1 (2021) 100002

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.elsevier.com/locate/ahjo

Review Article

Mechanical circulatory support with Impella in percutaneous coronary intervention: current status

Baskaran Chandrasekar

Cardiac Cath Lab, Chest Diseases Hospital, PO Box 4082, Safat 13041, Kuwait

ARTICLE INFO

Article history:
Received 3 September 2020
Received in revised form 25 October 2020
Accepted 11 November 2020

ABSTRACT

In patients with, or at risk of, hemodynamic instability during percutaneous coronary intervention, maintaining perfusion of vital organs is crucial. The intra-aortic balloon pump and Impella are the two most commonly used percutaneous mechanical circulatory support devices. Intra-aortic balloon pump has been in widespread use for over three decades. Mechanical circulatory support with Impella is being used increasingly often in patients with acute myocardial infarction complicated by cardiogenic shock, and in those undergoing high-risk percutaneous coronary intervention. Besides improving cardiac output and coronary perfusion, Impella has potential myocardial protective effects. Three key measures that determine the clinical utility of a device are clinical outcome, device-related complications, and cost impact. In this review, the current data on use of Impella in patients with acute myocardial infarction complicated by cardiogenic shock, in left ventricular unloading in acute myocardial infarction, and in those undergoing high-risk percutaneous coronary intervention is analyzed.

Contents

1. Introduction

The management of cardiogenic shock in patients with acute myocardial infarction remains a major challenge. The incidence of cardiogenic shock in acute myocardial infarction has been reported to range from 5% to 15%, reflecting the variation in defining cardiogenic shock [1]. Although the increase in use of primary percutaneous coronary intervention (PCI) has been associated with improved survival in patients with acute myocardial

Abbreviations: AMICS, acute myocardial infarction complicated by cardiogenic shock; HRPCI, high-risk percutaneous coronary intervention; MCS, mechanical circulatory support; IABP, intra-aortic balloon pump; MACCE, major adverse cardiac and cerebrovascular event; RCT, randomized control trial.

E-mail address: ani_chandra1@yahoo.com.

http://dx.doi.org/10.1016/j.ahjo.2020.100002

infarction complicated by cardiogenic shock (AMICS) [2], the mortality rate has been persistently high since over 2 decades. Hemodynamic deterioration, with multi-organ failure is the predominant cause of high mortality in such patients. Another subset of patients at risk of hemodynamic instability during PCI are those undergoing high-risk PCI (HRPCI). Clinical and angiographic variables, such as acute myocardial infarction, recent heart failure, renal failure, peripheral vascular disease, cerebrovascular disease, chronic lung disease, diabetes, advanced age, proximal left anterior descending artery disease, left main coronary artery disease, multivessel disease, chronic total occlusion, have been used to characterize HRPCI [3]. The current evidence for use of Impella in the above group of patients is reviewed.

2. Mechanical circulatory support in PCI: a preamble

Mechanical circulatory support (MCS) during PCI may have the potential to improve outcome in patients with, or, at high-risk of hemodynamic instability. The intra-aortic balloon pump (IABP) has been in use since over three decades to provide circulatory support in hemodynamically compromised patients. In the IABP-SHOCK II (Intra-aortic Balloon Pump in Cardiogenic Shock II) trial, MCS with IABP did not reduce 30-day mortality compared to conventional treatment in patients with AMICS (39.7% in IABP group versus 41.3% in control group, $p = 0.69$) [4]. This result was consistent in all the pre-specified subgroup analyses of primary end-point, including age (<50 years, 50 to 75 years, or >75 years). Long-term follow-up of IABP-SHOCK II trial patients (6.2 years, interquartile range 5.6–6.7) has revealed a high, but similar all-cause mortality in both IABP and control groups (66.3% versus 67.0%, $p = 0.98$) [5]. In patients undergoing HRPCI, elective IABP as compared to unplanned IABP-support did not reduce in-hospital major adverse cardiac events [6]. However, long-term follow-up of these patients did show a significant 34% relative reduction in all-cause mortality (hazard ratio 0.66; 95% CI 0.44–0.98, $p < 0.05$) at 51 months (interquartile range, 41–58) with elective pre-PCI support with IABP as compared to unplanned IABP-supported HRPCI [7]. There is no clear explanation from the data available for this observed benefit in long-term but not in in-hospital major adverse cardiac events with elective IABP. There were no differences in the extent of revascularization, number of vessels treated, or procedural success rate to explain the difference in long-term all-cause mortality. A difference was reported in the secondary outcome of procedural complications (defined as ventricular tachycardia/ventricular fibrillation, cardiorespiratory arrest, and sustained hypotension) which was lower in the elective IABP group (odds ratio 0.11; 95% CI 0.44–0.98, $p < 0.001$), but still cannot explain the difference in long-term mortality. The authors of the study have acknowledged the possibility that the difference in long-term mortality may reflect a chance finding [7].

Four basic characteristics for percutaneous MCS device have been proposed [8]. These include effective insertion with minimal surgical application, simplicity of initiation and maintenance for widespread use by minimally trained professional personnel, capability for aiding the coronary and peripheral circulation intermittently or continuously for hours or days, and significant support for the ischemic myocardium by reducing its work. The Impella system, designed to meet these basic characteristics has been available in Europe since 2004 and in the United States since 2008, and its use has been increasing rapidly. Over 15,000 implantations had been performed by 2013 and over 70,000 by 2018 in the United States alone, according to the manufacturer's (Abiomed) report. The approximate device cost of Impella is $23,000–$25,000 and that of IABP is $800–$1000. The CMS (Centers for MEDICARE and MEDICAID Services) has recently reduced the reimbursement rate for Impella by 11% (down to $71,950 from $80,650).

