Original scientific paper

Real-life use of left ventricular circulatory support with Impella in cardiogenic shock after acute myocardial infarction: 12 years AMC experience

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Abstract

Aims: Mortality in cardiogenic shock patients remains high. Short-term mechanical circulatory support with Impella can be used to support the circulation in these patients, but data from randomised controlled studies and 'real-world' data are sparse. The aim is to describe real-life data on outcomes and complications of our 12 years of clinical experience with Impella in patients with cardiogenic shock after acute myocardial infarction and to identify predictors of 6-month mortality.

Methods: We describe a single-centre registry from October 2004 to December 2016 including all patients treated with Impella for cardiogenic shock after acute myocardial infarction. We report outcomes and complications and identify predictors of 6-month mortality.

Results: Our overall clinical experience consists of 250 patients treated with Impella 2.5, Impella CP or Impella 5.0. A total of 172 patients received Impella therapy for cardiogenic shock, of which 112 patients had cardiogenic shock after acute myocardial infarction. The mean age was 60.1±10.6 years, mean arterial pressure was 67 (56–77) mmHg, lactate was 6.2 (3.6–9.7) mmol/L, 87.5% were mechanically ventilated and 59.6% had a cardiac arrest before Impella placement. Overall 30-day mortality was 56.2% and 6-month mortality was 60.7%. Complications consisted of device-related vascular complications (17.0%), non-device-related bleeding (12.5%), haemolysis (7.1%) and stroke (3.6%). In a multivariate analysis, pH before Impella placement is a predictor of 6-month mortality.

Conclusions: Our registry shows that Impella treatment in cardiogenic shock after acute myocardial infarction is feasible, although mortality rates remain high and complications occur.

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Introduction

Mechanical circulatory support devices provide support to the heart and overall circulation. Several percutaneous support devices are available, including the Impella devices (Abiomed Inc., Massachusetts, USA).[1] The Impella device is an axial pump placed across the aortic valve which retrieves blood from the left ventricle and expels it through a cannula into the ascending aorta.

In patients with cardiogenic shock (CS), the aim of Impella treatment is to support the heart and failing circulation by increasing mean arterial pressure (MAP) and cardiac output. Moreover, the Impella unloads the left ventricle by volume unloading, and reduces left ventricular wall stress which reduces myocardial oxygen consumption and improves myocardial perfusion.[2, 3]

The Impella 2.5 and Impella CP can be inserted percutaneously and provide a maximum support of 2.5 and 3.7 L/minute, respectively. The larger Impella 5.0 can provide 5.0 L/minute but its introduction requires surgical cut-down of the femoral or axillary artery.[4] These three types of Impella provide haemodynamic support to the left ventricle while the Impella RP provides circulatory support to the right ventricle.

The recently published 2017 European Society of Cardiology (ESC) guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation recommend that mechanical circulatory support may be considered in patients in whom therapy with vasopressor and inotropes is inadequate.[5] However, this recommendation is based on only limited data of small randomised controlled trials.[6, 7] Therefore, data on the real-life use of mechanical support devices in patients with CS after acute myocardial infarction, including outcomes, complication rates and predictors of adverse outcomes are important. The aim of this study is to report our outcomes and complications over 12 years of clinical experience with left ventricular Impella device, in patients with CS after acute myocardial infarction. The secondary aim is to identify predictors of 6-month mortality.

Methods

Patient population

The data analysed in this study were obtained from patients who received an Impella at the Academic Medical Center in Amsterdam between October 2004 and December 2016. Our centre is a high volume tertiary referral hospital with on-site cardiac surgery.

The Impella programme at our hospital started with the placement of the Impella 2.5 in patients undergoing elective high-risk percutaneous coronary intervention (PCI) with the aim of preventing haemodynamic compromise during complex PCI procedures.[8–12] After gaining experience with the Impella in this controlled elective setting in 24 patients, we expanded Impella usage into the acute setting in four patients with a large anterior myocardial infarction without major haemodynamic compromise. Only thereafter did we start using Impella in patients with CS.[13–16] More Impella devices have become available over the years. Initially, only the percutaneous Impella 2.5 and the Impella 5.0, which needs a surgical cut-down of the femoral artery, were available. After our first report on the outcomes of CS patients treated with an Impella 2.5 or Impella 5.0, we adhered to the strategy of either placing an Impella 5.0 immediately or, if not possible, initially to insert an Impella 2.5 and upgrade to an Impella 5.0 before the patient was transferred to the intensive care unit, with the aim of giving the patient more haemodynamic support than the 2.5 L/minute of the Impella 2.5.[15] In 2012, the percutaneous Impella CP, which supports up to 3.7 L/minute, became available whereafter patients were routinely treated with the Impella CP. As we deemed the difference in support provided by the Impella CP and the Impella 5.0 to be approximately 1 L/minute, the need to upgrade the Impella CP to a surgical Impella 5.0 was infrequent. However, the actual support provided by the Impella devices is also determined by patient characteristics (e.g. native heart pulsatile flow and vascular resistance). Veno-arterial extracorporeal life support was not readily available in our institution during the inclusion period of this study. Also, our institution is not a durable left ventricular assist device (LVAD) or heart transplantation centre. However, these patients are generally not deemed candidates for this therapy during the acute phase of CS. The study was approved by the Academic Medical Center's institutional review board and complies with the Declaration of Helsinki.

Treatment

Implantation of the Impella was according to instructions for use, and all operators received training prior to the start of the Impella programme. The use of the Impella device and the timing of the initiation of Impella therapy (before or after revascularisation) were left to the discretion of the treating cardiologist or cardiac surgeon.

