Use of mechaNical left ventricuLar unlOADing in Complex Higher-risk Indicated Procedures

UNLOAD-CHIP trial

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LIST OF ABBREVIATIONS

ACS Acute Coronary Syndrome

CHIP Complex high-risk and indicated percutaneous coronary interventions

ADHF Acute decompensated heart-failure

SCAI Society of cardiovascular angiography and interventions

LV Left ventricle

PCWP Pulmonary capillary wedge pressure

LVEDP Left ventricular end diastolic pressure

CO Cardiac output

CI Cardiac index

CPO Cardiac power output

SvO2 Mixed venous oxygen saturation

pVAD Percutaneous ventricular assist devices

IABP Intra-aortic balloon pump

MACCE Major adverse cardiovascular cerebral events

LVEF Left ventricular ejection fraction

IRB Institutional review board

MCS Mechanical circulatory support

IHCA: In-hospital cardiac arrest

OHCA: Out-hospital cardiac arrest

PCI: Percutaneous coronary intervention

RRT: Renal replacement therapy

ACT Activated clotting time

CPR Cardiopulmonary resuscitation

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1. PROTOCOL SUMMARY

Title:	Use of mechanical left ventricular unloading in complex higher-risk and indicated procedures (UNLOAD-CHIP)
Design:	A prospective, randomized, controlled, open-label, multicentre trial with an adaptive design
Hypothesis:	Mechanical left ventricular unloading through the PulseCath iVAC2L® during complex coronary stenting in patients with reduced LV function (<30%) is superior to a mechanical unassisted procedure (IABP class III, pVAD IIb)
Inclusion criteria:	Stabilized after admission for ACS/NSTEMI *OR* ADHF (SCAI A-B) **AND** EF <30% **AND** Complex left main disease (2-stent, calcium modifying techniques) *OR* equivalent (ostial LAD and RCX) *OR* last remaining vessel (native) with likely prolonged procedural ischemia.
Objective:	To assess the efficacy of mechanical left ventricular unloading in CHIP PCI.
Randomization:	PulseCath iVAC2L versus standard-of-care (no MCS)
Analysis:	Intention-to-treat
Primary endpoint:	***Combined (in-hospital) clinical endpoint*** All-cause death SCAI CSWG stage C-E Renal replacement therapy Mechanical ventilation Ventricular arrhythmias necessitating CPR
Secondary endpoints:	***Efficacy endpoints*** PCWP (Δ max) [Time Frame: peri-procedural] LVEDP (Δ max) [Time Frame: peri-procedural] CO / CI / CPO (Δ max) [Time Frame: peri-procedural] SvO2 [Time Frame: peri-procedural] Drop in MAP <60 for >10 minutes [Time Frame: peri-procedural] Clinical success of IVAC2L implantation [Time Frame: peri-procedural] Highest Vasoactive Inotropic Score [Time Frame: hospitalisation] Rescue pVAD implantation [Time Frame: hospitalisation] Length of hospital stay [Time Frame: hospitalisation]

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Major adverse cardiovascular cerebral events (MACCE) [Time Frame: hospitalisation]
Hospitalization for cardiovascular causes [Time Frame: 30-day]
SCAI CSWG stage C-E [Time Frame: 30-day]
Renal replacement therapy [Time Frame: 30-day]
Mechanical ventilation [Time Frame: 30-day]
Ventricular arrhythmias necessitating CPR [Time Frame: 30-day]

Safety endpoints

Major vascular events (Time Frame: 30-day)
Limb ischemia (Time Frame: 30-day)
Bleeding events (Time Frame: 30-day)
Aortic valve injury (Time Frame: 30-day)

Sub-analysis

A pre-specified sub analysis will be performed comparing patients with left sided congestion (PCWP > 18mmHg OR LVEDP > 15mmHg) versus those who do not.

Patients: Complex higher risk indicated patients (CHIP) with severely depressed LV (<30%) scheduled for anticipated prolonged procedural PCI of a large territory (distal LM or equivalent) during their admission for ADHF / ACS.

Number of patients: A total of 98 randomized patients. The cohort size may change based on the implementation of the adaptive rules.

Study flow: The Heart Team, including at least one interventional cardiologist and one cardiothoracic surgeon, reached consensus for PCI and identified all patients at risk for procedural haemodynamic compromise. If inclusion criteria were present and exclusion criteria were absent informed consent was obtained. Patients will be randomized and stratified based on severe mitral regurgitation. At baseline, all patients underwent standard clinical work-up with a coronary angiography, transthoracic echocardiography (TTE) and pre-procedural CT angiography or Doppler of the femoral arteries to determine the quality of the access vessel. A common femoral artery minimum diameter of 6 mm is required to accommodate the iVAC2L. In subjects randomized to

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the treatment arm, ultrasound-guided access to the common femoral artery is obtained. The PulseCath iVAC 2L catheter is introduced into the LV. PCI was routinely performed by radial artery access. All patients are simultaneously monitored by a pulmonary artery catheter, and blood pressure, heart rate, filling pressures, SvO2 and cardiac output (and derived parameters) are acquired at baseline, after pump insertion and activation and subsequently every 15 minutes during support, and after device removal. Postoperatively, patients will undergo echocardiography to investigate damage to the aortic valve or increase in aortic regurgitation. After 30 days follow-up by telephone is done.

Statistical Analysis:

Sample Size

Enrolment of 2 x 49 patients provides the trial with 80% power to show superiority of the iVAC2L regimen over standard-of-care under an assumed reduction of the combined clinical endpoint, that comprises in-hospital SCAI stage C-E cardiogenic shock, in-hospital all-cause death, mechanical ventilation, renal replacement therapy and CPR from an estimated 25% % to 5%.

Primary Endpoint

The study was designed to test the following hypothesis: The PulseCath iVAC2L is superior to the standard of care (No MCS) in terms of the incidence of the combined primary endpoint.

Main analysis of the primary endpoint is performed in the full analysis set population under application of the Intention-to-treat principle that is, events are counted irrespective of their occurrence relative to early or unanticipated termination of randomized regimen.

Superiority of the PulseCath iVAC2L regimen in terms of the primary endpoint is declared if the 95% confidence interval (CI) of the Rate Difference lies below 0%. The method of Farrington and Manning will be used to calculate the 95% confidence interval for the between-group Rate Difference of the primary end point. Use of the 95% CI is equivalent to superiority testing with the Farrington & Manning test for the Rate Difference (H0: RD = 0) with a two-sided type I error (α) of 0.05.

Clinical follow-up: Follow-up will take place at 30 days (by telephone) after randomization.

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2. INTRODUTION

2.1 Background

During the last three to four decades percutaneous coronary intervention (PCI) tools and techniques have improved immensely (1). Currently, PCI is the most widely used approach for myocardial revascularization. In general, elective PCI is considered a safe and relatively low-risk procedure(2). However, patients with left main or complex coronary lesions or impaired left ventricular function remain at high risk for peri-procedural and post-procedural hemodynamic instability and death (3, 4). Mechanical circulatory support (MCS) devices, such as intra-aortic balloon pump (IABP) and Impella (Impella 2.5 and CP), have emerged as potential tools to avoid hemodynamic instability during these CHIP coronary interventions. These devices have shown to improve hemodynamics / cardiac output during complex PCI procedures, although the benefit of mechanical circulatory support in CHIP PCI remains debated and no clear benefit on patient outcomes has been shown (5-7). A recent large scale analysis favoured Impella as opposed to IABP (8). The use of these devices, especially Impella, is associated with increased risk for complications such as bleeding (6, 9). The use of MCS for optimizing peri-procedural hemodynamic support needs to be balanced out against the potential risk for MCS related complications.

Recently the PulseCath iVAC 2L was introduced. This is a pulsatile pump, placed in the left ventricle, that ejects blood into the ascending aorta at a flow up to 2L/min (10). Theoretically, pulsatility maintains the physiological vascular responses and endothelial function at the level of the -systemic and –micro circulation and might offer benefit when compared to continues flow devices such as Impella (11). In contrast, IABP (which also offers pulsatile support), lacks the possibility of active unloading. Therefore, the combination of those features in the PulseCath iVAC2L is unique.

Recent studies performed with the PulseCath iVAC2L in the setting of CHIP PCI demonstrated hemodynamic advantages with afterload reduction, increased stroke volume and higher cardiac output. Also, the device was deemed safe in terms of complications (11, 12). Samol et al. showed in a prospective cohort study that the use of IVAC2L was non-inferior to Impella in terms of feasibility and safety, even if complications occur. (13) Other advantages of the IVAC2L are its relatively simple use and lower costs when compared to other mechanical circulatory support devices such as the Impella family. Considering that the IVAC2L is powered by an IABP console, the possibility of widespread use adds an even greater advantage.