3. Hemodynamics of Impella

Besides the augmentation in cardiac output generated by Impella, the potential benefits of Impella accrue from its favorable effects on hemodynamic support and left ventricular unloading, occurring at the device's outflow port and inflow port respectively (Fig. 1). The increase in mean aortic and diastolic coronary artery pressures and coronary flow velocity reserve, along with decrease in microvascular resistance together result in an increase in coronary blood flow [9]. A 47% increase in coronary blood flow with Impella-support has been demonstrated [10]. Left ventricular unloading with Impella-support during PCI significantly decreases left ventricular end-diastolic pressure and left ventricular end-diastolic wall stress, along with increase in left ventricular diastolic compliance [11]. These effects lead to a decrease in myocardial oxygen demand. The decrease in left ventricular end-diastolic pressure may improve coronary blood flow as high left ventricular end-diastolic pressure has been reported to be associated with subendocardial ischemia, probably related to extravascular compressive forces [12]. With a fall in left ventricular end-diastolic pressure, perfusion of myocardium also improves because of the resultant increase in coronary perfusion pressure (as coronary perfusion pressure = aortic diastolic pressure - left ventricular end-diastolic pressure).

Left ventricular unloading in the setting of acute myocardial infarction can reduce extent of myocardial necrosis in the area of infarction. In animal studies in the setting of acute myocardial infarction, left ventricular unloading with Impella just prior to reperfusion reduced the extent of myocardial necrosis compared to primary reperfusion group and in the group where unloading was initiated after reperfusion [13]. Left ventricular unloading with Impella 60 min before reperfusion reduced infarct-size by 43% compared to primary reperfusion in animal experiments [14]. Subsequently, even 30 min of left ventricular unloading with Impella followed by reperfusion was shown to reduce infarct-size compared to primary reperfusion in experimental studies [15]. Left ventricular unloading prior to reperfusion protects against ischemia/reperfusion injury and limits myocardial damage [16]. In their study Kapur et al. have shown that left ventricular unloading prior to reperfusion promotes activity (increases phosphorylation) of the protective proteins involved in the RISK pathway (Reperfusion Injury Salvage Kinases) – extracellular regulated kinase (ERK) and serine/threonine kinase Akt, leading to reduced myocardial injury [16]. Stromal-derived factor-1α, a cardio-protective cytokine, protects against apoptosis and maintains mitochondrial integrity by activating the reperfusion injury salvage kinases extracellular regulated kinase and Akt [17]. During ischemia/reperfusion injury, increased levels of the proteases matrix metalloproteinase and dipeptidylpeptidase-4 inactivate stromal-derived factor-1α, increasing myocardial cellular apoptosis and damaging mitochondrial integrity [18]. Left ventricular unloading, by reducing matrix metalloproteinase and dipeptidylpeptidase-4 levels, increases availability of stromal-derived factor-1α thereby improving myocardial cell survival [15].

4. Clinical studies with Impella: AMICS and HRPCI

A systematic review of medical literature databases including PUBMED, EMBASE, and CENTRAL was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [19]. The following key words were used for the search, 'mechanical circulatory support' and 'Impella', 'Impella' and 'cardiogenic shock', 'Impella' and 'high-risk percutaneous coronary intervention'. Randomized control trials (RCT), registries and retrospective series with more than 10 patients, reviews and meta-analyses were included in the systematic review (PRISMA flow diagram, Fig. 2).

4.1. Randomized controlled and pilot trials

Randomized control trials are valuable to determine the existence of cause-effect relationship between an intervention and an outcome. The planned randomized trials with Impella and their status are listed in Table 1. In a RCT of 25 patients with AMICS randomized to Impella-support or to IABP-support (ISAR-SHOCK), both groups showed a similar 30-day mortality, although cardiac-index was increased significantly with Impella-support compared to IABP-support [20]. An explorative RCT of 48 patients with AMICS comparing IABP with Impella (IMPRESS in Severe Shock) demonstrated similar 30-day and 6-month mortality with both treatment arms [21]. The ongoing DanGer Shock trial will test whether