After implantation, the Impella performance level was set to a maximum level without suction or position console alarms, usually P7–8. In case of positioning alarms, echocardiography was performed to verify the position of the Impella device. Duration of Impella support was at the discretion of the treating physician. Upgrade to an impella device with more haemodynamic support was considered when the device used was deemed to provide insufficient support. This was the case in patients who exhibited a combination of worsening haemodynamics and increased need for inotropes and vasopressors (dosages) despite high Impella performance, together with an overall assessment of the patient and his/her neurological status. During Impella support, all patients were treated with unfractionated heparin in order to maintain an activated clotting time level between 160 and 180 seconds. All patients were

treated with heparin (5000 IU), and aspirin (500 mg) pre-PCI. Adjunctive treatment with glycoprotein IIb/IIIa inhibitors was at the discretion of the interventional cardiologists. Post-PCI dual antiplatelet therapy was prescribed in all patients in accordance with the guidelines.

Weaning was not formally protocolled, but was evaluated daily by the treating physician and typically started on signs of haemodynamic recovery, usually 12–24 hours after PCI, when inotropes and vasopressors were reduced. Weaning usually occurred in two steps: from maximum possible support (P7–8) to approximately half support (P4–5) (if necessary patients were observed for several hours, typically overnight), to low-level Impella support (P2–3) before device removal. Device removal was typically also two-staged. First the device is pulled back from the left ventricle into the descending aorta. The device is not switched off, but set to level P1 in order to prevent thrombus formation. After 45–60 minutes of heparin cessation, the device is removed, followed by approximately 30 minutes of femoral compression.

Study population

We included all consecutive patients presenting with CS in the setting of acute myocardial infarction who underwent Impella 2.5, Impella CP or Impella 5.0 therapy and were treated with primary PCI. Patients were excluded from analysis if they were referred to our hospital while already on Impella support or received Impella therapy after revascularisation with coronary artery bypass grafting.

Data source

We retrieved baseline demographic variables, procedural and angiographic information that had been prospectively collected from our local electronic database. Data on complications were obtained by a dedicated researcher who performed a retrospective in-depth chart review for each individual patient, including the daily clinical course reports. Follow-up data were completed with information obtained from discharge letters and inpatient and outpatient charts from the hospitals or referring centres.

Definitions

CS was defined as a clinical diagnosis made by the treating physician, based on blood pressure criteria from the SHOCK trial, i.e. systolic blood pressure (SBP) of 90 mmHg or less for at least 30 minutes or the need for vasopressors to maintain a SBP greater than 90 mmHg.[17] Survival was defined as survival within the hospital admission or up to 30 days, whichever was longer. A device-related vascular complication was defined as limb ischaemia requiring extraction of the device, an access site infection, or an access site-related bleed. Access site-related bleeding was subdivided into minor and major bleeding. Major

bleeding was defined as bleeding associated with a serum haemoglobin level decrease of 3.1 mmol/L (5 g/dL), a bleed necessitating a minimum of two packed cells of blood product transfusion or the need for surgery to control the bleeding.[16] Access site bleeds that were reported on the patient's chart or the hospital discharge letter, but did not fit the definition of a major bleed, were noted as minor bleeds. Haemolysis was defined as clinically relevant haemolysis requiring extraction of the device or blood transfusion. Haemorrhagic or ischaemic stroke was confirmed by a neurologist and a concurring computed tomography scan. Renal insufficiency on admission was defined by means of the clinical threshold for impaired renal function (creatinine >95 μmol/L for women and >110 μmol/L for men). Low haemoglobin on admission was defined using the clinical threshold for anaemia (7.5 mmol/L for women and 8.5 mmol/L for men).

Analysis

Normally distributed continuous variables are reported as mean ± standard deviation (SD) and compared with analysis of variance (ANOVA) corrected for multiple testing by Bonferroni. Skewed distributed variables are presented as median (25th–75th percentile) and compared with the Wilcoxon rank sum test. Categorical variables are presented as proportions and compared using chi-square tests. Kaplan–Meier analyses were calculated and a log-rank test was used to compare the clinical outcomes between groups. Patients were compared according to the outcome (survivors vs. non-survivors) and the type of Impella device the patients first received. Confidence intervals (95% CIs) were calculated based on the Pearson–Clopper method.

Univariate Cox proportional hazard analyses were performed to identify predictors for 6-month mortality. The following parameters were included: age, laboratory values on admission (lactate, glucose, pH), haemodynamic variables on admission (MAP, SBP and heart rate (HR)), all continuous variables. Sex, low haemoglobin on admission, renal insufficiency on admission, cardiac arrest before Impella placement and traumatic injuries on admission were included as dichotomous variables. Variables that were significant in univariate analysis ($P<0.10$) were entered in a stepwise backward multivariate Cox regression analysis. A covariate was removed from the model if its significance level exceeded $P=0.10$. Analyses were performed using SPSS (version 23.0; Chicago, IL, USA).

