CLINICAL DOSSIER

Cardiogenic Shock
therapy with Impella®
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.¹ The latest approval adds to the prior FDA indication of Impella 2.5 for elective and urgent high-risk percutaneous coronary intervention (PCI), or Protected PCI™.

**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, cardiac output, CPO, CI, PCWP, SVO₂

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**Hemodynamic Effects of Impella Support**

![Hemodynamic Effects Diagram](image)

**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.”²⁻³¹


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**30-Day Survival**

![30-Day Survival Graph](image)

- **cVAD Registry**: Impella Pre-PCI
- **IABP/Inotropes Pre-PCI**: Log-Rank, p=0.004

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**Executive Summary**

**Improving Outcomes in Cardiogenic Shock**

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**Impella Devices**
- **Impella 2.5™**
- **Impella CP®**
- **Impella 5.0™**
- **Impella LD™**
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.\textsuperscript{13} Compensatory systemic vasoconstriction with high systemic vascular resistance (SVR) occurs in response to the depression of CO.\textsuperscript{21} Cotter, et al. categorized acute heart failure patients according to cardiac power and demonstrated its importance in risk stratification and selection of therapy.\textsuperscript{22} Cardiac power output (CPO), the product of cardiac output and mean arterial pressure, CPO=(CO x MAP/451), is a useful prognostic indicator in chronic heart failure.\textsuperscript{5}

In the SHOCK trial, CPO was the hemodynamic variable most strongly associated with in-hospital mortality (See Figure 1).\textsuperscript{5} 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\textsuperscript{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.\textsuperscript{5}

\textit{Figure 1: Cardiac Power Output \#1 Correlate to Mortality in AMI Cardiogenic Shock}\textsuperscript{5}
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. 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).

Figure 2: Incidence of Cardiogenic Shock Growing and STEMI Cardiogenic Shock in Medicare Age Increasing

The in-hospital mortality rate for AMI cardiogenic shock has remained constant at 50% for more than a decade. Those 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). The combined effect of the in-hospital and early post discharge hazard approaches a mortality rate of 60%.

Figure 3: Cardiogenic Shock Remains Leading Cause of Mortality in Acute Myocardial Infarction

Age ≥65 only; excludes non-Medicare population.
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.27 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 in small, often community, hospitals and in catheterization laboratories with smaller procedural volumes.27 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).27 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.

*Figure 4: AMI Cardiogenic Shock Often Treated Community in Hospitals*27
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. Randomized clinical trials have not shown a hemodynamic or mortality benefit with IABP when compared with medical therapy.

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 major drawback of this therapy resides in the increased mortality associated with the administration of inotropes and the temporary improvement of hemodynamic parameters and cardiac output at the 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 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 (See Figure 5).

**Figure 5: High-Dose Vasopressors/Inotropes Associated With Increased in-Hospital Mortality**

Mortality Risk  
(N=3462)

<table>
<thead>
<tr>
<th>Inotrope</th>
<th>Moderate Dose</th>
<th>One High Dose</th>
<th>Two High Dose</th>
<th>Three High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Inotrope</td>
<td>2%</td>
<td>7.5%</td>
<td>21%</td>
<td>80%</td>
</tr>
<tr>
<td>Low Dose</td>
<td>3%</td>
<td></td>
<td>42%</td>
<td></td>
</tr>
</tbody>
</table>

Inotropes and vasopressors increase the myocardial oxygen consumption (MVO$_2$). By increasing both contractility and afterload, they increase myocardial oxygen demand and mechanical work in an already compromised ventrical.

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. In fact, 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).

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. Addressing and treating the underlying etiology and use of effective mechanical circulatory support (MCS) will allow 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). The IABP must be timed with precision to the patient's EKG to provide benefit, and is not optimal in patients with tachycardia or heart rate irregularity. In IABP-SHOCK-I, there was no hemodynamic effect in AMI cardiogenic shock (See Figure 7A) likely due to the low native cardiac output, which is normally experienced during cardiogenic shock.

IABP-SHOCK-II (n=600), concluded no mortality benefit of IABP compared with medical therapy in the setting of AMI complicated by cardiogenic shock. 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 7B). At 12 month follow-up of these patients, there was no survival benefit observed between the IABP arm and control arm.