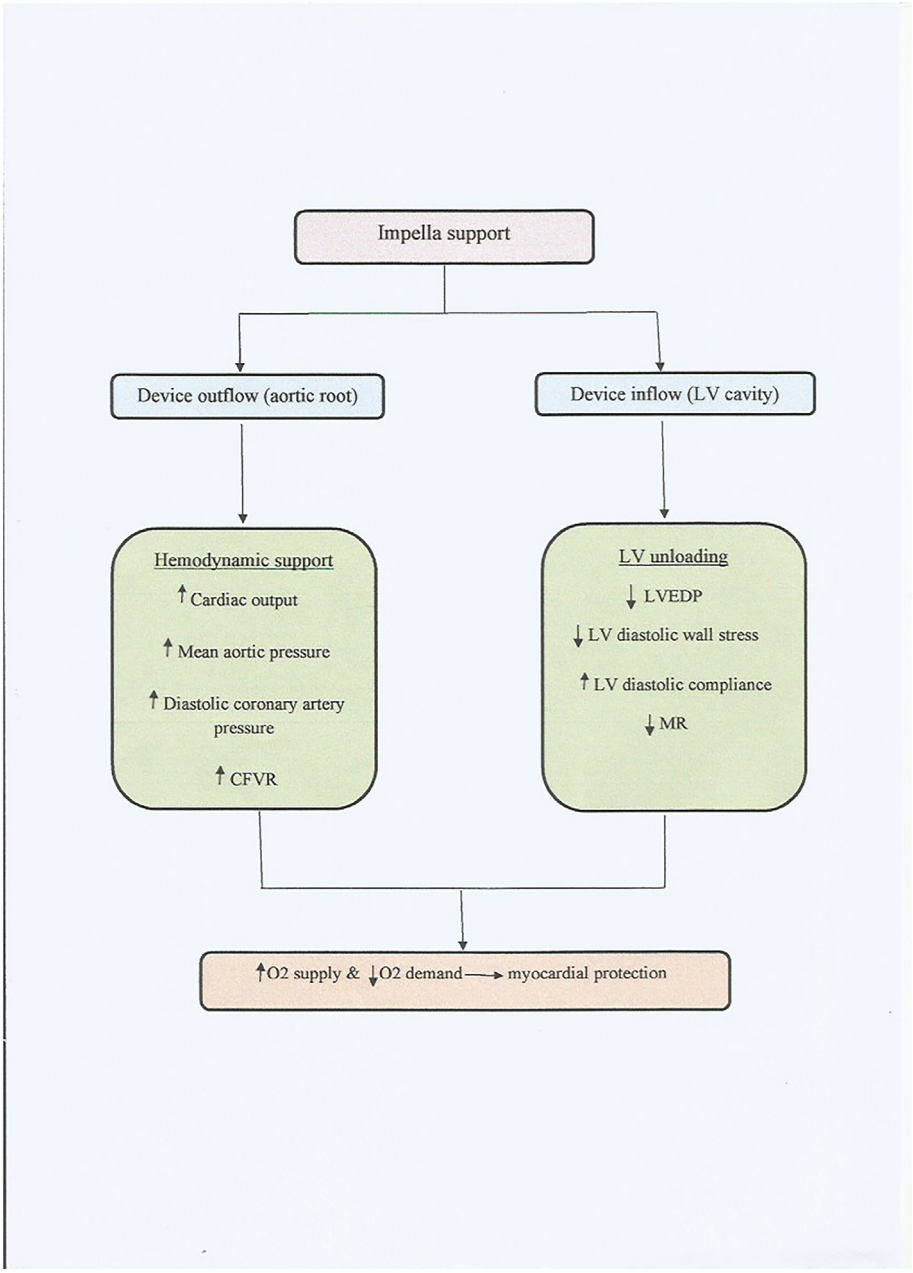

Fig. 1. Schematic representation of potential benefits of Impella-support underlying the perceived myocardial protective effects. LV = left ventricle, CFVR = coronary flow velocity reserve, EDP = end-diastolic pressure, MR = microvascular resistance.

Impella use (placed prior to PCI) can improve the 180-day survival in patients with AMICS, as compared to conventional guideline-driven treatment [22]. The study (ClinicalTrials.gov: NCT01633502) has an estimated primary completion date of September 2022 and an estimated study completion date of January 2023. The FRENCH trial (NCT00314847), the IMPRESS in STEMI trial (NTR1079), and the RECOVER II FDA trial (NCT00972270) were discontinued due to insufficient enrollment.

The PROTECT II study is the largest RCT with Impella reported thus far, which randomized HRPCI patients (n = 452) undergoing a nonemergent procedure to IABP-support (n = 226) or Impella-support (n = 226) [23]. The study showed no difference in 30-day mortality (6.2% for IABP versus 6.9% for Impella, p = 0.74) or major adverse cardiac and cerebrovascular events (MACCE) (40.1% for IABP versus 35.1% for Impella, p = 0.22) between the two groups. At 90 days, in the intent-to-treat population, there was a trend towards a decrease in MACCE with Impella (49.3% for IABP versus 40.6% for Impella, p = 0.06), MACCE was also lower in the per-protocol population (51.0% for IABP versus 40.0% for Impella, p < 0.05). Although 654 patients were planned to be enrolled, the study was discontinued after enrollment of 452 patients (69%) upon recommendation by the data safety monitoring board for futility, due to inability to demonstrate differences between the two groups in the primary-endpoint.

It should be delineated here that the above trials used different support platforms. The ISAR-SHOCK and PROTECT II trials utilized the Impella 2.5 support (capable of providing up to 2.5 l/min) while the IMPRESS in Severe Shock and DanGer Shock trials utilized the more robust Impella CP support (capable of providing up to 4.1 l/min). The different support platforms provide different degrees of hemodynamic support, however, there is no study distinguishing outcomes between the devices.

Also, the definition of shock varied across different trials. In the ISAR-SHOCK trial, cardiogenic shock was defined based on both clinical and hemodynamic criteria as described in the SHOCK trial [24]. The presence of

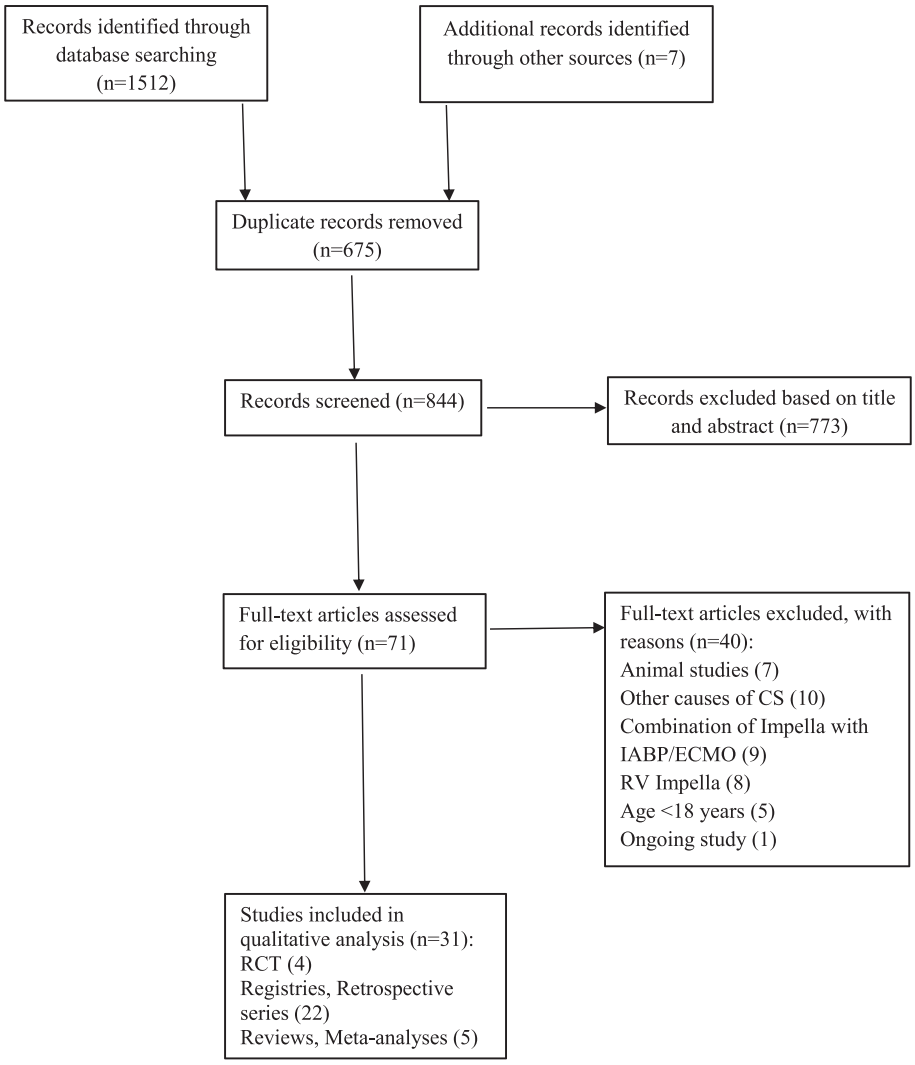

Fig. 2. Flow diagram showing study selection according to PRISMA principle. CS = cardiogenic shock, IABP = intra-aortic balloon pump, ECMO = extracorporeal membrane oxygenation, RV = right ventricle, RCT = randomized controlled trials, PRISMA = preferred reporting items for systematic reviews and meta-analyses.

