

Microaxial flow pump (Impella CP®) in patients with ST-elevation myocardial infarction complicated by cardiogenic shock

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ABSTRACT

Cardiogenic shock due to ST-elevation myocardial infarction remains a critical condition with a high mortality rate, even with current revascularization techniques. The use of mechanical circulatory support, such as the microaxial flow pump device (Impella CP®), presents a promising approach to enhance cardiac output and systemic perfusion. The DanGer Shock trial explored the efficacy of Impella CP® in addition to standard care compared to standard care alone in improving survival outcomes for these patients. Despite the potential for increased adverse events, the Impella CP® device significantly reduces mortality in patients with ST-elevation myocardial infarction complicated by cardiogenic shock. Future research should focus on refining patient selection criteria and minimizing device-related complications to maximize the therapeutic benefits of mechanical circulatory support in this critical population.

Key words: cardiogenic shock, Impella, mechanical circulatory support, myocardial infarction

CARDIOGENIC SHOCK DUE TO ACUTE MYOCARDIAL INFARCTION

Cardiogenic shock affects 5% to 10% of patients with ST-elevation myocardial infarction (STEMI) and is associated with a 30-day mortality rate of *circa* 50% even in the post-revascularization era [1–3]. Ischemic injury to the myocardium leads to a reduction in cardiac output, causing critical organ hypoperfusion and end-organ injury. The management of cardiogenic shock complicating acute myocardial infarction encompasses primary coronary revascularization, vasoactive drugs, and circulatory as well as ventilatory support [4]. However, many of these interventions are guided mainly by the treating physician's experience rather than evidence-based recommendations. Over the past 25 years, just two well-powered clinical trials have demonstrated clinically meaningful benefits through culprit vessel revascularization [5, 6]. Despite these efforts, high mortality rates

persist, indicating a need for further research into additional interventions that could improve hemodynamic stability and mitigate end-organ injury.

Augmenting cardiac output and restoring systemic perfusion with mechanical circulatory support seems intuitively beneficial. However, defining cardiogenic shock is complex, and predicting in which patients the myocardium will recover following revascularization and the speed of recovery is challenging [7]. Patients whose cardiac functions recover enough to ensure perfusion in the first hours are less likely to benefit from mechanical circulatory support, but are still exposed to the potential complications of the devices. On the other hand, the risk of complications may be acceptable in patients who have refractory cardiac shock in whom mechanical circulatory support may be life-saving. One particularly challenging group in this regard comprises patients resuscitated from out-of-hospital cardiac arrest. They often present with a car-

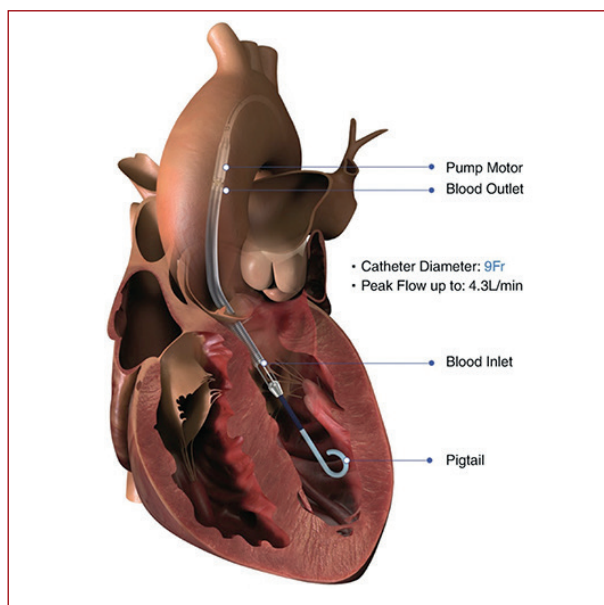


Figure 1. Impella CP device (from AbioMed)

diogenic shock phenotype (high lactate levels, requiring vasopressors, and with an initially stunned myocardium) but frequently become hemodynamically stable within hours [7, 8]. Additionally, cardiac arrest patients have already suffered prolonged hypoxia resulting in anoxic brain injury, a condition mechanical circulatory support is unlikely to improve. Thus, identifying patients who are likely to benefit from mechanical circulatory support is challenging [9].