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 cardiogenic shock patients. Subsequently, the European Society of Cardiology (ESC) downgraded the guidelines for the IABP to Class III (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. This is likely due to delayed care in AMI cardiogenic shock patients, according to the authors (See Figure 8).

Figure 8: Predictors of Mortality in AMI Cardiogenic Shock and Contemporary Trials With IABP

<table>
<thead>
<tr>
<th>Predictors of Mortality in AMI Cardiogenic Shock</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>
</tr>
</tbody>
</table>

Contemporary Trials With IABP

<table>
<thead>
<tr>
<th>Trial/First Author</th>
<th>Indications</th>
<th>Definition</th>
<th>N</th>
<th>Control or No IABP Survival</th>
<th>Prophylatic or IABP Survival</th>
<th>Routine Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>IABP-SHOCK-II</td>
<td>AMI and CS</td>
<td>SBP &lt;90 mm Hg for &gt;30 min or vasoactive medications needed to maintain SBP &gt;90, pulmonary edema, end-organ dysfunction (AMS, cool extremities, UOP &lt;30 mL/h, lactate &gt;2)</td>
<td>600</td>
<td>41.3%</td>
<td>39.7%</td>
<td>No difference in survival</td>
</tr>
<tr>
<td>TACTICs</td>
<td>AMI and CS</td>
<td>s/p fibrinolysis</td>
<td>57</td>
<td>67% at 30 days Killip III/IV; 20% at 6 months</td>
<td>73% at 30 days Killip III/IV; 61% at 6 months</td>
<td>No significant difference except in Killip III/IV patients who received IABP</td>
</tr>
<tr>
<td>Waksman et al.</td>
<td>AMI and CS</td>
<td>s/p fibrinolysis</td>
<td>45</td>
<td>19%</td>
<td>46%</td>
<td>In-hospital survival improved with IABP use in patients s/p fibrinolysis</td>
</tr>
<tr>
<td>NRMI</td>
<td>AMI and CS</td>
<td>Observational study: IABP compared to no IABP among patients given fibrinolysis or primary angioplasty</td>
<td>IABP=7,268 No IABP=15,912</td>
<td>Lytics: 67% in-hospital mortality PTCA: 42% in-hospital mortality</td>
<td>Lytics: 49% in-hospital mortality PTCA: 47% in-hospital mortality</td>
<td>IABP provided substantial benefit in patients with AMI and CS who received fibrinolysis</td>
</tr>
</tbody>
</table>

Table adapted from Atkinson et al.
Extracorporeal Membrane Oxygenation (ECMO):

In the past decade, the use of ECMO has grown rapidly; however, the data show no evidence of improved outcome in the setting of cardiogenic shock. Patients who may benefit the most from ECMO are those with primary pulmonary insufficiency, 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.

Additionally, a recent meta-analysis conducted by Cheng, et al. on 1,866 adult patients supported with ECMO for the treatment of cardiogenic shock and cardiac arrest showed that there is a significant morbidity associated with this treatment, including lower extremity amputation (4.7%), stroke (5.9%), neurological complications (13.3%), acute kidney injury (55.6%), major or significant bleeding (40.8%), rethoracotomy for bleeding or tamponade in postcardiotomy patients (41.9%), and significant infection (30.4%). Furthermore, recent studies have shown that outcomes with ECMO in the setting of cardiogenic shock were unacceptably high with in-hospital mortality exceeding 70%.

ECMO systems (which consist of pumps, oxygenators, heater and cooler systems, and tubing) allow high blood flow, but these systems do not unload the heart. Indeed, the retrograde flow generated from the outflow cannula in the descending aorta can lead to a dangerous rise in the left atrial and ventricular pressure in a notable proportion of cases. Consequently, this complication of ECMO can result in extreme heart dilation and pulmonary edema and lowers the ischemic threshold of the heart and reduces the likelihood of left ventricular recovery. 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. The resultant afterload increase imparted by the retrograde femoral blood flow can place the myocardium in greater jeopardy thereby minimizing the chances for myocardial recovery.

