A systematic literature review and meta-analysis of impella devices used in cardiogenic shock and high risk percutaneous coronary interventions

Introduction

Short-term mechanical circulatory support (MCS) is an established treatment option across a diverse range of clinical indications including cardiogenic shock and high risk percutaneous coronary interventions (HRPCI) [1-4]. The Impella platform of left ventricular assist devices (Abiomed, Inc., Danvers, Massachusetts) are minimally invasive, catheter-based, axial flow pumps which directly unload the left ventricle by driving blood from the left ventricle into the ascending aorta. Impella devices were introduced onto the market in 2003 in Europe and 2008 in the United States. Since the advent of the first generation of Impella pumps a number of revised devices have since become available, including the Impella 2.5, Impella CP (cardiac power), Impella 5.0 and Impella LD (Left direct) (Table 1) [5].

Whilst the current evidence base supporting the survival benefits and documenting complications associated with Impella support in cardiogenic shock and HRPCI is growing, these studies tend to be limited by under-powering and/or design, with the majority of the available data being sourced from small clinical trials or case series [6,7].

Whilst Impella has been available since 2003, no contemporary systematic overview of the combined safety and effectiveness profile...
of Impella is currently available. The objective of this study was to present a pooled and up-to-date review of the survival and safety profile associated with the use of Impella devices in the cardiogenic shock (CS) and high-risk percutaneous coronary intervention (HRPCI) indications.

**Methods**

A systematic literature search was performed in Medline, Medline In-Process, EMBASE and the CENTRAL bibliographic databases on the 30th April, 2017. Inclusion criteria are detailed in (Table 2). Only full-text peer-reviewed articles with 10 or more Impella patients supported for CS or HRPCI were included. The full search strategy is detailed in the Supplemental Material. Summary data for each included study is described in Supplemental Material. Benefit and safety outcomes analyzed and stratification groups used in the analysis are described in Table 3.

| Table 1: Types of Impella devices, included into the study |
|---------------------------------|----------------|----------------|
| **Impella 2.5**                 | **Impella CP** | **Impella 5.0** |
| Flow                            | < 2.5 L/min    | < 4.0 L/min    | < 5 L/min    |
| Catheter Size                   | 9F             | 9F             | 9F           |
| Pump Insertion Size             | 12F            | 14F            | 21F           |
| Approved Duration               | 4 days (US)    | 4 days (US)    | 6 days (US)  |
| FDA Approved Indications        | High Risk PCI  | High Risk PCI  | AMICS/PCCS   |
| Insertion Sheath                | 13cm Peal-Away | 13 cm/25cm Peal-Away | 6 cm Peal-Away |
| Valve Interaction               | Smooth Cannula | Smooth Cannula | Smooth Cannula |
| AMICS: Acute Myocardial Infarction complicated by Cardiogenic Shock; EU: European Union; FDA: US Food and Drug Administration; HTx: Heart Transplantation; LVAD: Left Ventricular Assist Device; PCCS: Postcardiotomy Cardiogenic Shock |

