SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Temporary Ventricular Support Device

Device Trade Name: Impella Ventricular Support Systems

Device Procode: OZD

Applicant's Name and Address: Abiomed, Inc.
22 Cherry Hill Drive
Danvers, MA 01923

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P140003/S018

Date of FDA Notice of Approval: February 7, 2018

The original PMA for the Impella 2.5 System (PMA P140003) was approved on March 23, 2015. The approved indication for use for the Impella 2.5 System is:

The Impella 2.5 System is a temporary (< 6 hours) ventricular support device indicated for use during high risk percutaneous coronary interventions (PCI) performed in elective or urgent, hemodynamically stable patients with severe coronary artery disease and depressed left ventricular ejection fraction, when a heart team, including a cardiac surgeon, has determined high risk PCI is the appropriate therapeutic option. Use of the Impella 2.5 in these patients may prevent hemodynamic instability which can result from repeat episodes of reversible myocardial ischemia that occur during planned temporary coronary occlusions and may reduce peri- and post-procedural adverse events.

The SSED to support the indication is available on the CDRH website and is incorporated by reference here: https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140003B.pdf.

On April 7, 2016 panel-track supplements (P140003/S004 and P140003/S005) were approved for patients experiencing ongoing cardiogenic shock immediately (<48 hours) following acute myocardial infarction or open heart surgery for the Impella Ventricular Support Systems. The SSEDs to support these indications are available on the CDRH website at: https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140003S004B.pdf and https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140003S005B.pdf, respectively. The current supplement (P140003/S018) was submitted to expand this indication to incorporate the setting of cardiomyopathy, including peripartum cardiomyopathy or myocarditis within the ongoing cardiogenic shock indication.

II. INDICATIONS FOR USE

The Impella 2.5, Impella CP, Impella 5.0, and Impella LD Catheters, in conjunction with the Automated Impella Controller, are temporary ventricular support devices intended for short term use (≤4 days for the Impella 2.5 and Impella CP, and ≤6 days for the Impella 5.0 and Impella LD) and indicated for the treatment of ongoing cardiogenic shock that occurs:

- immediately (<48 hours) following acute myocardial infarction or open heart surgery, or
- in the setting of cardiomyopathy, including peripartum cardiomyopathy, or myocarditis

as a result of isolated left ventricular failure that is not responsive to optimal medical management and conventional treatment measures.* The intent of the Impella Support Systems therapy is to reduce ventricular work and to provide the circulatory support necessary to allow heart recovery and early assessment of residual myocardial function.

**Optimal medical management and conventional treatment measures include volume loading and use of pressors and inotropes, with or without IABP.*

III. CONTRAINDICATIONS

The Impella Ventricular Support Systems are contraindicated for patients with the following conditions:

- Mural thrombus in the left ventricle
- Mechanical aortic valve or heart constrictive device
- Aortic valve stenosis/calcification (equivalent to an orifice area of 0.6 cm^2 or less)
- Moderate to severe aortic insufficiency (echocardiographic assessment graded as ≥ +2)
- Severe peripheral arterial disease that precludes the placement of an Impella Catheter
- Significant right heart failure
- Combined cardiorespiratory failure
- Presence of an atrial or ventricular septal defect (including post-infarct VSD)
- Left ventricular rupture
- Cardiac tamponade

IV. WARNINGS AND PRECAUTIONS

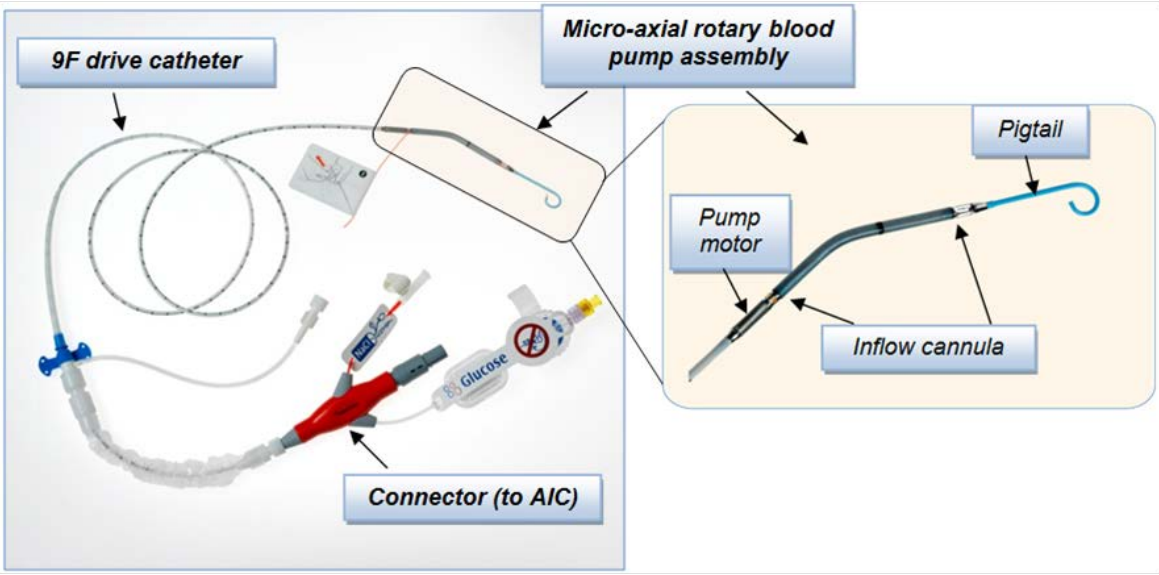
The warnings and precautions can be found in the Impella Ventricular Support Systems labeling.

V. DEVICE DESCRIPTION

To accommodate a range of cardiac flow requirements and implant techniques, four different Impella support Catheters are available. Figure 1 shows general overall design for the Impella Catheters. All of the Impella Catheters consist of a micro-axial rotary

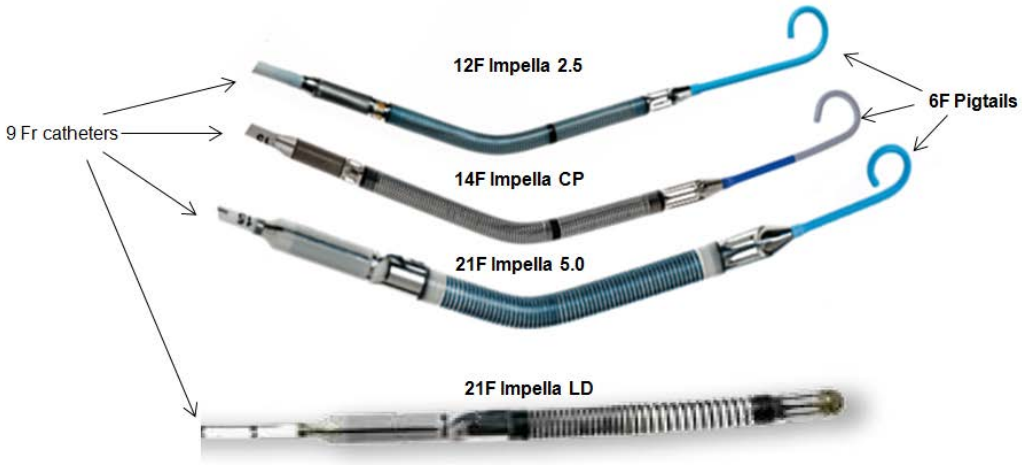
blood pump mounted on a 9F drive catheter, which is connected to an external controller, the Automatic Impella Controller (AIC).

