side support differs somewhat from the identification of isolated right heart failure. Left sided filling pressures may be low in a patient with isolated right ventricular (RV) failure, or LVAD flows may be compromised due to impaired delivery of volume to the left ventricle due to RV dysfunction.

Patients may have elevated CVP pressures out of proportion to the PCWP. CVP/PCWP ratio >0.63 is one metric of RV failure. Korabathina, et al. have demonstrated that the ratio of the pulmonary artery pulse pressure to the RA pressure, termed the Pulmonary Artery Pulsatility Index (PAPI; calculated as PA sys–PA diastolic/RA pressure) is predictive of the need for right heart support if the PAPI < 1.0. Initiation of left ventricular support may uncover the need for right side support. RV failure may become manifest by marked elevation of the RA pressure and the presence of new onset tricuspid regurgitation. Conversely, following right sided univentricular support, PCWP elevation, and onset of pulmonary edema often indicate the need for LV support. Continued requirement of multiple high-dose inotropes, elevated lactate, depressed CPO, and worsening end organ function should prompt the clinician to consider escalation of systemic support to a device capable of delivering more flow. Assessment of a patient’s hemodynamic requirements (BSA) along with the degree of hemodynamic compromise (LVEDP or EF) and the assessment of desired improvement of systemic flow should guide the therapy. A young muscular male with a BSA of 2.4 m² may require escalation from Impella 2.5 to Impella CP to wean inotropes or to increase CPO to the 0.7 Watt range. All these critical patient care decisions require invasive hemodynamic monitoring and continual intensive care monitoring, reassessment and decision making to optimize outcomes by appropriate escalation and de-escalation of left and right sided support.
Cost Effectiveness

Impella has been determined to be one of the most cost-effective treatments in cardiogenic shock. Maini et al. concluded that in addition to reduction in length of stay (LOS), patients treated with Impella devices had improved survival with reduced cost (See Figure 33). A systemic review of cost effectiveness studies also observed reduction in LOS across multiple patient populations.

![Reduction of Length of Stay Between PVADs and Respective Comparators](image)

*Figure 33: Reduction of Length of Stay Between PVADs and Respective Comparators*

The 2014 publication by Stretch, et al, which evaluated the records of 11,887 patients highlighted that IABP use was associated with cost increases of 25.2% (p < 0.001). However, the paper also noted that the “use of short-term MCS in the United States has increased rapidly, whereas rates of in-hospital mortality have decreased. These changes have taken place in the context of declining hospital costs associated with short-term MCS.”

*Not available/calculated.
Figure adapted from Manini et al.*
References:

73. Burkhoff D. Mechanical properties of the heart and its interaction with the vascular system. Cardiac Physiol. (White Paper) 2011.
In addition to the risks above, there are other WARNINGS and PRECAUTIONS associated with Impella devices. Learn more visit: www.abiomed.com/important-safety-information

### POTENTIAL ADVERSE EVENTS

**Acute renal dysfunction, Aortic valve injury, Bleeding, Cardiogenic shock, Cerebral vascular accident/ Stroke,Death, Hemolysis, Limb ischemia, Myocardial infarction, Renal failure, Thrombocytopenia and Vascular injury**

*In addition to the risks above, there are other WARNINGS and PRECAUTIONS associated with Impella devices. Learn more visit: www.abiomed.com/important-safety-information*

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### Right-Side Support

The Impella RP® System is indicated for providing temporary right ventricular support for up to 14 days in patients with a body surface area ≥1.5 m², who develop acute right heart failure or decompensation following left ventricular assist device implantation, myocardial infarction, heart transplant, or open-heart surgery.

**Important Risk Information for Impella RP System**

**CONTRAINDICATIONS**

The Impella RP System is contraindicated for patients with the following conditions: Disorders of the pulmonary artery wall that would preclude placement or correct positioning of the Impella RP device. Right ventricular failure with valvular stenosis or valvarular regurgitation. Mural thrombi of the right atrium or vena cava. Anatomic conditions precluding insertion of the pump. Heart failure and/or cardiogenic shock as a consequence of refractory ventricular arrhythmias, as well as a consequence of sustained supraventricular arrhythmias, causing haemodynamic compromise.