**Table 2: Inclusion criteria**

| Indication                     | Study type                                                                 | Outcomes reported                                        | Exclusion criteria                                                                                     |
|--------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Cardiogenic shock (CS)         | Multiple-patient observational and experimental studies of Impella device with ≥ 10 Impella casesb Patients implanted with Impella devices in 2004 and later | Complications and safety outcomes including stroke/ TIA, MACE, bleeding, hematoma, hemolysis, renal dysfunction, limb ischemia, device malfunction and revascularization | Reviews                                                                                              |
|                                |                                                                          |                                                          | Conference abstracts                                                                                   |
|                                |                                                                          |                                                          | Device name was not reported in study                                                                  |
|                                |                                                                          |                                                          | Study population of less than 10 patients                                                              |
|                                |                                                                          |                                                          | Studies of percutaneous ventricular assist devices other than Impella                                   |
| Prophylactic use in HRPCIa     | Multiple-patient observational and experimental studies of Impella device with ≥ 10 Impella casesb Patients implanted with Impella devices in 2004 and later |                                                          | No clinical outcomes or no clinical outcomes of interest reported                                     |
|                                |                                                                          |                                                          | Mixed devices (results of Impella reported combined with results of other devices)                    |
|                                |                                                                          |                                                          | Mixed indications (results of patients with CS or HRPCI reported combined with results of patients treated with other devices) |
|                                |                                                                          |                                                          | Other indication than cardiogenic shock and HRPCI                                                     |
|                                |                                                                          |                                                          | Health economic studies                                                                               |
|                                |                                                                          |                                                          | Prediatic population                                                                                  |
|                                |                                                                          |                                                          | Right ventricular support                                                                             |
|                                |                                                                          |                                                          | Concomitant use of Impella and ECMO                                                                  |
|                                |                                                                          |                                                          | Support during Balloon Aortic Valvuloplasty (BAV) procedure                                           |
|                                |                                                                          |                                                          | Support during Electrophysiology (EP) procedure                                                      |
| HRPCI: High Risk Percutaneous Coronary Intervention |                                                                          |                                                          | a. Patients treated for CS at the time of Impella support initiation were excluded                    |
|                                |                                                                          |                                                          | b. Studies which reported only surrogate outcomes (other than the ones above-mentioned) were excluded from the analysis. |
|                                |                                                                          |                                                          | c. All left ventricular assist Impella devices were considered                                       |

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Statistical analyses

Categorical variables were summarized using frequency and percentage. Continuous variables were summarized using mean and standard deviation (SD) or median and inter-quartile range (IQR) as appropriate. A random effects meta-analysis using DerSimonian–Laird method was used to pool the various benefits and safety outcomes across included studies and expressed as proportions with 95% confidence intervals. Arcsine transformation of proportions was made for analysis of data from single-arm studies [8,9]. Inter-study heterogeneity was analyzed by Cochran’s Q and I² statistics. A significant p-value of Q (p<0.05) indicated that there might be significant heterogeneity between studies. Heterogeneity measured by I² was quantified as low, moderate, and high (low: 0-25%; moderate 26-50%; high 51-100%) [9]. The primary results were limited to those outcomes associated with an I² of less than 50%. For all analyses, p-value <0.05 was considered significant. All analyses were conducted in R (R Foundation for Statistical Computing, Vienna, Austria) and validated in Stata version 15 (StataCorp, College Station, Texas) [10].

Results

Patient characteristics

A total of 33 publications [11-42] reported clinical outcomes for 2,827 patients with Impella support were included in the analysis (Tables 2 and 3). The mean (SD) age of patients in included studies was 64.9 (11.4) years. Males constituted 74.6% of patients. The median (IQR) number of patients treated with Impella devices in included studies was 36 (18-119). A total of 1,144 (40.5%) patients were supported for CS, of which 890 (78%) for AMICS (Acute Myocardial Infarction complicated by Cardiogenic Shock). A smaller group of 93 (8%) patients had CS secondary to acute decompensated heart failure (ADHF). The median (IQR) duration of support was 43 hours (25-53 hours) for AMICS, 295 hours (231-358 days) for ADHF. The median (IQR) duration of support was 1.9 hours (1.5-2.1 hours) in the 1,715 patients supported prophylactically with Impella for HRPCI.

Meta-analysis

The pooled proportions of selected survival and complications (survival, stroke/TIA, MI, revascularization, MACE, bleeding, hemolysis, renal dysfunction, limb ischemia and device malfunction) across Impella device types within the cardiogenic shock indications (CS of any etiology and AMICS, ADHF-CS, PCCS) and HRPCI, are summarized in Tables 4, 5 and Supplemental Figures.

Cardiogenic shock

The pooled proportions of survival and complications across Impella device types for cardiogenic shock indications are summarized in Table 4.