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So far, MCS facilitated CHIP has not been proven beneficial compared to a conservative (non-supported) high-risk procedure. Although high-risk criteria parameters such as coronary anatomy (location and complexity), co-morbid conditions, and concomitant cardiac disease (structural or valvular disease, left ventricular dysfunction) are well known, no intrinsic value of each of these components is determined. The recent PULSE trial shed some light on this gap of knowledge by showing possible additional hemodynamic benefit for patients with mitral regurgitation, who presented with an acute coronary syndrome (ACS) and who had higher cardiac filling pressures at baseline (11). Therefore, MCS-facilitated high-risk PCI might be beneficial if used in ACS patients or patients with (left-sided) congestion (stabilized acutely decompensated heart failure) with low hemodynamic tolerance. However, due to the low number of patients enrolled and non-randomized nature of this study, conclusions should be drawn with caution. To this day, no randomized controlled trials have been executed with the PulseCath iVAC2L in this subset of CHIP patients who are thought to benefit from an MCS-facilitated PCI. Its place in the setting of CHIP PCI remains to be elucidated.

2.2 Research hypothesis

Prophylactic percutaneous mechanical left ventricular unloading by insertion of the PulseCath iVAC2L® during complex coronary stenting (complex left main disease or equivalent or last remaining vessel) at risk for prolonged procedural ischemia in patients with reduced LV function (<30%) is superior to a mechanical unassisted PCI procedure.

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3. OBJECTIVES

The primary objective of the UNLOAD-CHIP is to investigate the combined clinical endpoint (all-cause mortality, SCAI C-E cardiogenic shock, need for mechanical ventilation, need for renal replacement therapy, -peri or –post procedural ventricular arrhythmias leading to loss of cardiac output requiring CPR) for patients undergoing CHIP PCI. We will assess the efficacy of the PulseCath iVAC2L versus standard-of-care (no-MCS) in those patients.

Secondary (peri-procedural) objectives that we are investigating are: PCWP, LVEDP, CO/CI/CPO, SvO2, prolonged drop in MAP.
Secondary objectives during hospitalisation are: highest vasoactive inotropic score, rescue pVAD implantation, length of hospital stay, cardiovascular death, clinical success of PulseCath iVAC2L implantation.
Objectives at 30 days are: MACCE, hospitalization for cardiovascular causes and durable LVAD/heart transplant.

A pre-specified subanalysis will be performed comparing patients with left sided congestion congestion (PCWP>18mmHg OR LVEDP >15mmHg) versus those who do not.

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4. STUDY DESIGN

The current study is an investigator initiated, randomized, open label, multi-center clinical trial.

All patients assigned to have a complex higher-risk indicated procedure (CHIP) based on a formal local heart team decision will be screened for potential inclusion in the study.

Patients will be eligible for after consideration of in- and exclusion criteria. Subsequently patients will be approached for study participation by their cardiologist. The patient information folder (PIF) and consent form will be provided to the patient by a study team member. Patients will have at least 24 hours to consider participation. An independent physician will be available for extra information, if desired. After this period of consideration, written informed consent is obtained and patients will be planned for CHIP PCI according to standard practice in adherence to international guidelines. Patients will also be randomized and stratified based on severe mitral regurgitation.

At baseline, all patients have undergone a clinical work-up consisting of a coronary angiogram, a transthoracic echocardiography (TTE) and/or pre-procedural CT angiography or Doppler of the femoral arteries to determine the quality of the access vessel. A common femoral artery minimum diameter of 6 mm is required to accommodate the iVAC2L. In the cathlab the pulmonary artery catheter (PAC) is placed and cardiac output and its derived parameters will be obtained before the procedure without an active PulseCath and after the procedure with an active PulseCath. Pulmonary capillary wedge pressure (PCWP), right arterial pressure (RAP), pulmonal artery pressure (PAP) and left ventricular end diastolic pressure (LVEDP) will be determined –pre –peri (every 15 minutes, with its first measurement 15 minutes after PulseCath activation) and -post procedural together with blood pressure and heart rate.

In subjects randomized to the treatment arm, ultrasound-guided access to the common femoral artery will be obtained. The 17 Fr PulseCath iVAC 2L catheter will be introduced into the left venticle. After this PCI will be routinely performed by radial artery access. After the procedure a vascular preclosure technique is used (two Perclose ProGlide®). Post-PCI, patients will undergo echocardiography to investigate aortic valve injury or increase in aortic regurgitation. Patients were followed up by phone after 30 days to assess outcomes. After this visit the study ends for the participant.

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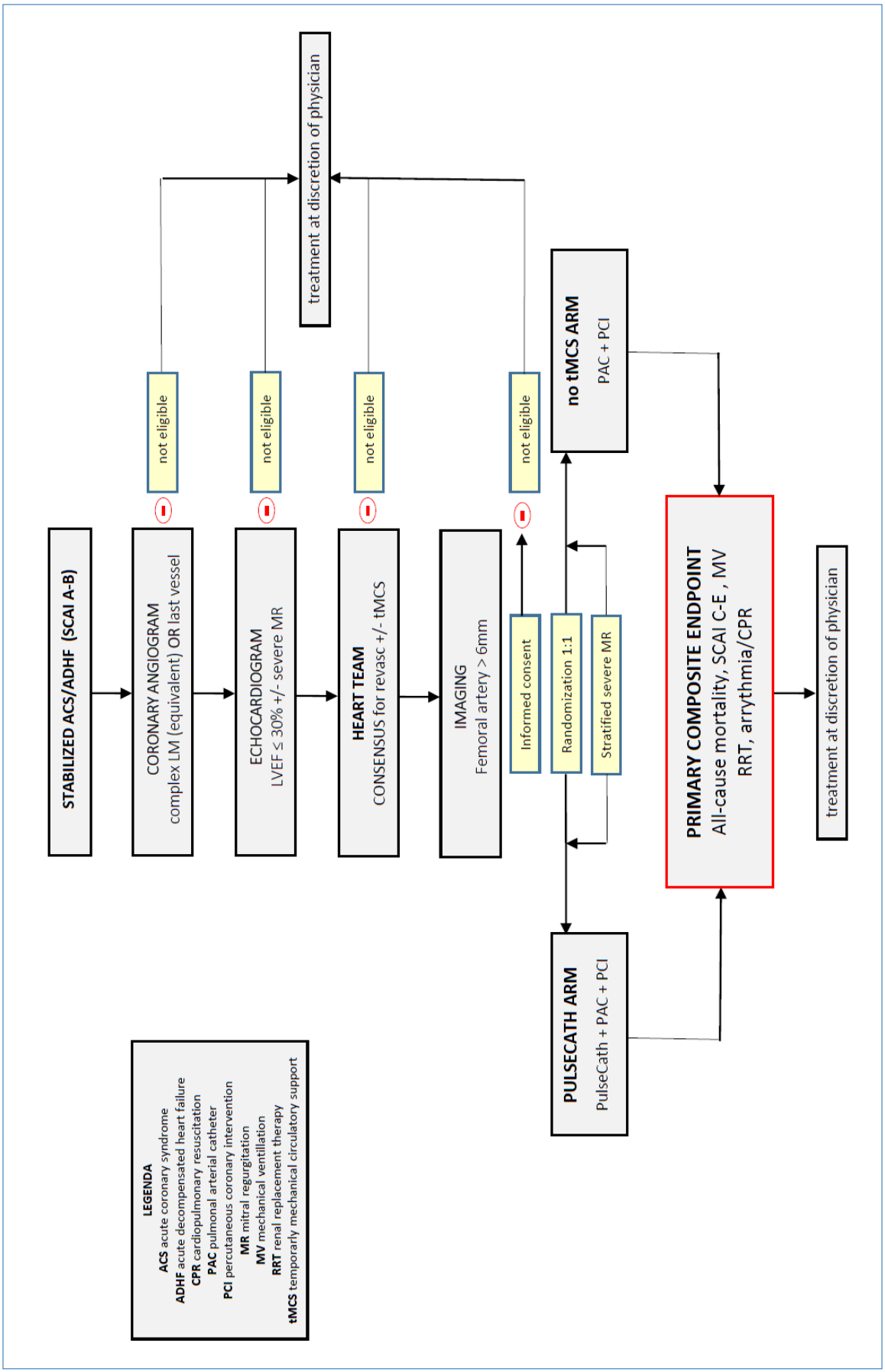
Figure 1. Flowchart UNLOAD CHIP trial



5. STUDY POPULATION

5.1 Population

Consecutive patients, aged ≥18 years who are stabilized after admission for ACS or ADHF (SCAI A-B) with a severely impaired LVEF (<30%) in whom a clinical coronary angiogram shows extensive anatomical coronary artery disease (CAD), as described below, and in whom coronary revascularization with mechanical support by heart team consensus is considered, will be screened for eligibility by the site Principal or Sub-Principal Investigator (an interventional cardiologist or its designee).

5.2 Inclusion criteria

- Age ≥18 years
- Multidisciplinary heart team consensus for MCS facilitated PCI **AND**
- Stabilized after admission for ACS/NSTEMI **OR** ADHF (SCAI A-B) **AND**
- LVEF <30% **AND**
- Complex left main disease (calcium modifying techniques deemed necessary OR 2-stent techniques) **OR** equivalent (ostial LAD and RCX) **OR** last remaining vessel (native) with likely prolonged procedural ischemia.

  Angiographic significant distal CAD within the index arterie(s) (with an anticipated normal coronary artery lumen of 3.0mm) may be revascularized during the index procedure.