**Important Risk Information for Impella RP System**

Learn more visit: www.abiomed.com/important-safety-information

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### EUROPE

**Left-Side Support**

**Impella 2.5® and Impella CP®**

- The Impella (intracardiac pump for supporting the left ventricle) is intended for clinical use in cardiology and in cardiac surgery for up to 5 days for the following indications, as well as others:
  - The Impella is a circulatory support system for patients with reduced left ventricular function, e.g., post-cardiotomy, low output syndrome, cardiogenic shock after acute myocardial infarction, or for myocardial protection after acute myocardial infarction.
  - The pump may also be used as a cardiovascular support system during coronary bypass surgery on the beating heart, particularly in patients with limited preoperative ejection fraction with a high risk of postoperative low output syndrome.
  - Support during high risk percutaneous coronary intervention (PCI).
  - Post PCI.

**Impella 5.0®, Impella LD®**

- The Impella (intracardiac pump for supporting the left ventricle) is intended for clinical use in cardiology and in cardiac surgery for up to 5 days for the following indications, as well as others:
  - The Impella is a cardiovascular support system for patients with reduced left ventricular function, e.g., post-cardiotomy, low output syndrome, cardiogenic shock after acute myocardial infarction.
  - The pump may also be used as a cardiovascular support system during coronary bypass surgery on the beating heart, particularly in patients with limited preoperative ejection fraction with a high risk of postoperative low output syndrome.

**CONTRAINDICATIONS**

- Mechanical aortic valves, severe aortic valvular stenosis or valvular regurgitation.
- Hematological disorder causing fragility of the blood cells or hemolysis.
- Hypertrophic obstructive cardiomyopathy (HOCM).
- Aneurysm or necrotomy or severe anomaly of the ascending aorta and/or the aortic arch.
- Mural thrombus in the left ventricle.
- Ventricular septal defect (VSD) after myocardial infarction.
- Anatomic conditions precluding insertion of the pump.
- Other illnesses or therapy requirements precluding use of the pump.
- Severe peripheral arterial occlusion disease (PAD). A relative contraindication.

**POSSIBLE COMPLICATIONS**

There are risks of complications with every procedure using a blood pump. These include among others:
- Hemolysis
- Bleeding
- Immune reaction
- Embolism, thrombosis
- Vascular injury through to anocerecotomy
- Positioning problems
- Infection and septicaemia
- Dislocation of the pump

In addition to the risks above, there are other WARNINGS and PRECAUTIONS associated with Impella devices. For more information please see the Instructions For Use Manual. Learn more visit: www.abiomed.com/important-safety-information

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### CANADA

**Left-Side Support**

**Impella 2.5® and Impella CP®**

- The Impella (intracardiac pump for supporting the left ventricle) is intended for clinical use in cardiology and in cardiac surgery for up to 5 days for the following indications:
  - The Impella is a circulatory support system for patients with reduced left ventricular function, e.g., post-cardiotomy, low output syndrome, cardiogenic shock after acute myocardial infarction, or for myocardial protection after acute myocardial infarction.
  - The pump may also be used as a cardiovascular support system during coronary bypass surgery on the beating heart, particularly in patients with limited preoperative ejection fraction with a high risk of postoperative low output syndrome.
  - Support during high risk percutaneous coronary intervention (PCI).
  - Post PCI.

**Impella 5.0®, Impella LD®**

- The Impella (intracardiac pump for supporting the left ventricle) is intended for clinical use in cardiology and in cardiac surgery for up to 10 days. Learning visit: www.abiomed.com/important-safety-information

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### Important Risk Information for Impella devices

**CONTRAINDICATIONS**

- Aortic dissection, in particular calcification or other disorders of the pulmonary artery wall.
- Mechanical valves, severe valvular stenosis or valvular regurgitation of the tricuspid valve or pulmonary valve.
- Mural thrombi of the right atrium or vena cava.
- Anatomic conditions precluding insertion of the pump.
- Other illnesses or therapy requirements precluding use of the pump.
- Presence of a vena cava filter or caval interruption device, unless there is clear access from the femoral vein to the right atrium that is large enough to accommodate a 22 Fr catheter.

**POTENTIAL ADVERSE EVENTS**

There are risks of complications with every procedure using a blood pump. These include among others:
- Hemolysis
- Bleeding
- Immune reaction
- Embolism, thrombosis
- Vascular injury through to angieroncetomy
- Infection and septicaemia
- Endocardiac injuries due to attachment of the pump to the valve system following incorrect positioning
- Cardiogenic shock due to acute myocardial infarction.

In addition to the risks above, there are other WARNINGS and PRECAUTIONS associated with Impella devices. For more information please see the Instructions For Use Manual. Learn more visit: www.abiomed.com/important-safety-information

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*CE-Zulassung: Impella 2.5, Impella CP 5 Tage, Impella 5.0, Impella LD: 10 Tage