In summary, high morbidity and mortality rates persist with ECMO, despite strategies often implemented to improve results and reduce complication rates. Provisions to prevent distal limb ischemia, left ventricular distention, and central hypoxia, often involve additional devices, procedures, and expense. Overall, these measures have been shown to be ineffective and detrimental to the long-term outcome of the patient.
Impella® Device Description and Hemodynamic Characteristics

The Impella® Ventricular Support System consists of a family of percutaneous heart pumps: the Impella 2.5™, Impella CP®, Impella 5.0™, and Impella RP® catheters. These pumps are the smallest, percutaneous ventricular support devices available. The left-sided Impella devices are inserted percutaneously and placed in the left ventricle across the aortic valve, generating forward blood flow in the ascending aorta and directly unloading the left ventricle. Use of Impella 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]) and augmenting peak coronary flow.17 These changes result in favorable alteration of the balance between myocardial oxygen supply and demand. In total, 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 needed to support more than 40,000 patients. The Impella platform, which includes the Impella 2.5, Impella CP, Impella 5.0 and the Impella RP (right percutaneous) devices, is approved by the U.S. Food & Drug Administration (FDA) for different device-specific indications. Since the U.S. market introduction in 2008, more than 1,000 hospitals have provided hemodynamic support with Impella to over 37,000 patients. In the past decade, 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) and China (2013) for indications including high-risk Percutaneous Coronary Intervention (PCI) and cardiogenic shock.
**Impella® Platform/FDA Approvals:**

In the United States, the Impella 2.5™ device has been used since 2006. The first investigation of Impella was the PROTECT 1, FDA trial for high-risk PCI. The Impella 2.5 device received U.S. FDA 510(k) clearance in 2008 and received Pre-Market Approval (PMA) in 2015, deeming it safe and effective in elective and urgent high-risk PCI, or Protected PCI™. The approved use for the Impella 2.5 in Protected PCI includes the treatment of hemodynamically stable patients with severe coronary artery disease and depressed left ventricular ejection fraction (LVEF) undergoing elective or urgent PCI. The FDA had determined that the use of the Impella 2.5 in connection with these patients may result in a reduction of peri- and post procedural adverse events.

In 2016, the Impella 2.5, Impella CP®, Impella 5.0™ and Impella LD™ devices received FDA approval for the treatment of ongoing cardiogenic shock, immediate (<48 hours) post-acute myocardial infarction (AMI) or postcardiotomy 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.

The most recently added device to the Impella platform is the Impella RP®, a percutaneous pump designed for right heart support. In 2015, the Impella RP received a Humanitarian Device Exemption (HDE) approval from the FDA for circulatory assistance in pediatric or adult 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 optimizes right heart hemodynamics, providing up to four liters per minute of blood flow.

**Hemodynamic Stabilization With Impella**

- Unloads Left Ventricle & Coronary Perfusion
- End Organ Perfusion
- Right Side Support
- Escalation & Ambulation
The Hemodynamic Benefits of Impella® Therapy in Cardiogenic Shock

The Impella left side heart pump propels blood forward from the left ventricle into the aorta. Impella’s active forward flow and systemic aortic pressure contribution, increases MAP. This increase in MAP and forward flow provides end-organ perfusion, which requires both pressure and flow. The objective measure of these parameters is their product (MAP x CO/451) is referred to as CPO. Impella’s action, directly unloading the left ventricle, is unique among MCS devices. The active removal of blood from the LV cavity reduces end-diastolic volume and pressure (LVEDV, LVEDP) and augments peak coronary flow. This leads to a favorable alteration of the balance of myocardial oxygen supply and demand. This cascade of hemodynamic effects has been described in the literature and validated in computational modeling in a variety of pre-clinical and clinical studies (See Figure 9).

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. LV wall tension (characterized by Laplace as Pressure x Diameter/wall thickness) falls leading to subsequent reduction in microvascular resistance. Simply put, the myocardial perfusion gradient improves with a rise in MAP and drop in LVEDP. Nellis, et al. demonstrated in an animal model that a 40 mmHg pressure gradient exists between coronary arterioles and venules. Sustained hypotension with coronary perfusion gradients <40 mmHg can lead to profound myocardial ischemia, which quickly depresses an already impaired left ventricle and may lead to cardiovascular collapse and arrest.

Figure 9: Principles of Impella Design

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*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 significant increased hyperemic flow velocity and CFVR with increasing levels of Impella support by Remmelink, et al. The myocardial perfusion effects of Impella can be 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 (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 10).

**Figure 10: Improved Myocardial Perfusion With Impella**

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 with the Impella device turned off (A) and turned on (B), in the setting of STEMI with shock (see Figure 11).