5.3 Exclusion criteria

- Contraindications for Pulsecath IVAC2L:
  a. moderate-severe aortic regurgitation
  b. known presence of an LV thrombus (contrast echo/MRI)
  c. aortic valve prosthesis
  d. severe aortic valve stenosis
  e. peripheral arterial disease that would preclude placement of the PulseCath iVAC2L device
- Cardiogenic shock defined as either SCAI CSWG stage C-E
- Patient is intubated and mechanically ventilated
- Stroke <3 months
- Major bleeding event <3 months
- History of bleeding diathesis or known coagulopathy (including heparin-induced thrombo-cytopenia), any recent GU or GI bleed, or will refuse blood transfusions.

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- Chronic kidney disease with eGFR <25.
- Pregnancy, or suspected thereof.
- BMI > 35
- Other medical, social, or psychological problems that, in the opinion of the Investigator, compromises the subject's ability to give written informed consent and/or to comply with study procedures.
- Subject belongs to a vulnerable population (defined as individuals with mental disability, persons in nursing homes, impoverished persons, homeless persons, nomads, refugees and those permanently incapable of giving informed consent; vulnerable populations also may include members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the Sponsor, members of the armed forces and persons kept in detention)

5.4 Sample size calculation

Since the magnitude of the effect, derived from limited observational studies and 2 RCT's (of which one was prematurely terminated) in the targeted population, can be misleading and the intervention is highly invasive with high ethical relevance, we opted for a trial design with 2-sided alternatives. The most relevant in-hospital clinical events as a result of coronary obstruction during HR-PCI in patients with low cardiac ejection fraction are hemodynamic compromise resulting in cardiogenic shock, death, need for renal replacement therapy / mechanical ventilation and peri-procedural arrhythmia.
The addressed clinical events reported in the present population vary according to differences in study design and definitions. Most data is retrospective.
Cardiogenic shock was reported to occur in 25% in a registry investigating the targeted population in patients revascularized without hemodynamic support versus 5% occurrence with MCS (14). Due to the low number of patients, 20, this must be interpreted with caution. In the PROTECT II, a prematurely terminated RCT, cardiogenic shock was observed in 4% and 5% of the IABP- and Impella 2.5 arm, respectively (5). No control arm (without MCS) was tested. In the only other RCT conducted, the BCIS I trial cardiogenic shock was not addressed (15).
Cardiac death at 30 days is reported to be in the order of 9-12% in the PROTECT II, whereas in-hospital death, being part of the current primary endpoint, is reported to occur in 1-2% in the BCIS I trial.
Renal replacement therapy, a surrogate marker for CS-severity and multi-organ failure, is a relevant endpoint for the current trial population / design. Only limited data on the need for dialysis is available. Sukul et al. reported an occurrence of 10% in an unsupported group vs 1% in the MCS-group (14). We could not trace data on the need for mechanical ventilation. Cardiac arrhythmia/CPR is

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reported to be in the order of 4% at 30-day in the PROTECT II study in the MCS arms. In-hospital or peri-procedural arrhythmia/CPR is not specified.
Contrary, the risks associated with the introduction and use of large bore assist devices are substantial. A large US registry analysing complications between 2009 and 2018 of tMCS in HR-PCI reports a combined complication rate (stroke, tamponade, major bleeding, or vascular complication requiring treatment) of 19% of which major bleeds and vascular complications are the main drivers (16). An European registry reported an 11% incidence of device related complications mainly consisting of major bleeds and vascular complications requiring treatment in a cohort from 2004-2018 (9).

The primary endpoint will be the composite of all-cause mortality, cardiogenic shock, (need for) renal replacement therapy / mechanical ventilation and arrhythmia requiring CPR. On review and extrapolation of available data together with advances in PCI tools and techniques used in HR-PCI during the last decade (the RCT's were performed > 10 years ago) we assume the primary combined clinical (in-hospital) event rate to be 25% in the unsupported arm and 5% in the MCS facilitated arm.

The study is designed as an adaptive two-stage randomized trial with a definitive determination of the sample size at the transition from stage 1 to stage 2. The funding of the trial at it first submission (per November 2022) permits a total inclusion of 98 (= 2 x 49) patients into the trial. We estimated that the standard-of-care regimen would be associated with an in-hospital event rate for the primary endpoint of 25%. Enrolment of 2 x 49 patients in stage 1 provides the trial with 80% power to show superiority of the PulseCath iVAC2L based regimen over the standard-of-care based regimen under an assumed reduction of the in-hospital combined clinical event rate from 25% to 5%, corresponding with relative risk reduction of 80%.
The adaptive design includes a definitive determination of the sample size when the in-hospital outcomes of the first 90 patients have been adjudicated by the Clinical Event Committee. We calculated that inclusion of 2 x 167 patients provides the trial with 80% power under an assumed reduction of the in-hospital event rate from 25% to 13%, being an absolute risk and a reduction (Relative Risk 0,5) that is still considered clinically relevant balancing the net clinical positive effect and the vascular/bleeding risks associated with the introduction and usage of the device.
The sample-size re-estimation will be carried out according to the following 3 steps by an independent statistician.

1. the sample size will not be increased if the interim data show a benefit for the PulseCath iVAC2L-based regimen with a conditional power of at least 90% for a sample size of 2 x 49 under the assumption of a relative risk reduction of 80%.

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2. the planned sample size will be increased to 2 x 167 in the presence of a positive signal in the observed event rates for primary endpoint (Relative Risk < 0.70) and a conditional power between 30% and 80%.
3. The definitive sample size will not be increased in the absence of sufficiently positive signals in the observed events for the primary endpoint and a conditional power < 30% (futility).

The Steering Committee will share the observed in-hospital event rates in the first 90 patients with potential grant givers. The determination of the sample size at 2 x 167 patients will only be effectuated if adequate funding is obtained.

No formal statistical testing is foreseen in the review of the in-hospital outcomes of the first 90 patients. Therefore, final testing of the superiority hypothesis for the primary endpoint is performed at an alpha level of 5%.

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6. TREATMENT OF SUBJECTS

The study will be performed according to the guidelines of the latest version of the Helsinki Declaration. The present study will follow the most recent International Good Clinical Practice guidelines. The primary procedure is considered standard clinical practice. All patients will undergo a standard clinical work-up including ecg, laboratory, echocardiogram, coronary angiogram and imaging of the femoral artery (echo or CT). The CHIP PCI is performed by either the radial or femoral approach with standard coronary catheterization techniques. The PulseCath iVAC2L is positioned via the femoral artery.

As for both groups additional assessments include:

- Pulmonary artery catheterization (PAC) and derived measurements: -pre and during (every 15 minutes, with the first measurement 15 minutes after PulseCath activation) and after the procedure and removal of the device.
- LVEDP measurements.
- 30 day follow-up by phone.

6.1 PulseCath iVAC2L group

The PAC will be placed under echographic guidance in the femoral vein. After PAC derived measurements including CO/CI/CPO and LVEDP, an interventional cardiologist will implant the Pulsecath iVAC2L by an echographic guided (femoral arterial) puncture. Unfractionated heparin in a therapeutic dose, with activated clotting time of >300s with check of the activated clotting time every 30 min, will be given, unless the patient had an indication for therapeutic anticoagulation.

After this the PulseCath iVAC2L will be placed. A vascular preclosure technique was used (two Perclose ProGlide® Suture-Mediated Closure systems; Abbott Vascular, Santa Clara, CA, USA). A 18 Fr SoloPath sheath was inserted. The aortic valve was crossed with a pigtail catheter; an Amplatz Super-Stiff™ guidewire (Boston Scientific, Marlborough, MA, USA) was shaped and inserted through the pigtail into the left ventricular apex. The pigtail was then exchanged for the 17 Fr PulseCath iVAC 2L catheter. Its distal tip should be seated halfway into the left ventricular cavity and the valve housing with its side opening in the ascending aorta. After introduction, the membrane pump was filled with heparinized saline and air-free connected to the catheter and the IABP console. In this study, we used the Datescope CS300® IABP console. In participating centers other devices may be used. The two-way valve would guide the blood during pump aspiration from the tip of the catheter to the membrane

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pump, and during pump ejection from the membrane pump to the side opening in the valve housing, thus generating pulsatile flow.

The PulseCath iVAC2L device will be activated. After the device is turned on, additional PAC measurements are obtained 15 minutes after pump activation and consecutive measurements every 15 minutes during the CHIP PCI. The CHIP PCI is thereafter executed according to standard clinical practice. After the procedure, the patient will be weaned from the device. The level of support is subsequently lowered to 1:2 or 1:3 for 15 minutes, and after this, additional PAC measurements are obtained. If deemed hemodynamically stable (systolic BP > 90 mmHg and MAP > 60mmHg and HR <100 and SvO2 >65%) the device could be safely removed together with the PAC after last PAC measurements are obtained. The femoral sheath was removed and the artery was closed using the closure technique mentioned above.
In case of inability to wean the patient from the device, the device is allowed to remain in situ for a maximum time frame of 24 hours. After the 24 hour time period the device has to be removed. Postoperatively, patients will undergo echocardiography to investigate aortic valve injury or increase in aortic regurgitation.
Further treatment is at the discretion of the treating physician.