Before the DanGer Shock trial [10], only two trials had been powered and completed to detect differences in mortality with the use of mechanical circulatory support in patients with cardiogenic shock complicating acute myocardial infarction, namely the IABP-SHOCK II [11] (intra-aortic balloon pump) and ECLS-SHOCK [12] (veno-arterial extracorporeal membrane oxygenation) trials. Both were neutral regarding the primary outcome, with 30-day mortality rates of 41.3% vs. 39.7% in the IABP-SHOCK II trial and 49.0% vs. 47.8% in the ECLS-SHOCK trial for standard of care vs. mechanical circulatory support, respectively.

DANGER SHOCK TRIAL

The microaxial flow pump Impella CP® (Abiomed, Johnson & Johnson Med. Tec., Danvers, MA, US) is a mechanical circulatory support device that provides unloading of the left ventricle and increases perfusion (Figure 1). The device draws blood from the left ventricle and expels it into the ascending aorta, thereby increasing cardiac output, lowering filling pressure, and lowering myocardial oxygen consumption [13]. The device can be rapidly inserted before or after revascularization through the femoral artery and provide a flow of up to 3.8 liters per minute.

The DanGer Shock trial [10] was the first trial adequately powered to compare mortality in patients randomized to standard of care vs. standard of care plus Impella CP. It was

an international, multicenter, randomized trial conducted in Denmark, Germany, and the UK, enrolling patients with STEMI (aged ≥ 18 years) complicated by cardiogenic shock. Cardiogenic shock was defined as hypotension (systolic blood pressure < 100 mm Hg or ongoing need for vasopressor support), combined with hypoperfusion with an arterial lactate level of ≥ 2.5 mmol per liter and a left ventricular ejection fraction below 45%. Patients who had been resuscitated from out-of-hospital cardiac arrest could only be included if they had regained consciousness (a Glasgow Coma Score ≥ 8) upon arrival at the catheterization laboratory. Other important exclusion criteria included a shock duration > 24 hours, other causes of shock (e.g., hypovolemia, sepsis, pulmonary embolism or anaphylaxis), shock due to mechanical complications to myocardial infarction, and evidence of severe right ventricular failure by echocardiography. Patients were randomized immediately when CS was identified, before or after revascularization, or up to 12 hours after exiting the catheterization laboratory, when CS developed later. The Impella CP device was placed immediately after randomization, and was set to run at the highest level for at least 48 hours. All patients could be escalated to additional mechanical support after randomization (Impella 5.0, Impella RP, or extracorporeal life support). The primary outcome in the DanGer Shock trial was all-cause mortality at 180 days. This specific timescale was based on the mortality difference observed in the SHOCK trial, which only became statistically significant after 180 days of follow-up [5].

