Observational multicentre registry of patients treated with IMPella mechanical circulatory support device in ITaly: the IMP-IT registry

Alaide Chieffo[1]*, MD; Marco B. Ancona[1], MD; Francesco Burzotta[2], MD; Vittorio Pazzanese[3], MD; Carlo Briguori[4], MD; Carlo Trani[2], MD; Tommaso Piva[5], MD; Federico De Marco[6], MD; Maurizio Di Biasi[7], MD; Paolo Pagnotta[8], MD; Gavino Casu[9], MD; Gennaro Giustino[10], MD; Matteo Montorfano[1], MD; Federico Pappalardo[3], MD; Giuseppe Tarantini[11], MD

1. Interventional Cardiology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; 2. Institute of Cardiology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; 3. Advanced Heart Failure and Mechanical Circulatory Support Program, San Raffaele Scientific Institute, Vita Salute University, Milan, Italy; 4. Interventional Cardiology Unit, Mediterranea Cardiocentro, Naples, Italy; 5. Interventional Cardiology Unit, Ospedali Riuniti di Ancona, Ancona, Italy; 6. Department of Clinical and Interventional Cardiology, IRCCS Policlinico San Donato, Milan, Italy; 7. Interventional Cardiology Unit, Ospedale Luigi Sacco, Milan, Italy; 8. Cardiovascular Department, Humanitas Research Hospital, Rozzano, Italy; 9. Interventional Cardiology Unit, Ospedale San Francesco, Nuoro, Italy; 10. The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; 11. Department of Cardiac, Thoracic and Vascular Science, University of Padua, Padua, Italy

A list of study collaborators can be found in the Appendix paragraph.

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00428

KEYWORDS

- acute heart failure
- cardiogenic shock
- left main
- multiple vessel disease
- ventricular assist device

Abstract

Aims: The aim of this study was to investigate nationwide trends and clinical outcomes of the Impella device for cardiogenic shock (CS) and high-risk percutaneous coronary intervention (HR-PCI).

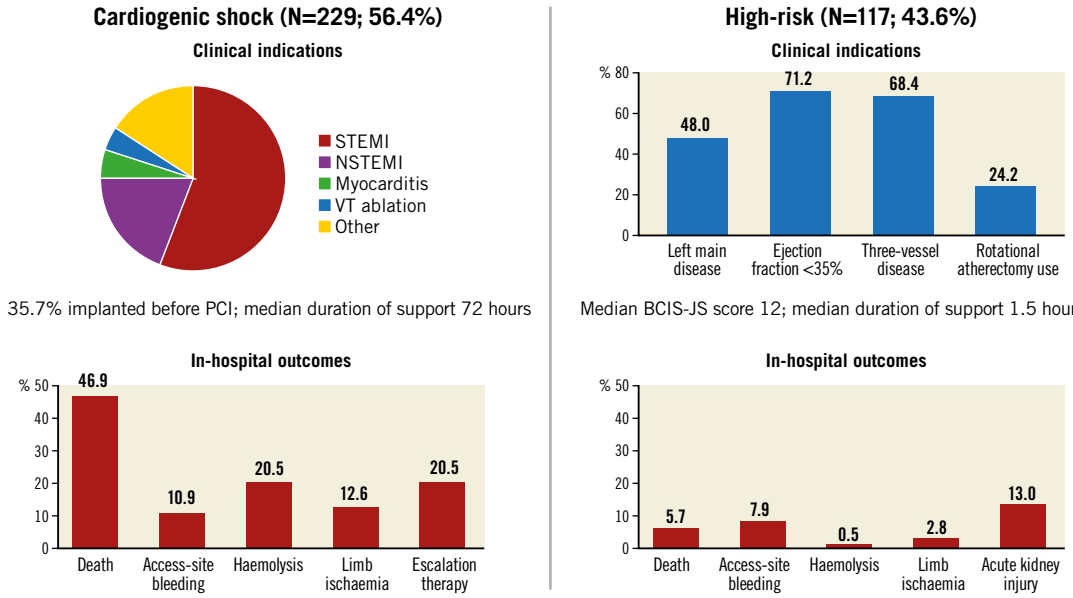
Methods and results: The IMP-IT study was a multicentre observational national registry which enrolled all patients treated with Impella 2.5, Impella CP, Impella 5.0 and Impella RP, both for CS and HR-PCI indications, across 17 Italian centres from 2004 to June 2018. A total of 406 patients were included: 229 had CS (56.4%) and 177 underwent HR-PCI (43.6%). The use of Impella increased significantly during the study period (average annual percent change 39.8%, 95% confidence interval: 30.4 to 49.9; p<0.0001) for both indications. The Impella 2.5 was the most commonly used device (N=242; 59.6%). Rates of in-hospital and one-year all-cause death in patients with CS were 46.9% and 57.0%, respectively; 18.5% underwent left ventricular assist device implantation or heart transplant at one year. Rates of in-hospital and one-year all-cause death in patients who underwent HR-PCI were 5.7% and 15.6%, respectively. Rates of device-related complications were 37.1% and 10.7% in the setting of CS and HR-PCI, respectively.

Conclusions: Use of the Impella for CS and HR-PCI is increasing substantially in Italy, despite relatively high rates of device-related complications.

**Corresponding author: Interventional Cardiology Unit, IRCCS San Raffaele Scientific Institute, 60, Via Olgettina, 20132 Milan, Italy. E-mail: chieffo.alaide@hsr.it*

© Europa Digital & Publishing 2020. All rights reserved.

SUBMITTED ON 29/04/2019 - REVISION RECEIVED ON 1st 10/06/2019 / 2nd 01/08/2019 - ACCEPTED ON 15/08/2019



Visual summary. *Impella Italian Registry (IMP-IT). 406 patients enrolled across 17 centres in Italy.*

Abbreviations

AMICS	acute myocardial infarction cardiogenic shock
HF	heart failure
HR-PCI	high-risk percutaneous coronary intervention
IABP	intra-aortic balloon pump
LVAD	left ventricular assist device
MCS	mechanical circulatory support
PCI	percutaneous coronary intervention
pLVAD	percutaneous left ventricular assist device

Introduction

The purpose of short-term percutaneous mechanical circulatory support (MCS) is to reduce left ventricular stroke work and myocardial oxygen demand while maintaining systemic and coronary perfusion in the setting of cardiogenic shock (CS) or to provide haemodynamic support during complex cardiac procedures such as high-risk percutaneous coronary intervention (HR-PCI)[1,2]. Historically, intra-aortic balloon pumps (IABP) have been used to provide haemodynamic support during CS and HR-PCI. However, evidence from randomised controlled trials does not support their use[3], and their use is no longer indicated by the current European Society of Cardiology guidelines[4]. Over the past decade, novel percutaneous left ventricular assist devices (pLVAD) have increasingly been used in place of IABP in these clinical cases[5]. Currently, the most commonly used pLVAD worldwide is the microaxial Impella® pump (Abiomed, Danvers, MA, USA) which received the CE mark for the Impella 2.5 device in 2004[5]. However, despite the widespread adoption of this technology, in both Europe and the USA, data about its efficacy and safety in a real-world population are limited to small case series and industry-sponsored registries[5-7]. Here we report the results of the IMP-IT registry (IMPella Mechanical Circulatory Support Device in Italy), an investigator-initiated, nationwide, all-comer, multicentre registry which evaluated the trends in use and clinical outcomes of the Impella in the setting of CS and HR-PCI in Italy.

Editorial, see page 1312

Methods

STUDY POPULATION

The IMP-IT study was a multicentre retrospective observational national registry that included all consecutive patients treated with Impella 2.5, Impella CP, Impella 5.0 and Impella RP, both for CS and HR-PCI, in 17 Italian centres from 2004 to June 2018. This was an investigator-initiated study promoted by the Italian Society of Interventional Cardiology (Società Italiana di Cardiologia Interventistica – GISE). GISE is a national scientific society that hosts a prospective nationwide registry that collects yearly procedural data from catheterisation laboratories in Italy. Through the GISE registry, we identified centres that have used Impella devices for the indications of CS and HR-PCI. These centres were invited to participate in the IMP-IT registry following formal invitation from the principal investigator of the study (A. Chieffo) and the president of GISE (G. Tarantini). The participating centres which agreed to participate in the IMP-IT registry and the respective number of patients per centre enrolled in the registry are reported in **Supplementary Table 1**. Data related to medical history, procedural characteristics, 30-day and one-year outcomes were collected from each centre and included in a pre-specified structured data set. Clinical follow-up data were collected by in-person visits, telephone interviews, and medical notes from any hospital admission or outpatient visits. Adverse events were then adjudicated by two independent cardiologists (M. Ancona,

V. Pazzanese) using source documents provided by each centre. PCI was performed according to each centre's standard clinical practice. Collection of data at each participating site was performed according to the policies of the local institutional review board/ethics committee.

STUDY ENDPOINTS

The objectives of the study were: (i) to analyse the trends in use of Impella overall and according to its two different clinical indications (CS and HR-PCI); and (ii) to evaluate in-hospital and one-year clinical outcomes of Impella use according to the indications (CS and HR-PCI). Given the considerable differences in the clinical risk profile between patients in the CS and HR-PCI cohorts, direct comparisons between these two groups were not performed. The primary clinical endpoint of interest included in-hospital mortality, one-year mortality and the composite of death, rehospitalisation for heart failure (HF), LVAD implantation or heart transplant at one year. The full list of endpoints and study definitions is provided in **Supplementary Appendix 1** and **Supplementary Appendix 2**.

DEVICES

The devices included in this study were the Impella 2.5, Impella CP, Impella 5.0 and Impella RP. A description of the devices used in the study is provided in **Supplementary Appendix 3**.