Survival

In the two RCTs identified in the systematic search, survival at 30-days was reported to be 54% in both (29, 33). Additionally, in the IMPRESS trial (n=24) survival
Table 4: Meta-analysis of survival and complications outcomes in cardiogenic shock patients

| Group                  | Outcome                  | Patients (N) | Studies pooled (N) | Pooled proportion (95%CI) | I² | Degree of I² | Q   | p-Value for Q |
|------------------------|--------------------------|--------------|-------------------|---------------------------|----|--------------|-----|---------------|
| **Survival**           |                          |              |                   |                           |    |              |     |               |
| CS – prospective studies | Survival to next therapy | 26           | 2                 | 0.887 (0.597-1)          | 0.74 | High         | 3.79| 0.052         |
|                        | Survival to discharge    | 35           | 3                 | 0.697 (0.383-0.933)      | 0.82 | High         | 10.82| 0.004        |
|                        | Survival at 30-days       | 25           | 2                 | 0.658 (0.334-0.916)      | 0.77 | High         | 4.38 | 0.036        |
| CS – observational retrospective studies | Survival to next therapy | 178          | 8                 | 0.717 (0.565-0.847)      | 0.83 | High         | 39.16| 0            |
|                        | Survival to discharge    | 352          | 10                | 0.63 (0.539-0.716)       | 0.75 | High         | 37.27| 0            |
| AMICS – observational retrospective studies | Survival to next therapy | 97           | 3                 | 0.704 (0.532-0.851)      | 0.64 | High         | 5.87 | 0.053        |
|                        | Survival to discharge    | 278          | 6                 | 0.563 (0.464-0.659)      | 0.71 | High         | 16.4 | 0.006        |
|                        | Survival at 30-days       | 158          | 5                 | 0.472 (0.361-0.584)      | 0.73 | High         | 11.41| 0.022        |
|                        | Survival at 6 months      | 20           | 2                 | 0.588 (0.421-0.746)      | 0   | Low          | 0   | 0.966        |
| ADHF – observational retrospective studies | Survival to next therapy | 59           | 3                 | 0.624 (0.27-0.915)       | 0.92 | High         | 26.41| 0            |
|                        | Survival to discharge    | 63           | 3                 | 0.678 (0.58-0.769)       | 0   | Low          | 0   | 0.743        |
|                        | Survival at 30-days       | 43           | 2                 | 0.672 (0.553-0.781)      | 0   | Low          | 0   | 0.945        |
| **Complications**      |                          |              |                   |                           |    |              |     |               |
| CS – prospective studies | Bleeding*                | 15           | 3                 | 0.247 (0.042-0.547)      | 0.82 | High         | 9.89 | 0.007        |
|                        | Hematoma**               | 3            | 2                 | 0.075 (0.015-0.175)      | 0   | Low          | 0.06 | 0.803        |
|                        | Device malfunction       | 2            | 3                 | 0.054 (0.006-0.144)      | 0.27 | Moderate     | 2.68 | 0.261        |
|                        | Hemolysis                | 3            | 3                 | 0.078 (0.023-0.162)      | 0   | Low          | 0.66 | 0.72         |
|                        | Limb ischemia            | 1            | 2                 | 0.059 (0.005-0.167)      | 0   | Low          | 0.8  | 0.372        |
| CS – observational retrospective studies | Bleeding*                | 106          | 10                | 0.157 (0.089-0.239)      | 0.8 | High         | 38.48| 0            |
|                        | Hematoma**               | 11           | 3                 | 0.048 (0.024-0.08)       | 0   | Low          | 0.72 | 0.699        |
|                        | Device malfunction       | 17           | 5                 | 0.051 (0.019-0.096)      | 0.59 | High         | 8.68 | 0.07         |
| AMICS – observational retrospective studies | Bleeding*                | 88           | 5                 | 0.214 (0.159-0.276)      | 0.42 | Moderate     | 8.31 | 0.081        |
|                        | Hematoma**               | 10           | 2                 | 0.049 (0.023-0.083)      | 0   | Low          | 0.69 | 0.406        |
|                        | Device malfunction       | 8            | 3                 | 0.025 (0.011-0.045)      | 0   | Low          | 0.92 | 0.63         |
|                        | Hemolysis                | 30           | 3                 | 0.081 (0.056-0.111)      | 0   | Low          | 0.26 | 0.879        |
|                        | Limb ischemia            | 10           | 4                 | 0.036 (0.017-0.063)      | 0   | Low          | 3.2  | 0.362        |
|                        | Renal Dysfunction        | 98           | 3                 | 0.459 (0.147-0.79)       | 0.97 | High         | 15.95| 0            |
| Stroke/TIA in-hospital | 10                       | 6             | 0.035 (0.018-0.057) | 0 | Low          | 2.97 | 0.705        |
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| Stroke/TIA in-hospital | 10                       | 6             | 0.035 (0.018-0.057) | 0 | Low          | 2.97 | 0.705        |