6.2 Control group

The PAC will be placed according to local practice. After PAC derived measurements are obtained the CHIP is executed according to standard clinical practice. During the procedure PAC measurements are obtained every 15 minutes. Fifteen minutes after the procedure is finished, additional PAC measurements will be obtained. Hereafter, the PAC will be removed.

6.3 Clinical deterioration

If study patients deteriorate (progression of HD parameters and biochemistry alterations as specifically defined for SCAI CSWG stage C, D or E) the primary endpoint is reached. Further treatment will be provided as deemed appropriate by the treating physician.

PulseCath iVAC2L arm:

If patients remain unable to wean from the device (<1h post-procedural) this is seen as clinical deterioration (SCAI C-E), and accordingly the primary endpoint is reached.

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If patient deteriorates during PulseCath iVAC2L, and escalation is required in the form of additional inotropes or another form of MCS, this is also seen as clinical deterioration and the primary endpoint is reached.

Control arm:

Either inotropic treatment or rescue MCS is not withhold if deemed necessary by the treating physician. If patients receive inotropes/rescue MCS during PCI this is considered clinical deterioration to SCAI C-E (depending on biochemical and hemodynamic parameters) and the primary endpoint is reached.

6.4 Long-term treatment

Subjects randomized to both the PulseCath iVAC2L and control arm will be treated based on the contemporary AHA/ACC/SCAI and ESC practice guidelines for Acute Coronary Syndromes (ACS) in Patients Presenting with (or without) Persistent ST-Segment Elevation AND/OR The diagnosis and Treatment of Acute and Chronic Heart Failure. Both during their index admission and over the duration of the follow-up period

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7. METHODS

7.1 Study parameters / endpoints

7.1.1 Primary endpoint

Combined Clinical endpoint:

- All-cause death (Time Frame: hospitalisation)
- SCAI stage C-E (Time Frame: hospitalisation)
- (Need for) renal replacement therapy (Time Frame: hospitalisation)
- (Need for) mechanical ventilation (Time Frame: hospitalisation)
- -Peri or –post procedural ventricular arrhythmias leading to loss of cardiac output requiring CPR (Time Frame: hospitalisation)

7.1.2 Secondary endpoints

Efficacy endpoints:

- PCWP (Δ max) (Time Frame: periprocedural)
- LVEDP (Δ max) (Time Frame: periprocedural)
- CO / CI / CPO (Δ max) (Time Frame: periprocedural)
- SvO2 (Time Frame: periprocedural)
- Drop in mean arterial pressure (MAP <60) for >10 minutes (Time Frame: periprocedural)
- Highest Vasoactive Inotropic Score (Time Frame: hospitalisation)
- Clinical success of IVAC2L implantation
- Rescue pVAD implantation (Time Frame: hospitalisation)
- Length of hospital stay (Time frame: hospitalisation)
- Cardiovascular death (Time frame: 30-day)
- Major adverse cardiovascular cerebral events (MACCE) (Time frame:30-day)
- Stroke (Time frame: 30-day)
- Myocardial infarction (Time frame: 30-day)
- Hospitalization for cardiovascular causes (time frame 30-day)

Safety endpoints:

- Major vascular events (Time Frame: 30-day)
- Limb ischemia (Time Frame: 30-day)
- Bleeding events (BARC 3 and 5) (Time Frame: 30-day)
- Aortic valve injury (Time Frame: 30-day)

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7.2 Randomization, blinding and treatment allocation

Prior to randomization, the site Principal or Sub-Principal Investigator will review the patient data and the Inclusion and Exclusion criteria to ensure that the patient is eligible for the study. Patients that meet the in- and exclusion criteria will be asked for informed consent (Time Frame: 24 hours). If informed consent is obtained. The patient will be randomised to the PulseCath iVAC2L arm or the standard of care (no-MCS) arm and are stratified based on the presence of severe mitral regurgitation. We will be using an interactive Web-based randomization system, Castor EDC. The trial design and intervention does not allow blinding. Hereafter the study continues as described in chapter 6.

7.3 Study procedures and observations

7.3.1 Baseline information

The data from the following assessments will be collected:

1. History and physical examination. This assessment at baseline is targeted to assess subject eligibility for study participation.
2. Echocardiogram (if not already present during admission)
3. 12-lead electrocardiogram.
4. Blood count and kidney function.
5. Cardiovascular medication.
6. CT-angiography or Doppler femoral arteries

7.3.2 Laboratory

- Baseline (before procedure), 2 hours after procedure and 24 hours after procedure: Hb, kreatinine (eGFR), ureum, ALT, BNP, lactate
- Cardiac enzymes (hs-troponin T and CK-MB) are measured at baseline (as described above) and every six hours until the highest levels were reached
- During admission laboratory parameters are collected to define SCAI CS stage only if deemed necessary by the treating physician. This consists of the following: creatinine, eGFR, arterial/venous blood gas (pH, lactate) and amino L-transferase.

7.3.3 Hemodynamic indices

Hemodynamics, i.e. vital parameters (mean arterial pressure (MAP, mmHg, heart rate), left ventricular end-diastolic pressure(LVEDP) pulmonary capillary wedge pressure (PCWP, mmHg) and pulmonary artery pressure (PAP, mmHg), pulmonary pulsatility index (PAPI), right atrial pressure (RAP, mmHg) and cardiac output / index (CO / CI / CPO) will be determined once the PAC is in situ.

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The PulseCath iVAC2L arm:

After insertion and activation of the device, additional PAC derived measurements will be obtained after 15 minutes. Hereafter, every 15 minutes PAC derived measurements and vital parameters will be obtained during the procedure. After the CHIP PCI, additional PAC derived measurements including CO/CI/CPO and vital parameters will be obtained, and the PulseCath iVAC2L will be weaned and another round of measurements is done after 15 minutes. If hemodynamically stable the device is turned off, and removed. It is not required to assess ACT before removal. Fifteen minutes after cessation of support the final PAC derived measurements will be obtained.

NOTE; If patient is unable to wean from the PulseCath iVAC2L additional PAC derived measurements and vital parameters will be retrieved each two hours until the PulseCath iVAC2L is removed.

Control arm:

During the procedure every 15 minutes PAC derived measurements and vitals will be obtained. Fifteen minutes after the CHIP PCI additional PAC derived measurements and vitals are obtained.

Inotropes & mechanical circulatory support(MCS)

Cumulative dose of inotropes, and MCS deployment will be monitored.

7.3.4 Index admission

Clinical stability will be evaluated for at least 1 day after the procedure before patient is discharged from the hospital.

7.3.5. Follow-up

After 30 (±5) days a follow-up by phone will be made to assess outcomes and SAE's.

7.3.6 Study completion

Study completion occurs when the subject has completed the final scheduled follow-up. At a minimum, every effort should be made to document subject vital status for every visit.

Subject participation in the trial will conclude upon completion of the 30-days follow-up, death or a withdraw of consent by the subject.

All reasonable efforts will be made to obtain complete data for all subjects; however, missing observations will occur due to loss to follow-up, withdrawal, or non-adherence with required assessments.

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Three attempts will be made to contact subjects who do not return for study follow-up visits. The final attempt shall include a certified letter to the subject regarding study participation. If these subjects cannot be located, they will be considered lost to follow-up. If they are contacted but refuse to return for visits, they will be considered withdrawals. If possible subjects who withdraw from the study should have a final study visit with physical examination and evaluation of concomitant medications and adverse events. This visit information will be maintained in the study database and used for analysis purposes, as appropriate. No additional subjects will be recruited to replace any subjects lost to follow-up.

7.4 Withdrawal of individual subjects

Subjects may withdraw from the clinical trial at any time without jeopardy or prejudice. If a subject prematurely terminates from the study, the reason for study termination will be recorded and the results will be tabulated by number and percent for each arm of the study. If termination is a result of an serious adverse event (not being a clinical endpoint), an serious adverse Event eCRF will also be completed. Subjects who withdraw consent after treatment will have their data evaluated until the time of their withdrawal.

7.5 Replacement of individual after withdrawal

Subjects will not be replaced after withdrawal from the trial unless a subject withdraw his or her consent before the randomization process.

7.6 Follow-up of subjects withdrawn from treatment

Subjects that withdraw from the trial will be offered guideline directed care and will be followed up by their treating physician according to local protocol/policy as deemed necessary.

7.7 Premature termination of the study

The Sponsor reserves the right to temporarily suspend or prematurely discontinue the study either at a single site, multiple sites, or at all sites at any time for reasons including, but are not limited to, safety or ethical issues, inaccurate or incomplete data recording, non-compliance, or unsatisfactory enrolment with respect to quality or quantity. The follow-up visits will continue for all randomized subjects. The DSMB can advise the principal investigator on safety issues. If the study is prematurely terminated or suspended, the sponsor will, as soon as possible but within 15 days, provide a written statement to the METC and the Investigators of the participating centers to enable prompt notification of their METC.