STATISTICAL ANALYSIS

Individual patient data were pooled in a single pre-specified structured data set. Trends in the use of the Impella during the study period are reported as average annual percent change (AAPC) with 95% confidence intervals (CIs). Baseline characteristics are reported as number (%), mean±standard deviation, or median (interquartile range), for descriptive purposes. Event rates with 95% CIs at one year of follow-up were estimated using the Kaplan-Meier method as time-to-first event. Predictors of death and the composite of death, rehospitalisation for HF, LVAD implantation or heart transplant at one year were estimated using multivariable Cox regression analysis including all variables with a p-value <0.10 at univariate analysis and using a rule of 1:8 covariates per number of events to avoid overfitting. We accounted for inter-centre heterogeneity by including the clinical centre identifier as a covariate in the multivariable models. Due to the low number of events in the HR-PCI cohort, we performed multivariable Cox regression modelling only in the CS cohort. A level of $p<0.05$ was set as statistically significant. Analyses were performed with Stata, version 14.0 (StataCorp, College Station, TX, USA) and Joinpoint software, version 4.6.0.0 (National Cancer Institute, Bethesda, MD, USA).

Results

A total of 406 patients were enrolled across 17 Italian centres. Of these, 229 patients received the Impella in the setting of CS (56.4%) and 177 patients in the setting of HR-PCI (43.6%). The study flow diagram is shown in **Supplementary Figure 1**. Most of the patients were treated with the Impella 2.5 in both the CS and HR-PCI groups. Trends in the use of Impella in situations of CS, HR-PCI and overall are illustrated in **Figure 1A**, **Figure 1B** and **Supplementary Figure 2**, respectively. Overall, the use of the Impella increased exponentially during the study period (AAPC 39.8%, 95% CI: 30.4 to 49.9; $p<0.0001$). The use of the Impella 2.5 increased steadily from 2004 to 2018 (AAPC 31.4%, 95% CI: 22.7-40.7; $p<0.0001$). Conversely, the use of Impella CP increased exponentially after its introduction (AAPC 104.3%, 95% CI: 73.1-141.2; $p<0.0001$). Use of the Impella 5.0 increased slightly over the study period, but this was not statistically significant (AAPC 5.1%, 95% CI: -0.8 to 11.3; $p=0.10$). Finally, the use of the Impella RP increased significantly after 2013 (AAPC 66.0%, 95% CI: 30.4 to 111.4; $p<0.0001$).

IMPELLA FOR CARDIOGENIC SHOCK

Baseline characteristics in patients with CS are reported in **Table 1**. In patients presenting with CS, the mean age was 63.7±13.2 years, 72.9% were male, 32.9% had diabetes mellitus and 26.8% had prior chronic heart failure (HF). The cause of CS was mostly acute myocardial infarction CS (AMICS), with ST-segment elevation and non-ST-segment elevation myocardial infarction accounting for 55.0% and 20.1% of cases, respectively. At the time of the index presentation, 23.9% of patients had experienced out-of-hospital cardiac arrest, 75.5% were on mechanical ventilation and 58.9% were in INTERMACS class I. The procedural characteristics of patients with CS are reported in

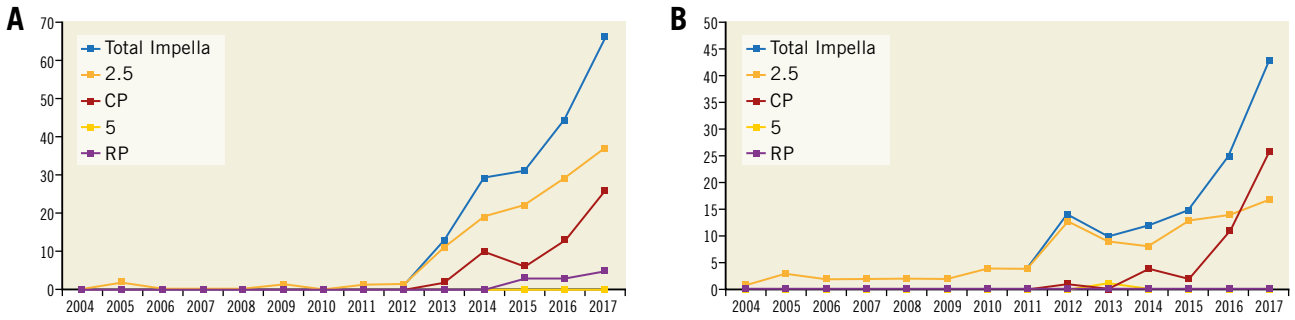


Figure 1. *Trends in use of Impella in the IMP-IT registry. A) Number of Impella used during the study period in patients presenting with cardiogenic shock. B) Number of Impella used during the study period for patients undergoing high-risk percutaneous coronary intervention.*

Table 1. Baseline characteristics.

	Cardiogenic shock (N=229; 56.4%)	High-risk PCI (N=177; 43.6%)
Clinical characteristics		
Age	63.7±13.2	72.9±9.5
Male	167 (72.9%)	148 (83.6%)
Hypertension	116 (54.7%)	146 (82.5%)
Dyslipidaemia	88 (41.5%)	108 (61%)
Diabetes mellitus	70 (32.9%)	82 (46.3%)
Chronic pulmonary disease	25 (11.7%)	35 (20%)
Prior myocardial infarction	72 (33.8%)	74 (41.7%)
Previous percutaneous coronary intervention	69 (32.2%)	43 (24.3%)
Previous coronary artery bypass graft	11 (5.1%)	26 (14.7%)
Chronic kidney disease	56 (26.3%)	67 (38.1%)
Dialysis	6 (2.8%)	9 (5.1%)
Atrial fibrillation	25 (11.7%)	29 (16.5%)
Prior transient ischaemic attack or stroke	13 (6.1%)	19 (10.8%)
Peripheral artery disease	29 (13.6%)	46 (26%)
Chronic heart failure	57 (26.8%)	95 (54%)
Left ventricular ejection fraction, %	24.9±11.9	31.3±10.4
Right ventricular dysfunction	65 (32.0%)	22 (12.9%)
INTERMACS class I	135 (58.9%)	–
Out-of-hospital cardiac arrest	51 (23.9%)	–
Aetiology of cardiogenic shock		
ST-elevation myocardial infarction	126 (55.0%)	–
Non-ST-elevation myocardial infarction	46 (20.1%)	–
Acute myocarditis	11 (4.8%)	–
Post-ventricular tachycardia ablation	9 (3.9%)	–
Other	37 (16.2%)	–
Laboratory values		
pH	7.28±0.5	7.4±0.1
Heart rate, bpm	93.6±24.1	78.8±15.5
Mean arterial pressure, mmHg	63.9±19.7	81.9±14.8
Serum lactate, mmol/l	6.1±4.8	1.99±2.01
Haemoglobin, g/dL	12.1±0.2	12.4±0.1
Serum creatinine, mg/dL	1.6±0.1	1.3±0.1

Results reported as n (%) and mean±standard deviation as appropriate. *Defined as eGFR <60 ml/min/1.73 m^2.

Table 2. Procedural characteristics and in-hospital management.

	Cardiogenic shock (N=229; 56.4%)	High-risk PCI (N=177; 43.6%)
Impella		
Use of Impella 2.5	134 (58.5%)	108 (61%)
Use of Impella CP	84 (36.7%)	66 (37.3%)
Use of Impella 5.0	2 (0.8%)	3 (1.7%)
Use of isolated Impella RP	9 (3.9%)	–
Use of Impella RP plus left-side Impella	6 (2.6%)	–
Timing of Impella placement		
Impella implanted before PCI	77 (35.7%)	118 (66.7%)
Impella implanted during PCI	42 (19.4%)	57 (32.2%)
Impella implanted after PCI	78 (36.1%)	1 (0.56%)
Impella removed immediately after PCI	21 (10.1%)	143 (82.7%)
Duration of Impella support, hours	72 (24-144)	1.5 (1.5-3.0)
Other cardiopulmonary support used		
Use of inotropes	155 (74.9%)	14 (8.2%)
Use of mechanical ventilation	165 (75.7%)	30 (17.2%)
Length of mechanical ventilation, hours	120 (48-248)	4 (1-12)
Use of extracorporeal membrane oxygenation	66 (29.3%)	0 (0.0%)
Use of intra-aortic balloon pump	79 (36.1%)	3 (1.7%)
Intensive care length of stay, days	10 (5-20)	3 (1-8)
Angiographic and procedural characteristics		
Coronary angiography performed	187 (81.6%)	177 (100%)
PCI performed	154 (67.2%)	177 (100%)
Left main disease	62 (33.5%)	82 (48.0%)
Left anterior descending artery disease	137 (74.1%)	162 (94.2%)
Left circumflex disease	98 (53.6%)	149 (87.7%)
Right coronary artery disease	105 (56.8%)	138 (81.2%)
Number of diseased vessels	1.9±1.1	2.6±0.7
Three-vessel disease	78 (39.4%)	121 (68.4%)
BCIS myocardial jeopardy score	8 (6-12)	12 (10-12)
Number of vessels treated	1.2±0.9	1.9±0.9
Three vessels treated	22 (12.0%)	41 (24.7%)
Number of stents implanted	1.8±1.6	2.8±1.5
Use of rotational atherectomy	11 (6.0%)	43 (24.2%)
Use of vascular closure device	50 (22.3%)	162 (95.3%)
Resuscitation required during index procedure	42 (19.5%)	6 (3.5%)
Resuscitation required after index procedure	62 (28.6%)	7 (3.9%)

Results reported as n (%) for categorical variables and median (interquartile range) or mean±standard deviation for continuous variables as appropriate. BCIS: British Cardiovascular Intervention Society

Table 2. Most of the patients (58.5%) received an Impella 2.5, while 36.7% received an Impella CP and only a few patients received an Impella 5.0 or Impella RP. Coronary angiography was performed in the majority of patients (81.6%) and subsequent PCI in 67.2%. The Impella device was implanted before PCI in 35.7%. Among patients who underwent PCI, 12.0% of patients had three vessels treated. The median duration of Impella support was 72 hours (interquartile range [IQR]: 24-144).