* any type of bleeding

** any type of hematoma
at 6-months was 50% (29). Survival at 90-days in the CS of any etiology in retrospective cohort was 62.6% (95%CI: 53.9%-70.9%) and survival at 6 months was 58.3% (95%CI: 44.2%-71.8%). Other survival outcomes including survival to next therapy and survival to discharge were associated with unacceptably high heterogeneity and were thus considered unreliable. Similarly, in prospective studies of CS of any etiology, the outcomes on survival were similarly limited by excessive heterogeneity. Survival at 6 months in the AMICS subgroup was 58.8% (95%CI: 42.1%-74.6%). In the subgroup of ADHF patient’s survival to discharge was 67.8% (95%CI: 58%-76.9%), whilst 30-day survival was 67.2% (95%CI: 55.3%-78.1%).

| Group                                | Outcome                      | Patients (N) | Studies pooled (N) | Pooled proportion (95%CI) | I2 | Degree of I2 | Q | p-Value for Q |
|--------------------------------------|-------------------------------|--------------|--------------------|--------------------------|----|--------------|---|--------------|
| HRPCI – Prospective studies          | Survival                      | 235          | 3                  | 0.922 (0.886-0.951)       | 0  | Low          | 0.2| 0.906        |
|                                      | Survival at 30-days           | 39           | 3                  | 0.153 (0.112-0.2)        | Low| 0.56         | 0.754         |
|                                      | MACE at 30-days               | 33           | 2                  | 0.135 (0.095-0.18)       | Low| 0.25         | 0.616         |
|                                      | Revascularization at 30-days  | 0            | 2                  | 0.003 (0-0.014)          | Low| 0.89         | 0.344         |
|                                      | Stroke/TIA at 30-days         | 0            | 2                  |                         |    |              |               |
| HRPCI – observational retrospective studies | Survival                      | 587          | 9                  | 0.99 (0.981-0.997)       | 0  | Low          | 2.75| 0.949        |
|                                      | Survival to next therapy      | 938          | 6                  | 0.979 (0.964-0.99)       | Low| 5.39         | 0.37          |
|                                      | Survival to discharge         | 398          | 6                  | 0.961 (0.94-0.977)       | Low| 3            | 0.7           |
|                                      | Bleeding*                     | 35           | 7                  | 0.074 (0.035-0.126)      | Low| 18.93        | 0.004         |
|                                      | Hematoma**                    | 21           | 6                  | 0.075 (0.036-0.127)      | Low| 10.21        | 0.069         |
|                                      | Device malfunction            | 1            | 5                  | 0.007 (0.001-0.017)      | Low| 3.25         | 0.516         |
|                                      | Hemolysis                     | 12           | 7                  | 0.014 (0.008-0.021)      | Low| 3.69         | 0.719         |
|                                      | Limb ischemia                 | 4            | 3                  | 0.046 (0.002-0.139)      | High| 5.64        | 0.06          |
|                                      | MACE at 30-days               | 17           | 3                  | 0.051 (0.03-0.077)       | Low| 0.76         | 0.685         |
|                                      | MI at 30-days                 | 1            | 4                  | 0.008 (0.001-0.02)       | Low| 1.42         | 0.701         |
|                                      | Renal Dysfunction             | 45           | 6                  | 0.033 (0.015-0.059)      | High| 14.28       | 0.014         |
|                                      | Revascularization in-hospital  | 5            | 3                  | 0.009 (0.003-0.017)      | Low| 0.18         | 0.912         |
|                                      | Revascularization at 30-days   | 3            | 4                  | 0.019 (0.004-0.044)      | Low| 3.54         | 0.316         |
|                                      | Stroke/TIA peri-procedural     | 0            | 2                  | 0.006 (0-0.022)          | Low| 0.31         | 0.578         |
|                                      | Stroke/TIA in-hospital         | 0            | 4                  | 0.002 (0-0.008)          | Low| 3.42         | 0.49          |
|                                      | Stroke/TIA at 30-days          | 1            | 4                  | 0.008 (0.001-0.02)       | Low| 1.15         | 0.764         |