Figure 1: Impella ventricular support catheter design



There are four different Impella Catheters, as shown in Figure 2. The peripherally placed catheters are the Impella 2.5, the Impella CP and the Impella 5.0, which have blood pump diameters of 12F, 14F and 21F, respectively. In addition, a fourth 21F surgically placed Impella Catheter, the Impella LD is available.

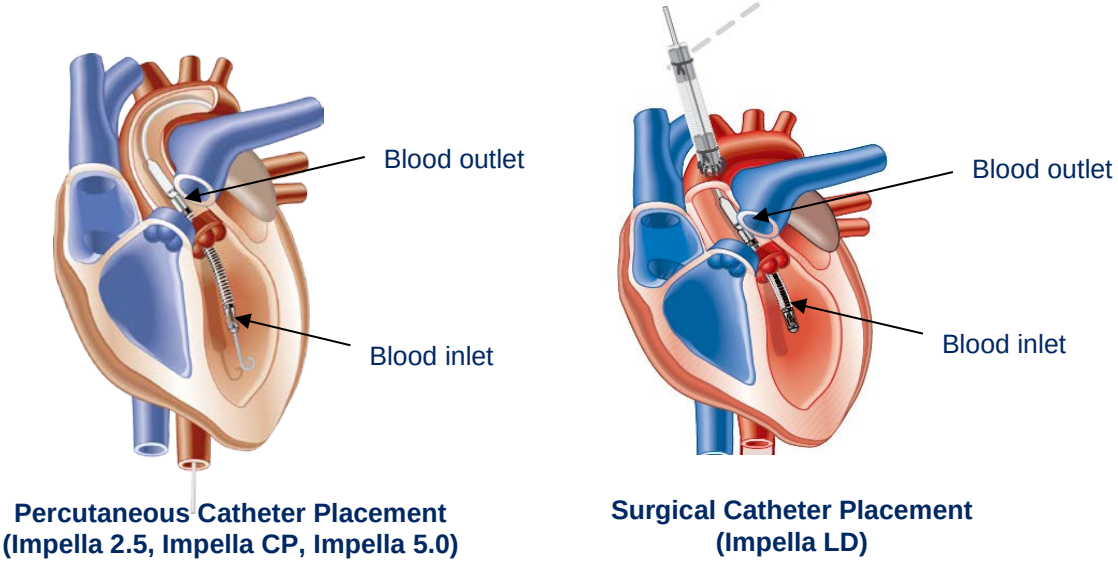
Figure 2: The Impella Ventricular Support Catheters



The Impella Catheters shown above are all placed with the cannula inflow located in the left ventricle and the outflow located in the ascending aorta, as shown in Figure 3. Blood

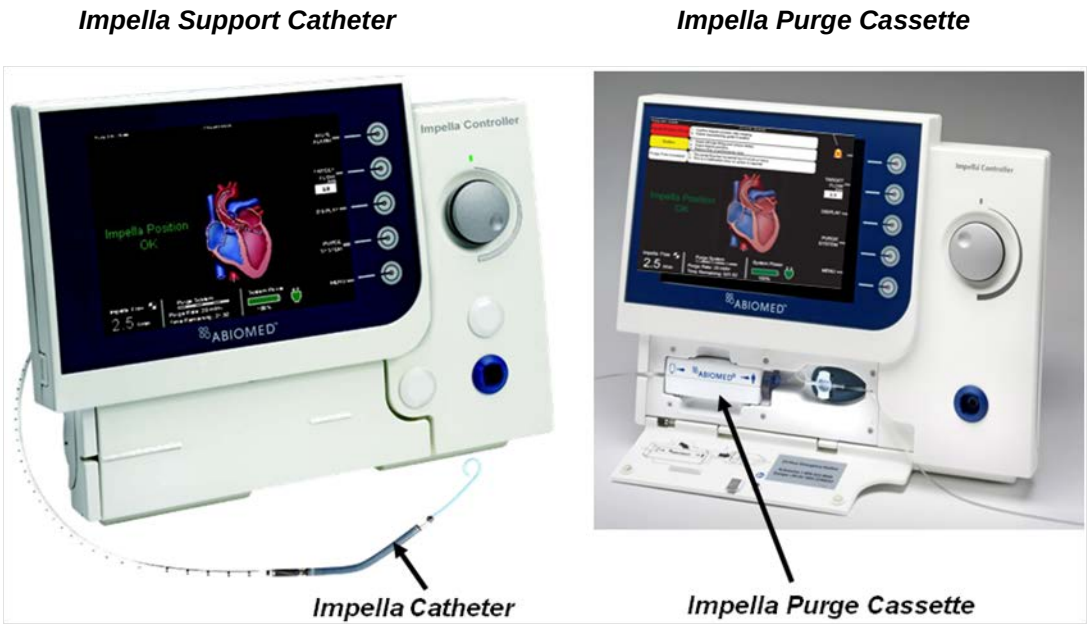
is drawn through the cannula situated in the left ventricle and expelled into the aorta. As shown in Figures 2 and 3, the three peripherally placed pumps (the Impella 2.5, Impella CP and Impella 5.0) have 6F pigtails attached to their tips, to enable device placement over the wire and positioning in the correct anatomical position. When placing an Impella Catheter peripherally (via a guidewire), the device is loaded over the wire through the pigtail. The Impella 5.0, while placed peripherally, requires a graft and a surgical cut-down and can access the circulation through either the femoral or axillary artery. Alternatively, the Impella LD is surgically placed directly through the aorta into the heart (see Figure 3).

Figure 3: Ventricular placement of the Impella Catheters



The Impella Catheters are operated by the same external drive console, the Automatic Impella Controller (AIC), shown in Figure 4. The AIC generates signals required to power the drive motor of the Impella Catheters and provides a user interface. The AIC also incorporates the disposable Impella Purge Cassette system, which provides a fluid pressure barrier to prevent blood from entering the Impella Catheter's drive motor. A dextrose (5-40% with 50 Units/ml of heparin added) solution is used as a purge fluid. The AIC is portable and can be used for patient transport by trained healthcare professionals within healthcare facilities and during medical transport between hospitals (i.e., ambulance, helicopter or fixed-wing aircraft).

Figure 4: The AIC with an Impella Catheter and its Impella Purge Cassette



Additional sterile, disposable implant accessories are provided with the Impella Catheters to assist in their percutaneous insertion. For the Impella 2.5, these components are a 13F peel-away introducer kit (manufactured by Merit Medical) and a 0.018" placement guidewire (manufactured by Lake Region Medical). The Impella CP accessories are a 14F peel-away introducer kit (manufactured by Oscor Medical) and the identical placement guidewire packaged with the Impella 2.5. The Impella 5.0 is packaged with a 23F peel-away introducer kit (manufactured by Oscor Medical), a 0.018" guidewire (manufactured by Lake Region Medical) and a surgical clamp to assist in hemostasis.

A reusable cart for the AIC is also provided for ease of patient transport within the hospital.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of ongoing cardiogenic shock. These alternatives include inotropic support, intra-aortic balloon pump (IABP) counterpulsation therapy, and surgical left ventricular assist devices. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Impella pumps have received CE mark in the European Union as well as approval in Canada to treat all patients with reduced left ventricular function, including those in cardiogenic shock (of any origin). Neither the AIC nor any of the Impella support

catheters have been withdrawn from marketing for any reason related to their safety or effectiveness.

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the probable adverse effects (e.g., complications) associated with the use of the device.