In-hospital outcomes of CS patients are reported in **Table 3**. Overall, the rate of in-hospital mortality was 47.2%. Median in-hospital stay was 15 days (IQR: 8-29 days). Escalation therapy to extracorporeal membrane oxygenation, LVAD or transplant was required in 20.5% of patients. Life-threatening or severe bleeding occurred in 15.7% of patients; 12.6% of patients had limb ischaemia, 6.9% of which required endovascular treatment. The rates of device-related complications did not change significantly during

Table 3. In-hospital and one-year outcomes.

	Cardiogenic shock (N=229; 56.4%)	High-risk PCI (N=177; 43.6%)
In-hospital outcomes		
Death	107 (46.9%)	10 (5.7%)
Life-threatening or severe bleeding	36 (15.7%)	8 (5.1%)
Number of red blood cell transfusions	5.5±9.3	0.3±1.7
Device-related complications	85 (37.1%)	19 (10.7%)
Access-site bleeding	25 (10.9%)	14 (7.9%)
Haemolysis	47 (20.5%)	1 (0.5%)
Limb ischaemia	29 (12.6%)	5 (2.8%)
Need for endovascular intervention	16 (6.9%)	5 (2.8%)
Aortic injury	1 (0.5%)	0 (0.0%)
Left ventricular perforation	1 (0.5%)	0 (0.0%)
Sepsis	70 (30.5%)	7 (4.1%)
Acute kidney injury*	101 (50.5%)	19 (13%)
Need for renal replacement therapy	62 (27.1%)	6 (3.5%)
Escalation therapy¶	47 (20.5%)	0 (0.0%)
LVEF at discharge, %	34.5±13.9	33.8±10.3
One-year outcomes		
All-cause death	122 (57.0% [50.2-64.0])	23 (15.6% [10.6-22.7])
Cardiac death	111 (53.4% [46.5-60.7])	22 (14.8% [10.0-21.8])
Hospitalisation for heart failure	15 (18.2% [11.1-28.9])	13 (11.9% [7.0-19.9])
Myocardial infarction	1 (1.7% [0.2-11.6])	8 (6.9% [3.5-13.5])
Stroke	9 (6.6% [3.2-13.3])	3 (2.0% [0.6-6.0])
LVAD or heart transplant	21 (18.5% [12.2-27.5])	1 (1.2% [0.2-8.3])
Death, hospitalisation for heart failure, LVAD or heart transplant	147 (69.7% [63.0-76.2])	33 (23.3% [17-32])

In-hospital outcomes are reported as n (%) or mean±standard deviation as appropriate. One-year outcomes are reported as number of events (Kaplan-Meier failure estimate [95% confidence interval]). *Defined as a serum creatinine increase ≥0.3 mg/dL from baseline. ¶Defined as the need for extracorporeal membrane oxygenation, left ventricular assist device implantation or heart transplant.

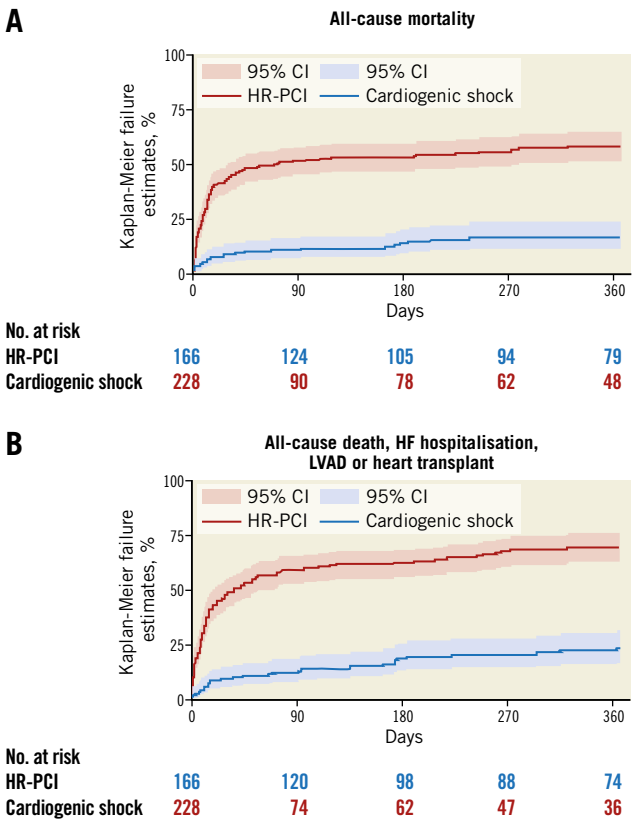


Figure 2. *One-year outcomes in the IMP-IT registry. A) All-cause mortality. B) Composite of all-cause mortality, rehospitalisation for heart failure, need for left ventricular assist device or heart transplant. HF: heart failure; LVAD: left ventricular assist device*

the study period (AAPC 5.1%, 95% CI: -19.9% to 37.9%; p=0.60). One-year outcomes are reported in **Table 3**, **Figure 2A**, **Figure 2B**, **Supplementary Figure 3A** and **Supplementary Figure 3B**. Overall, patients who presented with CS had a one-year mortality rate of 57.0% **(Figure 2A)**. Among those who presented with AMICS, the 30-day and one-year mortality rates were 41.1% and 54.3%, respectively. Among all CS patients, the one-year rate of LVAD or heart transplant was 18.5% and of the composite of death, hospitalisation for HF, LVAD or heart transplant 69.7% **(Figure 2B)**. By using a smoothed hazard function, the highest risk of mortality was within 30 days, which then declined markedly beyond 90 days **(Supplementary Figure 4A, Supplementary Figure 4B)**. Independent predictors of one-year all-cause death and the composite of death, hospitalisation for HF, LVAD or heart transplant are reported in **Figure 3** and **Supplementary Figure 5**, respectively. There were no significant differences in all-cause mortality by type of Impella device used **(Supplementary Table 2, Supplementary Figure 6)**.

IMPELLA FOR HIGH-RISK PCI

Baseline characteristics in patients who underwent HR-PCI are reported in **Table 1**. Mean age was 72.9±9.5 years, 83.6% were male, 46.3% had diabetes mellitus and 41.7% had prior chronic HF. Mean left ventricular ejection fraction was 31.3±10.4%. The Impella 2.5 was used in 61% of patients and the Impella CP in 37.3%. The Impella device was implanted before PCI in 66.7%, during PCI in 32.2% and post PCI in 0.6% of patients. Patients had three-vessel disease in 68.4% of cases and the left main coronary artery was involved in 48.0%. Rotational atherectomy was used in 24.2% of cases and 24.7% had three-vessel PCI. The Impella device was removed immediately after PCI in 82.7% of patients. The overall duration of Impella support was 1.5 hours (IQR: 1.5-3.0).

In-hospital outcomes in patients with HR-PCI are reported in **Table 3**. Overall, the rate of in-hospital mortality was 5.7%. Life-threatening or severe bleeding complications occurred in 5.1% of patients. Patients had limb ischaemia in five cases (2.8%). The rates of device-related complications did not change significantly during the study period (AAPC 12.0%, 95% CI: -9.6% to 38.8%; p=0.20). The rate of all-cause mortality at one year was 15.6% **(Figure 2A)** and that of death, hospitalisation for HF, LVAD or heart transplant 23.3% **(Figure 2B)**. There were no significant differences in all-cause mortality by type of Impella device used **(Supplementary Table 2)**.

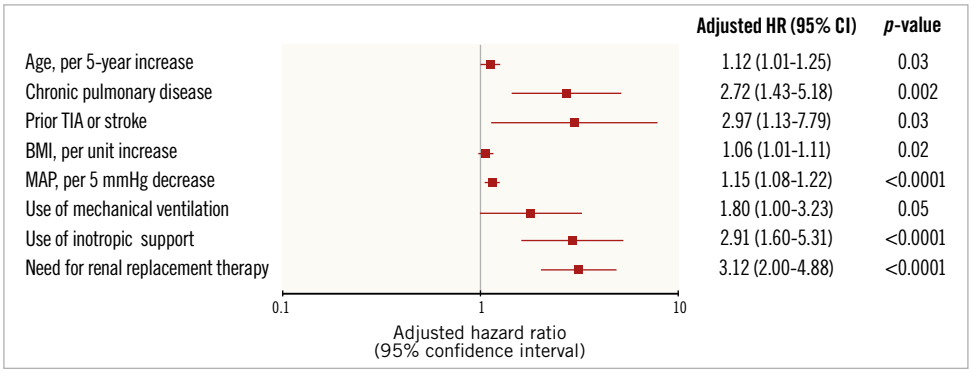


Figure 3. *Predictors of all-cause mortality in patients with cardiogenic shock. A) All-cause mortality. B) Composite of all-cause mortality, heart failure hospitalisation, LVAD or heart transplant. MAP: mean arterial pressure*

Discussion

The main findings of the IMP-IT registry, the largest European series (n=406) of patients undergoing Impella implantation in the setting of CS or HR-PCI, are the following: (i) the use of Impella devices for CS and HR-PCI has grown exponentially over the last few years; (ii) more than half of the patients (56.4%) had an Impella implanted for CS and, in the majority of CS cases, the cause was AMICS; (iii) in 43.6% of the patients the indication for Impella use was HR-PCI; as expected, more than half of the patients had impaired left ventricular ejection fraction and most of them had severe three-vessel disease with concomitant left main disease; (iv) overall, the Impella 2.5 was most commonly used for both indications; however, the Impella CP was rapidly adopted after its introduction; (v) the rates of device-related complications including access-site bleeding and limb ischaemia were relatively high and in line with prior published reports.