BASELINE CHARACTERISTICS AND MANAGEMENT OF STEMI AND CARDIOGENIC SHOCK IN DANGER SHOCK TRIAL

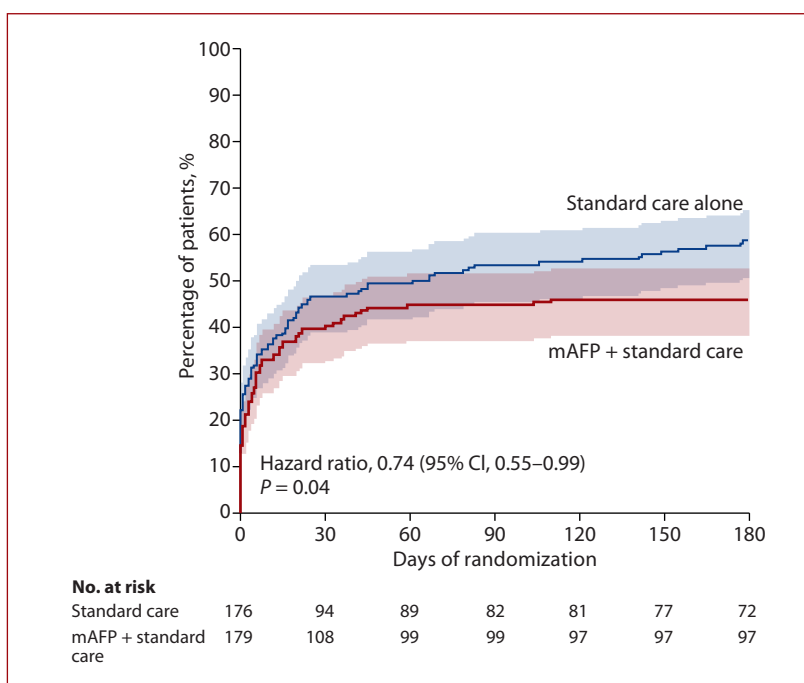
Over a period of 10 years, 355 patients were included in the final analysis. The patient population was primarily male (79.2%), with a median age of 67 years (IQR 59–76). Most patients suffered from an anterior acute myocardial infarction (71.8%), and 20.3% had been resuscitated from a cardiac arrest with regained consciousness (Glasgow Coma Scale ≥ 8) before entering the catheterization laboratory. At the time of randomization, median systolic blood pressure was 82 mm Hg (IQR 82–91) and heart rate was 95 beats per minute (IQR 77–110). Median lactate level was 4.5 mmol per liter (IQR 3.3–7.0). The vast majority had a percutaneous coronary intervention (96.6%), and 5 patients (1.4%) underwent acute coronary artery bypass grafting. Among the 355 patients, 179 were randomized to a standard of care plus microaxial flow pump group and 176 to a standard of care only group. The device was successfully placed in 170/179 patients in the microaxial flow pump group, with 3 patients (1.7%) crossing over to standard of care, and in 6 patients device placement was attempted but unsuccessful. In the microaxial flow pump group, 82.1% of the patients were randomized in the catheterization laboratory, mainly before revascularization (67% of the patients randomized in the catheterization

Table 1. Completed trials powered to assess differences in mortality with mechanical circulatory support devices in patients suffering from cardiogenic shock complicating acute myocardial infarction

Trial (PMID)	Intervention	No. of patients	Baseline characteristics	Primary outcome (device vs. standard of care)	Adverse Events (device vs. standard of care)
IABP-II (22920912)	Intra-aortic balloon pump vs. standard of care	600	Age: c. 69 years Male sex: 68.8% STEMI: 68.6% OHCA: 45.0%	30-day all-cause mortality: 39.7% vs. 41.3%	Bleeding*: 20.6% vs. 20.8% Peripheral ischemia: 3.4% vs. 4.3% AKI: No difference in creatinine clearance first 4 days
ESCL-SHOCK (37634145)	Veno-arterial extracorporeal membrane oxygenation vs. standard of care	420	Age: c. 62.5 years Male sex: 80.7% STEMI: 65.9% OHCA: 77.9%	30-day all-cause mortality: 47.8% vs. 49.0%	Bleeding*: 23.4% vs. 9.6% Peripheral ischemia: 11.0% vs. 3.8% AKI: Renal replacement therapy in 8.1% vs. 13.9%
DanGer-Shock (38587239)	Microaxial flow pump vs. standard of care	355	Age: 67 years Male sex: 79.1% STEMI: 100% OHCA: 20.3% (all regained consciousness before randomization)	180-day all-cause mortality: 45.8% vs. 58.5%	Bleeding*: 21.8% vs. 11.9% Peripheral ischemia: 5.6% vs. 1.1% AKI: Renal replacement therapy in 41.9% vs. 26.7%

*Moderate or severe

Abbreviations: AKI, acute kidney injury; OHCA, out-of-hospital cardiac arrest; STEMI, ST-segment elevation myocardial infarction

**Figure 2.** Time to all-cause death until 180 days in patients with ST-elevation myocardial infarction complicated by cardiogenic shock randomized to standard of care or standard of care plus microaxial flow pump [mAFP] device (Impella CP®). Shaded areas indicate 95% confidence interval (reprinted with permission from the New England Journal of Medicine [12])

laboratory). In the standard of care group, 3 patients (1.7%) received an Impella CP device and were thus considered as crossover patients. Escalation to another mechanical circulatory support system was done in 28 patients (15.6%) in the microaxial flow pump group vs. 37 patients (21.0%) in the standard of care group.