hypotension (systolic blood pressure <90 mmHg for longer 30 min or the need for inotropes or vasopressors to maintain systolic blood pressure >90 mm hg) fulfilled the eligibility criteria for cardiogenic shock in the IMPRESS in Severe Shock trial, but the patients also needed to be on mechanical ventilation before randomization. In the DanGer trial, the definition of cardiogenic shock was based on presence of persistent hypotension, tissue hypoperfusion, increase in arterial blood lactate and reduced left ventricular ejection fraction on echocardiography. Although the different randomized trials used varying definitions of cardiogenic shock, the same criterion was applied to both the arms of randomization within a trial, thus eliminating any potential bias.

Table 1
Impella – randomized trials and their status.

FRENCH trial (NCT00314847); Status – Discontinued
ISAR-SHOCK (NCT00417378); Status – Completed (ref #20)
IMPRESS in STEMI (NTR1079); Status – Discontinued
RECOVER II FDA (NCT00972270); Status – Discontinued
IMPRESS in Severe Shock (NTR3450); Status – Completed (ref #21)
DanGer SHOCK (NCT01633502); Status – Ongoing
PROTECT II (NCT00562016); Status – Completed (ref #23)
DTU-STEMI Pilot trial (NCT03000270); Status – Completed (ref #42)
DTU-STEMI trial (NCT03947619); Status – Ongoing

4.2. Retrospective series, registries, meta-analysis

Over the past few years, several observational studies have documented the use of Impella-support in AMICS and HRPCI [25–29]. In a meta-analysis of MCS (Impella and TandemHeart) supported HRPCI or cardiogenic shock, Rios et al. reported no short-term (6-month) or long-term (1-year) all-cause mortality benefit over IABP [30]. In a recent meta-analysis of patients who had received Impella-support for cardiogenic shock (acute myocardial infarction, acute decompensated heart failure, post-cardiotomy) or for HRPCI [31], after adjustment for considerable heterogeneity between studies for several key outcomes, the 90- and 180-days survival rates in cardiogenic shock patients were 62.6% and 58.3% respectively. The 30-day survival in the HRPCI patients was 92.2% with a MACCE rate of 15.3%. While some of the above studies analyzed data from both shock patients and elective HRPCI patients, none of the studies were designed for comparison of data between shock patients and elective HRPCI patients. Vetrovec et al. [25], and Chieffo et al. [29] aimed to analyze trends and outcomes of Impella for cardiogenic shock and HRPCI in clinical practice, while Rios et al. [30] attempted to compare IABP versus Impella during cardiogenic shock or HRPCI, and Hill et al. [31] analyzed the survival and complication rates of Impella use in cardiogenic shock and HRPCI.

An analysis of MCS use in the United States between 2004 and 2011 involving 6 devices (non-percutaneous and percutaneous, including Impella)

observed a 1511% increase in the use of percutaneous MCS and a 101% increase in the use of non-percutaneous MCS from 2007 to 2011 [32]. Compared to the period 2004–2007, the period 2008–2011 was accompanied by decreased in-hospital mortality and hospital costs. The authors, however, were unable to attribute this decrease in in-hospital mortality to the increase in use of MCS. They acknowledge the difficulty in differentiating the impact of MCS from other treatment strategies for cardiovascular diseases evolving during the period. Furthermore, the analysis of outcome was not device-specific, and IABP and extracorporeal membrane oxygenation were excluded as MCS devices.

Patients undergoing HRPCI or PCI for AMICS are at high risk for periprocedural acute kidney injury. The association between Impella use and acute kidney injury is unclear. A protective effect of Impella-support during HRPCI on renal function as compared with unsupported HRPCI has been described in some studies [33,34]. However, when compared to IABP-support, a trend towards higher acute kidney injury with Impella-support has also been reported [30,35].

The timing of initiation of Impella-support, whether early (pre-PCI or during PCI) or delayed (post-PCI), is thought to have an effect on patient outcome. In patients with AMICS, Impella implantation pre-PCI favorably influenced survival to hospital discharge as compared to Impella implantation post-PCI [36]. Flaherty et al. in a meta-analysis of 3 studies reported a 48% decrease in in-hospital/30-day mortality with early (implantation before or during PCI) versus late initiation of Impella (implantation post-PCI) in AMICS [37]. Long-term survival rates also appear to be higher with early implantation of Impella compared to delayed implantation in patients with AMICS undergoing PCI [38]. It is possible that late initiation of Impella in the setting of HRPCI could be associated with further hemodynamic compromise and collapse, with higher rates of MACE expected. However, there is no report till date evaluating the effect of timing of initiation of Impella-support in the setting of HRPCI.

4.3. Comparative studies

The aforementioned studies did not perform comparative analysis with a matched group of controls without Impella-support. In the absence of a published adequately powered RCT, recently several investigators have attempted to compare the outcome of Impella-support in AMICS and HRPCI, to matched control groups (Table 2).

In a retrospective study by Schrage et al., patients with AMICS treated with Impella were compared to matched patients from the IABP-SHOCK II trial [39]. The study found no difference in 30-day all-cause mortality, but higher complications with Impella treatment. The result was consistent upon comparison of Impella with both the medical treatment, and, the IABP arms of the IABP-SHOCK II trial. In an analysis by Helgestad et al. of patients with AMICS undergoing PCI, patients who received early Impella or early IABP were compared with their respective control groups [40]. The early-Impella group had a lower 30-day mortality compared with its control group. No difference in mortality was seen in the early-IABP group on comparison with its control group. There was, however, significant unevenness in matching of the treatment groups with their respective controls. The incidence of cardiogenic shock before start of PCI was markedly higher in the control groups (55% for early-Impella group versus 85% for control group, $p < 0.01$) and (62.5% for early-IABP group versus 85% for control group, $p = 0.02$), rendering interpretation of the results of this study challenging.