IMPELLA IN CS

Patients suffering from CS remain at high risk of morbidity and mortality. Since the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial, conducted more than 20 years ago, demonstrated improved survival with early reperfusion of the infarct-related coronary artery by PCI in AMICS patients[8], no other therapies have been proven to improve outcomes[9]. Percutaneous LVADs have been developed and introduced into clinical practice to overcome the limitations of IABPs by providing a greater reduction in cardiac preload and afterload, and enhance end-organ perfusion[5]. However, while these devices have been approved for commercial use, and their uptake worldwide is increasing[10], evidence from rigorous randomised controlled trials supporting their use is lacking. In addition, these devices are associated with high costs, necessitate highly specialised care, and published data have reported high device-related complication rates. According to our data, more than half (56.4%) of the Impella devices were implanted in the setting of CS, mostly due to AMICS. Device-related complications such as life-threatening bleeding or limb ischaemia were relatively high and in line with prior reported rates. For example, in the USpella registry, among 154 consecutive patients with AMICS who underwent Impella 2.5 support and PCI, the rate of vascular complications requiring surgical repair was 9.7%, the rate of bleeding requiring transfusion was 17.5% and that of haemolysis was 10.3%[11]. More recently, in a large propensity-matched analysis comparing IABP versus Impella in the setting of AMICS, the rates of life-threatening or severe bleeding and peripheral ischaemic complications with the Impella were 8.5% and 9.8%, respectively[12]. In the setting of AMICS, the rate of 30-day mortality in our registry was 41.1%, which compares relatively favourably with other prior reports[11]. Finally, we investigated factors associated with increased mortality at one year in CS. Independent predictors of one-year mortality, such as inotropic support, mechanical ventilation use and need for renal replacement therapy have been described previously, and correlate with the severity of clinical presentation.

IMPELLA IN HR-PCI

Patients with complex multivessel or unprotected left main coronary artery disease and ischaemic cardiomyopathy are a challenging subset of patients with poor prognosis and few treatment options. Within this setting, prophylactic MCS during PCI is used with the rationale of providing haemodynamic stability during the procedure and allowing complete revascularisation[1,2]. The uptake of Impella for this clinical indication is also increasing worldwide[6], despite the lack of randomised trials establishing the role of MCS-supported PCI versus unprotected PCI. In our series, HR-PCI was an indication for Impella use in 43.6% of the study cohort. As expected, most of these patients had low left ventricular ejection fraction and high-risk anatomical features including three-vessel disease, left main disease and/or left anterior descending coronary artery disease. Similar patient characteristics were observed in the USpella (N=175) and German (N=154) HR-PCI registries[13,14]. The rates of life-threatening bleeding and vascular complications in our registry were comparable to prior reports[13,14]. For example, in the HR-PCI cohort of the USpella registry, the rates of bleeding requiring transfusion and major vascular complications were 9.7% and 4.0%, respectively. In the Prospective, Multicenter, Randomized Controlled Trial of the IMPELLA RECOVER LP 2.5 System

Versus Intra-Aortic Balloon Pump in Patients Undergoing Non Emergent High Risk PCI (PROTECT II) trial[15], Impella-supported PCI was associated with lower rates of major adverse cardiac events at three months compared with IABP-supported PCI in the per protocol population (but not in the intention-to-treat population). No randomised trials have compared Impella-supported PCI versus unprotected PCI in case of equipoise as to whether or not haemodynamic support is required. Therefore, evidence from appropriately designed randomised trials is needed to guide the application of this technology in non-CS indications further.

Limitations

This study has several limitations that need to be disclosed. Given its observational, non-randomised design, our findings remain hypothesis-generating. However, they may be used to inform further studies in this field. Data collection was retrospective and therefore subject to recall and ascertainment bias. In addition, in view of its retrospective design, event monitoring was not standardised across clinical centres which could have led to underreporting of adverse events; however, the rates of adverse events in our study were largely in line with other studies in comparable patient populations.

Conclusions

The use of Impella devices for both CS and HR-PCI indications is growing exponentially in Italy; however, the rates of device-related complications remain high, especially in CS patients. Considering their increasing uptake in clinical practice without clear guidance from scientific societies, adequately powered randomised clinical trials and large national/multinational registries are warranted in order to define better the patients who may benefit from Impella implantation, especially for AMICS indications.

Impact on daily practice

The IMP-IT study was a multicentre nationwide registry that enrolled 406 patients from 17 centres in Italy. Rates of in-hospital and one-year all-cause death in patients with CS (N=229) were 46.9% and 57.0%, respectively. Rates of in-hospital and one-year all-cause death in patients who underwent HR-PCI (N=177) were 5.7% and 15.6%, respectively. Rates of device-related complications were 37.1% and 10.7% in the setting of CS and HR-PCI, respectively. Randomised clinical trials are needed in order to define better those patients who may benefit from Impella implantation.

Appendix. Study collaborators

Roberto Garbo, MD, *Interventional Cardiology, Ospedale San Giovanni Bosco, Turin, Italy*; Gerlando Preti, MD, *Interventional Cardiology Unit, Ospedale di Conegliano, Italy*; Elisa Nicolini, MD, *Interventional Cardiology Unit, Ospedali Riuniti di Ancona, Ancona, Italy*; Rocco Sclafani, MD, *Interventional Cardiology Unit, Azienda Ospedaliera di Perugia, Italy*; Giuseppe Colonna, MD, *Interventional Cardiology Unit, Vito Fazzi Hospital, Lecce, Italy*; Marco Mojoli, MD, *SS Emodinamica Interventistica, AAS5, Ospedale di Pordenone, Italy*; Massimo Siviglia, MD, *Interventional Cardiology Unit, A.O. Bianchi Melacrino Morelli, Reggio Calabria, Italy*; Cristiana Denurra, MD, *Interventional Cardiology Unit, Ospedale SS Annunziata, Sassari, Italy*; Francesco Caprioglio, MD, *Interventional Cardiology Unit, Mestre General Hospital, Mestre, Italy*.

Funding

This was an investigator-driven study promoted by the Italian Society of Interventional Cardiology (GISE). No specific funding was allocated for this study.

Conflict of interest statement

A. Chieffo and G. Tarantini have received speakers' fees from Abiomed and GADA. M.B. Ancona has received speaker's fees from Cordis. F. Burzotta and C. Trani have received speakers' fees from Abiomed, Abbott and Medtronic. P. Pagnotta has received speaker's fees from Boston Scientific and Cardia. The other authors have no conflicts of interest to declare. The study collaborators have no conflicts of interest to declare.

References

1. Rihal CS, Naidu SS, Givertz MM, Szeto WY, Burke JA, Kapur NK, Kern M, Garratt KN, Goldstein JA, Dimas V, Tu T; Society for Cardiovascular Angiography and Interventions (SCAI), Heart Failure Society of America (HFSA), Society of Thoracic Surgeons (STS), American Heart Association (AHA), and American College of Cardiology (ACC). 2015 SCAI/ACC/HFSA/STS Clinical Expert Consensus Statement on the Use of Percutaneous Mechanical Circulatory Support Devices in Cardiovascular Care: Endorsed by the American Heart Association, the Cardiological Society of India, and Sociedad Latino Americana de Cardiologia Intervencionista; Affirmation of Value by the Canadian Association of Interventional Cardiology-Association Canadienne de Cardiologie d'intervention. *J Am Coll Cardiol.* 2015;65:2140-1.

2. Chieffo A, Burzotta F, Pappalardo F, Briguori C, Garbo R, Masiero G, Nicolini E, Ribichini F, Trani C, Álvarez BC, Leor OR, Moreno R, Santos R, Fiarresga A, Silveira JB, de Prado AP, Musumeci G, Esposito G, Tarantini G. Clinical expert consensus document on the use of percutaneous left ventricular assist support devices during complex high-risk indicated PCI: Italian Society of Interventional Cardiology Working Group Endorsed by Spanish and Portuguese Interventional Cardiology Societies. *Int J Cardiol.* 2019;293:84-90.

3. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Fuhrmann J, Bohm M, Ebelt H, Schneider S, Schuler G, Werdan K; IABP-SHOCK II Trial Investigators. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med.* 2012;367:1287-96.

4. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J.* 2018;39:119-77.

5. Burkhoff D, Sayer G, Doshi D, Uriel N. Hemodynamics of Mechanical Circulatory Support. *J Am Coll Cardiol.* 2015;66:2663-74.

6. Vetrovec GW, Anderson M, Schreiber T, Popma J, Lombardi W, Maini B, Moller JE, Schafer A, Dixon SR, Hall S, Ohman EM, Mindrescu C, Moses J, O'Neill W. 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.* 2018;199:115-21.

7. Cohen MG, Matthews R, Maini B, Dixon S, Vetrovec G, Wohns D, Palacios I, Popma J, Ohman EM, Schreiber T, O'Neill WW. Percutaneous left ventricular assist device for high-risk percutaneous coronary interventions: Real-world versus clinical trial experience. *Am Heart J.* 2015;170:872-9.

8. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, LeJemtel TH. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med.* 1999;341:625-34.

9. Werdan K, Gielen S, Ebelt H, Hochman JS. Mechanical circulatory support in cardiogenic shock. *Eur Heart J.* 2014;35:156-67.

10. Shah M, Patnaik S, Patel B, Ram P, Garg L, Agarwal M, Agrawal S, Arora S, Patel N, Wald J, Jorde UP. Trends in mechanical circulatory support use and hospital mortality among patients with acute myocardial infarction and non-infarction related cardiogenic shock in the United States. *Clin Res Cardiol.* 2018;107:287-303.