* any type of bleeding
** any type of hematoma
Complications

In the IMPRESS trial, bleeding incidence among Impella patients was 33.3% and hemolysis 8.3% (29), while in the ISAR-SHOCK trial (n=26) no bleeding was observed (33). Across prospective CS studies, the pooled rates of hemolysis (7.8%; 95%CI: 2/3%-16.2%) and limb ischemia (5.9%; 95%CI: 0.5%-16.7%) were low. Similarly, in the retrospective CS studies the low rates of in-hospital stroke (3.5%; 95%CI: 1.8%-5.7%) and limb ischemia (4.2%; 95%CI: 2.3%-6.7%) were observed. When retrospective studies were pooled for the subgroup of AMICS patients, event rates within the observational retrospective studies were generally low (device malfunction 2.5% (1.1%-4.5%); in-hospital stroke 3.7% (95%CI: 1.8%-6.2%); limb ischemia 3.6% (95%CI:1.7%-6.3%), hematoma 4.9% (95%CI:2.3%-8.3%), hemolysis 8.1% (95%CI: 5.6%-11.1%). The exception was bleeding, observed in 21.4% of patients (95%CI: 15.9%-27.6%). In the ADHF group in-hospital stroke rate was 2.7% (95%CI: 0.01%-8.5%).

High-risk percutaneous coronary intervention

The pooled proportions of survival and complications across Impella device types for high risk PCI are summarized in Table 5.

Survival

A single RCT (PROTECT II) comparing HRPCI patients on Impella 2.5 (n=225) to patient on intra-aortic balloon pump (n=223) reported 92.4% of patients randomized to Impella 2.5 had survived to 30-days post insertion, decreasing marginally to 87.9% at 90-days (28). For the HRPCI prospective group, 30-day survival was 92.2% (95%CI: 88.6%-95.1%). Survival was very high within retrospective studies of patients supported prophylactically with Impella 2.5 for HRPCI. Survival to next therapy was 99% (95%CI: 98.1%-99.7%), 97.9% at discharge was (95%CI: 96.4%-99%) and 96.1% at 30-days (95%CI: 94%-97.7%).

Complications

In-hospital stroke/TIA was again low, associated with only 2.9% (95%CI: 1.1%-5.7%) of Impella 2.5/CP insertions and 2.7% (95%CI: 0.1%-8.5%) of Impella 5.0 supports. Consistent with the other indications and study types analyzed, in-hospital bleeding was associated with 23.1% (95%CI: 16.7%-30.3%) of Impella 2.5/CP insertions. Similarly, device malfunction was again low associated with just 2.3% of Impella 2.5/CP insertions (95%CI: 0.9%-4.3%). For Impella 2.5/CP hemolysis was reported in 8.6% (95%CI: 5.7%-12%) of insertions while for Impella 5.0 it was 6.9% (95%CI: 1.8%-15%). The rates of limb ischemia in Impella 2.5/CP was 4.7% (95%CI: 2.1%-8.2%) and 3.6% (95%CI: 0.3%-10%) in Impella 5.0.