- Acute renal dysfunction
- Aortic insufficiency
- Aortic valve injury
- Atrial fibrillation
- Bleeding
- Cardiogenic shock
- Cardiac tamponade
- Cardiopulmonary resuscitation
- Cerebral vascular accident/Stroke
- Death
- Device malfunction
- Failure to achieve angiographic success
- Hemolysis
- Hepatic failure
- Insertion site infection
- Limb ischemia
- Myocardial infarction
- Need for cardiac, thoracic or abdominal operation
- Perforation
- Renal failure
- Repeat revascularization
- Respiratory dysfunction
- Sepsis
- Severe hypotension
- Thrombocytopenia
- Thrombotic vascular (non-CNS) complication
- Transient ischemic attack
- Vascular injury
- Ventricular arrhythmia, fibrillation or tachycardia

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

Preclinical testing was conducted on the Impella 2.5 Catheter, the AIC, and the Impella Purge Cassette in support of P140003 and summaries can be found in the original SSED, here: http://www.accessdata.fda.gov/cdrh_docs/pdf14/P140003b.pdf. The testing to support the increased duration of use for the ongoing cardiogenic shock indication (the original indication was for < 6 hours, while the ongoing cardiogenic shock indication is for 4-6 days) and to support the additionl Impella Catheters (Impella CP, Impella 5.0, and Impella LD) can be found in the P140003/S004 and P140003/S005 SSED, here https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140003S004B.pdf and https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140003S005B.pdf , respectively.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

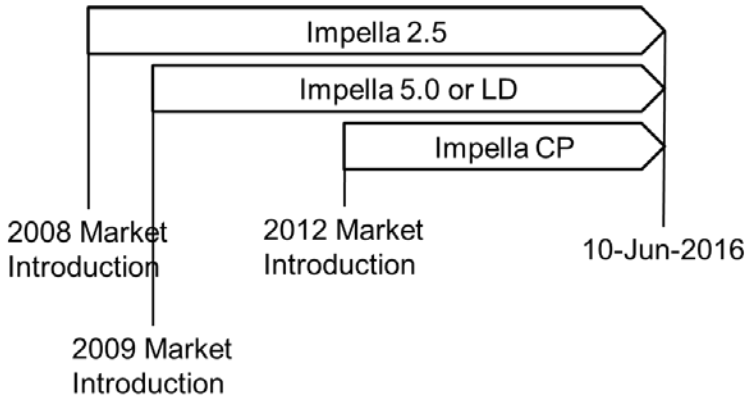
The applicant performed an analysis of real-world, use data captured in the Impella Registry to establish a reasonable assurance of safety and effectiveness in the treatment of patients suffering from cardiomyopathy, myocarditis, or peripartum cardiomyopathy with ongoing cardiogenic shock with the Impella Ventricular Support Systems. Additionally, a detailed literature review of the treatment outcomes for the new patient group was used to further support the overall safety and effectiveness of the Impella devices in the new patient group. Data from the Impella Registry and the literature review were the basis for the PMA approval decision. A summary of the clinical study and literature review are presented below.

A. Study Design

The Impella Registry is an ongoing, multi-center, retrospective, observational registry for collection of de-identified data for patients treated with the Impella 2.5, Impella CP, Impella 5.0, Impella LD and Impella RP Support Systems. The registry, which was started by ABIOMED in 2009, is open for participation by qualifying sites in the U.S., Canada and Europe. A total of 88 sites have participated in the registry since its initiation. As of December 31, 2016, there were 58 open sites of which 44 were U.S. sites. All patients identified for this analysis were U.S. patients. The 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, almost entirely from the United States. Data are collected at all participating sites retrospectively without pre-selection of patients, and include cardiomyopathy, myocarditis, and peripartum cardiomyopathy (PPCM) patients treated with the Impella 2.5, Impella CP and Impella 5.0/LD Systems.

The data collection from the Impella Registry includes IRB approval, complete data monitoring, adverse events (AEs) monitoring, and CEC adjudication of major AEs. All data are entered electronically by the sites. The time during which the Impella Registry data were collected is shown in Figure 5. Eligible patients were those who were reported in the Impella Registry as having presented with ongoing cardiogenic shock in the setting of cardiomyopathy, myocarditis, or peripartum cardiomyopathy, and required mechanical circulatory support with Impella devices, through June 10, 2016.

Figure 5: Time intervals for Impella implants data collection by type of device



The database for this Panel Track Supplement included 93 patients treated with an Impella Ventricular Support System. These included 50 patients with cardiomyopathy (4 Impella 2.5, 29 Impella CP, and 17 Impella 5.0), 34 patients with myocarditis (14 Impella 2.5 , 12 Impella CP and 8 Impella 5.0), and 9 patients with PPCM (5 Impella 2.5, 2 Impella CP and 2 Impella 5.0). The cardiomyopathy patients included the 50 most recent consecutive cardiomyopathy with ongoing cardiogenic shock patients enrolled in the Impella Registry. The patients with myocarditis and PPCM included all such patients enrolled in the Impella Registry.

1. Clinical Inclusion and Exclusion Criteria

   Eligible patients were those who were reported in the Impella Registry as having presented with ongoing cardiogenic shock in the setting of cardiomyopathy, myocarditis, or peripartum cardiomyopathy. They were deemed as requiring mechanical circulatory support and were treated off-label with the Impella devices based on the clinical judgement of their treating physician.

2. Follow-up Schedule

   All patients were followed post implantation according to their local standards of care. The Impella Registry collects follow-up data at discharge and 30 days.

3. Clinical Endpoints

   Data entered into the Impella Registry were collected electronically through standardized data collection forms. The endpoints analyzed in this application included: survival to discharge, myocardial recovery, survival to 30 days post Impella implant, hemodynamic improvement, and device-related and procedure-related adverse events. The analyses in this application focused on the discharge and 30-day post-implant time points.

B. Accountability of PMA Cohort

At the time of database extract, 93 patients were available for analysis . The number of patients in each analysis population for each Impella device is shown in Table 1.

Table 1: Analysis Populations

Analysis Population	Total Cases	Impella 2.5	Impella CP	Impella 5.0	Impella LD
All Subjects	93	23	43	27	0
Cardiomyopathy	50	4	29	17	0
Myocarditis	34	14	12	8	0
Peripartum Cardiomyopathy	9	5	2	2	0

C. Study Population Demographics and Baseline Parameters

The demographics and baseline characteristics of all the cardiomyopathy, myocarditis and PPCM patients are shown below in Table 2 and 3. Ninety-two of the 93 patients were in cardiogenic shock at the time of Impella implant. One of the PPCM patients was not in cardiogenic shock at the time of Impella implant and the device was implanted to improve left ventricular function and prevent further hemodynamic deterioration.