PRIMARY OUTCOME OF DANGER SHOCK TRIAL

At 180 days, 82/179 patients (45.8%) in the microaxial flow pump group vs. 103/176 patients (58.5%) in the standard of care group had died (hazard ratio 0.74; 95% confidence interval [CI], 0.55–0.99; $P = 0.04$) (Figure 2). This translates to a 12.7% absolute reduction in mortality at 180 days

with the microaxial flow pump device, and thus a number needed to treat of 8. The Kaplan–Meier curve in Figure 2 indicates an early separation in mortality between the two groups, which continued to separate from day 30 until day 180. Predefined subgroup analyses suggested a greater benefit in patients with lower mean arterial blood pressure and in those with multivessel disease, whereas the effect in women seemed less. These issues will be analyzed in forthcoming sub-studies.

ADVERSE EVENTS IN DANGER SHOCK TRIAL

The risk of adverse events was higher in the microaxial flow group. Moderate or severe bleeding occurred in 39 patients (21.8%) in the microaxial flow group vs. 21 pa-

tients (11.9%) in the standard of care group (relative risk [RR] 2.06; 95% CI, 1.15–3.66). Limb ischemia was seen in 10 patients (5.6%) vs. 2 patients (1.1%) in the microaxial flow group and the standard of care group, respectively (RR 5.15; 95% CI, 1.11–23.84). Renal replacement therapy was initiated in 75 patients (41.9%) in the microaxial flow group and 47 (26.7%) in the standard of care group (RR, 1.98; 95% CI, 1.27–3.09).

LESSONS FROM DANGER SHOCK TRIAL

The DanGer Shock trial was the first study ever to demonstrate a survival benefit from an intervention beyond revascularization in patients with cardiogenic shock complicating STEMI. This raises the crucial question as to whether this was driven by the device or by patient selection.

IS A MICROAXIAL FLOW PUMP DEVICE BETTER AND SAFER THAN OTHER MECHANICAL CIRCULATORY SUPPORT DEVICES?

The DanGer Shock trial was the first to compare a microaxial flow pump device alone against standard of care in a study powered to detect differences in mortality. Microaxial flow pump devices may provide a favorable balance between the benefits of unloading the left ventricle and ensuring end-organ perfusion in patients with predominantly left ventricular failure [14]. Indeed, a comprehensive understanding of how Impella CP affects hemodynamic stability and end-organ perfusion in this population is warranted, including an evaluation as to whether the effect is sustained over a longer follow-up. Subsequent studies should hopefully provide indications of the hemodynamic effects. Regarding the risk of complications, it is noteworthy that the incidence of bleeding outcomes with a mechanical support device in the DanGer Shock trial (21.8%) was similar to those in the IABP-SHOCK II (20.6%) and ECLS-SHOCK trials (23.4%), lower for peripheral ischemia (5.6% with microaxial flow pump devices in DanGer vs. 11.0% with veno-arterial extracorporeal membrane oxygenation in extracorporeal life support [ECLS]), and higher for acute kidney injury (AKI) or renal replacement therapy (41.9% with microaxial flow pump devices in DanGer vs. 8.1% with veno-arterial extracorporeal membrane oxygenation in ECLS) [11, 12]. This underscores the critical condition that cardiogenic shock represents, and highlights the need to better understand the development of any complications and measures to reduce them in order to improve patient outcomes.

WHICH PATIENTS TO TREAT?

