

The ULYSS trial design - Supplementary material

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Supplementary data 1: Protocol of care for acute myocardial infarction complicated by cardiogenic shock in the ULYSS trial whatever the group of randomizations.

CS, cardiogenic shock; LVAD, left ventricular assist device; MBP, mean blood pressure; PAC, pulmonary artery catheter; SBP, systolic blood pressure; SVO₂, venous saturation in oxygen; TTE, transthoracic echocardiography; UFH, unfractionated heparin

The following protocol is adapted from available European and American guidelines and consensus recently published [1–5].

Optimal medical care of CS:

Fluid Challenge as first line therapy if no sign of overt fluid overload (1C)
Invasive blood pressure monitoring (1C)
Pulmonary artery catheter (IIb/C)
Ventilatory support/O ₂ according to blood gases (1C)
Intravenous inotropes to increase cardiac output (IIb/C)
Vasopressors (norepinephrine preferable over dopamine in presence of persistent hypotension (IIb/B)
Ultrafiltration in refractory congestion not responding to diuretics (IIb/C)

For inotropes and vasopressors management, the following protocol of care will be proposed:

- Start by dobutamine except in case of profound hypotension (MBP < 65 mmHg and/or SBP < 80 mmHg) where Norepinephrine should be preferred first.
- **Dobutamine** (IIbC ESC guidelines 2021): Start at 2.5 µg/kg/min and increase by 2.5 µg/kg/min each 5-10min to restore cardiac output (CI ≥ 2.2L/min/m²) and perfusion (ScVO₂ ≥ 60% and/or diuresis ≥ 1ml/kg/h and/or lactate clearance and/or disappearance of mottling and disorders of consciousness)
- **Norepinephrine** (IIbB ESC guidelines 2021): Start at 0.1 µg/kg/min if MAP < 55mmHg (start at 0.05 µg/kg/min if MBP between 55 and 60mmHg). Adapt norepinephrine and increase by 0.05 µg/kg/min every 3-5 minutes to restore MBP ≥ 65 mmHg in case of hypotension not responding to dobutamine and/ or fluid challenge.
- Use of epinephrine is discouraged but in the case of cardiac arrest.

In certain cases, renal replacement therapy should be used based on the medical team discussion: untreatable overload, severe metabolic acidosis ($\text{pH} < 7.2$) or refractory hyperkalemia ($\geq 6\text{mmol/L}$)

CS monitoring:

- A central venous line (preferentially on superior vena cava territory) is recommended for drugs infusion, continuous monitoring of central venous pressure and serial ScVO₂ measurement.
- Arterial line with continuous monitoring of invasive blood pressure and serial lactates measurement is mandatory.
- Consider using PAC early in the treatment course in patients not responsive to initial therapy or in cases of diagnostic or therapeutic uncertainty or in case of transplant/LVAD project. Continuous and/or intermittent monitoring of atrial, pulmonary artery and pulmonary capillary wedge pressure, and cardiac index may be useful as serial measurement of SVO₂.

Supplementary data 2: Protocol of Impella® implantation, management and weaning in the experimental group

CS, cardiogenic shock; HRT, heart replacement therapy; PAC, pulmonary artery catheter; TOE, transesophageal echocardiography; tPA, Tissue Plasminogen Activator; TTE, transthoracic echocardiography; UFH, unfractionated heparin

The following protocol is adapted from available European and American guidelines and consensus recently published [2, 5–9]

- Impella® implantation

Although the Impella® device could be implanted without fluoroscopy in rare cases, we recommend puncture of the common femoral artery under fluoroscopic and ultrasound guidance [10]. For implantation of the peel-away sheath, a stiff wire (eg, Amplatz extra stiff) should be used under fluoroscopy to avoid wire misplacement that can cause arterial perforation or severe groin or retroperitoneal bleeding. It is also recommended to leave the stiff wire in place while the introducer of the peel-away sheath is removed.