11. O'Neill WW, Schreiber T, Wohns DH, Rihal C, Naidu SS, Civitello AB, Dixon SR, Massaro JM, Maini B, Ohman EM. The current use of Impella 2.5 in acute myocardial infarction complicated by cardiogenic shock: results from the USpella Registry. *J Interv Cardiol.* 2014;27:1-11.

12. Schrage B, Ibrahim K, Loehn T, Werner N, Sinning JM, Pappalardo F, Pieri M, Skurk C, Lauten A, Landmesser U, Westenfeld R, Horn P, Pauschinger M, Eckner D, Twerenbold R, Nordbeck P, Salinger T, Abel P, Empen K, Busch MC, Felix SB, Sieweke JT, Moller JE, Pareek N, Hill J, MacCarthy P, Bergmann MW, Henriques JPS, Mobius-Winkler S, Schulze PC, Ouarrak T, Zeymer U, Schneider S, Blankenberg S, Thiele H, Schafer A, Westermann D. Impella Support for Acute Myocardial Infarction Complicated by Cardiogenic Shock. *Circulation.* 2019;139:1249-58.

13. Maini B, Naidu SS, Mulukutla S, Kleiman N, Schreiber T, Wohns D, Dixon S, Rihal C, Dave R, O'Neill W. Real-world use of the Impella 2.5 circulatory support system in complex high-risk percutaneous coronary intervention: the USpella Registry. *Catheter Cardiovasc Interv.* 2012;80:717-25.

14. Baumann S, Werner N, Ibrahim K, Westenfeld R, Al-Rashid F, Sinning JM, Westermann D, Schafer A, Karatolios K, Bauer T, Becher T, Akin I. Indication and short-term clinical outcomes of high-risk percutaneous coronary intervention with microaxial Impella(R) pump: results from the German Impella(R) registry. *Clin Res Cardiol.* 2018;107:653-7.

15. O'Neill WW, Kleiman NS, Moses J, Henriques JP, Dixon S, Massaro J, Palacios I, Maini B, Mulukutla S, Dzavik V, Popma J, Douglas PS, Ohman M. 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.* 2012;126:1717-27.

Supplementary data

Supplementary Appendix 1. Study definitions.

Supplementary Appendix 2. Study endpoints and definitions.

Supplementary Appendix 3. Devices.

Supplementary Figure 1. Study flow diagram of the IMP-IT registry.

Supplementary Figure 2. Trends in use of the Impella in the IMP-IT registry.

Supplementary Figure 3A. Rates of heart failure hospitalisations at 1 year.

Supplementary Figure 3B. Rates of LVAD or heart transplant at 1 year.

Supplementary Figure 4A. Instantaneous hazard of all-cause mortality over one year.

Supplementary Figure 4B. Instantaneous hazard of all-cause death, HF hospitalisation, LVAD or heart transplant over one year.

Supplementary Figure 5. Predictors of 1-year all-cause death, hospitalisation for HF, LVAD or heart transplant in patients with cardiogenic shock.

Supplementary Figure 6. Kaplan-Meier curves for one-year mortality according to the type of Impella device in patients with cardiogenic shock.

Supplementary Table 1. Participating centres in the IMP-IT registry.

Supplementary Table 2. Crude rates of all-cause mortality at one year according to the type of Impella device used.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00428

Supplementary data

Supplementary Appendix 1. Study definitions

Cardiogenic shock. Criteria for CS included a systolic blood pressure of less than 90 mmHg for longer than 30 minutes or the use of catecholamine therapy to maintain a systolic pressure of at least 90 mmHg, clinical signs of pulmonary congestion, and signs of impaired organ perfusion with at least one of the following manifestations: altered mental status, cold and clammy skin and limbs, oliguria with a urine output of less than 30 ml per hour, or an arterial lactate level of more than 2.0 mmol per litre.

High-risk PCI. HR-PCI was defined according to the presence of at least of one clinical and one anatomical high-risk criterion as defined below. High-risk clinical characteristics and comorbidities were defined as: advanced age (>75 years), diabetes mellitus, heart failure with left ventricular ejection fraction ≤35%, acute coronary syndromes, previous cardiac surgery, peripheral vascular disease, advanced chronic kidney disease (glomerular filtration rate <30 ml/min/1.73 m^2), chronic obstructive pulmonary disease, concomitant severe aortic valvulopathy or severe mitral regurgitation. Complexity of coronary anatomies/lesions included: unprotected left main disease, degenerated saphenous vein grafts, severely calcified lesions with need for rotational atherectomy, last patent conduit, and chronic total occlusions in patients with multivessel disease.

Supplementary Appendix 2. Study endpoints and definitions

In-hospital death was defined as any patients who died during the hospital stay.

Need for renal replacement therapy (RRT) is the utilisation of any modality of RRT in case of little or no residual kidney function.

Acute kidney injury was defined as any of the following: increase in serum creatinine by ≥0.3 mg/dl (≥26.5 lmol/l) within 48 hours; or increase in serum creatinine to ≥1.5 times from baseline, which is known or presumed to have occurred within the prior seven days; or urine volume <0.5 ml/kg/hr for six hours.

Need for mechanical ventilation was defined as the need for invasive ventilatory support by endotracheal tube placement.

Need for support escalation due to haemodynamic deterioration was defined as left or right ventricular failure that is not responsive to Impella support and requires the use of advanced short-term mechanical support such as ECMO or the need of, in patients dependent on mechanical support, transplantation or long-term mechanical support such as surgical implantation of LVAD.

Need for LVAD/transplantation defined as cardiac transplantation or long-term mechanical circulatory support (LVAD) in patients in INTERMACS class I, II or III during hospital stay or in patients in INTERMACS class IV after discharge.

Device-related complications were defined as vascular access complications in terms of bleeding or limb ischaemia, vascular complications requiring endovascular interventions, neurological events (stroke), life-threatening bleeding, haemolysis, number of RBC transfused after Impella insertion, aortic injury such as dissection or left ventricular perforation.

Neurological events were defined as:

- Stroke: duration of a focal or global neurological deficit ≥24 hrs; or <24 hrs if available neuroimaging documents a new haemorrhage or infarct; or the neurological deficit results in death.
- Transient ischaemic attack: duration of a focal or global neurological deficit <24 hrs, any variable neuroimaging does not demonstrate a new haemorrhage or infarct.

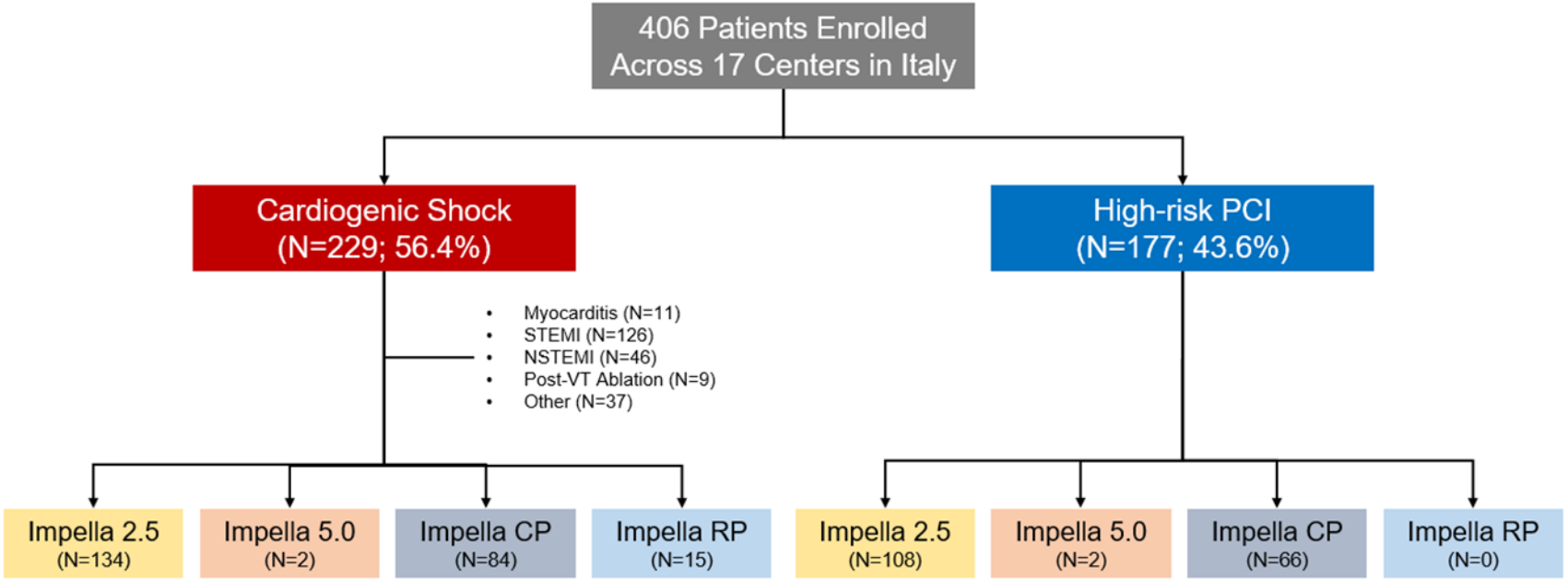
Bleeding was defined according to the Global Use of Strategies to Open Occluded Arteries (GUSTO) criteria as: (i) severe or life-threatening: intracerebral haemorrhage or bleeding resulting in substantial haemodynamic compromise requiring treatment; (ii) moderate: requiring

blood transfusion but not resulting in haemodynamic compromise; (iii) mild: bleeding that does not meet the above criteria.