Table 2: Demographics and baseline characteristics

Parameter	All Subjects (N=93)	Cardio-myopathy (N=50)	Myocarditis (N=34)	Peripartum Cardiomyopathy (N=9)
Age, years (mean +/- SD)	48 +/- 17	55 +/- 12	42 +/- 17	27 +/- 8
Male, % (N)	59% (55)	76% (38)	50% (17)	0% (0)
Left ventricular ejection fraction (LVEF), % (mean +/- SD) (N)	16% +/- 8% (77)	15% +/- 6 (39)	18% +/- 10 (29)	17% +/- 7 (9)
Number of inotropes at baseline (mean +/- SD)	2 +/- 1	3 +/- 1	2 +/- 1	2 +/- 1
Diabetes, % (N)	28% (26)	44% (22)	9% (3)	11% (1)
Smoking, % (N)	26% (24)	22% (11)	33% (11)	22% (2)
Hypertension, % (N)	53% (49)	62% (31)	44% (15)	33% (3)
Arrhythmia, % (N)	39% (36)	56% (28)	21% (7)	11% (1)
Congestive heart failure, % (N)	59% (54)	88% (44)	26% (9)	13% (1 of 8)
NYHA III/IV. % (N)	95% (41 of 43)	100% (28 of 28)	83% (10 of 12)	100% (3 of 3)
Renal insufficiency	33% (30)	54% (26)	12% (4)	0% (0)
Known history of cardiomyopathy, % (N)	52% (47)	82% (41)	15% (5 of 33)	13% (1 of 8)
Prior myocardial infarction, % (N)	11% (10)	18% (9)	3% (1)	0% (0)
Prior AICD/pacer, % (N)	33% (31)	54% (27)	9% (3)	11% (1)

Table 3: Baseline hemodynamics

Parameter	All Subjects (N=93)	Cardio-myopathy (N=50)	Myocarditis (N=34)	Peripartum Cardiomyopathy (N=9)
Cardiac index (L/min/m^2) Mean +/- SD (N)	1.97 +/- 0.74 (48)	1.98 +/- 0.76 (20)	1.82 +/- 0.46 (23)	2.60 +/- 1.37 (5)
Heart rate (bpm) Mean +/- SD (N)	104.5 +/- 27.8 (89)	102.0 +/- 27.8 (48)	107.8 +/- 28.0 (32)	106.2 +/- 28.8 (9)
Systolic arterial pressure (mmHg) Mean +/- SD (N)	98.0 +/- 20.9 (90)	95.5 +/- 20.2 (48)	100.4 +/- 21.5 (33)	102.8 +/- 22.2 (9)
Diastolic arterial pressure (mmHg) Mean +/- SD (N)	65.7 +/- 15.2 (90)	65.2 +/- 16.4 (48)	66.1 +/- 13.7 (33)	66.5 +/- 16.1 (9)
Mean arterial pressure (mmHg) Mean +/- SD (N)	76.3 +/- 16.4 (90)	74.3 +/- 17.3 (48)	78.3 +/- 15.2 (33)	79.9 +/- 16.2 (9)
Pulmonary capillary wedge pressure (mmHg) Mean +/- SD (N)	25.9 +/- 9.8 (35)	27.9 +/- 14.0 (13)	25.2 +/- 6.6 (20)	21.5 +/- 3.5 (2)
Central venous pressure (mmHg) Mean +/- SD (N)	24.6 +/- 5.1 (7)	27.5 +/- 9.2 (2)	22.3 +/- 2.6 (4)	28.0 (1)

Additionally, Impella support characteristics are provided below (Table 4). Impella CP was the most used device (46%), followed by Impella 5.0 (29%) and Impella 2.5 (25%). Femoral access site was predominantly used (70%). Mean duration of support was 123 +/- 200 hours (5±8 days) for the full cohort. For the full patient cohort, the 90^{th} percentile of support duration was 120 hours (5 days), 233 hours (9.7 days), and 384 hours (16 days) for patients supported with the Impella 2.5, Impella CP, and Impella 5.0, respectively.

Table 4: Impella support characteristics

Parameter	All Subjects (N=93)	Cardio-myopathy (N=50)	Myocarditis (N=34)	Peripartum Cardiomyopathy (N=9)
Impella device type (first device)				

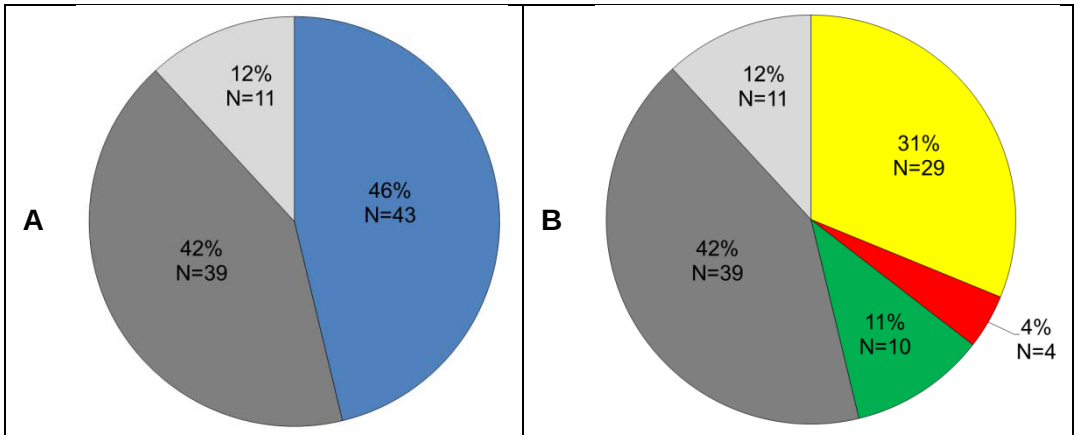
Parameter	All Subjects (N=93)	Cardio-myopathy (N=50)	Myocarditis (N=34)	Peripartum Cardiomyopathy (N=9)
Impella 2.5, % (N) Impella CP, % (N) Impella 5.0, % (N)	25% (23) 46% (43) 29% (27)	8% (4) 58% (29) 34% (17)	41% (14) 35% (12) 24% (8)	56% (5) 22% (2) 22% (2)
Impella access (% femoral), % (N)	70% (65)	64% (32)	79% (27)	75% (6)
Duration of device support, hours (mean +/- SD) (N)	123 +/- 200 (80)	115 +/- 101 (46)	91 +/- 74 (28)	338 +/- 670 (6)
90^{th} percentile of support duration Impella 2.5, hours Impella CP, hours Impella 5.0, hours	 120 233 384	 78 233 384	 72 72 1704	 120 241 216

D. Safety and Effectiveness Results

Outcomes were defined as survival to discharge and survival to 30 days after device implant. Survival to discharge and patient cardiac status at discharge for the full patient cohort, and all three cohorts separately, are shown in Figures 6-9.

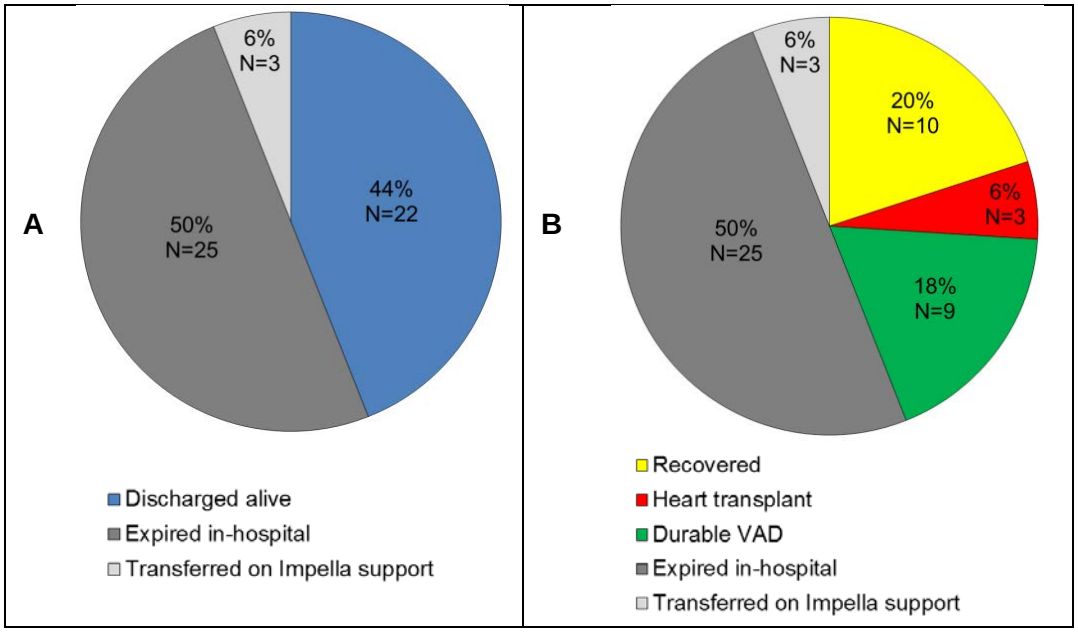
For the full patient cohort, 54 patients (58%) were either discharged alive (N=43, 46%) or transferred on Impella support to another medical facility for escalation of care (N=11, 12%); 39 (42%) expired during index hospitalization (Figure 6A). Of the 43 patients discharged alive, 29 recovered their cardiac function (67% of the discharged patients), 10 received a durable VAD (23% of the discharged patients), and 4 received a heart transplant (9% of the discharged patients) (Figure 6B).