We recommend the utilization of compresses to maintain an access angle in a $\approx 30^\circ$ to $\approx 45^\circ$ configuration between the access sheath and patient's skin to avoid femoral artery lifting. Furthermore, the access channel can be "compressed" by a circular suture around the repositioning sheath to reduce access site bleeding.

- Impella® associated anticoagulation management

Anticoagulation should be started as recommended by the manufacturer by the addition of 25 000 IU of heparin (UFH) in 500 mL 5% glucose in the purge solution. Potential systemic anticoagulation may be added if necessary/indicated to obtain anticoagulation targets: aPTT 40-70s and antiXa 0.3-0.5 in absence of bleedings.

Anti-Xa and aPTT should be monitored every 3h after each change until obtention of two measurements in the anticoagulation target. After obtention of stability, aPTT and anti-Xa should be measured at least two times a day.

In case of bleedings:

- Impella® sheath disruption/displacement should be searched, and anticoagulation level controlled in an urgent fashion.

- In case of over anticoagulation, UFH infusion should be stopped and next adapted.
- In case of low antiplatelets count (<50000/mm³) or fibrinogen (< 2g/l) supplementation should be made
- In absence of modifiable bleedings' associated factor = anticoagulation target may be adapted and decrease to aPTT 40-60s and antiXa 0.2-0.4.
- The volume of purge fluid and hence the UFH dose administered can be reduced by increasing the viscosity of the solution (i.e., 10% dextrose instead of 5%), which according to Poiseuille's law, increases the resistance to purge flow and/or the concentration of UFH in the purge solution could be decreased (for example change for 12 500 IU of heparin in 500 mL 5% glucose or less if necessary).
- In some cases anticoagulation should be stopped and an alternative purge solution with bicarbonates may be used (25mEq/L prepared by adding 12.5ml of sodium bicarbonate 8.4% to a 500ml solution of glucose 5%) [11].
- In some cases, bleedings at the access site can be controlled by tranexamic acid– or adrenalin-soaked gauze (1:100 concentration, only 20 minutes to avoid skin necrosis) in conjunction with pressure.

- Impella® monitoring

- A daily TTE is recommended for systematic Impella® position monitoring and myocardial, recovery evaluation. More prompt TTE should be done in case of alarms and/or clinical-biological deterioration. TOE may be used in absence of contraindication if necessary.
- Systematic chest X-ray is not mandatory for daily monitoring but may be realized as necessary based on team in charge of the patient decision.
- Hemolysis should be monitored at least one time a day associating LDH and plasmatic free hemoglobin.
- Fibrinogen, hemoglobin and platelets should be monitored one time a day. Recommended targets are fibrinogen > 2g/l, hemoglobin > 8g/dl and platelets > 50000/mm³.

- Impella® support management

- The support with Impella® CP for more than 24 hours is encouraged. If weaning leads to hemodynamic instability, the device should be maintained, and daily weaning attempts performed.
- In case of hemolysis, Impella® positioning should immediately be checked with bedside echocardiography (TTE and if necessary, TOE), and stringent pfHb/ LDH follow-up is mandatory. In some cases, chest Xray may be helpful. Evaluation of ventricular preload is also pivotal by TTE and if available PAC evaluation. According to Impella® position and left/right ventricular preload, management consist in [7]:
 - First reducing the Impella® pump speed
 - Pump repositioning if necessary (most often pullback under echo guidance).
 - Increasing ventricular preload by fluid challenge if needed and/or inotropes implementation in case of RV failure.
 - Exchanging pump in some cases
- If pump thrombosis was suspected, Tissue Plasminogen Activator (tPA, Alteplase®) was administered via the purge system based on the discretion of the multi-disciplinary team comprised of a cardiac surgeon, a heart failure cardiologist, an intensivist and a clinical pharmacist [12].
 - Note: dosing and duration remain undefined. Be conscious of the total amount of tPA patient is receiving (purge flow rate × concentration × time infused). Refer to reference below for examples.
 - If first time patient requiring alteplase, consider 0.04 mg/ml concentration.
 - If purge flow rate < 5 ml/hr: 2 mg alteplase in 48 ml sterile water, total volume 50 ml
 - If purge flow rate ≥ 5 ml/hr: 4 mg alteplase in 96 ml sterile water, total volume 100 ml
 - If patient requires a second course of alteplase, consider 0.08 mg/ml concentration.