**Figure 11: Improved End-Organ Perfusion With Impella**
Clinical Evidence of Safety and Effectiveness for Impella® in Cardiogenic Shock

Clinical scientific 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 Registry, incorporating data from all Impella devices at participating sites
- Benchmarking data from the AB5000 registry
- Prospective randomized controlled trial data from the ISAR-SHOCK trial
- Clinical trial data from the RECOVER I trial
- Literature review of scientific publications

**USpella/cVAD Registry Results (for All Impella Devices):**

All data for US PMA approvals came out of 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 purpose of the cVAD Registry is to capture data reflecting "real-world" use of Impella devices in current clinical practice and provide insights into patient characteristics, comorbid conditions, outcomes, patterns of care, and performance metrics of participating institutions to guide improvement efforts (See Figure 12). The registry, started by Abiomed® in 2009, enrolls patients at qualifying sites in the United States and Canada. The current sites include high- and low-volume 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. Recently, European sites have been added to the registry, and Japanese sites are expected to be added following regulatory approval of the Impella devices in Japan.

In addition to the PROTECT II clinical trial data, Abiomed used the cVAD Registry data for the PMA approval submission as supporting evidence of safety and efficacy of Impella 2.5 used for the high-risk PCI indication in routine daily clinical practice.
Furthermore, 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 3.5 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. 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 have been excluded from this trial. 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 are shown in Figure 13. As expected, the “salvage” group of patients had poorer outcomes than the RCT group, which is more representative of patients chosen for cardiogenic shock RCTs. In addition, the outcomes data for both 30-day survival and survival to discharge are provided in Figures 14 and 15, respectively, for each Impella® device.

*Formerly known as USpella Registry.
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)

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)
The Need for Early Identification of Cardiogenic Shock Patients

Poor outcomes and ineffective or detrimental treatments for cardiogenic shock patients require a call to action for the clinical community to find better solutions when treating this patient population. 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 (See Figure 17).

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.\(^53\)

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.\(^54\)

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.

**Figure 16: 30-Day Survival**\(^60\)

Door to Balloon Time Metric - Cardiogenic shock and hemodynamic support cases are excluded from Door to Balloon (DTB) metrics. Source: CMS, SCAI & ACC

*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*
Cardiac Output
LVEDP
End Organ Perfusion
Coronary Perfusion
Ischemia
End Organ Failure
Progressive Myocardial Dysfunction
Death Spiral of Cardiogenic Shock

GOAL: Myocardial Recovery Patients

Reverse Spiral

Figure 17: Reverse The Cardiogenic Shock Spiral
Benchmark Data from the AB5000/BVS 5000 Registry:

Further data was provided to the FDA through a benchmark analysis of cVAD Registry™ patients supported with Impella® for AMI cardiogenic shock with comparable patients included in the Abiomed® AB5000/BVS5000 Registry. The Abiomed BVS5000 extracorporeal surgical pump was the first VAD approved by the FDA in 1992 to support patients with left, right, or biventricular failure in the setting of cardiogenic shock. In 2003, following the completion of a post market approval (PMA) study including 60 patients, the FDA granted marketing approval for use of the AB5000 VAD in patients suffering from postcardiotomy cardiogenic shock or acute cardiac disorder leading to hemodynamic instability. The AB5000 is similar to the BVS5000 in that it can produce a stroke volume of 80 mL and flows of up to 6 L/min, but different in that it has higher reliability and it allows for patient ambulation.

The data source for this benchmark analysis included the review of 2,152 patients enrolled in the AB5000/BVS5000 Registry. Of these, 115 patients supported with the AB5000 pump for AMI cardiogenic shock were found to be an eligible match with the 324 cVAD Registry patients supported with Impella for the same indication. The results of this benchmark analysis demonstrated a significantly better survival to discharge (p=0.036) in the patient supported with Impella.

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.48 This prospective randomized study demonstrated that the Impella 2.5 provided superior hemodynamic improvement compared with IABP for cardiogenic shock patients (See Figure 18).48 The Impella 2.5 device was found to significantly increase cardiac index compared to IABP, while simultaneously unloading the left ventricle.