Figure 6: Survival to discharge (A) and patient status at discharge (B) – All patients (N=93)



For the cardiomyopathy patients, 25 patients were either discharged alive (N=22, 44%) or transferred on Impella support to another medical facility for escalation of care (N=3, 6%); 25 (50%) expired during index hospitalization (Figure 7A). Of the 22 patients discharged alive, 10 recovered their cardiac function, 9 received a durable VAD, and 3 received a heart transplant (Figure 7B).

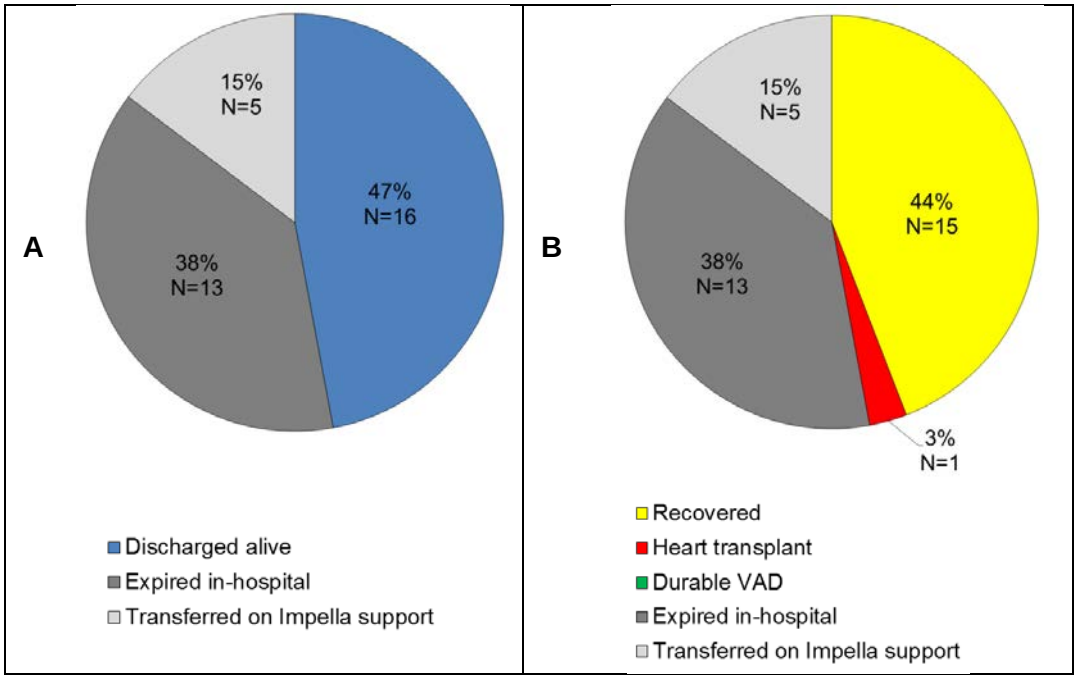
Figure 7: Survival to discharge (A) and patient status at discharge (B) – Cardiomyopathy patients (N=50)



For the myocarditis patients, 21 patients were either discharged alive (N=16, 47%) or transferred on Impella support to another medical facility for escalation of care (N=5, 15%); 13 (38%) expired during index hospitalization (Figure 8A). Of the 16 patients

discharged alive, 15 recovered their cardiac function and one received a heart transplant (Figure 8B).

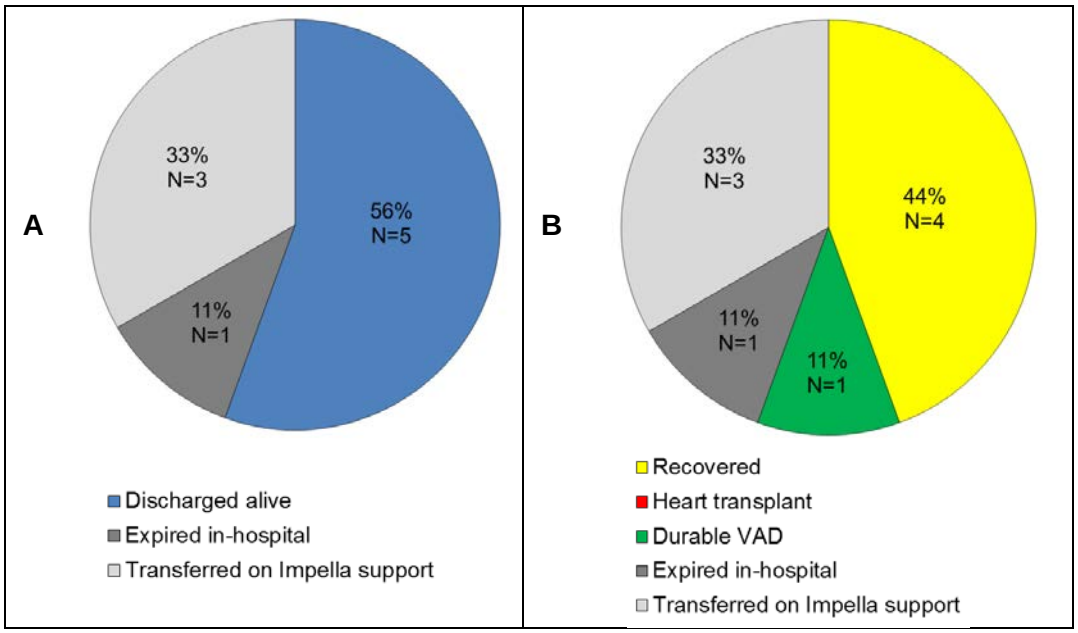
Figure 8: Survival to discharge (A) and patient status at discharge (B) – Myocarditis patients (N=34)



For the PPCM patients, 8 patients were either discharged alive (N=5, 56%) or transferred on Impella support to another medical facility for escalation of care (N=3,

33%); one (11%) expired during index hospitalization (Figure 9A). Of the 5 patients discharged alive, 4 recovered their cardiac function and one received a durable left ventricular assist device (Figure 9B).

Figure 9: Survival to discharge (A) and patient status at discharge (B) – PPCM patients (N=9)



Patient Hemodynamics

Hemodynamic parameters on Impella support compared to baseline are shown in Table 5. Impella support increased cardiac index and systolic, diastolic, and mean arterial blood pressure, and reduced pulmonary capillary wedge pressure, consistent with previous reports.