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Table 1. Schedule of measurements and observations

	Baseline	Procedure	Day procedure	Day after procedure	Other days randomization	Discharge	30 day follow-up
Informed Consent	x						
Clinical In-/exclusion criteria	x						
Demographics	x						
Medical History	x						x
Physical Examination	x		x	x	x		
Concomitant Medication	x						
12-lead ECG	x						
Hematology panel	x	x	x	x			
Echocardiogram	x						
Imaging for assessing femoral access	x						
Hemodynamic assessment	x	x	x	X	X		
PAC measurements		x	x	X	X		
Randomization	x						
Bleeding, site assessment	x	x	x	X			
Diuresis assessment	x		x	X	X		
Inotrope assessment		x	x	X	X		
Adverse Events	x	x	x	x	X	x	x

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8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs, UADEs and DFs

8.2.1 Adverse Event (AE)

An adverse event (AE) is any undesirable clinical occurrence (any sign, symptom, illness, abnormal laboratory value or other medical event) that occurs in a subject (or an event that worsens) during the study, whether or not considered related to intervention. During admission all procedural related or (coronary) adverse event will be reported to the principal investigator within 24 hours after knowledge of the event.

8.2.2 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

The investigator shall report serious adverse events to the sponsor without undue delay after obtaining knowledge of the events, unless, for certain serious adverse events, the protocol provides that no immediate reporting is required. The sponsor will report the SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

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8.2.3 Unanticipated Adverse Device Effect

An Unanticipated Adverse Device Effect (UADE) is defined as any adverse effect on the study subject's health or safety, or any life-threatening problem or death caused by or associated with the device. Also, the effect must not have been previously identified in the Investigational Plan or Instructions for Use (IFU) in its nature, frequency or severity. UADEs may also include other serious problems associated with the device that affect the rights or welfare of study subjects.

Any Unanticipated Adverse Device Effect occurring during the study must be reported to the study Sponsor or its agent, within 7 days after the investigator learns of the event.

8.2.4 Device Failures and Malfunctions

Investigators are instructed to report all possible device failures or malfunctions observed during the trial. A device malfunction is an unexpected change in study device performance that is contradictory to the IFU and IDE and/or negatively impacts the treatment when used according to the IFU and IDE. All device failures and malfunctions will be documented on the appropriate CRF.

In case of a malfunction the device must be sent back to the manufacturer for investigation. This process is independent of the clinical trial and must be done every time a malfunction occurs. The trial will be continued and is unaffected by a malfunction of the device. The device must be returned to the manufacturer within 5 working days. Instructions for returning the investigational device will be provided. If a device malfunction occurs during the mandatory support period of the trial, an immediate device exchange has to be performed.

The report of study results will include information on all device failures and malfunctions.

NOTE: Device failures or malfunctions are NOT to be reported as serious adverse events. However, if there were an serious adverse event that results from a device failure or malfunction, that specific event would be recorded in the usual manner on the SAE eCRF.

8.3 Annual safety report

The accredited IRB will receive an overview of all SAE's annually.

8.4 Follow-up of serious adverse events

The Investigator should follow all serious adverse events until the events are resolved, the subject is lost to follow-up, the subject has withdrawn consent, the subject completes the study, or the serious adverse event is otherwise explained. All SAEs will be followed until they have abated, or until a stable

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situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

8.5 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) provides periodic data safety monitoring. This Committee is designed to comply with policies and guidelines of regulatory bodies under which the clinical investigation is performed and Good Clinical Practices (GCP).
The DSMB will carefully review individual safety events and examine any statistical analyses presented from the composite trial data. Through direct interaction and meeting minutes, the DSMB will alert the Steering Committee to any areas of concern but does not make decisions about the trial.
The committee initially reviews safety issues after 25 patients. The review includes unexpected serious adverse events, mortality, stroke and bleeding. After the initial review the DSMB will meet after inclusion of 50 patients. The wishes of the DSMB and needs of the trial office will be considered when planning each meeting.
The advice(s) of the DSMB will only be sent to the sponsor of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

8.6 Steering Committee

The Steering Committee is an expert advisory leadership group that provides scientific and medical input on trial design, data collection, data analyses and interpretation of results. The Steering Committee includes all the National Principal Investigators. The Steering Committee is the main policy and decision-making committee of the study and has final responsibility for the scientific conduct of the study. It represents the opinion from the Investigators. The specific tasks of the Steering committee are to (1) approve the study protocol; (2) approve amendments to the protocol; (3) establish the organizational structure; (4) select the Clinical Centers; (5) select the members of the various committees; (6) review the activities of the study committees and change these committees if found necessary, (7) act upon recommendations of the Data Safety Monitoring Board; (8) review (performance) results / reports of the clinical centers; (9) resolve operational problems; (10) approve study reports and papers for publication.
The Steering Committee is charged with driving commitment to the trial, motivating investigational sites, encouraging patient recruitment, and producing high quality data.

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The Steering Committee meets at least 2 times per year and at the request of the Data and Safety Monitoring Board.

8.7 Clinical Events Committee

The independent Clinical Events Committee (CEC) will be responsible for adjudicating defined clinical events (all clinical efficacy and safety endpoints) for the study. The CEC will be comprised of physicians from the fields of cardiology/interventional cardiology experienced with the safety issues specific to mechanical circulatory support, who are not investigators in the trial, nor are they part of another committee.

A designated reviewer, either a highly experienced clinician or a physician, will review all SAEs, UADE's, device failures and malfunctions and related event data to determine whether the event could potentially meet the protocol definition for a primary endpoint, secondary endpoints or safety endpoint. If the event could potentially meet the protocol definition, the clinical event is coded and summarized for presentation to the (blinded) CEC.

The members of the CEC will review all data, adjudicate the event and determine whether a causal relationship to the investigational treatment or device exists. The CEC adjudication will then be incorporated into the clinical trial database for statistical analysis.

The CEC will meet regularly to review and adjudicate defined SAEs and defined Adverse Events and clinical study endpoints according to the CEC Manual of Procedures. The CEC will also review and rule on all deaths that occur throughout the trial.

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9. STATISTICAL METHODS AND ANALYSIS

9.1 General considerations

Statistical analysis is performed using IBM SPSS statistics. If not stated otherwise, all efficacy and the safety analyses are based on findings as confirmed by the Clinical Event Committee (CEC).

9.2 Analyses sets

Full analysis population (FAS) consists of all randomized subjects. Subjects are categorized according to the group to which they were assigned by the randomization process.

9.3 Main analysis of the primary endpoint

The study was designed to test the following hypothesis: The PulseCath iVAC2L is superior to the standard of care (No MCS) in terms of the incidence of the primary endpoints.

Main analysis of the primary endpoint is performed in the FAS population under application of the Intention-to-treat principle that is, events are counted irrespective of their occurrence relative to early or unanticipated termination of randomized regimen.

Rates of primary endpoints are estimated as the proportion of patients in whom one of the primary endpoints has occurred during hospitalisation.

Rate Differences (RD) are defined as the rate under the PulseCath iVAC2L regimen minus that under the standard-of-care regimen.

Superiority of the PulseCath iVAC2L-based regimen in terms of the primary endpoint(s) is declared if the 95% confidence interval (CI) of the Rate Difference lies below 0%. The method of Farrington and Manning will be used to calculate the 95% confidence interval for the between-group Rate Difference of the primary end point. Use of the 95% CI is equivalent to superiority testing with the Farrington & Manning test for the Rate Difference (H0: RD = 0) with a two-sided type I error (α) of 0.05.

9.4 Analyses of the secondary endpoints

No formal statistical analyses with hypothesis testing are foreseen for secondary endpoints. The statistical analyses are focused on effect estimation with corresponding 95%-confidence intervals. P-values may be provided for descriptive purposes.

Binary secondary endpoints are analysed with the methodology that is being used for the primary endpoint. Time-to-event secondary endpoints are analysed as 95% confidence intervals for the designated time point. Rate Differences are calculated according to the method of Com-Nougue, with the use of the Kaplan-Meier estimates and Greenwood estimators of the standard error. Quantitative

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secondary endpoints are analysed with the methodology of the two-sample t-test or the Mann-Whitney U-test, as appropriate.

For the vital parameters and PAC derived measurements (peri-procedural) a mean value will be calculated for each parameter. The mean value will be used for statistical testing.

9.5 Interim analyses

No formal interim analysis for efficacy is planned for this study. Interim study reports with descriptive analysis will be produced by an independent statistician for sample size calculation, for reimbursement purposes and are shared with the DSMB.

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10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The trial will be conducted in compliance with the protocol, principles of the Declaration of Helsinki (Fortaleza, 2013), WMO, ICH-Good Clinical Practice, as well as local regulations and applicable regulatory requirements.

10.2 Recruitment and consent

The treating cardiologist will approach potential eligible patients to participate in the study. After agreement to participate patients are being asked by the cardiologist if an investigator may approach them to ask for informed consent.

An Informed consent approved by the Institutional Review Board (IRB) will be reviewed with the patient and all patients will be required to confirm their consent with their signature. Consent signature will be obtained for all patients prior to any study-specific screening/baseline tests or procedures (like a femoral angiogram or LVEDP measurement). This does not include those procedures or tests that may be obtained in the normal course of the patient's non-study related care and are considered standard-of-care (like admission biochemistry, echocardiogram, CT etc).