Discussion

Impella devices were associated with good survival and generally low rates of complications and safety outcomes across all combinations of indication and study types analyzed. In the absence of sufficiently powered randomized clinical trials covering relevant indications and patient cohorts, the presented meta-analysis provides the best evidence to date and confirms observations from individual studies that the use of Impella in CS is likely to be safe and effective. It further
extends the existing evidence base by demonstrating that these low event rates and favorable survival outcomes are generally consistent across both the indication and the study design used to study Impella outcome data.

Survival in CS secondary to either ADHF or AMI supported with Impella was particularly encouraging, with pooled 90-day survival across both indications at 62.6%. When the analysis was limited to the ADHF cohort, an indication characterized by the use of the more powerful Impella 5.0 device, survival to discharge was 67.8% (with an upper limit high of 83.0%) whilst survival at 30-days was 67.2%. In the context of ADHF, the 5.0 device is employed to reverse tissue hypoxemia, end organ dysfunction, and cardiorenal syndrome facilitating bridge to recovery, durable LVAD insertion of heart transplantation [25].

The relatively high rates of survival consistently observed across these often severely decompensated patients supports the effectiveness of the Impella 5.0 as a “bridge to decision” in ADHF [25]. Survival in the AMICS patients at 6 months was 58.8% (when the meta-analysis was limited to case series). Elsewhere, prophylactic Impella support for patients undergoing HRPCI was associated consistently high survival rates at 30-days (92.2% in prospective studies and 96.1% in retrospective studies), in line with expectations.

Notably, the rate of stroke/TIA was particularly low – regardless of indication, device type or study design. The maximum inpatient stroke rate observed amongst those pooled analyses associated with acceptable heterogeneity was 2.7% in both the ADHF case series and in the pooled CS retrospective observational studies it was 3.5%. In-hospital stroke rate was 3.7% in the AMICS and just 0.02% of the HRPCI retrospective studies group. This is broadly consistent with the low rates of stroke/TIA reported in the Impella arm of the pivotal PROTOCOL II study; which observed 0.0% and 0.9% stroke or TIA rates at 30 and 90-days respectively.

Limb ischemia is a significant risk for CS patients managed with a combination of mechanical support and catecholamine therapy. However, our meta-analysis suggests that limb ischemia is a relatively infrequent event at 5.9% of patients in the pooled CS prospective studies group (upper limit 16.7%) and 4.2% in CS retrospective group (upper limit 6.7%). In the AMICS subgroup limb ischemia rate was 4.4%. Bleeding events were reported in 23.5% of the AMICS subgroup.

Hemolysis rates were consistently low across indication/study type groups, ranging from a high of 8.8% in the AMICS PCI case series cohort to just 1.4% of the HRPCI retrospective subgroup. In the retrospective studies device malfunction was low in both the AMICS PCI s (2.5%) and the HRPCI subgroups (0.7%).

Whilst this meta-analysis provides the largest pooling of survival and complications to date in CS and HRPCI patients on Impella support, it does have a number of limitations. Firstly, it is not a comparative analysis and thus should not be used to make inferences around the exact benefit attributable to Impella relative to any other left ventricular support device in these specific clinical scenarios, with regards to either efficacy or in terms of harm avoided. Secondly, a large proportion of eligible studies included in the meta-analyses were low-quality case series. This led, in part, to the unacceptably high levels of heterogeneity for several key outcomes. However, by stratifying the meta-analysis by the level of evidence (i.e. study type) we were able to statistically demonstrate for the first time that those favorable survival and low incidence of adverse event signals previously only observed in individual studies were broadly consistent across study types (randomized trial, prospective cohort, retrospective, case series) – suggesting these signals are genuine. An appropriately powered clinical trial and/or larger prospective cohort study, preferably of longer follow-up duration than the studies included here, would be required to better characterize the benefit of Impella in these patient cohort, particularly in relation to competitor support devices.

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Conflicting Interests

Natalia M Stelmaszek-Zadykowicz, Sun Sun and Tim Spelman are employees of Synergus AB – MedTech consulting company and received consulting fees from Abiomed Inc. Jonathan Hill, Bernhard Schieffer, Andreas Schäfer have received honoraria for speaking and chairing at symposia. The other authors report no conflicts.

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