*Figure 18: Hemodynamic Stability and LV Unloading With Impella*48

<table>
<thead>
<tr>
<th></th>
<th>Impella 2.5</th>
<th>IABP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Augmented CI</td>
<td>2.20 ± 0.64</td>
<td>1.84 ± 0.71</td>
</tr>
<tr>
<td>Ventricular Unloading</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Native CI</td>
<td>1.71 ± 0.45</td>
<td>1.73 ± 0.59</td>
</tr>
<tr>
<td>Pre-Support Native Heart</td>
<td>p=0.02</td>
<td>N.S.</td>
</tr>
</tbody>
</table>
**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 19: 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>IIb</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>IIb</td>
<td>2013</td>
<td>2016</td>
</tr>
<tr>
<td>STEMI and Urgent CABG</td>
<td>IIa</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>2015/16</td>
</tr>
</tbody>
</table>

** Categories referencing Impella include Percutaneous LVAD, PVAD, Non-durable MCS, TCS and percutaneous MCSO
* Excludes Protect II Randomized Controlled Trial, and FDA PMA approval studies due to timing of available data in 2011
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 20).

Figure 20: Impella® Best Practices in AMI Cardiogenic Shock

- **Identify (Protocols)**
  - SBP <90 mmHg or on Inotropes/Pressors
  - Cold, clammy, tachycardia
  - Lactate elevated >2 mmol/L

- **Stabilize Early**
  - Impella Support pre-PCI
  - Reduce Inotropes/Pressors

- **Complete Revascularization**
  - PCI Guidelines based in Cardiogenic Shock

- **Assess for Myocardial Recovery**
  - Weaning and Transfer Protocols
  - Cardiac Output
  - Cardiac Power Output
  - Urine Output
  - Lactate
  - Inotropes

- **Myocardial Recovery**
  - Ongoing Left heart failure

- **No Recovery Escalate & Ambulate**
  - Assess for Right heart failure

- **Cardiogenic etiology evaluation**
  - EKG (STEMI / NSTEMI)
  - Echocardiography
  - If available, PA Catheter, Cardiac Output, CPO, CI, PCWP, Svo₂
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.

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 aforementioned 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. 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. 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 time frame 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 20), 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, 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.

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)

*Figure 21: Culprit Artery—Only Versus Multivessel PCI*

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>B-R</td>
<td>PCI of a noninfarct artery may be considered in selected patients with STEMI and multivessel disease who are hemodynamically stable, either at the time of primary PCI or as a planned staged procedure.¹</td>
</tr>
</tbody>
</table>

¹ Modified recommendation from 2013 Guideline (changed class from III: Harm to IIb and expanded time frame in which multivessel PCI could be performed).
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 are allowed to 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® 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 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 (PAp; calculated as PA sys-PA diastolic/RA pressure) is predictive of the need for right heart support if the PAp <1.0.58 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® in order to wean inotropes or to increase CPO to the 0.7 Watt range. All of 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.¹ A systemic review of cost effectiveness studies also observed reduction in LOS across multiple patient populations.

Figure 22: Reduction of Length of Stay Between PVADs and Respective Comparators¹

*Not available/calculated.
Figure adapted from Maina et al.¹
References:


The Impella RP® System is indicated for providing circulatory assistance for up to 14 days in pediatric or adult 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.

CONTRAINDICATIONS
The Impella RP is contraindicated for use with patients experiencing any of the following conditions: (1) Disorders of the pulmonary artery wall that would preclude placement or correct positioning of the Impella RP device; (2) Mechanical valves, severe valvular stenosis or valvular regurgitation of the tricuspid valve or pulmonary valve; (3) Mural thrombus of the right atrium or vena cava; (4) Anatomic conditions precluding insertion of the pump; (5) Other illnesses or therapy requirements precluding use of the pump; and (6) Presence of a vena caval 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
Additionally, potential for the following risks has been found to exist with the use of the Impella RP: Arrhythmia; Atrial fibrillation; Bleeding; Cardiac tamponade; Cardiogenic shock; Death; Device Malfunction; Hemolysis; Hepatic failure; Insertion site infection; Perforation; Phlegmasia cerulea dolens (a severe form of deep venous thrombosis); Pulmonary valve insufficiency; Respiratory dysfunction; Sepsis; Thrombocytopenia; Thrombotic vascular (non-central nervous system) complication; Tricuspid valve injury; Vascular injury; Venous thrombosis; Ventricular fibrillation and/or tachycardia

The Impella RP is approved for use as a Humanitarian Device. It’s effectiveness for the above indication has not been demonstrated.