Prior to inclusion in the study, it is the responsibility of the Investigator to give each patient (or subject's representative) full and adequate verbal and written information about the objectives and the procedures of the study and the possible risks involved. The patients will be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which they are otherwise entitled and that withdrawal from the study will not jeopardize future medical care. The consent form must be signed and dated by both the investigator and the patient. Furthermore, it is the responsibility of the Investigator to obtain a signed Informed Consent form from each patient prior to performing any study-related procedures. Informed consent documents will be written to be understandable to the subject. All patients providing informed consent are to receive copies of their signed informed consent documentation. The information is intended to give each participant a thorough understanding of the purpose and the nature of the trial, the cooperation required, anticipated benefits, and potential hazards of the study. The investigator also explains that the patient is completely free to refuse or to withdraw from the trial and that if he does so he receives standard treatment with the same degree of care.

Patients will have at least 24 hours to consider participation. An independent physician will be available for extra information, if desired.

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10.3 Benefits and risk assessment

All patients who have consented and who are included in trial will have an indication for CHIP PCI as decided in the heart team. The clinical equipoise of mechanical circulatory support (in this case, PulseCath iVAC2L) use during CHIP PCI for hemodynamic support on the one hand, but the risks for device related complications on the other allows for use of the PulseCath iVAC2L or use of no support. Percutaneous mechanical circulatory support is a widely accepted and applied treatment modality in high-risk, complex PCI. Further explanation about evidence is given in chapter 2.1. In patients with a high-risk for peri-and post procedural hemodynamic instability the benefit outweighs the associated complications. Since there are no randomized controlled trials which prefers no-MCS support over MCS support during CHIP PCI, patients will not be exposed to extra known risk due to randomization in the trial.

Conclusion: The benefits outweigh the associated risks

10.4 Compensation for injury

The investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor has also an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.5 Incentives

There will be no reimbursement for study participation.

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11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

Standardized electronic case report forms (eCRF) will be used to collect complete and accurate records of the clinical data from the UNLOAD-CHIP trial according to GCP requirements. The Investigator and/or study staff under his/her direction is responsible for accurately recording the clinical data and submitting it to the Sponsor in a timely manner. CRF and source documentation will be monitored following the monitor plan as provided by the Clinical Monitor Center (CMC) in conjunction with the Clinical Research Unit (CRU) of the AUMC.

Data entry for the study will only be performed by trained site staff (i.e. local Clinical Research Coordinator and/or Research Fellow Cardiology (PhD candidate or designee) of the Principal Institute). All enrolled subjects and screen failures will be entered into the database. The pertinent data to be collected will be captured in the medical record and entered into the electronic CRF by the designee at the participating site. Data will be retained for 15 year.

The Institution and the Principal Investigator shall prepare, maintain and retain complete, current, accurate, organized and legible Study Documentation (as defined below) in a manner acceptable for the collection of data for submission to, or review by, the regulatory, competent or governmental authorities, and in full compliance with the Protocol and all Applicable Laws.
"Study Documentation" includes all records (related to the Study Device or Protocol), accounts, notes, reports and data, collected, generated or used in connection with the Study and all reports and records necessary for the evaluation and reconstruction of the Study.

Data entered in the EDC system will be automatically saved to a central database and changes tracked to provide an audit trail. The Principal Investigator will be notified to sign the CRF electronically as per the agreed project process and data will be locked to prevent further editing. The Principal Investigator's electronic signature shall be the legally binding equivalent to a handwritten signature. If medical records of Study Subjects are held in a computerized medical system, such system must be in full compliance with European regulations on electronic medical records and signatures.

To handle data confidentially and encoding, a subject identification code (existing out of 5 numbers, according to CCMO guidelines) list will be used to link the data to the subject. This code will not be based on patient initials and birth-date. The key to the code will be safeguarded by the investigator.
The investigator will maintain all Study Documentation / records pertaining to this trial for fifteen years following trial completion, or as otherwise instructed by the CRU, or per local requirements whichever is longer. Published data will not be traceable to the individual patient.

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11.2 Monitoring and Quality Assurance

A Clinical Research Organization (CURIUS) and a Clinical Monitoring Center (CMC) will be appointed to collect (e.g. Uploading redacted source documentation to a study portal) of the necessary source documents for the evaluation and reconstruction of the clinical and hospital course of the subjects. Source documents include, but are not limited to, death certificate, autopsy report, laboratory reports, echocardiograms, ultrasound report, cardiac catheterization logs and cardiac catheterization reports, subject discharge reports. Additional records may be requested for any other procedure performed in accordance with the study protocol.

A Clinical Monitoring Center (CMC) will be appointed to monitor and oversee the conduct of the study. The Sponsor and/or CMC designee will conduct investigational site monitoring in conjunction with the CRU of the AUMC to ensure that all Investigators are in compliance with the Protocol and the Investigators' agreements. In cases of the COVID-19 pandemic impacting the study sites' ability to allow for site visits, as well as travel restrictions that may be in place by the Sponsor and/or CMC, these visits may be done remotely, as outlined in the Monitoring Plan.

The Sponsor and/or CMC designee will monitor the sites to ensure that the completed eCRFs agree with the source documentation and other records and resolve any differences. Periodic phone contacts and site visits will be conducted to ensure that the Protocol is being followed.

For record verification purposes, the clinical monitor will be provided access to hospital records, original laboratory data, and other records and data as they relate to the study and as agreed to with the Investigator prior to the initiation of the trial. The Investigator will also make available to the clinical monitor all regulatory documents, all completed eCRFs, informed consent documents, and source documents for screened and enrolled subjects at the site. It is important that the Investigator and other relevant site personnel are available for consultation with the clinical monitor during the monitoring visits and that sufficient time is devoted at the site to the monitoring process.

If the Sponsor and/or their authorized representative become aware that an Investigator is not complying with the study Protocol, the Investigator Agreement, competent authority's Regulations, the Declaration of Helsinki (if applicable), applicable privacy standards, or any condition of the study imposed by the IRB, the Sponsor or their authorized representative may immediately secure compliance or halt study enrollment. An inability to secure compliance and/or to complete an investigation to identify factors contributing to non-compliance may result in the Investigator and site termination from the study participation by the Sponsor.

The CRU / CMC will review significant new information, including unanticipated serious adverse events and ensure that such information is provided to the national regulatory agencies (as applicable), the Investigators, and to all reviewing IRBs.

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11.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited IRB has been given. All amendments will be notified to the IRB that gave a favourable opinion.

11.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited IRB once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events, other problems, and amendments.

11.5 End of study (report)

Study close-out visits will be conducted after the final follow-up visit is completed at each site following the resolution of any outstanding data discrepancies and adverse events. The investigator will notify the accredited IRB of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the IRB immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the investigator will notify the accredited IRB within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited IRB and the appropriate study oversight authorities.

11.6 Public disclosure and publication policy

The results of this scientific research involving will be disclosed unreservedly. The trial is registered in a public trial registry ClinicalTrials.gov (xxxxxxxxxx).

The results of this prospective, multicentre, randomised investigator-initiated trial with a superiority design are intended to be published in a peer-reviewed journal and as abstracts/presentations at national and international scientific meetings, including those from the Nederlandse Vereniging voor Cardiologie, European Society of Cardiology etc.

The publication rights in regard to the main results of the trial, i.e., regarding the primary and secondary objectives, belong to the sponsor. No individual investigator may publish on the results of this trial, or their own patients, without prior approval from the sponsor.

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12. STRUCTURED RISK ANALYSIS

The joint EAPCI/ACVC expert consensus document on percutaneous ventricular assist devices state that micro-axial flow pumps hold class IIb indication in patients with complex, high-risk coronary artery disease revascularization. This means that MCS 'may be considered in highly selected patients undergoing high-risk PCI in case of acceptable femoral access.' Furthermore, the PulseCath iVAC2L is currently being used within the field of interest and considered a viable option for CHIP PCI.

Given the actual existing evidence about the clinical significance of the PulseCath iVAC2L use in the field of interest there exists equipoise about its potential benefits, which is reflected in actual international guidelines and therefore justifies the rationale and need for this trial.

Important to state is that control patients are not withheld from rescue MCS during and after the procedure if deemed necessary by the interventional/treating cardiologist.

There is clear evidence that the PulseCath iVAC2L system improves the hemodynamic status. However, there is no evidence whether the improved hemodynamic support outweighs the associated risks in patients with an indication for CHIP PCI.

Therefore our trial is justified in an attempt to clarify this, but without exposing the patient to risks that would outweigh the benefits of the device.

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14. DEFINITIONS

14.1 Primary endpoint definitions

14.1.1 All-cause mortality

All-cause mortality is defined as cardiac death, non-cardiac death and undetermined death (see 14.4)

14.1.2 SCAI CSWG stage C- E

Progression to SCAI CS stage C, D OR E is defined according to the following criteria:

Intervention arm (PulseCath iVAC2L):

1. HD parameters and biochemistry alterations as specifically defined for each stage, **OR**
2. Unable to wean from the PulseCath iVAC2L (cathlab <1h) **OR**
3. Start of inotropes and/or vasopressors **OR**
4. Upgrade to temporary MCS during PulseCath iVAC2L support or initiation after its removal (IABP, Impella CP, Impella 5.5 or RP, temporary VAD or BiVAD, ECLS). Elective VAD implantation is not considered progression to SCAI C- E.