Results

Patient population

Between October 2004 and December 2016, a total of 250 patients received Impella 2.5, Impella CP or Impella 5.0 at
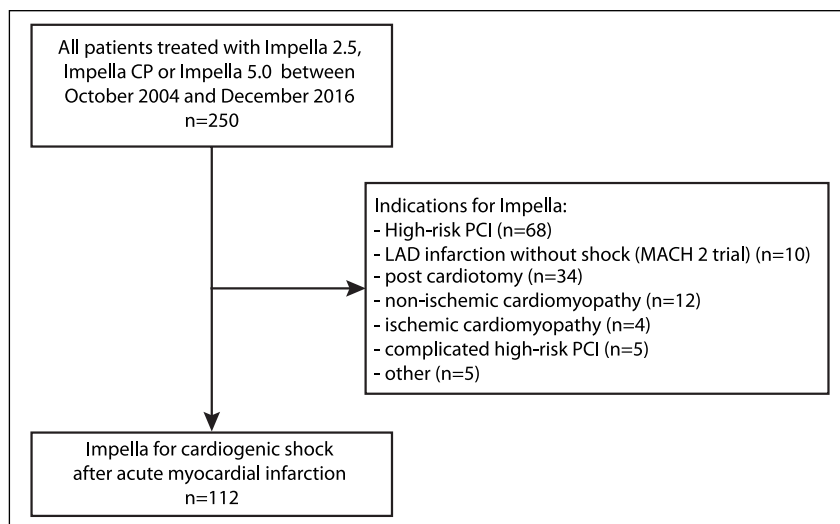
Figure 1. Flow diagram of the patients treated with Impella therapy at the Academic Medical Center, Amsterdam.

our institution (Figure 1). A total of 112 patients with CS in the setting of acute myocardial infarction were treated with primary PCI and Impella. Baseline characteristics are summarised in Table 1. In the total population, patients were 60±10 years old and 80% were men. A total of 60% of patients had experienced a cardiac arrest before Impella placement. A total of 89% of patients were mechanically ventilated and 87% were treated with catecholamines or inotropes during primary PCI. The median ischaemic time was 153 minutes and 81% had an anterior myocardial infarction. Angiographic success was achieved in 98% of patients, defined as thrombolysis in myocardial infarction (TIMI) flow post-PCI of 2/3.

Clinical course

Characteristics of the clinical course are summarised in Table 2. The initial Impella strategy consisted of Impella 2.5 in 40 patients (35.7%), Impella CP in 52 patients (46.4%) and Impella 5.0 in 20 patients (17.9%). The Impella device was placed before primary PCI in 18.8% of the patients. In 58%, the Impella was placed directly after the primary PCI (during the initial procedure), and in 23.2% of patients the Impella was placed in a separate procedure (after having left the cardiac catheterisation laboratory). The median Impella support time was 53 hours. A total of 12 patients (10.7%) underwent an upgrade to a higher-flow support device (Impella 5.0 or veno-arterial extracorporeal membrane oxygenation (ECMO)). One patient received a durable LVAD after Impella and ECMO treatment. The majority of the patients were treated with inotropic or vasopressor agents (95%), mechanical ventilation (95%), and were admitted to the intensive care unit (ICU) (89%) (Table 3). Renal replacement therapy was necessary in 38% of patients and 59% required blood products.

Complications and adverse outcome

The clinical outcomes for patients with CS after acute myocardial infarction are summarised in Table 3. A total of 65 patients (58%) died during the admission. The cause of death was refractory CS (67.7%), post-anoxic brain injury (20.0%), or other reasons (12.3%). Four patients were diagnosed with stroke during admission (3.6%). Device-related vascular complications occurred in 19 patients (17%), of whom 14 had an access site-related bleed (11 major and three minor bleeds), four patients had limb ischaemia requiring surgery and one patient had an access site infection requiring surgery. Clinically relevant haemolysis occurred in 7.1% of patients. Non-device-related bleeding occurred in 14 patients (12.5%).

Survivors versus non-survivors

Non-survivors had lower pH levels (7.14 (6.94–7.25) vs. 7.26 (7.17–7.35), *P*=0.002), and higher lactate (7.6 (4.1–10.9) vs. 4.2 (2.2–8.1) mmol/L, *P*=0.012) and glucose levels (14.1 (11.7–20.6) vs. 11.5 (8.9–17.0) mmol/L, *P*=0.028) before device placement (Table 1). However, non-survivors did not differ in age (60.7±11.4 vs. 59.3±9.5, *P*=0.503), MAP (66 (52–76) vs. 68 (57–80), *P*=0.289), cardiac arrest (60.0% vs. 59.6%, *P*=0.998), ischaemic time (161 (119–232) vs. 140 (95–266), *P*=0.517), mechanical ventilation (89.2% vs. 89.4, *P*=0.982).

Survivors required less inotropic or vasopressor therapy during admission (98.5% vs. 89.4%, *P*=0.035), a longer duration of Impella support (80 (51–150) vs. 36 (12–72) hours, *P*<0.001), and had a longer length of ICU stay (12 (7–25) vs. 3 (2–7) days, *P*<0.001) (Table 2). All strokes occurred in the non-survivors (6.2% vs. 0%, *P*=0.083) (Table 3). There were no differences in device-related vascular complications (17.0% in survivors vs. 16.9% in the

Table 1. Baseline characteristics of patients with Impella support for acute myocardial infarction.