In a retrospective cohort study of 28,304 patients undergoing PCI for AMICS by Dhruva et al., 3360 patients who received either Impella or IABP were matched for demographics, clinical history and presentation, infarct location, coronary anatomy and laboratory data [41]. Impella use was associated with a higher risk of in-hospital mortality (45.0% versus 34.1%, absolute risk difference 10.9 percentage points [95% CI, 7.6–14.2]; $p < 0.01$) and in-hospital major bleeding complications. The above findings were consistent regardless whether device implantation was performed early (before or during PCI), or delayed (post-PCI). In the largest reported study of patients undergoing PCI with MCS (Impella or IABP), Amin et al. analyzed 48,306 patients undergoing PCI with MCS between 2004 and 2016 [35]. The use of Impella was found to increase rapidly from the time of its availability in 2008, to 31.9% of MCS implanted by 2016. After propensity adjustment and to account for any variations across different hospitals, Impella use was observed to be associated with increased in-hospital mortality (odds ratio, 1.24 [95% CI, 1.13–1.36]) and complications, as compared with IABP use. Additionally, the authors reported higher hospitalization costs despite a shorter length of stay in Impella-supported patients.

Any comparison of data between cardiogenic shock patients and patients undergoing elective HRPCI has limitations, as both conditions differ prognostically. Among the above four comparative studies only the study by Amin et al. included cardiogenic shock and elective HRPCI, the remaining studies were confined to patients with cardiogenic shock. In the study, cardiogenic shock was present in 50% of patients. While patients receiving Impella had a higher prevalence of diabetes, heart failure, chronic kidney disease, chronic obstructive pulmonary disease, and multivessel disease

Table 2
Impella – recent comparative studies.

Authors (ref #, year)	Study cohort (n)	Comparison	Statistics	Outcome for Impella
Schrage et al. (ref #39, 2019)	PCI for AMICS (372)	Impella vs IABP-SHOCK II trial patients	48.5% vs 46.4% ($p = 0.64$)	↔in-hospital mortality
			8.5% vs 3.0% ($p < 0.01$)	↑severe bleeding
			9.8% vs 3.8% ($p = 0.01$)	↑limb ischemia
			35.3% vs 19.4% ($p < 0.01$)	↑sepsis
Helgestad et al. (ref #40, 2020)	PCI for AMICS (40 in each group, out of a cohort of 903)	Early-Impella vs its control	40% vs 77.5% ($p < 0.01$)	↓30-day mortality with early Impella[a]
		Early-IABP vs its control	27.5% v 37.5% ($p = 0.35$)	↔30-day mortality with early IABP
Dhruva et al. (ref #41, 2020)	PCI for AMICS (1680 in each group, out of a cohort of 28,304)	Impella vs IABP	45.0% vs 34.1% ($p < 0.01$)	↑in-hospital mortality
			31.3% vs 16.0% ($p < 0.01$)	↑bleeding
Amin et al. (ref #35, 2020)	PCI with MCS (48,306 of which 4782 received Impella, and the remaining IABP)	Impella vs IABP	OR 1.24 [95% CI, 1.13–1.36]	↑in-hospital mortality
			OR 1.10 [95% CI, 1.00–1.21]	↑bleeding
			OR 1.34 [95% CI, 1.18–1.53]	↑stroke

PCI = percutaneous coronary intervention; AMICS = acute myocardial infarction with cardiogenic shock; IABP = intra-aortic balloon pump; MCS = mechanical circulatory support; OR = odds-ratio; CI = confidence-interval.

[a] Significant unevenness in matching (please refer text).

than those receiving IABP, they had a lower prevalence of ST-segment elevation acute myocardial infarction, cardiogenic shock, cardiac arrest, and mechanical ventilation than those receiving IABP. The objective of the study by Amin et al., as highlighted by the authors, was to analyze the outcome with Impella use in patients undergoing PCI with MCS in contemporary practice, and was not an attempt to compare data between cardiogenic shock and elective HRPCI patients.

5. Clinical studies with Impella: Left ventricular unloading

Left ventricular unloading prior to reperfusion in experimental studies led to a significant reduction in the extent of myocardial necrosis in acute myocardial infarction [13–15]. The DTU-STEMI (Door-to-Unload in STEMI) Pilot trial was a feasibility study to assess left ventricular unloading prior to reperfusion in acute myocardial infarction [42]. Twenty-five patients with anterior ST-segment elevation acute myocardial infarction were assigned to Impella implantation followed by immediate reperfusion, and a further 25 patients were randomized to Impella implantation followed by delayed reperfusion after 30 min of left ventricular unloading. At 30 days, the mean infarct-size as measured by cardiac magnetic resonance imaging was similar in both groups. A larger RCT with planned enrolment of 668 patients, the DTU-STEMI trial (ClinicalTrials.gov: NCT03947619), is in progress. The estimated primary completion date of the study is October 2023, and estimated study completion date is October 2027.

6. Complications with Impella use

Both access site and remote complications have been reported with Impella use (Table 3). The relatively large introducer vascular sheath size may play a role, as incidence of access site complications during cardiac catheterization is directly related to vascular sheath size [43]. The Impella 2.5, Impella CP, and Impella 5.0 require 13 French, 14 French, and 23 French introducer sheaths respectively. Recently, MCS with Impella or extracorporeal membrane oxygenation was identified as the major risk-factor for bleeding in patients with AMICS by Freund et al. [44]. In the study, bleeding was independently associated with higher mortality (hazard ratio 2.11; 95% CI 1.63 to 2.75; $p < 0.01$), and with peripheral ischemia, sepsis, new-onset atrial fibrillation and ventricular fibrillation. The recently published Italian registry has observed that the use of Impella is increasing substantially, with an annual percent increase of 39.8% (95% CI 30.4 to 49.9; $p < 0.01$), despite high rates of device-related complications [29]. Device-related complications were seen in 37.1% of patients with cardiogenic shock (limb ischemia 12.6%, access-site bleeding 10.9%, hemolysis 20.5%) and in 10.7% of patients with HRPCI (limb ischemia 2.8%, access-site bleeding 7.9%, hemolysis 0.5%). The incidence of limb ischemia is much higher in patients with cardiogenic shock than HRPCI patients receiving Impella as those patients are likely to be hypoperfused to begin with, more likely to be on inotropes/vasopressors, and would need the device for a longer period.