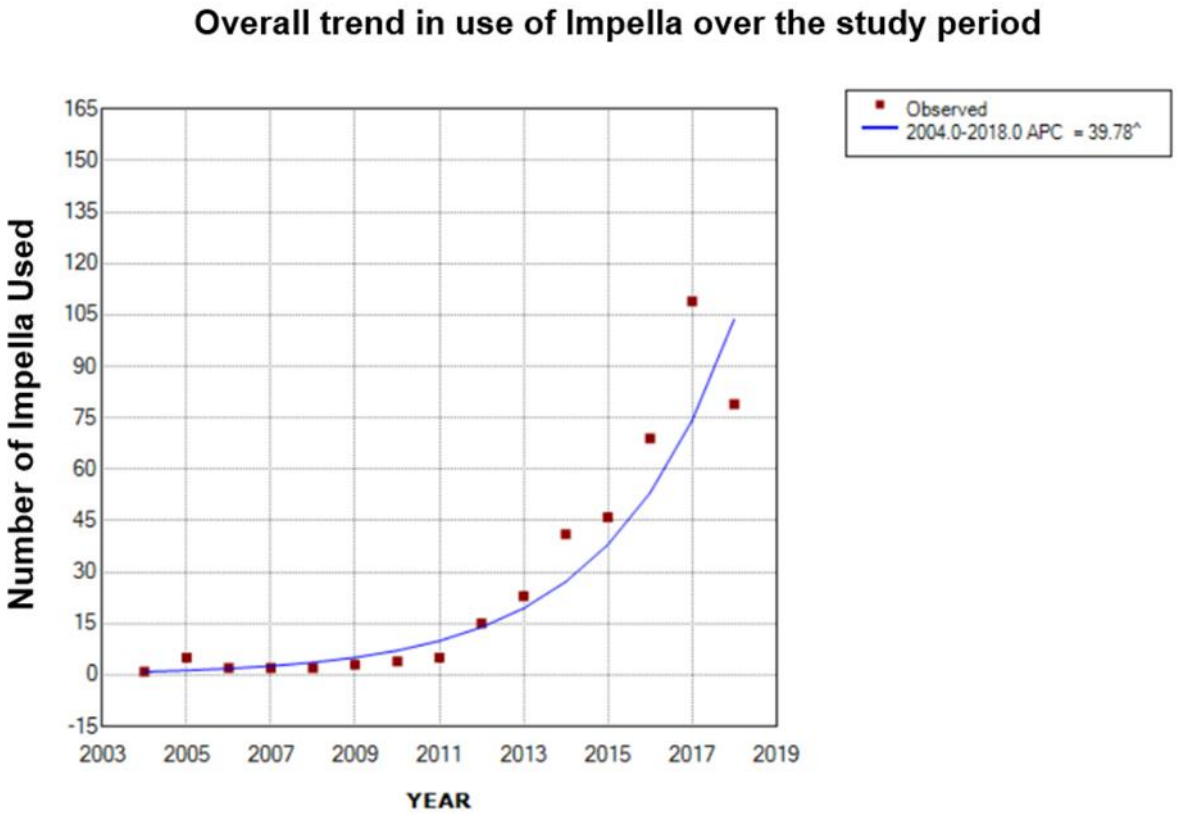
Haemolysis was defined according to the INTERMACS definitions as: (i) major haemolysis: plasma-free haemoglobin value greater than 20 mg/dl or a serum lactate dehydrogenase (LDH) level greater than two and one-half times (2.5x) the upper limits of the normal range at the implanting centre occurring after the first 72 hours post implant and associated with clinical symptoms or findings of haemolysis or abnormal pump function. Major haemolysis requires the presence of one or more of the following conditions: haemoglobinuria ("tea-coloured urine"); anaemia (decrease in haematocrit or haemoglobin level that is out of proportion to levels explainable by chronic illness or usual post-VAD state); hyperbilirubinaemia (total bilirubin above 2 mg%, with predominately indirect component); pump malfunction and/or abnormal pump parameters; (ii) minor haemolysis: plasma-free haemoglobin value greater than 20 mg/dl or a serum lactate dehydrogenase (LDH) level greater than two and one-half times (2.5x) the upper limits of the normal range at the implanting centre occurring after the first 72 hours post implant in the absence of clinical symptoms or findings of haemolysis or abnormal pump function.

Supplementary Appendix 3. Devices

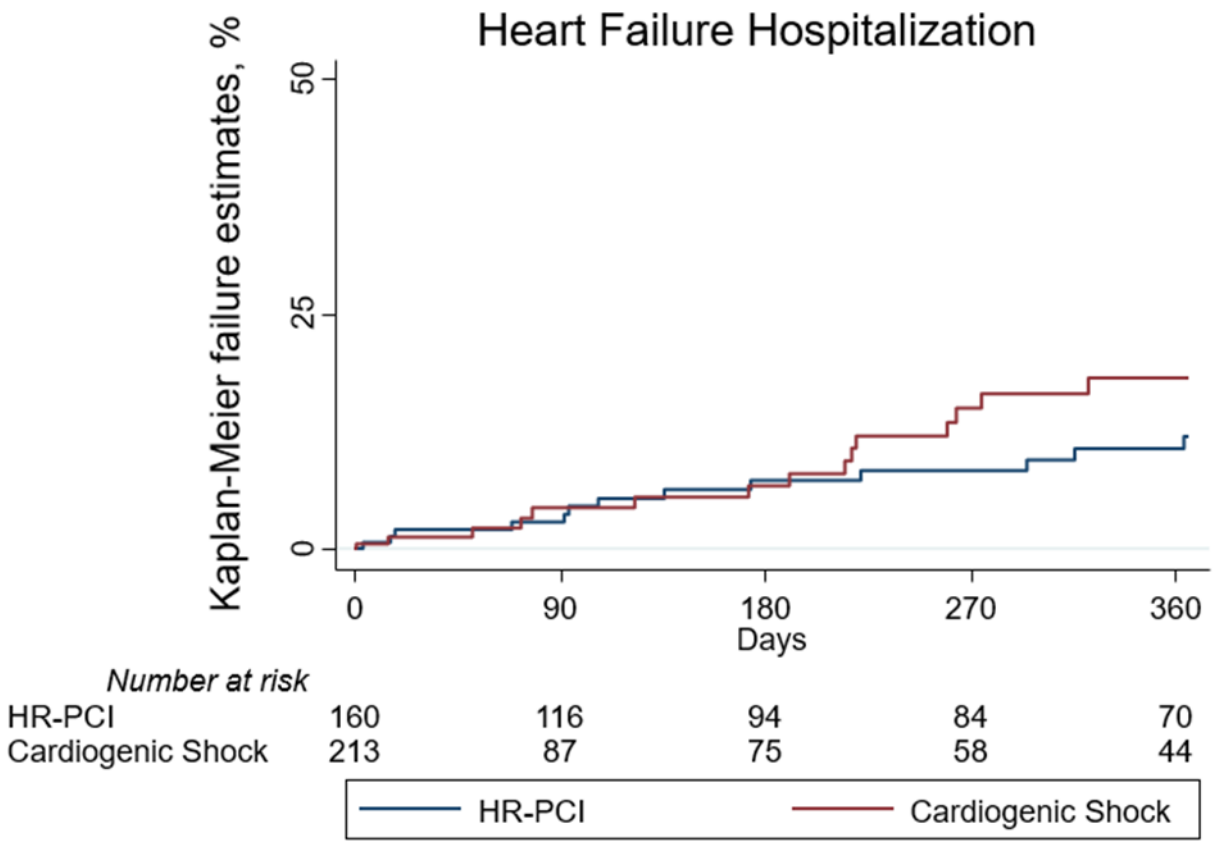
The Impella 2.5 device (Abiomed) is a 12 Fr micro-axial pump mounted on a 9 Fr catheter. It is inserted through the femoral artery using a modified Seldinger technique. The pump is advanced retrogradely across the aortic valve into the left ventricle; fluoroscopy guidance is usually used. The Impella 2.5 generates up to 2.5 L/min of flow in the ascending aorta. An activated thrombin time of 160–180 seconds during pump support is usually recommended for both devices. From 2012 the Impella CP device also became available: it is able to generate up to 4.0 L/min and requires a 14 Fr percutaneous vascular access. The Impella 5.0 device requires a surgical 21 Fr access and is able to generate up to 5.0 L/min. The Impella RP is a right ventricular assist device: it requires a 23 Fr percutaneous femoral vein access and is advanced into the right atrium, across the tricuspid and pulmonic valves, and into the pulmonary artery. It delivers blood from the inlet area, which sits in the inferior vena cava, through the cannula to the outlet opening near the tip of the catheter in the pulmonary artery; it is able to generate up to 4.0 L/min. Selection of each device and support level depends on the clinical scenario, preload status, and body size, disease severity and presence of peripheral artery disease.