	All patients	Survivors	Non-survivors	*P* value
	(*n*=112)	(*n*=47)	(*n*=65)	
Clinical characteristics and risk factors				
Age (years)	60.1 ± 10.6	59.3 ± 9.5	60.7 ± 11.4	0.503
Male sex, *n* (%)	90 (80.4)	40 (85.1)	50 (76.9)	0.282
Body mass index (kg/m²)	26.0 (23.7–27.8)	26.0 (23.4–27.8)	25.8 (24.2–27.8)	0.850
Cardiovascular risk factors, *n* (%)				
Current smoking	41 (42.7)	21 (48.8)	19 (35.8)	0.131
Hypertension	38 (35.2)	14 (29.8)	24 (39.3)	0.302
Hypercholesterolemia	15 (14.2)	6 (12.8)	9 (15.3)	0.715
Diabetes mellitus	17 (15.3)	6 (12.8)	11 (17.2)	0.070
Prior myocardial infarction, *n* (%)	17 (15.7)	4 (8.5)	13 (21.3)	0.070
Prior TIA or stroke, *n* (%)	4 (3.7)	2 (4.3)	2 (3.2)	0.777
Known peripheral arterial disease, *n* (%)	6 (5.7)	1 (2.1)	5 (8.6)	0.154
Prior PCI or CABG, *n* (%)	15 (13.6)	5 (10.6)	10 (15.9)	0.429
Clinical characteristics on admission				
Cardiac arrest, *n* (%)	67 (59.8)	28 (59.6)	39 (60.0)	0.998
Out of hospital cardiac arrest, *n* (%)	49 (74.2)	22 (78.6)	27 (71.1)	0.490
Witnessed arrest, *n* (%)	58 (90.6)	27 (96.4)	31 (86.1)	0.160
First rhythm VT/VF/AED, *n* (%)	56 (86.2)	26 (92.9)	30 (81.1)	0.173
Time till return of spontaneous circulation (min)	21 (11–50)	16 (10–25)	30 (19–54)	0.025
Traumatic injuries at admission, *n* (%)	7 (6.3)	3 (6.4)	4 (6.2)	0.961
Primary percutaneous coronary intervention				
Ischaemic time (min)	153 (107–240)	140 (95–266)	161 (119–232)	0.517
Infarct-related artery, *n* (%)				0.879
Left main	29 (25.9)	14 (29.8)	15 (23.1)	
Left anterior descending	62 (55.4)	25 (53.2)	37 (56.9)	
Left circumflex	13 (11.6)	5 (10.2)	8 (12.3)	
Right coronary artery	8 (7.1)	3 (6.4)	5 (7.7)	
Multi-vessel disease, *n* (%)ᵃ	74 (66.1)	28 (59.6)	46 (70.8)	0.217
Mechanical complications, *n* (%)	3 (2.7)	0 (0)	3 (4.6)	0.135
TIMI flow 0/1 pre-PCI, *n* (%)	90 (81.8)	35 (77.8)	55 (84.6)	0.361
TIMI flow 2/3 post-PCI, *n* (%)	101 (91.0)	43 (93.5)	58 (89.2)	0.441
Cardiogenic shock during primary PCI	103 (92.0)	44 (93.6)	59 (90.8)	0.584
Catecholamines or inotropes, *n* (%)	94 (83.9)	37 (78.7)	57 (87.7)	0.202
Mechanical ventilation, *n* (%)	98 (87.5)	41 (87.2)	57 (87.7)	0.942
Primary PCI in other hospital	9 (8.0)	5 (10.6)	4 (6.2)	0.389
Before device placement				
Catecholamines or inotropes, *n* (%)	102 (91.1)	41 (87.2)	61 (93.8)	0.226
Mechanical ventilation, *n* (%)	100 (89.3)	42 (89.4)	58 (89.2)	0.982
Intra-aortic balloon pump before Impella placement, *n* (%)	22 (19.6)	6 (12.8)	16 (24.6)	0.119
Blood pressure values				
Mean arterial pressure (mmHg)	67 (56–77)	68 (57–80)	66 (52–76)	0.289
Systolic blood pressure (mmHg)	86 (73–102)	89 (79–104)	83 (70–100)	0.202
Diastolic blood pressure (mmHg)	58 (44–65)	60 (48–66)	56 (40–65)	0.215
Heart rate (beats per minute)	96 (78–113)	95 (75–108)	97 (80–115)	0.274
Blood values				
Lactate (mmol/L)	6.2 (3.6–9.7)	4.2 (2.2–8.1)	7.6 (4.1–10.9)	0.012
Haemoglobin (mmol/L)	8.4 (7.5–9.4)	8.8 (7.4–9.5)	8.3 (7.5–9.1)	0.285
Creatinine (µmol/L)	114 (90–136)	104 (87–129)	123 (95–140)	0.080
Glucose (mmol/L)	13.4 (9.8–18.3)	11.5 (8.9–17.0)	14.1 (11.7–20.6)	0.028
Arterial pH	7.21 (7.07–7.30)	7.26 (7.17–7.35)	7.14 (6.94–7.25)	0.002

Data are displayed as count (percentage), mean ± standard deviation or median (25th percentile to 75th percentile).
P value for the comparison between survivors versus non-survivors.
TIA: transient ischaemic attack; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; VT: ventricular tachycardia; VF: ventricular fibrillation; AED: automated external defibrillator; TIMI: thrombolysis in myocardial infarction.
ᵃ>50% stenosis in non-culprit vessel.

Table 2. Clinical course of patients with cardiogenic shock after acute myocardial infarction.