Several comparative studies have demonstrated a higher complication rate with Impella-support (Table 2). In a comparative study of Impella treatment with the medical treatment and IABP arms of IABP-SHOCK II trial, life-threatening or severe bleeding, peripheral ischemic complications requiring intervention in hospital, and sepsis were more often seen with Impella-support [39]. In a matched comparison of patients with Impella- or IABP-support for AMICS, a higher risk of major bleeding with Impella has been reported [41]. In addition to higher bleeding, an increased incidence of stroke was seen in Impella-supported patients as compared to IABP-support [35]. Azzalini et al. have reported that patients undergoing HRPCI with Impella-support have a higher incidence of major bleeding (6.8% versus 2.8%, $p = 0.04$) and need for blood transfusion (11.2% versus 4.8%, $p < 0.01$) than those patients undergoing HRPCI without MCS [45]. The incidence of peri-procedural myocardial infarction was higher in the Impella-supported group (14.0% versus 6.4%, $p < 0.01$) which was partly attributed by the authors to more aggressive PCI in the Impella-supported group.

Table 3
Complications with Impella use.

Access site bleeding
Acute limb ischemia
Stroke
Sepsis
Intravascular hemolysis
Increased mean platelet volume
Acquired von Willebrand syndrome

Hematological complications have also been reported with Impella use. Impella-related intravascular hemolysis occurs in up to 30% of patients, with evidence of hemolysis detectable within 24 h [29,46]. An association between Impella use and increased mean platelet volume has been described by Harutyunyan et al. in patients undergoing HRPCI [47]. Increase in mean platelet volume was observed in all patients by 24 h post-implantation. Every 1% increase in % change in mean platelet volume was associated with 11% increased risk of mortality (odds ratio 1.11, 95% CI 1.015–1.216, $p < 0.02$). Contact with foreign surface and pump-flow are thought to promote the increase in mean platelet volume. Another potential factor contributing towards increased bleeding complications with Impella is acquired von Willibrand syndrome. Acquired von Willibrand syndrome has been detected in 95% of patients on Impella-support [48], with a mean time from device implantation to diagnosis of von Willibrand syndrome of 10.6 ± 10.8 h.

7. Cost impact of Impella

7.1. Studies favoring cost-effectiveness of Impella

Two studies have reported Impella to be cost-effective as compared to IABP in patients undergoing HRPCI [49,50], both studies were funded by the manufacturer. In the study by Roos et al., data was obtained data from the Europella and USpella registries [49]. The authors have acknowledged key limitations in their study which had used unadjusted, indirect comparisons between the interventions that may have led to bias in the estimation of cost-effectiveness. For instance, the probability data for 30-day mortality used for the IABP-group was almost twice as high as the Impella-group, which would undoubtedly favor the Impella-group. In the study by Gregory et al. which analyzed data from the PROTECT II trial, while the hospital costs for index admission were lower for IABP, Impella was calculated to have a long-term projected higher quality-adjusted life-year and an incremental cost-effectiveness ratio [50]. This model assumed a projected long-term probability of MACCE requiring readmissions for the IABP-group that was significantly higher than that for the Impella-group. These projections were based on the PROTECT II study per-protocol population, rather than the intent-to-treat population. Given the fact that the PROTECT II study was a shortened trial that enrolled only 69% of the planned number of patients, this does raise an element of concern [51].

7.2. Studies disfavoring cost-effectiveness of Impella

In a comparative effectiveness research, Shah et al. have shown that treatment with the percutaneous ventricular assist devices Impella and TandemHeart was associated with higher incremental hospital cost as compared to IABP [52]. Both Impella and TandemHeart had similar costs, and Impella represented 92% of the percutaneous ventricular assist devices deployed. The study also offers insight into the total incremental annual hospital impact for migration from IABP to Impella for the United States, estimated at different % migration levels (10% migration – approx. $254 million; 25% migration – approx. $635 million; 50% migration – approx. $1.27 billion; and 100% migration – approx. $2.54 billion). Shah et al. then performed a separate analysis of readmissions data from the Intercontinental Medical Statistics Health Database from January 2012 through March 2013 for any cardiac-related readmissions occurring at 30, 60, or

90 days after the index procedure [48]. A total of 2559 Impella-supported and 52,364 IABP-supported PCI were identified and analyzed for readmissions. No statistical difference was observed between the two groups for cardiac readmissions.

In a publicly-funded cost analysis by Health Quality Ontario, Canada [53], using the PROTECT II model (intent-to-treat population) as the base-case scenario, the authors found higher incremental cost and lower incremental quality-adjusted life-year for Impella over IABP. Even in the simulated scenario of a 50% lower mortality with Impella and a 50% higher mortality with IABP from the base-case scenario, Impella was not cost-effective. Impella as an alternative to IABP for Ontario province was projected to lead to an additional annual cost of 2.9–11.5 million $Canadian.

8. Conclusion

Use of Impella-support during percutaneous coronary intervention has seen a rapid increase over the past few years. Mechanical circulatory support with Impella has potential favorable hemodynamic and myocardial protective effects. These perceived effects, however, have not translated to significant clinical outcomes. Available clinical data till date suggest that Impella-support for acute myocardial infarction complicated by cardiogenic shock, and for high-risk percutaneous coronary intervention is not associated with improved survival over conventional treatment. Contrarily, even increased mortality, significant device-related complications, and incremental cost associated with Impella use have been reported. The results of clinical efficacy of left ventricular unloading with Impella prior to revascularization in acute myocardial infarction are awaited.