Control arm:

1. HD parameters and biochemistry alterations as specifically defined for each stage, OR
2. Initiation of temporary MCS (IABP, Impella CP, Impella 55 or RP, temporary VAD or BiVAD, ECLS) during or after the CHIP procedure. Elective VAD implantation is not considered progression to SCAI C-E.

14.1.3 Need for mechanical ventilation

Mechanical ventilation is defined as a combination of clinical or laboratory signs that the patient cannot maintain an airway or adequate oxygenation or ventilation. Concerning findings include:

1. Respiratory rate > 30/minute OR
2. Inability to maintain arterial oxygen saturation > 90% with fractional inspired oxygen (FIO2) > 0.60 OR
3. pH < 7.25 OR
4. Partial pressure of carbon dioxide (PaCO2) > 50 mm Hg (unless chronic and stable)

The decision to initiate mechanical ventilation should be based on clinical judgment that considers the entire clinical situation and not simple numeric criteria. However, mechanical ventilation should not be delayed until the patient is in extremis.

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14.1.4 Need for renal replacement therapy

Renal replacement therapy is defined as initiation of dialysis (hemodialysis or peritoneal dialysis), hemofiltration, and hemo-diafiltration in case of acute kidney injury (AKI) stage 3

14.1.5 Peri or -post procedural ventricular arrhythmias

Peri or -post procedural ventricular arrhythmias leading to hemodynamic instability/collapse necessitating CPR (defined as electrical defibrillation and/or basic life support)
Ventricular arrhythmias are defined as either one of the following:

1. Ventricular fibrillation
2. Ventricular tachycardia with loss of output
3. Pulseless electrical activity (PEA)
4. Asystole

Receiving CPR is not mandatory in order to fulfil the endpoint as it states 'necessitating CPR'. Therefore, if a patient (suffering from ventricular arrhythmias) is withhold from CPR due to treatment plan restrictions and/or other medical reasons the primary endpoint is met.

14.2 Secondary outcomes

14.2.1 PAC derived measurements and (invasive) LVEDP

Consists of PCWP, LVEDP, CO, CI, CPO, SvO2.
For values collected during the CHIP (as stated in the protocol, every 15 minutes) a mean value will be calculated and used for statistical analysis

14.2.2 Drop in mean arterial pressure

Drop in mean arterial pressure below <60mmHg for >10 minutes

14.2.3 Highest vasoactive inotropic score(VIS)

The VIS is calculated as follows: dopamine dose (µg/kg/min) + dobutamine dose (µg /kg/min) + 100 x epinephrine dose (µg /kg/min) + 100 x norepinephrine dose (µg /kg/min) + 10,000 x vasopressin dose (U/kg/min) + 10 x milrinone dose (µg /kg/min) + enoximone dose (µg /kg/min)

14.2.4 Clinical success of PulseCath iVAC2L implantation

Proper placement and circulatory support and successfully weaned from the device within 1 hours post CHIP procedure.

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14.2.5 Rescue MCS implantation

The need to implant a MCS device during and/or after the CHIP.

Note: Durable LVAD is not seen as rescue MCS implantation.

14.2.6 Myocardial infarction

Myocardial infarction is defined according to the fourth universal definition of myocardial infarction:

Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL.

In addition, one of the following elements is required:

1. Symptoms of acute myocardial ischaemia
2. New ischaemic ECG changes
3. Development of pathological Q waves
4. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology
5. Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy

14.2.7 Stroke or TIA

Stroke or TIA will be adjudicated according to the criteria below:

Stroke diagnostic criteria:

1. Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke
2. Duration of a focal or global neurological deficit ≥24 hours; OR <24 hours, if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; OR the neurologic deficit results in death
3. No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences)

Confirmation of the diagnosis by at least one of the following:

   a. Neurology or neurosurgical specialist
   b. Neuroimaging procedure (MR or CT scan or cerebral angiography)
   c. Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)
   d. TIA (transient ischemic attack), TIA will be adjudicated according to the criteria below:

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TIA diagnostic criteria:

1. Brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour, and without evidence of acute infarction

Definitions of TIA versus stroke syndromes:

1. TIA: New focal neurologic deficit with rapid symptom resolution (usually 1-2 hours), always within 24 hours; neuroimaging without tissue injury
2. Stroke: diagnosis as above, preferably with positive neuroimaging study
3. Subjects with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.

14.2.8 Heart failure hospitalization

Criteria for a heart failure admission include ALL of the following:

1. Requires in-hospital stay for >24 hours
2. Demonstrates signs and/or symptoms of heart failure such as new/worsening dyspnea, orthopnea, PND, increasing fatigue, worsening functional capacity or activity intolerance, or signs and/or symptoms of volume overload
3. Results in IV or invasive treatment for heart failure (includes ICD or CRT placement)
4. NT-ProBNP ≥300 ng/L or pro-BNP≥100

14.2.9 Major adverse cardiac and cerebrovascular events-

- Death, myocardial infarction, stroke, or transient ischemic attack

-

14.3 Safety outcomes

14.3.1 Vascular events

All vascular complications (major or minor) are adjudicated by the CEC to verify whether they are major or minor.

1. Major vascular events determined as PulseCath iVAC2L related by the CEC, will be analyzed as part of the Performance Goals. If relatedness cannot be determined, the CEC will rule the event as “PulseCath iVAC2L related”
2. All bleeding events will be reported on as outlined in section 4.2.2

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Major vascular events

1. Significant thoracic aortic dissection requiring surgical intervention
2. Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudo-aneurysm, hematoma, irreversible nerve injury, compartment syndrome, or arterial thrombosis) leading to either death, need for significant blood transfusions (≥4 units), unplanned surgical intervention, or irreversible end-organ damage (e.g. hypogastric artery occlusion causing visceral ischemia or spinal artery injury causing neurologic impairment)
1. Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage

Minor vascular events

1. Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudo-aneurysm, or hematoma requiring compression, thrombin injection therapy, or arterial thrombosis) not requiring unplanned percutaneous or surgical intervention and not resulting in irreversible end-organ damage
2. Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage
3. Failure of percutaneous access site closure resulting in interventional (e.g. stent-graft) or surgical correction and not associated with death, need for significant blood transfusions (≥ 4 units), or irreversible end-organ damage
4. Simple balloon inflation for treatment of small dissection

14.3.2 Limb ischemia

New incidences of hypoperfusion of the leg defined by such symptoms as decreased skin temperature of the limb or decreased peripheral pulses and requiring device retrieval and/or surgery.

14.3.3 Bleeding events

Document and record all BARC and TIMI bleeding. Reportable, Major Bleeding is defined as BARC >=3.

1. Bleeding events determined as Impella Related by the CEC, will be analyzed as part of the Performance Goals. If relatedness cannot be determined, the CEC will rule the event as “Impella related”

2. All bleeding events will be reported on as outlined in section 4.2.2

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BARC bleeding

1. Classification of bleeding will be according to the Bleeding Academic Research Consortium (BARC) definitions.
2. Type 0 (no evidence of bleeding) and Type 1 (bleeding that is not actionable and does not cause the subject to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional) will not be reported.
3. Type 2: any clinically overt sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that is actionable but does not meet criteria for type 3, type 4 (CABG-related), or type 5 (fatal bleeding) BARC bleeding. The bleeding must require diagnostic studies, hospitalization, or treatment by a healthcare professional. In particular, the bleeding must meet at least one of the following criteria: First, it requires intervention, defined as a healthcare professional–guided medical treatment or percutaneous intervention to stop or treat bleeding, including temporarily or permanently discontinuing a medication or study drug. Second, the bleeding leads to hospitalization or an increased level of care, defined as leading to or prolonging hospitalization or transfer to a hospital unit capable of providing a higher level of care. Or third, the bleeding prompts evaluation, defined as leading to an unscheduled visit to a healthcare professional resulting in diagnostic testing (laboratory or imaging). A visit or phone call to a healthcare professional during which neither testing nor treatment is undertaken does not constitute type 2 bleeding.
4. Type 3: clinical, laboratory, and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below:

   Type 3a:

   a. Any transfusion with overt bleeding
   b. Overt bleeding plus hemoglobin drop of 3 to 5 g/dL* (provided hemoglobin drop is related to bleeding).

   Type 3b:

   a. Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)
   b. Cardiac tamponade
   c. Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/ hemorrhoid)
   d. Bleeding requiring intravenous vasoactive agents

   Type 3c:

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a. Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal); subcategories confirmed by autopsy or imaging or lumbar puncture
b. Intraocular bleed compromising vision

Type 4: coronary artery bypass graft (CABG)-related bleeding

a. Perioperative intracranial bleeding within 48 hours
b. Reoperation after closure of sternotomy for the purpose of controlling bleeding
c. Transfusion of ≥5 U whole blood or packed red blood cells within a 48-hour period (only allogeneic transfusions are considered transfusions for CABG-related bleeds)
d. Chest tube output >2L within a 24-h period

5. Type 5: fatal bleeding

Type 5a: Probable

a. Clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging

Type 5b: Definite

- Bleeding that is directly observed (by either clinical specimen or imaging) or confirmed on Autopsy

14.3.4 Aortic valve injury

Injury to the aortic valve regardless of the cause, defined as any significant change compared to baseline and assessed at grade 2 (moderate) or higher regurgitation on a 4-point scale.