	All patients	Survivors	Non-survivors	P value
	(n=112)	(n=47)	(n=65)	
Mechanical circulatory support				
First Impella device				0.053
Impella 2.5	40 (35.7)	13 (27.7)	27 (41.5)	
Impella CP	52 (46.4)	21 (44.7)	31 (47.7)	
Impella 5.0	20 (17.9)	13 (27.7)	7 (10.8)	
Change of mechanical support device, n (%)	12 (10.7)	4 (8.5)	8 (12.3)	0.521
Upgrade to Impella 5.0	9 (75)	3 (75.0)	6 (75.0)	
Upgrade to ECMO	3 (25)	1 (25.0)	2 (25.0)	
Device replacement by similar device, n (%)	2 (1.8)	1 (2.1)	1 (1.5)	0.816
Time of device placement				0.546
Impella placement before primary PCI, n (%)	21 (18.8)	11 (23.4)	10 (15.4)	
Impella placement directly after primary PCI, n (%)	67 (59.8)	26 (55.3)	41 (63.1)	
Impella placement in separate procedure after primary PCI, n (%)	24 (21.4)	10 (21.3)	14 (21.5)	
Time between revascularisation and Impella placement (hours)	13 (8–23)	13 (10–29)	14 (7–20)	0.752
IABP between primary PCI and Impella placement, n (%)	10 (41.7)	5 (50.0)	5 (35.7)	0.484
Duration of Impella support (hours)[a]	52 (22 – 122)	80 (51–150)	36 (12–72)	<0.001
Device failure requiring extraction of the device, n (%)	1 (0.9)	1 (2.1)	0 (0)	0.237
During admission				
Inotropic or vasopressor therapy, n (%)	106 (94.6)	42 (89.4)	64 (98.5)	0.035
Renal replacement therapy, n (%)	43 (38.4)	19 (40.4)	24 (36.9)	0.707
Mechanical ventilation, n (%)	106 (94.6)	43 (91.5)	63 (96.9)	0.208
Peak CKMB (µmol/L)	457 (184 – 934)	354 (120–781)	623 (251–1029)	0.051
Blood products, n (%)	68 (60.7)	29 (61.7)	39 (60.0)	0.856
Number of patients in the intensive care unit, n (%)	100 (89.3)	42 (89.4)	58 (89.2)	0.982
Days on the intensive care unit	5 (3–15)	12 (7–25)	3 (2–7)	<0.001

P value for the comparison between survivors versus non-survivors.
[a]Sum of support duration of all given support devices, including upgrades.
ECMO: extracorporeal membrane oxygenation; PCI: percutaneous coronary intervention; IABP: intra-aortic balloon pump; CKMB: creatine kinase myocardial type.

non-survivors, P=0.989), non-device-related bleeding (14.9% vs. 10.8%, P=0.280), but higher rates of clinically relevant haemolysis in the survivors (12.8% vs. 3.1%, P=0.049).

6-Month mortality

The mortality at 6 months follow-up was 60.7%. There was no difference within age groups of 10 years, or tertiles of peak creatine kinase myocardial type, lactate, MAP and HR (Figure 3). There was a higher mortality when patients had lower pH levels or higher glucose levels before Impella insertion. Placement of the Impella device before revascularisation compared with directly after the revascularisation did not show a significant difference in 6-month mortality (52.4% vs. 64.2%, HR 1.45, 95% CI 0.75–2.81, P=0.273) (Table 4). The type of Impella device was not associated with a significant difference in mortality. In a

Cox univariate analysis, lactate, glucose, pH and renal insufficiency before Impella insertion were predictors of 6-month mortality (Table 5). In a multivariate Cox regression analysis, only pH before Impella insertion was a predictor of 6-month mortality.

Differences between Impella devices

The initial Impella strategy consisted of Impella 2.5 in 40 patients (35.7%), Impella CP in 52 patients (46.4%) and Impella 5.0 in 20 patients (17.9%) (Supplementary Table 1). There were some differences in the baseline characteristics of patients with Impella 2.5, CP and 5.0 (Supplementary Table 2). Patients treated with Impella 2.5 experienced an out-of-hospital cardiac arrest (OHCA) less frequently. In the Impella 5.0 group, biochemical values at admission were compatible with a less severe state of CS, although there was no difference in MAP. Also, patients who had undergone

Table 3. Clinical outcome for patients with cardiogenic shock after acute myocardial infarction.

	All patients	Survivors	Non-survivors	P value
	(*n*=112)	(*n*=47)	(*n*=65)	
In-hospital outcome				
In-hospital mortality, *n* (%)	65 (58.0% CI 48.3–67.3)	0 (0% CI 0.0–7.5)	65 (100% CI 94.5–100)	
Refractory cardiogenic shock	44 (67.7)	–	44 (67.7)	
Post-anoxic brain injury	13 (20.0)	–	13 (20.0)	
Other reason	8 (12.3)	–	8 (12.3)	
Stroke, *n* (%)	4 (3.6% CI 1.0–8.9)	0 (0% CI 0.0–7.5)	4 (6.2% CI 1.7–15.0)	0.083
Haemorrhagic stroke	1 (25.0)	0 (0)	1 (25.0)	
Ischaemic stroke	3 (75.0)	0 (0)	3 (75.0)	
Device-related vascular complication, *n* (%)	19 (17.0% CI 10.5–25.2)	8 (17.0% CI 7.6–30.8)	11 (16.9% CI 8.8–28.3)	0.989
Limb ischaemia	4 (21.1)	3 (37.5)	1 (9.1)	
Access site-related bleeding	14 (73.7)	4 (50.0)	10 (90.9)	
Major bleeding	11 (78.6)	3 (75.0)	8 (80.0)	
Minor bleeding	3 (21.4)	1 (25.0)	2 (20.0)	
Access site infection	1 (5.3)	1 (12.5)	0 (0)	
Non-device-related bleeding	14 (12.5% CI 7.0–20.1)	7 (14.9% CI 6.2–28.3)	7 (10.8% CI 4.4–20.9)	0.280
Gastrointestinal bleeding	6 (42.9)	4 (57.1)	2 (28.6)	
Other location	8 (57.1)	4 (42.9)	5 (71.4)	
Clinically relevant haemolysis, *n* (%)	8 (7.1% CI 3.1–13.6)	6 (12.8% CI 4.8–25.7)	2 (3.1% CI 0.4–10.7)	0.049
Surgical LVAD placement, *n* (%)	1 (0.9% CI 0.0–4.9)	1 (2.1% CI 0.1–11.3)	0 (0% CI 0.0–5.5)	0.237
Heart transplantation, *n* (%)	0 (0% CI 0.0–3.2)	0 (0% CI 0.0–7.5)	0 (0% CI 0.0–5.5)	–

P value for the comparison between survivors versus non-survivors.
LVAD: left ventricular assist device; CI: confidence interval was calculated based on the Pearson–Clopper method.

primary PCI at another centre more often received an Impella 5.0 on arrival at our institution (Supplementary Table 3). Impella 5.0 was more frequently placed at a separate procedure and not at primary PCI. There were differences in the number of patients who were upgraded to another support device, the number of patients receiving blood products and the number of days on the ICU. There was no difference in stroke, device-related vascular complications or haemolysis between patients treated with Impella 2.5, CP or 5.0 (Supplementary Table 4).