- Impella® weaning protocol

Inotropes should be weaned first as soon as possible after Impella® implantation and hemodynamic stabilization in most cases. We recommend do not attempt weaning before 24h of support and before inotropes removal.

Vasopressors as norepinephrine may be used to maintain MBP and peripheral organ perfusion but at low to moderate level. High vasopressors/inotropes need should indicate the need to escalate therapy.

After hemodynamic stabilization with lactate clearance and normalization, ScVO₂ correction, weaning trials may be realized each day under continuous hemodynamic (invasive arterial pressure and TTE monitoring +/- CVP and PAC monitoring if available).

According to the patient context (previous cardiomyopathy, severity of myocardial damage, isolated LV or biventricular dysfunction), age, heart replacement therapy (HRT) possibility (heart transplantation or durable VAD),...) and potential associated complications, weaning protocol may be quick or more prudent. Schematically, it could consist in step-by-step pump speed decrease from full support to lowest support at P2. P1 should only used temporarily for few minutes before weaning. In case of failure defined as SBP and/or MBP drop, electrical instability, respiratory degradation, lactate level increase and/or ScVO₂ drop), the weaning trial must be stopped, and the pump level must be raised to its initial level. Future weaning trials may be attempted the day after. For some selected patients, the failure of one or more weaning trial should lead to heart team discussion of potential HRT project.

Preclosing is suggested probably by Proglide® over Manta® systems [13], but Impella® direct removal with manual compression or specific devices such as the FemoStop™ (St. Jude Medical) may be used. In patients with a high bleeding risk (extensive vessel calcification or tortuosity), the dry closure technique with a crossover balloon may be used to achieve hemostasis [14].

We recommend leaving patient in bed for 24 hours following removal. Systematic veno-arterial doppler should be made 12 to 24h after Impella® weaning to exclude local complication.

Supplementary Table 1: Comparative description of published, ongoing and future studies about Impella CP® device in cardiogenic shock.

	IMPRESS	DangerShock	ULYSS	RECOVER-IV
Trial's identifier	NTR3450	NCT01633502	NCT05366452	NCT05506449
Country	Denmark	Germany and Denmark	France	US
Trial's type	RCT, two-arms, open-label	RCT, two-arms, open-label	RCT, two-arms, open-label	RCT, two-arms, open-label
Sponsor	Academic	Academic	Academic	Abiomed
Primary end-point	30-day mortality	6-month all cause mortality	30-day survival free from mechanical circulatory support or heart transplantation	30-day mortality
Control group	SOC + IABP	SOC	SOC	SOC
Patients planned	100	360	206	560
Patients enrolled	24 per group	–	–	Not recruiting
Medico Economic analysis	No	No	Yes	No
Impella type	Impella CP	Impella CP	Impella CP	Impella CP
Timing of implantation	At the discretion of the treating physician	Up to 12h after PCI	Pre-PCI	Pre-PCI
IABP	In the control group	Not specified	Not allowed	At the discretion of the treating physician in the control group / Not allowed in the interventional group
	Not specified	ECMO for control group vs Impella 5.0/LVAD or HTx for interventional group	ECMO	Impella 5.5 and/or Impella RP in the interventional group vs Others not specified device in the control group
Escalation				

ECMO, extracorporeal membrane oxygenation; HTx, heart transplantation; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; SOC, standard of care