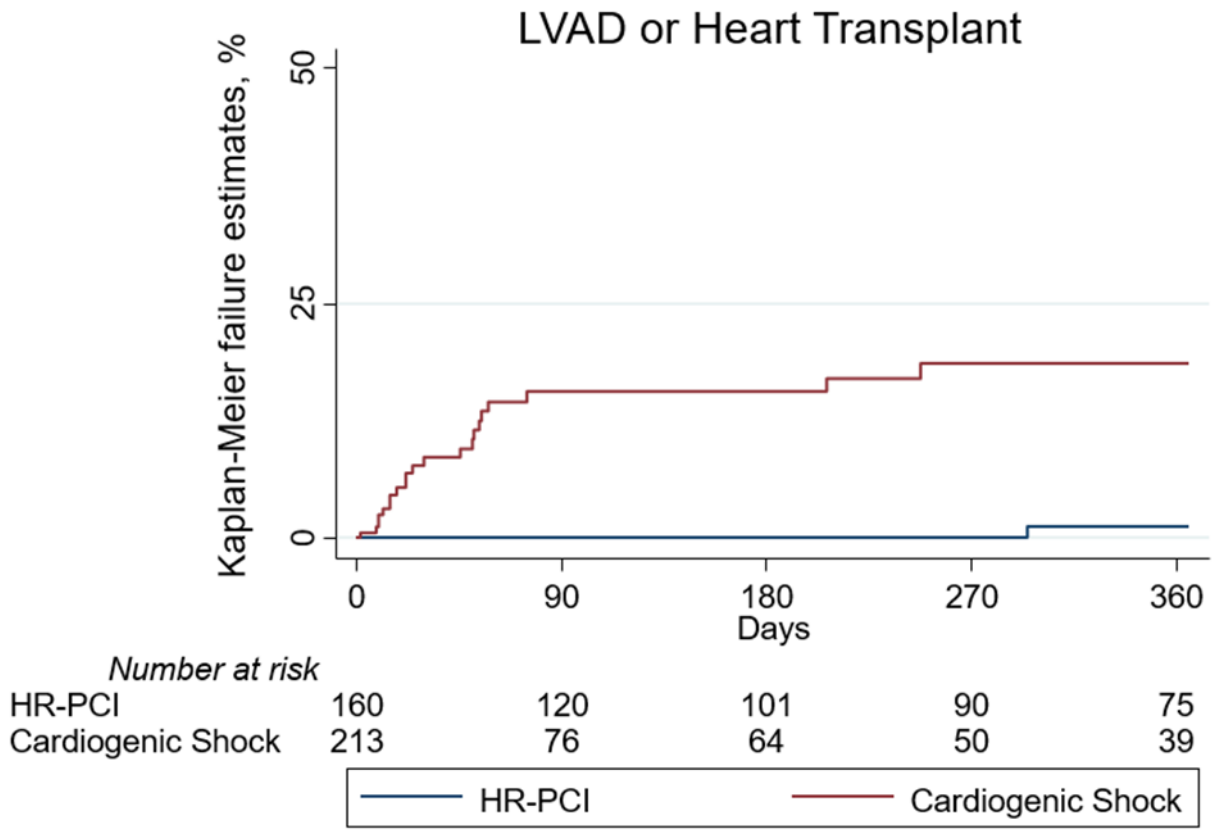
Supplementary Figure 1. Study flow diagram of the IMP-IT registry.



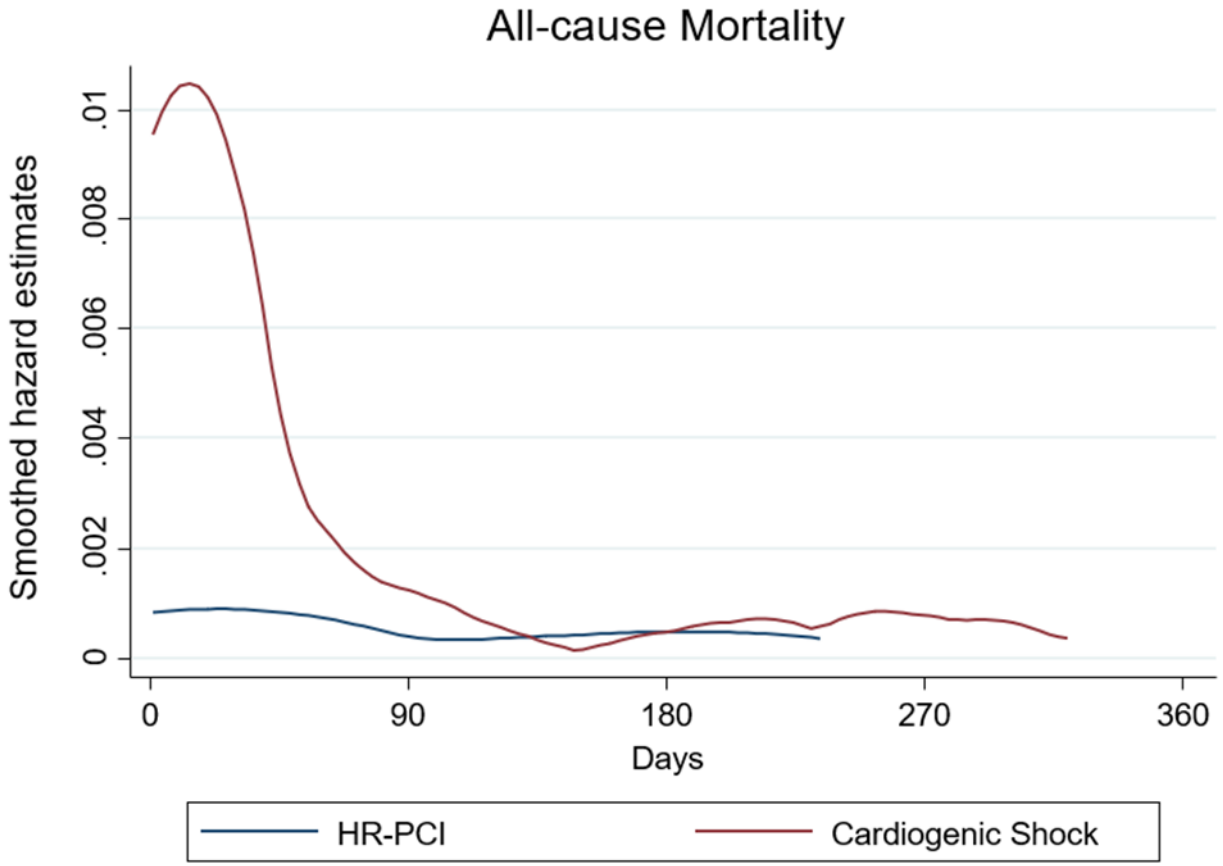
Supplementary Figure 2. Trends in use of the Impella in the IMP-IT registry.



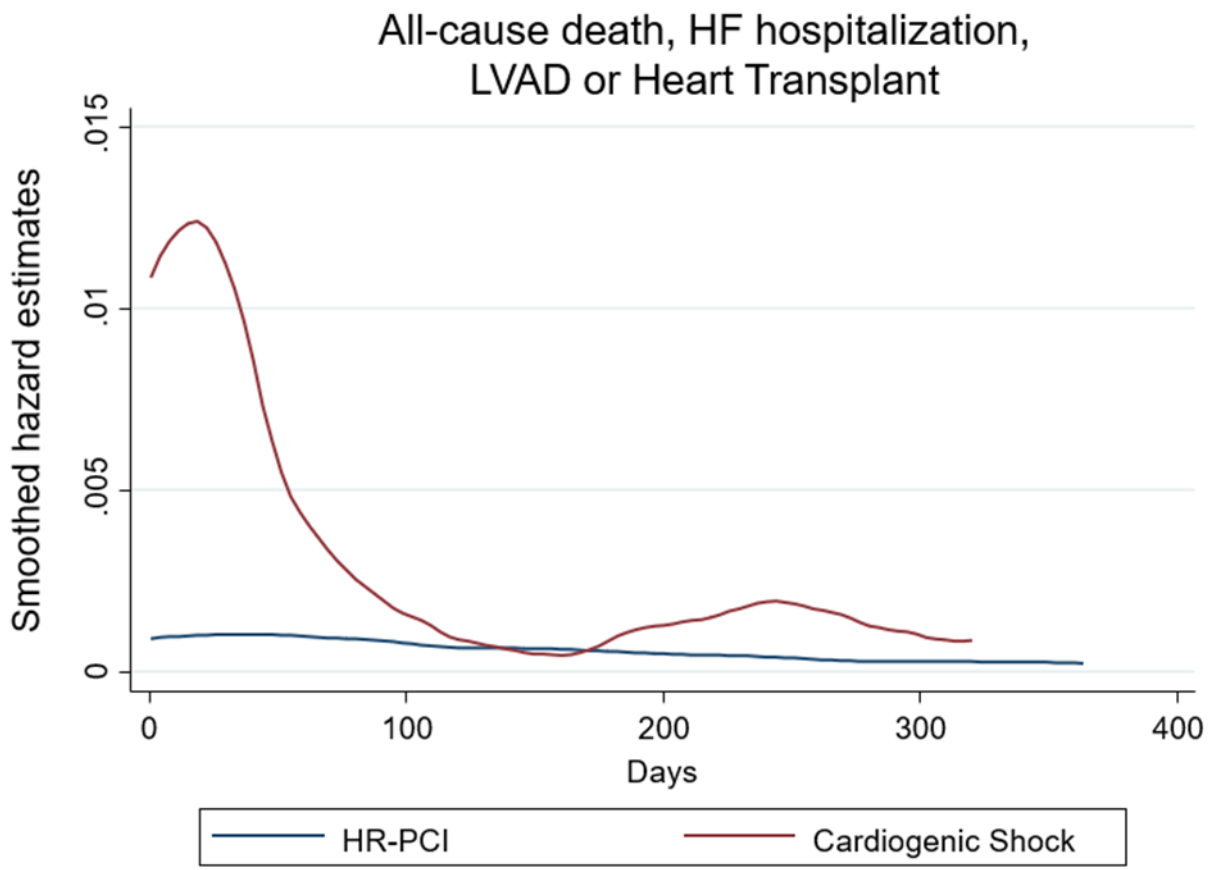
Supplementary Figure 3A. Rates of heart failure hospitalizations at 1 year.