Discussion

This analysis describes the largest single-centre experience with Impella technology in CS over 12 years. It provides an insight into the treatment strategy, outcomes and complications of patients treated with Impella at an experienced centre. We describe an overall 30-day mortality of 56.2% (Figure 2), of which 67.7% was due to refractory CS. Complications consisted of device-related vascular complications (17.0%), non-device-related bleeding (12.5%), haemolysis (7.1%) and stroke (3.6%). In a multivariate analysis, pH before Impella placement is a predictor of 6-month mortality.

Impella has been on the market since 2004 but with little (randomised) evidence on its effectiveness in CS. Three small and underpowered randomised trials compare the Impella with intra-aortic balloon pump (IABP) in CS, and

although the Impella can provide more haemodynamic support than an IABP, this was not translated into reduced mortality in randomised trials.[6, 16, 18, 19] However, comparing the outcomes is hampered by the fact that a large percentage of the randomly assigned patients had had a cardiac arrest before admission, resulting in a high percentage of neurological damage. This might have resulted in the treatment effect of Impella support being underestimated. Furthermore, one study was prematurely discontinued due to slow inclusion.[18]

Mortality rates in real-world cohorts are higher than in randomised controlled trials of mechanical circulatory support in CS patients.[16, 19–21] Registries that describe the real-world usage of devices actually describe an unselected patient cohort.[15, 22–31] Randomised controlled trials are particularly difficult to conduct in critically ill patients in an emergency situation. Also, severely ill patients with a very poor prognosis are often excluded from randomised studies. This is why registries are of interest in these severely ill patients, as they provide important hypothesis-generating rationales for future clinical trials. Furthermore, as data from randomised trials are sparse, real-world registries have an important role in reporting on complications and other safety outcomes.

We described the largest single-centre cohort on Impella therapy in CS patients after myocardial infarction. Several multi-centre registries also reported on Impella therapy in

this particular patient group, but only described the use of Impella 2.5 (O'Neill *N*=154; Lauten *N*=120) or Impella CP (Basir *N*=287). [24, 25, 32] It is also important to report results on outcomes and complications in patients treated with Impella CP, and especially Impella 5.0. Patient selection may result in more severely ill patients treated with an Impella CP or 5.0, and the Impella 5.0 requires surgical cut-down of the artery, which may lead to more complications. The largest Impella cohort to our knowledge (Basir; multi-centre *N*=287) described the use of Impella CP in CS patients after myocardial infarction. [32] However, they only reported the rate of vascular complications requiring surgical repair, and did not provide complication rates on other important complications such as leg ischaemia, haemolysis or the need for renal replacement therapy. Other studies that
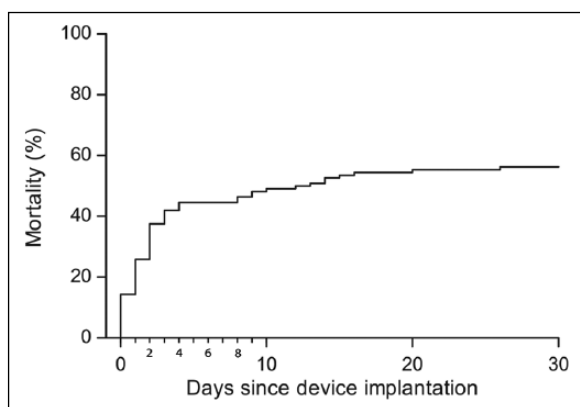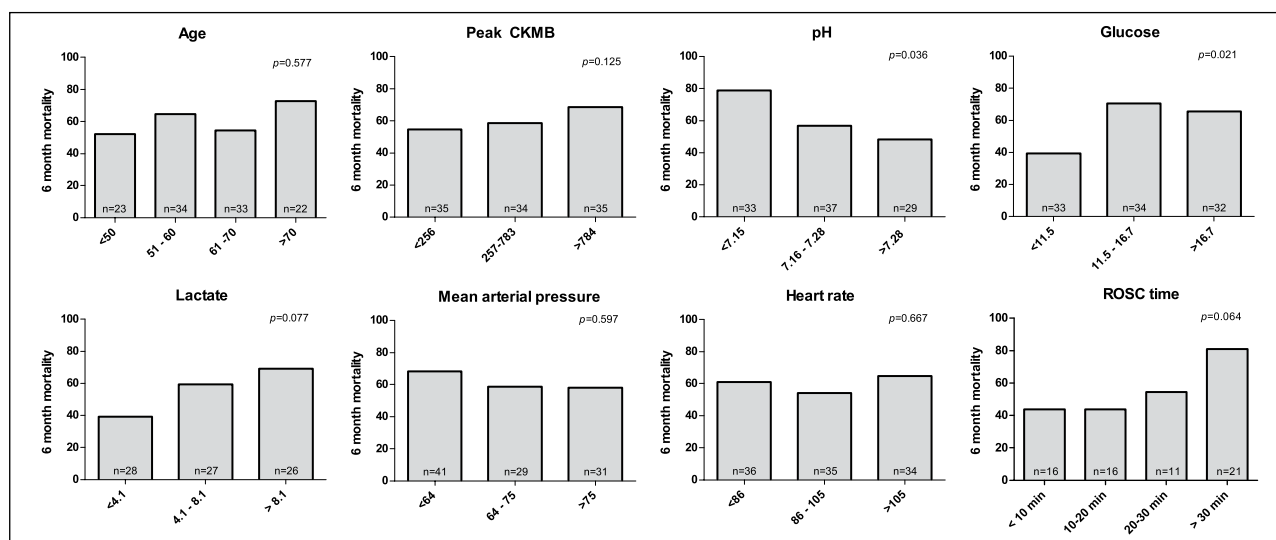
described the outcomes and complications of Impella CP or 5.0 therapy consisted of a small number of patients, a mixed population, or both. [15, 22, 27–29]