Secondly, and perhaps even more importantly, the population in the DanGer Shock trial differed from that in previous trials [11, 12]. When designing a clinical trial, there is often a balance to be struck between including homogenous patients with a theoretically high likelihood of benefiting from the intervention, and ensuring that the results apply to real-world scenarios [9]. In contrast to

the IABP-SHOCK II and ECLS-SHOCK trials, the DanGer Shock trial only included acute myocardial infarction patients with ST-elevation. These patients have a higher risk of developing cardiogenic shock, and registries have shown higher mortality in patients with cardiogenic shock complicating STEMI compared to non-STEMI (NSTEMI) [3]. Also, NSTEMI patients are older and have a higher comorbidity burden.

Patients who remain comatose after resuscitation for cardiac arrest often present at hospital in a shock-like state with reduced left ventricular function, low blood pressure, and elevated lactate. However, in these patients, the lactate level likely reflects the duration of the low-flow period during resuscitation and the quality of chest compression, rather than hypoperfusion on admission. Thus, lactate levels in the arrested patient will likely reflect O₂-debt and will normalize faster than in patients with LV-predominant failure. Further, the cause of death differs where the cardiac arrest phenotype is dominated by hypoxic brain injury, when mechanical circulatory support is unlikely to ameliorate the brain injury [15]. Thus, the DanGer Shock trial, in contrast to the IABP-SHOCK II and ECLS-SHOCK trials, excluded unconscious patients who had been resuscitated from a cardiac arrest. These would be more likely to have post-arrest stunning, less likely to benefit from circulatory support, and would inherit a huge burden of potential anoxic brain damage being unsusceptible to circulatory support. In the IABP-SHOCK II trial, 45% had been resuscitated before randomization, and in the ECLS-SHOCK trial, this figure was 77.7%. Compare these figures to only 20.3% of patients in the DanGer Shock trial. Moreover, all cardiac arrest patients included in the DanGer Shock trial had regained consciousness before randomization, and were thus unlikely to die due to anoxic brain injury. Selecting the appropriate patients is crucial for demonstrating efficacy, but may constrain the ability to generalize the results to other cohorts of cardiogenic shock patients, such as those with NSTEMI or non-ischemic acute heart failure. Future randomized trials will need to investigate whether microaxial flow pump devices confer benefits in populations beyond those studied in the DanGer Shock trial.

The patients in the DanGer Shock trial were slightly older (67 years) compared to those in the Polish retrospective registry of Impella-treated cardiogenic shock patients (63 years, n = 55), as reported by Pietrasik et al. [16]. In the Polish registry, STEMI was the precipitating cause in 72.7% of cases. The annual number of cases has generally been low, and patients have had a very severe cardiogenic shock, with a left ventricular ejection fraction of 22.5% (15.0%–29.5%) and lactate levels of 7.4 mmol/l. The proportion of patients who experienced cardiac arrest was 47.3%, although it is unknown whether these patients remained unconscious. The critical condition of cardiogenic shock patients in the Polish registry likely contributes to the high 12-month mortality rate of 80%, along with high rates of renal replacement therapy (32.7%) and bleeding (34.5%).

Timely intervention is crucial; although approximately half of the patients had the microaxial flow pump device implanted before percutaneous coronary intervention, it might have been futile due to the severity of shock, as also suggested by Pietrasik et al. [16].

LONG-TERM BENEFITS OF UNLOADING LEFT VENTRICLE

As evident from the Kaplan–Meier curve (Figure 2), the separation between the two groups would not have been sufficient to reject the null hypothesis at 30 days. This is significant because both the IABP-SHOCK II and ECLS-SHOCK trials evaluated the primary outcome at 30 days, suggesting that a longer follow-up period might be necessary to detect differences in survival. Indeed, registries and unpublished data from previous trials indicate that when excluding out-of-hospital cardiac arrest patients, the mortality rate does not transition to a plateau as seen in cardiac arrest cohorts from discharge (or 30 days) up to day 180 [17–19]. Clinically, this underscores the severity of the patient's condition and the extended need for professional care. Additionally, it also suggests that early interventions to unload the left ventricle could prevent maladaptive remodeling, offering both short-term and long-term benefits [20].