References

1. Chioncel O, Parissis J, Mebazaa A, et al (2020) Epidemiology, pathophysiology and contemporary management of cardiogenic shock - a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 22:1315–1341. <https://doi.org/10.1002/ejhf.1922>
2. McDonagh TA, Metra M, Adamo M, et al (2021) 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 42:3599–3726. <https://doi.org/10.1093/eurheartj/ehab368>
3. Bernhardt AM, Copeland H, Deswal A, et al (2023) The International Society for Heart and Lung Transplantation/Heart Failure Society of America Guideline on Acute Mechanical Circulatory Support. *J Heart Lung Transplant Off Publ Int Soc Heart Transplant* S1053-2498(22)02211–2. <https://doi.org/10.1016/j.healun.2022.10.028>
4. Henry TD, Tomey MI, Tamis-Holland JE, et al (2021) Invasive Management of Acute Myocardial Infarction Complicated by Cardiogenic Shock: A Scientific Statement From the American Heart Association. *Circulation* 143:e815–e829. <https://doi.org/10.1161/CIR.0000000000000959>
5. Chieffo A, Dudek D, Hassager C, et al (2021) Joint EAPCI/ACVC expert consensus document on percutaneous ventricular assist devices. *Eur Heart J Acute Cardiovasc Care* 10:570–583. <https://doi.org/10.1093/ehjacc/zuab015>
6. Lüsebrink E, Kellnar A, Krieg K, et al (2022) Percutaneous Transvalvular Microaxial Flow Pump Support in Cardiology. *Circulation* 145:1254–1284. <https://doi.org/10.1161/CIRCULATIONAHA.121.058229>
7. Balthazar T, Vandenbrielle C, Verbrugge FH, et al (2021) Managing Patients With Short-Term Mechanical Circulatory Support: JACC Review Topic of the Week. *J Am Coll Cardiol* 77:1243–1256. <https://doi.org/10.1016/j.jacc.2020.12.054>
8. Karatolios K, Hunziker P, Schibilsky D (2021) Managing vascular access and closure for percutaneous mechanical circulatory support. *Eur Heart J Suppl J Eur Soc Cardiol* 23:A10–A14. <https://doi.org/10.1093/eurheartj/suab002>

9. Vandenbriele C, Arachchilage DJ, Frederiks P, et al (2022) Anticoagulation for Percutaneous Ventricular Assist Device-Supported Cardiogenic Shock: JACC Review Topic of the Week. *J Am Coll Cardiol* 79:1949–1962. <https://doi.org/10.1016/j.jacc.2022.02.052>
10. Seto AH, Tyler J, Suh WM, et al (2017) Defining the common femoral artery: Insights from the femoral arterial access with ultrasound trial. *Catheter Cardiovasc Interv Off J Soc Card Angiogr Interv* 89:1185–1192. <https://doi.org/10.1002/ccd.26727>
11. Van Edom C, Van Puyvelde T, Jacobs S, Vandenbriele C (2023) Switch to a bicarbonate-based Impella® CP™ purge solution in a patient with haemothorax: a case report. *Eur Heart J Case Rep* 7:ytad022. <https://doi.org/10.1093/ehjcr/ytad022>
12. Bashline M, DiBridge J, Klass WJ, et al (2023) Outcomes of systemic bivalirudin and sodium bicarbonate purge solution for Impella® 5.5. *Artif Organs* 47:361–369. <https://doi.org/10.1111/aor.14428>
13. Dumpies O, Jobs A, Obradovic D, et al (2023) Comparison of plug-based versus suture-based vascular closure for large-bore arterial access: a collaborative meta-analysis of observational and randomized studies. *Clin Res Cardiol Off J Ger Card Soc*. <https://doi.org/10.1007/s00392-022-02145-5>
14. Genereux P, Kodali S, Leon MB, et al (2011) Clinical outcomes using a new crossover balloon occlusion technique for percutaneous closure after transfemoral aortic valve implantation. *JACC Cardiovasc Interv* 4:861–867. <https://doi.org/10.1016/j.jcin.2011.05.019>