We describe an in-hospital mortality rate of 58%, with a high percentage of patients having experienced cardiac arrest before Impella treatment (59.8%). Comparable mortality rates are described in other registries: Basir et al. [32] describe a 56% in-hospital mortality rate in patients with acute myocardial infarction but with 40% of patients with cardiac arrest, and Lackermair et al. [22] describe a 30-day mortality rate of 64% in a mixed patient cohort.

Although the aim of Impella therapy is to provide systemic haemodynamic support, the majority of the patients may still die from refractory CS (67%). Refractory shock is a complex disease in which haemodynamic support only is unlikely to be the complete answer, especially once the inflammatory shock reaction emerges and multiple organ failure becomes severe.

The Impella strategy at our hospital has changed over time. The Impella 2.5 was the standard therapy in patients with CS, until the Impella CP became available in 2012. The Impella CP requires a slightly larger insertion sheath than the Impella 2.5 (14 F versus the 13 F), but provides more flow (3.7 L/minute vs. 2.5 L/minute).

There was a trend towards a lower mortality rate in patients treated with larger Impella devices (Impella 2.5 70.0%, Impella CP 61.5%, Impella 5.0 40.0% at 6 months). However, comparison of baseline characteristics between patients treated Impella 2.5 and patients treated with Impella CP shows a much more extensive use of Impella CP, resulting in the treatment of more severely ill patients, who may already have more severe neurological damage

Figure 2. Kaplan–Meier curve for patients treated with Impella for cardiogenic shock after acute myocardial infarction.

Figure 3. Mortality at 6 months according to age, peak creatine kinase myocardial type (CKMB), pH, glucose, lactate, mean arterial blood pressure (MAP) and heart rate (HR) before Impella placement and time to return of spontaneous circulation (ROSC).
Glucose, pH, lactate, MAP, HR and peak CKMB were dichotomised by dividing them into tertiles. Age was dichotomised per 10 years of age and time to ROSC by 10 minutes. Comparison between groups was made by Pearson chi-square analysis.

Table 4. Mortality at 6 months according to Impella device, time of Impella placement, sex, cardiac arrest, traumatic injuries, renal impairment and haemoglobin on admission.

	n	6-Month mortality	Hazard ratio (95% CI)	*P* value
Impella device				
Impella 2.5	40	70.0	Reference	–
Impella CP	52	61.5	0.84 (0.51–1.39)	0.838
Impella 5.0	20	40.0	0.46 (0.21–1.00)	0.455
Timing of Impella placement				
Before revascularisation	21	52.4	Reference	–
Directly after revascularisation	67	64.2	1.45 (0.75–2.81)	0.273
Delayed (in separate procedure)	24	58.3	1.31 (0.59–2.88)	0.510
Sex				
Male	90	57.8	Reference	–
Female	22	72.7	1.56 (0.89–2.73)	0.123
Cardiac arrest				
Yes	67	59.7	Reference	–
No	45	62.2	1.03 (0.63–1.67)	0.912
Traumatic injuries before admission				
Absent	105	61.0	Reference	–
Present	7	57.1	0.875 (0.32–2.40)	0.796
Renal impairment				
Creatinine lower than normal reference value	46	50.0	Reference	–
Creatinine higher than normal reference value	57	70.2	1.68 (1.01–2.82)	0.046
Haemoglobin				
Higher than normal reference value	53	54.7	Reference	–
Lower than normal reference value	49	65.3	1.30 (0.78–2.14)	0.312

CI: confidence interval.

Table 5. Univariate and multivariate Cox regression of parameters on the association with mortality at 6-month follow-up.

Parameter	*n*	Univariate analysis			Multivariate analysis		
		HR	95% CI	*P* value	HR	95% CI	*P* value
Age	112	1.015	0.99–1.04	0.224	–	–	–
Male sex	112	1.556	0.89–2.73	0.123	–	–	–
Lactate (mmol/L)	81	1.071	1.01–1.14	**0.021**	–	–	–
Glucose (mmol/L)	99	1.046	1.01–1.09	**0.035**	–	–	–
pH	99	0.087	0.02–0.34	**<0.001**	0.087	0.02–0.34	**<0.001**
Low haemoglobin on admission	102	1.296	0.78–2.14	0.155	–	–	–
Renal insufficiency on admission	103	1.688	1.01–2.82	**0.046**	–	–	–
MAP before Impella placement	107	0.996	0.98–1.01	0.531	–	–	–
SBP before Impella placement	108	0.998	0.99–1.01	0.675	–	–	–
HR before Impella placement	105	1.073	0.79–1.01	0.650	–	–	–
Cardiac arrest	112	1.028	0.63–1.67	0.912	–	–	–
Traumatic injury on admission	112	0.947	0.34–2.61	0.916	–	–	–