Table 5: Comparison of hemodynamics pre-support and on-support (paired data)

Parameter	Pre-Support (N=93)	On-Support (N=93)	P-value
Cardiac index (L/min/m^2) Mean +/- SD (N)	1.93+/- 0.51 (25)	2.27 +/- 0.83 (25)	**0.05**
Heart rate (bpm) Mean +/- SD (N)	104.8+/- 28.7 (75)	110.6 +/- 41.5 (75)	0.24
Systolic arterial pressure (mmHg) Mean +/- SD (N)	97.5 +/- 18.8 (71)	104.4 +/- 23.0 (71)	**0.02**
Diastolic arterial pressure (mmHg) Mean +/- SD (N)	65.2 +/- 13.8 (70)	70.8 +/- 18.4 (70)	**0.04**
Mean arterial pressure (mmHg) Mean +/- SD (N)	75.5 +/- 15.0 (72)	83.1 +/- 18.4 (72)	**0.003**
Pulmonary capillary wedge pressure (mmHg)	23.5 +/- 7.3 (14)	18.7 +/- 6.7 (14)	**0.02**

Parameter	Pre-Support (N=93)	On-Support (N=93)	P-value
Mean +/- SD (N)			
Central venous pressure (mmHg) Mean +/- SD (N)	24.6 +/- 6.2 (5)	19.5 +/- 10.4 (5)	0.34

In-Hospital Adverse Events

Site-reported in-hospital adverse events are shown in Table 6. There were no valve injuries or valve dysfunction adverse events reported. The major complications reported for the full cohort included cerebrovascular accident (4%), acute renal dysfunction (35%), acute hepatic failure (5%), hemolysis (13%), bleeding requiring transfusion (10%), anemia requiring transfusion (11%), infection (13%), limb ischemia (4%), vascular complication with (3%) or without (4%) surgery, respiratory dysfunction/failure (4%), and ventricular arrhythmia (9%). Based on the site-reported data (local PI assessment of event causality), only a fraction of these rates were attributed to the Impella device and the events resolved without residual effect in most of the cases, unless the event of death occurred. Overall, the results did not show any evidence of increased morbidity associated with the Impella support in cardiomyopathy, myocarditis, and PPCM patients.

Table 6: Site-reported adverse events (to discharge)

In-Hospital Adverse Events	All Subjects (N=93)	Cardiomyopathy (N=50)	Myocarditis (N=34)	Peripartum Cardiomyopathy (N=9)
Death	42% (39/93)	50% (25/50)	38% (13/34)	11% (1/9)
Cerebrovascular Accident (CVA)/Stroke	4% (4/93)	4% (2/50)	6% (2/34)	0% (0/9)
Transient Ischemic Attack (TIA)	0% (0/93)	0% (0/50)	0% (0/34)	0% (0/9)
Acute Renal Dysfunction/Failure	35% (33/93)	30% (15/50)	47% (16/34)	22% (2/9)
Acute Hepatic Failure	5% (5/93)	6% (3/50)	6% (2/34)	0% (0/9)
Hemolysis	13% (12/93)	16% (8/50)	12% (4/34)	0% (0/9)
Valve Injury (Any Valve)	0% (0/93)	0% (0/50)	0% (0/34)	0% (0/9)
Anemia Requiring Transfusion	11% (10/93)	2% (1/50)	18% (6/34)	33% (3/9)
Bleeding Requiring Transfusion	10% (9/93)	2% (1/50)	21% (7/34)	11% (1/9)
Infection	13% (12/93)	12% (6/50)	9% (3/34)	33% (3/9)

In-Hospital Adverse Events	All Subjects (N=93)	Cardiomyopathy (N=50)	Myocarditis (N=34)	Peripartum Cardiomyopathy (N=9)
Limb Ischemia	4% (4/93)	0% (0/50)	9% (3/34)	11% (1/9)
Vascular Complication Requiring Surgery	3% (3/93)	2% (1/50)	3% (1/34)	11% (1/9)
Vascular Complication Without Surgery	4% (4/93)	4% (2/50)	3% (1/34)	11% (1/9)
Respiratory Dysfunction/Failure	4% (4/93)	2% (1/50)	6% (2/34)	11% (1/9)
Ventricular Arrhythmia	9% (8/93)	2% (1/50)	15% (5/34)	22% (2/9)

There were 39 in-hospital deaths (42%). The causes of death for each subgroup are categorized in Table 7. The majority of the deaths (N=25, 64%) were attributed to heart failure or cardiogenic shock.

Table 7: Causes of in-hospital death

Cause of Death	Impella Registry Population		
	Cardiomyopathy (N=50)	Myocarditis (N=34)	Peripartum Cardiomyopathy (N=9)
Heart Failure or Cardiogenic Shock	30% (15)	26.47% (9)	11.11% (1)
Myocardial Infarction	4% (2)	0	0
CVA/Stroke	0	2.94% (1)	0
Procedural Complication	0	2.94% (1)	0
Heart Failure with MSOF	16% (8)	2.94% (1)	0
Unknown	0	2.94% (1)	0
Total	**50% (25)**	**38.23% (13)**	**11.11% (1)**

CVA – cerebrovascular accident; MSOF – multi-system organ failure

Relatedness to the Device and Procedure

The Clinical Events Committee (CEC) determined the potential relationship to the device (Table 8) and procedure (Table 9) for each death. All deaths were adjudicated by the CEC as not related to the Impella device.

Two deaths in the myocarditis cohort were adjudicated by the CEC as probably related to the procedure. One myocarditis patient underwent an endomyocardial biopsy complicated by perforation of the inferior free wall of the right ventricle leading to cardiac tamponade and requiring emergent mediastinal exploration to suture the laceration and stop the bleeding. The patient expired four days later during the index hospitalization, and this death was adjudicated as probably related to the endomyocardial biopsy procedure. A second myocarditis patient was supported initially with an Impella CP but did not significantly improve. Consequently, the patient was escalated to an AB5000 LVAD. While on LVAD support, the patient developed multiple complications and support was withdrawn upon the request from the patient's family. This death was adjudicated as probably related to the LVAD implant procedure.

Table 8: In-hospital deaths CEC-adjudicated as related to the device

Deaths: CEC Device Relatedness	Definite	Probable	Possible	Remote	Not-Related	Unknown	Total
Cardiomyopathy	0	0	0	0	25	0	25
Myocarditis	0	0	0	0	13	0	13
PPCM	0	0	0	0	1	0	1

Table 9: In-hospital deaths CEC-adjudicated as related to the procedure

Deaths: CEC Procedure Relatedness	Definite	Probable	Possible	Remote	Not-Related	Unknown	Total
Cardiomyopathy	0	0	0	0	25	0	25
Myocarditis	0	2	0	0	11	0	13
PPCM	0	0	0	0	1	0	1

Patient Survival at 30 Days

The overall results (Kaplan-Meier curve estimates) for 30-day survival for the patients are shown in Figure 10 (full patient cohort), Figure 11 (cardiomyopathy patients), Figure 12 (myocarditis patients), and Figure 13 (PPCM patients). Overall outcome results appear favorable for this sick patient group, particularly when compared to the published results for similar patients (see the supplemental clinical information section below).