Funding

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] R.J. Goldberg, F.A. Spencer, J.M. Gore, et al., Thirty year trends (1975-2005) in the magnitude, management, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction: a population-based perspective, Circulation 119 (2009) 1211–1219.
[2] A. Babaev, P.D. Frederick, D.J. Pasta, NRMI investigators, et al., Trends in management and outcomes of patients with acute myocardial infarction complicated by cardiogenic shock, JAMA 294 (2005) 448–454.
[3] J.M. Brennan, J.P. Curtis, D. Dai, et al., Enhanced mortality risk prediction with a focus on high-risk percutaneous coronary intervention (results from 1,208,137 procedures in the National Cardiovascular Data Registry), JACC Cardiovasc. Interv. 6 (2013) 790–799.
[4] H. Thiele, U. Zeymer, F.J. Neumann, for the IABP-SHOCK II trial investigators, et al., Intraaortic balloon support for myocardial infarction with cardiogenic shock, N. Engl. J. Med. 367 (2012) 1287–1296.
[5] H. Thiele, U. Zeymer, N. Thelemann, et al., Intra-aortic balloon pump in cardiogenic shock complicating acute myocardial infarction: long-term 6-year outcome of the randomized IABP-SHOCK II trial, Circulation 139 (2019) 395–403.
[6] D. Perera, R. Stables, M. Thomas, et al., Elective intra-aortic balloon counterpulsation during high-risk percutaneous coronary intervention: a randomized controlled trial, JAMA 304 (2010) 867–874.
[7] D. Perera, R. Stables, T. Clayton, et al., BCIS-1 investigators. Long-term mortality data from the balloon pump-assisted coronary intervention study (BCIS-1): a randomized, clinical trial of elective balloon counterpulsation during high-risk percutaneous coronary intervention, Circulation 127 (2013) 207–212.
[8] A. Myat, N. Patel, S. Tehrani, A.P. Banning, S.R. Redwood, D.L. Bhatt, Percutaneous circulatory assist devices for high-risk coronary intervention, JACC Cardiovasc. Interv. 8 (2015) 229–244.
[9] M. Remmelink, K.D. Sjauw, J.P.S. Henriques, et al., Effects of left ventricular unloading by Impella recover LP2.5 on coronary hemodynamics, Catheter. Cardiovasc. Interv. 70 (2007) 532–537.
[10] L.D.C. Sauren, R.E. Accord, K. Hamzeh, et al., Combined Impella and intra-aortic balloon pump support to improve both ventricular unloading and coronary blood flow for myocardial recovery: an experimental study, Artif. Organs 31 (2007) 839–842.
[11] M. Remmelink, K.D. Sjauw, J.P.S. Henriques, et al., Effects of mechanical left ventricular unloading by Impella on left ventricular dynamics in high-risk and primary percutaneous coronary intervention patients, Catheter. Cardiovasc. Interv. 75 (2010) 187–194.
[12] A.K. Elhabyan, B. Reyes, O. Hallak, et al., Subendocardial ischemia without coronary artery disease: is elevated left ventricular diastolic pressure the culprit? Curr. Med. Res. Opin. 20 (2004) 773–777.
[13] H. Achour, F. Boccalandro, P. Felli, et al., Mechanical left ventricular unloading prior to reperfusion reduces infarct size in a canine infarction model, Catheter. Cardiovasc. Interv. 64 (2005) 182–192.
[14] N.K. Kapur, X. Qiao, V. Paruchuri, et al., Mechanical pre-conditioning with acute circulatory support before reperfusion limits infarct size in acute myocardial infarction, JACC Heart Fail. 3 (2015) 873–882.
[15] M.L. Esposito, Y. Zhang, X. Qiao, et al., Left ventricular unloading before reperfusion promotes functional recovery after acute myocardial infarction, J. Am. Coll. Cardiol. 72 (2018) 501–514.
[16] N.K. Kapur, V. Paruchuri, J.A. Urbano-Morales, et al., Mechanically unloading the left ventricle before coronary reperfusion reduces left ventricular wall stress and myocardial infarct size, Circulation 128 (2013) 328–336.
[17] D.I. Bromage, S.M. Davidson, D.M. Yellon, Stromal derived factor 1α: a chemokine that delivers a two-pronged defence of the myocardium, Pharmacol. Ther. 143 (2014) 305–315.
[18] S. Kanki, V.F.M. Segers, W. Wu, et al., Stromal cell-derived factor-1 retention and cardioprotection for ischemic myocardium, Circ. Heart Fail. 4 (2011) 509–518.
[19] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, PRISMA group, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, J. Clin. Epidemiol. 62 (2009) 1006–1012.
[20] M. Seyfarth, D. Sibbing, I. Bauer, et al., A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction, J. Am. Coll. Cardiol. 52 (2008) 1584–1588.
[21] D.M. Ouweneel, E. Eriksen, K.D. Sjauw, et al., Percutaneous mechanical circulatory support versus intra-aortic balloon pump in cardiogenic shock after acute myocardial infarction, J. Am. Coll. Cardiol. 69 (2017) 278–287.
[22] N.J. Udesen, J.F. Moller, M.G. Lindholm, et al., Rationale and design of DanGer shock: Danish-German cardiogenic shock trial, Am. Heart J. 214 (2019) 60–68.
[23] W.W. O'Neill, N.S. Kleiman, J. Moses, et al., A prospective, randomized clinical trial of hemodynamic support with Impella 2.5 versus intra-aortic balloon pump in patients undergoing high-risk percutaneous coronary intervention, the PROTECT II study, Circulation 126 (2012) 1717–1727.
[24] J.S. Hochman, L.A. Sleeper, J.G. Webb, for the SHOCK investigators, et al., Early revascularization in acute myocardial infarction complicated by cardiogenic shock, N. Engl. J. Med. 341 (1999) 625–634.
[25] G.W. Vetrovec, M. Anderson, T. Schreiber, et al., The cVAD registry for percutaneous temporary hemodynamic support: a prospective registry of Impella mechanical circulatory support use in high-risk PCI, cardiogenic shock, and decompensated heart failure, Am. Heart J. 199 (2018) 115–121.
[26] F. Burzotta, G. Russo, F. Ribichini, et al., Long-term outcomes of extent of revascularization in complex high risk and indicated patients undergoing Impella-protected percutaneous coronary intervention: report from the Roma-Verona registry, J. Interv. Cardiol. (2019)https://doi.org/10.1155/2019/5243913.
[27] S. Baumann, N. Werner, K. Ibrahim, et al., Indication and short-term clinical outcomes of high-risk percutaneous coronary intervention with microaxial Impella pump: results from the German Impella registry, Clin. Res. Cardiol. 107 (2018) 653–657.
[28] T. Schreiber, W.W. Htun, N. Blank, et al., Real-world supported unprotected left main percutaneous coronary intervention with Impella device; data from the USpella registry, Catheter. Cardiovasc. Interv. 90 (2017) 576–581.
[29] A. Chieffo, M.B. Ancona, F. Burzotta, et al., Observational multicentre registry of patients treated with Impella mechanical circulatory support device in Italy: the IMP-IT registry, Eurointervention 15 (2020) e1343–e1350.
[30] S.A. Rios, C.A. Bravo, M. Weinreich, et al., Meta-analysis and trial sequential analysis comparing percutaneous ventricular assist devices versus intra-aortic balloon pump during high-risk percutaneous coronary intervention or cardiogenic shock, Am. J. Cardiol. 122 (2018) 1330–1338.
[31] J. Hill, A. Banning, F. Burzotta, et al., Systematic literature review and meta-analysis of Impella devices used in cardiogenic shock and high risk percutaneous coronary interventions, Interv. Cardiol. 11 (2019) 161–171.
[32] R. Stretch, C.M. Sauer, D.D. Yuh, P. Bonde, National trends in the utilization of short-term mechanical circulatory support: incidence, outcomes, and cost analysis, J. Am. Coll. Cardiol. 64 (2014) 1407–1415.
[33] M.P. Flaherty, S. Pant, S.V. Patel, et al., Hemodynamic support with a microaxial percutaneous left ventricular assist device (Impella) protects against acute kidney injury in patients undergoing high-risk percutaneous coronary intervention, Circ. Res. 120 (2017) 692–700.
[34] M.P. Flaherty, J.W. Moses, R. Westenfeld, et al., Impella support and acute kidney injury during high-risk percutaneous coronary intervention: the global cVAD renal protection study, Catheter. Cardiovasc. Interv. 95 (2020) 1111–1121.
[35] A.P. Amin, J.A. Spertus, J.P. Curtis, et al., The evolving landscape of Impella use in the United States among patients undergoing percutaneous coronary intervention with mechanical circulatory support, Circulation 141 (2020) 273–284.
[36] W.W. O'Neill, T. Schreiber, D.H.W. Wohns, et al., The current use of Impella 2.5 in acute myocardial infarction complicated by cardiogenic shock: results from the USpella registry, J. Interv. Cardiol. 27 (2014) 1–11.