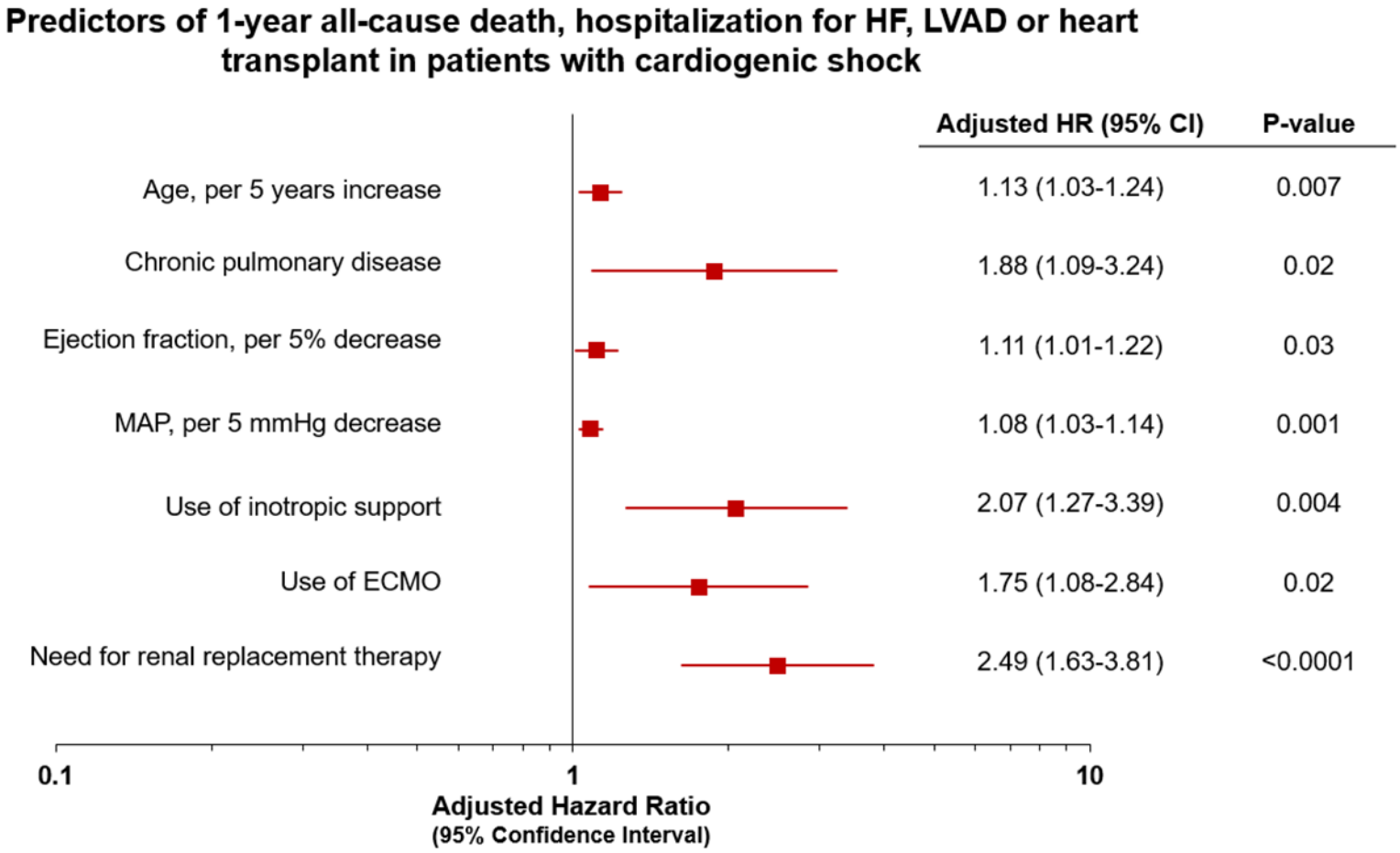
Supplementary Figure 3B. Rates of LVAD or heart transplant at 1 year.



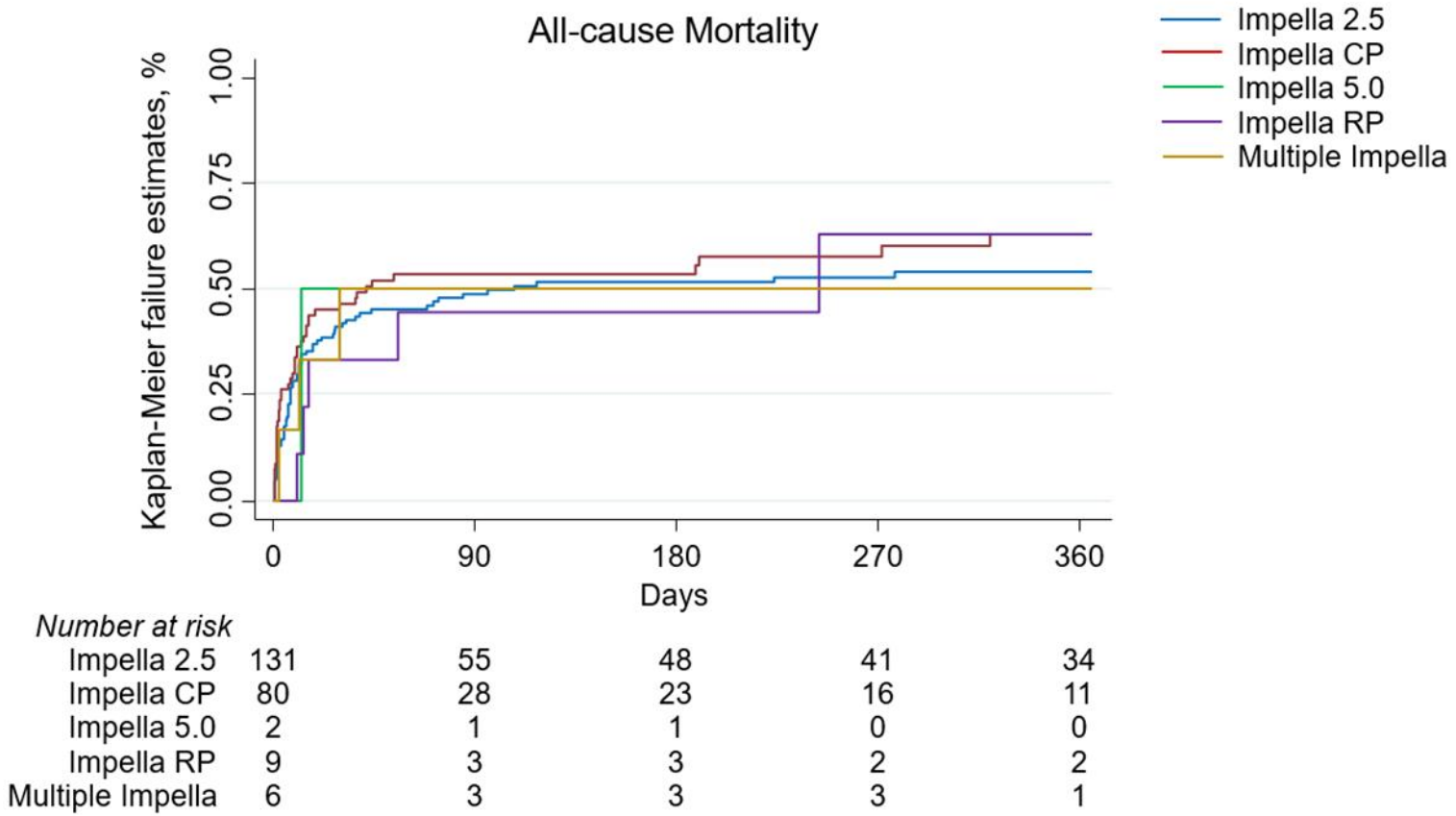
Supplementary Figure 4A. Instantaneous hazard of all-cause mortality over one year.



Supplementary Figure 4B. Instantaneous hazard of all-cause death, HF hospitalization, LVAD or heart transplant over one year.



Supplementary Figure 5. Predictors of 1-year all-cause death, hospitalization for HF, LVAD or heart transplant in patients with cardiogenic shock.



Supplementary Figure 6. Kaplan-Meier curves for one-year mortality according to the type of Impella device in patients with cardiogenic shock.

Supplementary Table 1. Participating centres in the IMP-IT registry.

List of centres	Patients per centre (n)
IRCCS San Raffaele Scientific Institute, Milan, Italy	144
Institute of Cardiology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome	107
Interventional Cardiology Unit, Mediterranea Cardiocentro, Naples	46
Interventional Cardiology Unit, Ospedali Riuniti di Ancona, Ancona	22
Department of Cardiac, Thoracic and Vascular Science, University of Padua Department of Clinical and Interventional Cardiology	15
IRCCS Policlinico San Donato, Milan	11
Interventional Cardiology Unit, Ospedale Luigi Sacco, Milan	10
Cardiovascular Department, Humanitas Research Hospital, Rozzano	8
Interventional Cardiology Unit, Ospedale San Francesco, Nuoro	8
Interventional Cardiology, Ospedale San Giovanni Bosco, Turin	7
Interventional Cardiology Unit, Ospedale di Conegliano	6
Interventional Cardiology Unit, Azienda Ospedaliera di Perugia	5
Interventional Cardiology Unit, Vito Fazzi Hospital, Lecce	4
SS Emodinamica Interventistica, AAS5, Ospedale di Pordenone	4
Interventional Cardiology Unit, A.O. Bianchi Melacrino Morelli, Reggio Calabria	4
Interventional Cardiology Unit, Ospedale SS Annunziata, Sassari	3
Interventional Cardiology Unit, Mestre General Hospital, Mestre	2

Supplementary Table 2. Crude rates of all-cause mortality at one year according to the type of Impella device used.

	Cardiogenic shock (N=229)	High-risk PCI (N=177)
Impella 2.5	68 (53.9%)	13 (14.6%)
Impella CP	48 (61.9%)	10 (17.6%)
Impella RP	8 (55.6%)	-

Results are reported as number of events (Kaplan-Meier estimates). Impella 5 is not shown due to low numbers.