Figure 10: Kaplan-Meier curve estimates for 30-day survival – all patients (N=93)

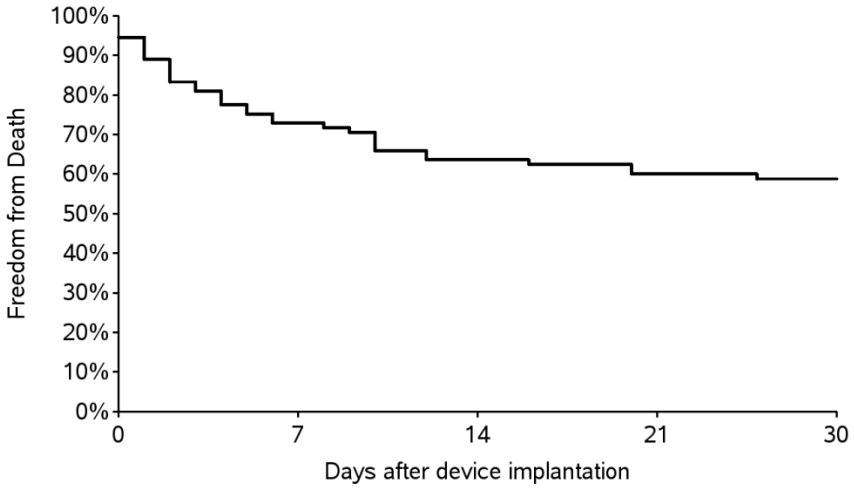


Figure 11: Kaplan-Meier curve estimates for 30-day survival – cardiomyopathy patients (N=50)

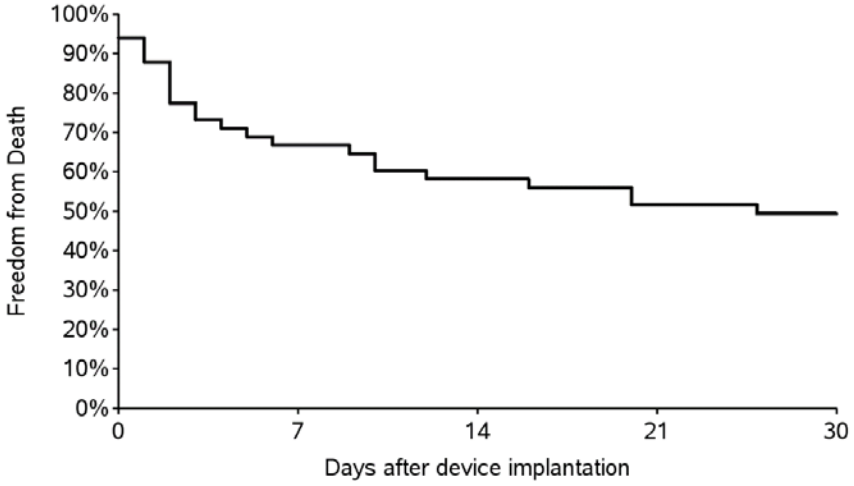


Figure 12: Kaplan-Meier curve estimates for 30-day survival – myocarditis patients (N=34)

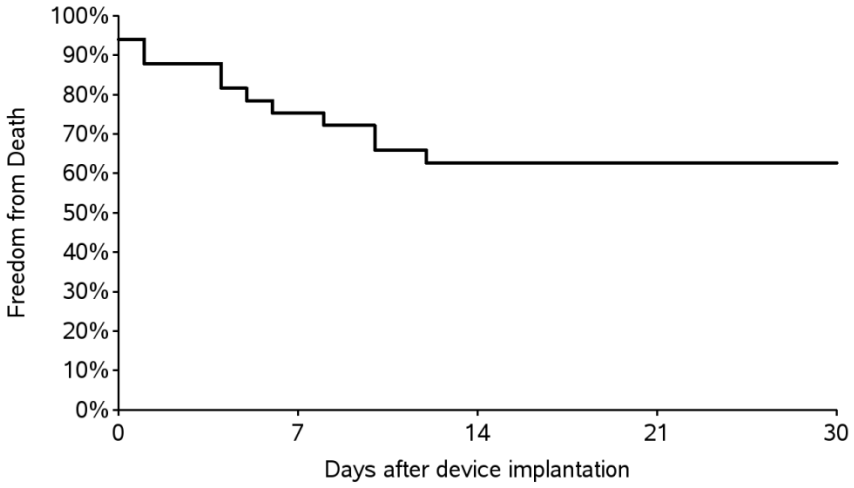
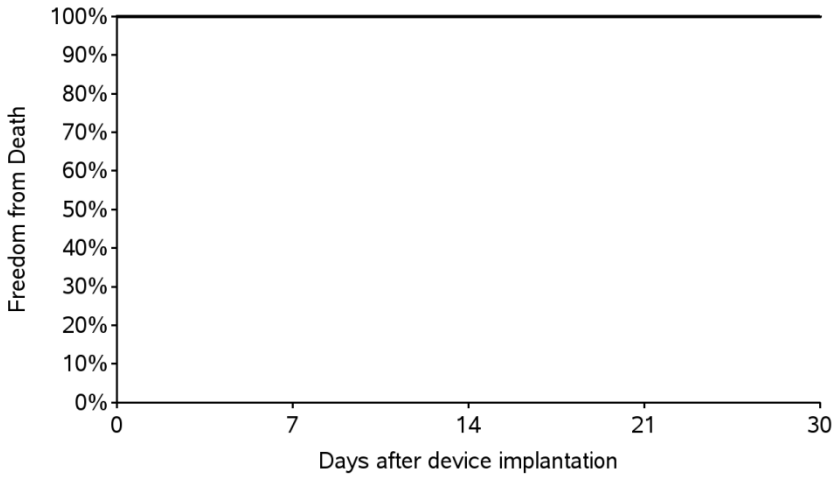


Figure 13: Kaplan-Meier curve estimates for 30-day survival – PPCM patients (N=9)



Device Failures and Replacements

There was one device failure reported during the study. One myocarditis patient experienced device failure after 12 days on support. The device was explanted without clinical sequelae. No device failures were reported for the cardiomyopathy or PPCM patients. One cardiomyopathy patient underwent a device replacement after the initial device migrated and could not be repositioned across the aortic valve.

3. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The applicant conducted a comprehensive literature review on the use of mechanical circulatory support in the setting of cardiogenic shock secondary to cardiomyopathy, myocarditis, or PPCM, to further enhance the body of evidence from the Impella Registry supporting the reasonable assurance of safety and effectiveness for the Impella family of devices. The literature review includes two parts: 1) a review of the literature for Impella use in the above setting, along with the FDA approved AB/BVS5000 VAD use in the same setting; and 2) a review of the literature for the use of other mechanical circulatory support devices in the same setting.

1. Impella

   The Impella review yielded 31 publications on the use of Impella devices for hemodynamic support in the setting of cardiomyopathy (16 publications) (1-16), myocarditis (13 publications) (8,17-28), or PPCM (3 publications) (29-31). The publications were either case reports on single patients (21 publications), single-center studies on hemodynamic support using Impella in the setting of cardiogenic shock where one or more of the patients presented with cardiomyopathy or myocarditis as the underlying cause (10 publications), or multi-center series on the use of Impella devices specifically for cardiomyopathy with ongoing cardiogenic shock (1 publication). For the cardiomyopathy patients, survival to explant was 72% (78 of 109). Ten of the reported cardiomyopathy patients were also included in the Impella Registry cohort. For the myocarditis patients, survival to explant was 71% (10 of 14 patients). One of the reported myocarditis patients was also included in the Impella Registry cohort. For the PPCM patients, recovery and survival to explant was 100% (3 patients).

2. Surgical VAD

   The BVS/AB5000 review yielded only one publication, a retrospective multi-center study using data collected in the ABIOMED voluntary registry, on 11 patients supported with the BVS 5000 for cardiogenic shock secondary to acute myocarditis. The BVS/AB5000 System is the only FDA-approved system for use in patients suffering from acute cardiac disorders such as viral myocarditis. Survival to explant was 82%, with high rates of bleeding (73%), stroke (27%) and infection (18%).