[37] M.P. Flaherty, A.R. Khan, W.W. O'Neill, Early initiation of Impella in acute myocardial infarction complicated by cardiogenic shock improves survival, a meta-analysis, JACC Cardiovasc. Interv. 10 (2017) 1805–1806.
[38] T. Loehn, W.W. O'Neill, B. Lange, et al., Long-term survival after early unloading with Impella CP in acute myocardial infarction complicated by cardiogenic shock, Eur. Heart J. Acute Cardiovasc. Care 9 (2020) 149–157.
[39] B. Schrage, K. Ibrahim, T. Loehn, et al., Impella support for acute myocardial infarction complicated by cardiogenic shock, Circulation 139 (2019) 1249–1258.
[40] O.K.L. Helgestad, J. Josiassen, C. Hassager, et al., Contemporary trends in use of mechanical circulatory support in patients with acute MI and cardiogenic shock, Open Heart 7 (2020), e001214.
[41] S.S. Dhruva, J.S. Ross, B.J. Mortazavi, et al., Association of use of an intravascular microaxial left ventricular assist device vs intra-aortic balloon pump with in-hospital mortality and major bleeding among patients with acute myocardial infarction complicated by cardiogenic shock, JAMA 323 (2020) 734–745.
[42] N.K. Kapur, M.A. Alkhouli, T.J. DeMartini, et al., Unloading the left ventricle before reperfusion in patients with anterior ST-segment-elevation myocardial infarction. A pilot study using the Impella CP, Circulation 139 (2019) 337–346.
[43] W.J. Cantor, K.W. Mahaffey, Z. Huang, et al., Bleeding complications in patients with acute coronary syndrome undergoing early invasive management can be reduced with radial access, smaller sheath sizes, and timely sheath removal, Catheter. Cardiovasc. Interv. 69 (2007) 73–83.
[44] A. Freund, A. Jobs, P. Lurz, et al., Frequency and impact of bleeding on outcome in patients with cardiogenic shock, JACC Cardiovasc. Interv. 13 (2020) 1182–1193.
[45] L. Azzalini, G.S. Johal, U. Baber, et al., Outcomes of Impella-supported high-risk nonemergent percutaneous coronary intervention in a large single-center registry, Catheter. Cardiovasc. Interv. (2020)https://doi.org/10.1002/ccd.28931.
[46] M.L. Esposito, K.J. Morine, S.K. Annamalai, et al., Increased plasma-free hemoglobin levels identify hemolysis in patients with cardiogenic shock and a transvalvular micro-axial flow pump, Artif. Organs 43 (2019) 125–131.
[47] M. Harutyunyan, K. Doshi, H. Nazeer, et al., Increased mean platelet volume is associated with decreased survival in patients supported with Impella, J. Heart Lung Transplant. 39 (4S) (2020) S407–S408.
[48] U. Flierl, J. Tongers, D. Berliner, et al., Acquired von Willebrand syndrome in cardiogenic shock patients on mechanical circulatory microaxial pump support, PLoS One 12 (2017), e0183193.
[49] J.B. Roos, S.N. Doshi, T. Konorza, et al., The cost-effectiveness of a new percutaneous ventricular assist device for high-risk PCI patients: mid-stage evaluation from the European perspective, J. Med. Econ. 16 (2013) 381–390.
[50] D. Gregory, D.J. Scotti, G. de Lissovoy, et al., A value-based analysis of hemodynamic support strategies for high-risk heart failure patients undergoing a percutaneous coronary intervention, Am. Health Drug Benefits 6 (2013) 88–99.
[51] P. Ranganathan, C.S. Pramesh, R. Agarwal, Common pitfalls in statistical analysis: intention-to-treat versus per-protocol analysis, Perspect. Clin. Res. 7 (2016) 144–146.
[52] A.P. Shah, E.M. Retzer, S. Nathan, et al., Clinical and economic effectiveness of percutaneous ventricular assist devices for high-risk patients undergoing percutaneous coronary intervention, J. Invasive Cardiol. 27 (2015) 148–154.
[53] Health Quality Ontario, Percutaneous ventricular assist devices: a health technology assessment, Ont. Health Technol. Assess Ser. 17 (2017) 1–97.