MAP: mean arterial blood pressure (mmHg); SBP: systolic blood pressure (mmHg); HR: heart rate (beats/min).

on admission. Despite this, the mortality rates of the patients treated with the Impella CP are numerically lower than the mortality rates in patients treated with Impella 2.5. Also, the Impella 5.0 is more often used when the Impella was inserted in a separate procedure, because of the need for surgical cut-down of the femoral or axillary artery in order to introduce a 21 F catheter. This delayed Impella placement induces patient selection bias, as the most severely ill patients will be treated with a percutaneous Impella at primary PCI because they may have been deemed too ill to wait for surgical cut-down. Patients admitted to the ICU without an Impella may be deemed to be less ill, and may either recover or deteriorate and require delayed mechanical support. Unfortunately, our sample

size is too small to take all possible confounders into account in a multivariate analysis and therefore we cannot fully evaluate our hypothesis.

The introduction of Impella 2.5 and CP requires 13 F and 14 F sheaths and therefore some vascular complications may be expected. In our cohort, device-related vascular complications occurred in 19 patients (17%), of which the majority had access site-related bleeding (*n*=14). Limb ischaemia occurred in four patients (3.6%). The largest Impella cohort that reports complications (*n*=154) describes 9.7% vascular complications requiring surgery, 3.9% limb ischaemia and 17.5% bleeding requiring transfusion.[10] Other smaller cohorts report limb ischaemia of 25%,[27] 12%,[22, 28] 10%[31] and 3%.[26]

Access site-related bleeding occurred in 14 patients (12.5%), of which 11 were a major bleed. Non-device-related bleeding occurred in 14 patients (12.5%). During mechanical support, patients receive heparin in addition to standard dual antiplatelet therapy after PCI (aspirin and a P2Y12 receptor blocker), which, in combination with larger-bore sheaths, facilitates bleeding. In a registry of post-cardiac arrest patients (*n*=78), the bleeding rate was 26% and three CS registries (*n*=120, *n*=154, *n*=66) describe bleeding rates of 24%, 18% and 35%.[24–26, 28] Jensen et al. describe groin bleeding in 13% and higher rates of minor (29%), moderate (19%) and severe (5%) bleeding.[31] Haemolysis occurred in 7.1% of treated patients. Earlier reports describe haemolysis in 6.0%, 7.5% and 10.3% of patients treated with Impella 2.5.[24–26] Our cohort describes a stroke rate of 3.6%, which is comparable with other cohorts (5%,[28] 1.9%,[24] 0%,[26] 1.7%).[25]

Previous described cohorts suggest a favorable outcome in patients in whom the Impella devices is placed before the revascularisation.[16, 23, 31, 33, 34] Impella placement before primary PCI may enable stable haemodynamics during the intervention. It may prevent deterioration during the procedure and when opening the occluded vessel. Several animal studies have shown that unloading the left ventricle before reperfusion reduces infarct size despite the longer ischaemic time.[35–37] These studies demonstrate that the use of Impella before revascularisation activates the neurohormonal cascade associated with reperfusion injury. This results in a cardioprotective signalling cascade which limits myocardial damage. In our cohort, 21 of the patients with acute myocardial infarction received an Impella before revascularisation (19%), 60% received it directly after the revascularisation and 21% received the Impella in a separate procedure. Our registry did not show a difference in 6-month mortality (52.4% vs. 64.2% durable, *P*=0.273). The time of device placement was at the discretion of the operator and therefore might be biased by the severity of the patient's condition.

Currently, there is no (randomised) evidence that either Impella or ECMO support is associated with improved clinical outcomes in CS patients after acute myocardial infarction. In our institution, Impella was the support device of choice, based on local availability and expertise. A total of four patients were transferred for ECMO (*N*=3) and LVAD placement (*N*=1). Although only a few patients required ECMO/LVAD/heart transplantation in another centre, it is possible that these techniques would have been deployed earlier if available in our centre.

Analysis of the PROTECT II trial, comparing IABP with Impella 2.5 in the setting of high-risk PCI, suggests a learning curve associated with the introduction of the Impella.[12] Our experience describes a stepwise introduction of the Impella in the setting of elective high-risk PCI, followed by the use of Impella in the emergency setting of CS and placement of Impella prior to emergency revascularisation. A stepwise introduction is important to allow the successful introduction of a new technology into the clinical setting.

There are several limitations to consider. This is an observational study with its associated limitations. Selection bias might play a significant role in the selection of patients to receive an Impella, the time of Impella placement, the selection of the device and the course of treatment. Multivariate analysis was limited due to the sample size of our cohort and did not include all variables that influence mortality in the model, such as the timing of device placement and myocardial infarction location.

In addition, there are many factors that might have influenced the results, such as experience of the device, change of therapy over time, improvement of general treatment of CS and ST-segment elevation myocardial infarction patients over time, and change in patient selection over time. Moreover, we performed two randomised controlled trials comparing Impella with IABP.[16, 18] During the inclusion period of these trials, half the patients were randomly assigned to IABP and the type of Impella therapy was defined by the study protocol.

Also, we could only retrieve complications that were noted in the patient records and only reported on haemolysis that led to device removal or transfusion. However, we are aware of the fact that important complications, such as bleeding or haemolysis, are not always captured well in the patient records. Therefore it is very likely that we underestimated the rate of some complications.

This registry shows that in patients with CS due to acute myocardial infarction, mechanical circulatory support with Impella is feasible, although mortality and complication rates remain high. Future studies should focus on the selection of the patient population that may have the most benefit from this therapy.

Conflict of interest

Funding

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