14.4 Death

14.4.1 Cardiovascular death

Cardiovascular death is defined as death resulting from cardiovascular causes. The following categories will be collected:

1. Death caused by acute MI
2. Death caused by sudden cardiac, including unwitnessed, death
3. Death resulting from heart failure
4. Death caused by stroke
5. Death caused by cardiovascular procedures
6. Death resulting from cardiovascular hemorrhage
7. Death caused by other cardiovascular organ failure
8. Death caused by arrhythmia

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9. Death resulting from other cardiovascular cause (needs to be specified)

14.4.2 Non-cardiovascular death

Non-cardiovascular death is defined as any death that is not thought to be the result of a cardiovascular cause. The following categories may be identified:

1. Death resulting from malignancy
2. Death resulting from pulmonary causes
3. Death caused by infection (includes sepsis)
4. Death resulting from gastrointestinal causes
5. Death resulting from accident/trauma
6. Death caused by other non-cardiovascular organ failure
7. Death resulting from other non-cardiovascular cause

14.4.3 Undetermined

Undetermined cause of death is defined as a death not attributable to any other category because of the absence of any relevant source documents. Such deaths will be classified as cardiovascular for end point determination

1. Death due to Acute Myocardial Infarction refers to a death by any CV mechanism (e.g., arrhythmia, sudden death, HF, stroke, pulmonary embolus, peripheral arterial disease) ≤ 30 days [1] after a MI, related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. We note that there may be assessable mechanisms of CV death during this time period, but for simplicity, if the CV death occurs ≤ 30 days of the MI, it will be considered a death due to MI.
2. Sudden Cardiac Death refers to a death that occurs unexpectedly and not within 30 days of an acute MI.
3. Death due to Heart Failure refers to a death in association with clinically worsening symptoms and/or signs of HF regardless of HF etiology. Deaths due to HF can have various etiologies, including single or recurrent MIs, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.
4. Death due to Stroke refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.
5. Death due to Cardiovascular Procedures refers to death caused by the immediate complications of a cardiac procedure.

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6. Death due to Cardiovascular Hemorrhage refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage (e.g., subdural hematoma), non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.
7. Death due to Other Cardiovascular Causes refers to a CV death not included in the above categories but with aspecific, known cause (e.g., pulmonary embolism or peripheral arterial disease).

14.5 SCAI CSWG definitions

General information:

Drugs are considered inotropes, inodilators or vasopressors

Devices are considered mechanical circulator support

A. hemodynamically stable

B. hypotensive OR hypoperfusing AND untreated

- *a. SBP 60-90 mm Hg, MAP 50-65 mm Hg **OR***
- *b. lactate 2-5 mmol/L OR ALT 200-500 U/L OR Creatinine rise ≥ 0.3 mg/dl during first 24h (26,53 µmol/L) OR Oliguria (≤ 0,5 ml/kg/h, ≤ 720 ml/24 h) **AND***
- *c. no drugs, no devices*

C. hypotensive AND hypoperfusing OR treated

- *a. SBP 60-90 mm Hg, MAP 50-65 mm Hg **AND***
- *b. lactate 2-5 mmol/L OR ALT 200-500 U/L OR Creatinine rise ≥ 0.3 mg/dl during first 24h (26,53 µmol/L) OR Oliguria (≤ 0,5 ml/kg/h, ≤ 720 ml/24 h) **AND***
- *c. no drugs, no devices **OR***
- *d. 1 drug or 1 device without hypotension or hypoperfusion*

D. Failure to stabilize with initial therapy

- *a. SBP 60-90 mm Hg, MAP 50-65 mm Hg **AND***
- *b. lactate 5 - 10mmol/L OR ALT >500 U/L OR Creatinine rise ≥ 0.3 mg/dl during first 24h (26,53 µmol/L) OR Oliguria (≤ 0,5 ml/kg/h, ≤ 720 ml/24 h) **OR***
- *c. 2-5 drugs or devices **OR***
- *d. 1 drug or 1 device with persistent hypotension or hypoperfusion*

E. Extremis /refractory shock

- *a. SBP <60 mm Hg, MAP<50 mm Hg **OR***
- *b. Lactate >10 mmol/L **OR***

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c. pH <7.2 ***OR***

d. ≥3 drugs OR ≥3 devices ***OR***

e. out of hospital cardiac arrest / in-hospital cardiac arrest

14.6 Left main distal bifurcation (2-stent) strategy

PCI of the left main distal bifurcation using a strategy that requires two stents: Double Kissing (DK)-Crush, Culotte, or T-and-Protrude (TAP).

14.7 Complex left main distal bifurcation

Complex LM bifurcation lesions were defined as those meeting a major risk factor: Side branch diameter stenosis ≥ 70% and side branch lesion length ≥ 10 mm, or any 2 minor risk factors: moderate to severe calcification, multiple lesions, bifurcation angle < 45°, main vessel reference vessel diameter < 2.5 mm, thrombus-containing lesions, and main branch lesion length ≥ 25 mm.

14.8 Acute Kidney Injury (AKI)

Stage Criteria:

2. Stage 1
    a. Increase in serum creatinine of ≥0.3 mg/dL (≥ 26.4 µmol/l) or 50 to 100% (1.5- to 2-fold) OR
    b. Urine output of <0.5 mL/kg/hour for 6 to 12 hours
3. Stage 2
    a. Increase in serum creatinine of >100 to 200% (> 2- to 3-fold) OR
    b. Urine output of <0.5 mL/kg/hour for 12 to 24 hours
4. Stage 3
    a. Increase in serum creatinine of >200% (> 3-fold) OR
    b. Increase in serum creatinine by >0.5 mg/dL to ≥4.0 mg/dL (≥ 354 µmol/l) OR
    c. Urine output of <0.3 mL/kg/hour for >24 hours or anuria for >12 hours OR
    d. Initiation of renal replacement therapy

14.9 Insertion site infection

Clinical manifestation of infection at the insertion site of the Pulsecath iVAC2L device distinguished by such signs as pain, fever, elevated temperature, drainage and/or leukocytosis.

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15.10 ICU dependency and SOFA scores

Patients can be transferred to the ICU as deemed necessary by the treating cardiologist and an intensive care specialist of a participating center.

ICU dependency is defined as either one of the following:

- patients receiving advanced respiratory support alone, i.e. invasive mechanical ventilator support applied via a trans-laryngeal tracheal tube or applied via a tracheostomy
- patients receiving a minimum of 2 organs supported, i.e. advanced cardiovascular and renal support and/or advanced respiratory support

Advanced cardiac support (i.e. inotropes, vaso-active drugs, temporary pacemaker and MCS) is defined as non-ICU dependent.

Advanced cardiac support and basic (non-ventilated) respiratory support is considered as non-ICU dependent.

Patients that are escalated to VA-ECMO as deemed necessary by the treating heart failure specialist are considered as ICU dependent.

If renal replacement can be provided on the coronary critical care unit this is considered as non-ICU dependent.

Sequential Organ Failure Assessment (SOFA) will be registered.

The SOFA score was initially designed to sequentially assess the severity of organ dysfunction in patients who were critically ill from sepsis. Since multiple organ dysfunction is common in critically ill patients, it has since been used to predict mortality in those with organ failure from other causes including those with acute liver failure from acetaminophen overdose, chronic liver failure (CLIF-SOFA), and cancer, as well as in patients who have undergone cardiac surgery or hematopoietic stem cell transplant.

SOFA uses simple measurements of major organ function to calculate a severity score. The scores are calculated 24 hours after admission to the ICU and every 48 hours thereafter (thus, the term "Sequential" Organ Failure Assessment). The mean and the highest scores are most predictive of mortality. In addition, scores that increase by about 30 percent are associated with a mortality of at least 50 percent.

The SOFA severity score is based upon the following measurements of organ function

1. Respiratory system – the ratio of arterial oxygen tension to fraction of inspired oxygen (PaO2/FiO2)
2. Cardiovascular system – the amount of vasoactive medication necessary to prevent hypotension

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3. Hepatic system – the bilirubin level
4. Coagulation system – the platelet concentration
5. Neurologic system – the Glasgow coma score
6. Renal system – the serum creatinine or urine output

The SOFA score has been endorsed by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) as a tool to facilitate the identification of patients at risk of dying from sepsis

15.11 Device Relatedness

Complications associated with the device (pump) as is relates to placement, efficacy, durability or removal (these involve the implanted device)

15.12 Procedure Relatedness

Complications associated with the procedure from initial placement of the device or any necessary secondary interventions. This includes morbidity or complications associated with either anesthesia or surgical/interventional procedure. This also includes inappropriate subject selection and errors attributed to inappropriate operator techniques, measurements, or judgment.

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