3. Other Mechanical Support Devices

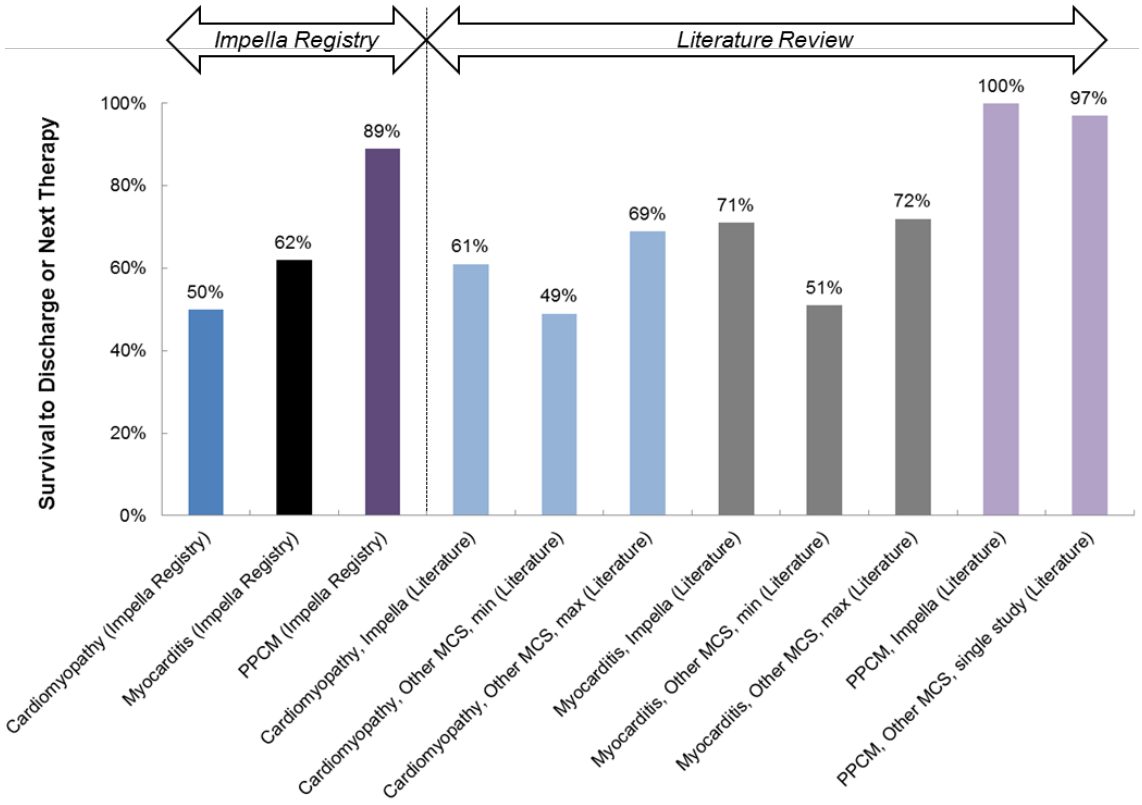
   The review on the use of other MCS devices in cardiomyopathy or myocarditis yielded 18 retrospective single-center (n=16) or multi-center (n=2) studies on patients who required mechanical circulatory support due to cardiogenic shock in the setting of cardiomyopathy (32-40) or myocarditis (41-49) (910 patients total). Most studies reported the use of Extracorporeal Membrane Oxygenation (ECMO) only (10 of 18 studies). Survival to discharge ranged from 49% to 96%. For ECMO, the most widely reported support modality, survival to discharge ranged from 54% to 72%. Many of these articles did not report adverse events. When reported, the rates of stroke, bleeding, and infection were consistently higher in all other MCS devices than in

Impella. The rates of limb ischemia were comparable. Hemolysis rate was absent in these data except for one non-Impella study.

The review on the use of other MCS devices in PPCM yielded one prospective multi-center study on patients who required VAD implant secondary to PPCM, using the INTERMACS registry (50). Survival to 1 month was 97%. Of note, only 66% of the patients described in the article above were in cardiogenic shock (INTERMACS 1 or 2) at the time of MCS device implant.

In conclusion, for available data on both Impella in these populations and other devices (pulsatile VADs and ECMO) the survival rates are comparable to the survival rates reported in the Impella Registry analyses (Figure 13). In addition for those articles where AEs were reported, the Impella Registry shows lower rates of morbidities associated with Impella than ECMO and surgical VADs. This is attributed to the relative low profile of Impella as a percutaneous device in this setting.

Figure 13: Survival comparisons of Impella Registry data, Impella literature, and other MCS reviewed in literature review



XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the population of patients experiencing ongoing cardiogenic shock in the setting of cardiomyopathy, myocarditis, or peripartum cardiomyopathy, the primary outcomes of interest are survival and myocardial recovery. In the Impella Registry Study, 50% of the cardiomyopathy patients were either discharged alive (44%) or transferred on Impella support (6%); 62% of the myocarditis patients were either discharged alive (47%) or transferred on Impella support (15%); and 89% of the PPCM patients were either discharged alive (56%) or transferred on Impella support (33%). The 30-day survival rates were 49% in cardiomyopathy, 63% in myocarditis, and 100% in PPCM. For the full cohort, for those patients who were discharged alive, 67% of the patients experienced myocardial recovery (29 of 43 patients).

Additionally, the Impella Registry Study showed improvement in hemodynamic status (including cardiac index; systolic, diastolic, and mean arterial blood pressure; and pulmonary capillary wedge pressure) from baseline to on-support.

In conclusion, given the totality of the information available for the Impella Ventricular Support Systems, the data demonstrate a beneficial therapeutic effect in patients experiencing ongoing cardiogenic shock in the setting of cardiomyopathy, myocarditis, or peripartum cardiomyopathy.

B. Safety Conclusions

The risks of the device are based on data collected in the Impella Registry as described above. There were no device-related serious adverse events in the Impella Registry Study. The safety profile of the Impella devices was favorable when compared with published results for the BVS/AB5000 surgical VAD, the only FDA approved system for use in patients suffering from acute cardiac disorders such as viral myocarditis, and with published results for other mechanical circulatory devices when used in similar patients.

C. Benefit-Risk Determination

The probable benefits of the device included potential survival to discharge and improved hemodynamic support.

The probable risks of the device in patients who were suffering from ongoing cardiogenic shock in the setting of cardiomyopathy, including peripartum cardiomyopathy, and myocarditis were evaluated using the Impella Registry Study. The safety profile was comparable to that of the BVS/AB5000 surgical VAD and other mechanical circulatory support devices.

The benefit-risk evaluation is favorable for use of the Impella 2.5, Impella CP and Impella 5.0/LD as temporary ventricular support devices to support hemodynamics and augment the circulation in patients who are suffering from ongoing acute cardiogenic shock in the setting of cardiomyopathy, including peripartum cardiomyopathy, or myocarditis, where other standard therapies (pressors, inotropes, IABP) have failed.

1. Patient Perspectives

   This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for short term use (≤4 days for the Impella 2.5 and Impella CP, and ≤6 days for the Impella 5.0 and Impella LD) for the treatment of ongoing cardiogenic shock that occurs:

- immediately (<48 hours) following acute myocardial infarction or open heart surgery, or
- in the setting of cardiomyopathy, including peripartum cardiomyopathy, or myocarditis

as a result of isolated left ventricular failure that is not responsive to optimal medical management and conventional treatment measures, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the Impella Ventricular Support Systems for patients who are experiencing ongoing cardiogenic shock in the setting of cardiomyopathy, myocarditis, or peripartum cardiomyopathy.

XIV. CDRH DECISION

CDRH issued an approval order on February 7, 2018.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

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