HOW TO REDUCE RISK OF ADVERSE EVENTS

The incidence of adverse events was high, and significantly higher in the microaxial flow pump group compared to the standard of care group, in the DanGer Shock trial. Regardless of potential survival bias, it is imperative to reduce these complications. Some are directly related to the placement of a large bore device in the femoral artery, but much bleeding also occurred after removal of the device, indicating that the device itself may have affected coagulation. Access site bleeding is probably unavoidable, but should be reduced to a minimum. It seems likely that ultrasound-based arterial puncture, and careful evaluation of the placement sheath especially when the patient is in the intensive care unit, could reduce access site bleeding, but there is a need to better understand late bleeding [during the course of the trial access and closure techniques developed (e.g., single access, Manta closure after side-port access)]. Renal replacement therapy was significantly higher in the microaxial flow pump group and though no patients required replacement therapy at 180 days, AKI injury is associated with a worse outcome, greater expense, and longer stay in the intensive care unit [21]. Consequently, future studies should focus on understanding the mechanism for kidney injury to develop strategies to mitigate the risk of AKI associated with mechanical circulatory support devices. In the DanGer Shock trial, the micro axial flow pump device was set to run on the highest performance level possible, unless suction, for the first 48 hours. Adopting a patient-directed treatment mode could potentially reduce device flow, possibly avoiding some hemolysis and thus less AKI, as reported in

observational studies of high-risk percutaneous coronary intervention with an Impella 2.5 or Impella CP device [22].

WHICH DEVICE TO CHOOSE FOR THE PATIENTS

Having two neutral trials with an intra-aortic balloon pump and a veno-arterial extracorporeal membrane oxygenation, alongside a positive trial with a microaxial flow pump device does not establish definitive evidence of superiority of the microaxial flow pump device over other mechanical devices. Firstly, the study populations differed across the 3 studies, making direct comparison challenging. To address the question of superiority, a dedicated trial comparing microaxial flow pump to veno-arterial extracorporeal membrane oxygenation or intra-aortic balloon pump would be necessary. Currently, several international studies powered for mortality assessment are recruiting to mechanical circulatory support devices, including *ULYSS* (NCT05366452) investigating the implantation of the Impella CP device prior to emergent percutaneous coronary intervention in patients with acute myocardial infarction complicated by cardiogenic shock vs. emergent percutaneous coronary intervention plus standard medical therapy. That trial is expected to be completed by the end of 2026. The UNLOAD ECMO trial (NCT05577195) will investigate the addition of the Impella device to veno-arterial extracorporeal membrane oxygenation compared to veno-arterial extracorporeal membrane oxygenation alone in patients with cardiogenic shock. UNLOAD ECMO is expected to be completed in 2025. The results of both are highly anticipated, and will hopefully shed light on new aspects of treating cardiogenic shock.

CONCLUSION

The routine use of a microaxial flow pump, compared to standard of care, reduced the risk of mortality at 180 days in patients with STEMI complicated by cardiogenic shock. However, it is important to note that the incidence of adverse events was higher in patients treated with a microaxial flow pump, while nevertheless providing a strong mortality benefit in the interventional group. The strict eligibility criteria in the DanGer Shock trial necessitate caution when assessing potential use in other patient cohorts.

TAKE-HOME MESSAGE

Microaxial flow pump reduced the risk of 180-day mortality by 12.7% in patients with STEMI complicated by cardiogenic shock, translating to a number needed to treat of 8 patients.

The DanGer Shock trial did not include unconscious patients who had been resuscitated from out-of-hospital cardiac arrest.

The risk of adverse events is high in cardiogenic shock patients, and even higher in patients receiving a microaxial flow pump device.

The strict eligibility criteria in the DanGer Shock trial necessitate caution when assessing potential use in other patient cohorts.

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