

# Effects of different modes of cardiopulmonary bypass in patients undergoing cardiac surgery

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<b>Registration date</b> 21/05/2024	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 21/05/2024	<b>Condition category</b> Surgery	<input type="checkbox"/> Individual participant data <input type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

Cardiac (heart) surgery is a high-risk procedure commonly performed with cardiopulmonary bypass (CPB), a machine that temporarily takes over the function of the heart and lungs, which is associated with disturbances in microcirculation (circulation of the blood in the smallest blood vessels). This can lead to complications such as decreased tissue perfusion (blood flow) and hypoxia (low blood oxygen) with organ dysfunction which can complicate the course of the patient's recovery. Cardiac surgery causes inflammation, ischemia-reperfusion injury (damage caused when blood supply returns to tissue) and acute trauma that contribute to endothelial dysfunction (impaired functioning of the lining of blood vessels).

The surface of the vascular (blood vessel) endothelium is covered with glycocalyx, a gel-like layer lining. It has an important role in maintaining vascular tone and permeability. The endothelial glycocalyx is a dynamic structure with a tenuous balance between degradation and synthesis. Under pathological conditions or trauma, such as cardiac surgery, the inflammatory response can adversely affect this balance. Increased levels of degradation markers are associated with organ dysfunction and poor outcomes in critically ill patients. Degraded endothelial glycocalyx components can be measured to estimate the degree of endothelial degradation and possible organ dysfunction.

Although CPB is a non-physiological procedure, it is widely accepted as a safe and effective method for open heart surgery. One of the most non-physiological features of CPB is the non-pulsatile flow generated by the pump. Recent evidence suggests that pulsatile CPB might be more physiological but the role of pulsatile versus non-pulsatile CPB is still far from being completely understood.

This study aims to investigate the difference between non-pulsatile and pulsatile CPB on endothelial dysfunction, oxidative stress, inflammatory response, and clinical outcomes in patients undergoing cardiac surgery.

### Who can participate?

Adult patients aged 18 years and over undergoing cardiac surgery with CPB (see detailed inclusion and exclusion criteria)

### What does the study involve?

Participants are randomly allocated to be treated with pulsatile or non-pulsatile CPB. Otherwise,

the patients' perioperative care is the same for all three participating centres and both groups. At seven predefined times blood samples will be taken and stored for tests.

What are the possible benefits and risks of participating?

Both methods of CPB are used in practice, but the non-pulsatile CPB is most commonly used. Thus, the risks of surgery and CPB as such are not supposed to differ between the groups. The potential expected benefits of pulsatile CPB would include less endothelial glycocalyx degradation, less pronounced pro-inflammatory response, less oxidative stress and possibly improved organ function.

Where is the study run from?

The study is run in three university hospitals: Ljubljana (Slovenia), Rijeka (Slovenia), and Maribor (Croatia)

When is the study starting and how long is it expected to run for?

January 2023 to January 2027

Who is funding the study?

1. Slovenian Research and Innovation Agency
2. Croatian Science Foundation

Who is the main contact?

1. Assist Prof Marko Zdravkovic, marko.zdravkovic@ukc-mb.si
2. Prof. Vlatka Sotosek, vlatkast@medri.uniri.hr

## Contact information

### Type(s)

Public, Scientific, Principal investigator

### Contact name

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## Additional identifiers

### Clinical Trials Information System (CTIS)

Nil known

### Protocol serial number

## Study information

### Scientific Title

Endothelial Dysfunction, Inflammation and Oxidative Stress (EDIOS) in patients undergoing cardiac surgery with pulsatile or non-pulsatile cardiopulmonary bypass: a multi-centric randomised controlled trial

### Acronym

EDIOS

### Study objectives

H1: Pulsatile cardiopulmonary bypass reduces endothelial dysfunction in patients undergoing cardiac surgery when compared with non-pulsatile cardiopulmonary bypass.

H2: Pulsatile cardiopulmonary bypass reduces inflammatory response in patients undergoing cardiac surgery when compared with non-pulsatile cardiopulmonary bypass.

H3: Pulsatile cardiopulmonary bypass reduces oxidative stress in patients undergoing cardiac surgery when compared with non-pulsatile cardiopulmonary bypass.

H4: Pulsatile cardiopulmonary bypass improves microcirculatory function in patients undergoing cardiac surgery when compared with non-pulsatile cardiopulmonary bypass.

H5: Pulsatile cardiopulmonary bypass improves clinical outcomes in patients undergoing cardiac surgery when compared with non-pulsatile cardiopulmonary bypass.

### Ethics approval required

Ethics approval required

### Ethics approval(s)

1. approved 01/03/2024, Komisiji Republike Slovenije za medicinsko etiko (KME RS) (Štefanova ulica 5, Ljubljana, 1000, Slovenia; +386 (0)1478 69 06; kme.mz@gov.si), ref: 0120-33/2024-2711-3

2. approved 28/02/2023, Klinicki bolnicki centar Rijeka, Eticko povjerenstvo (Kresimirova 42, Rijeka, 51000, Croatia; +385 (0)51658808; pravna-ivanaa@kbc-rijeka.hr), ref: 2170-29-02/1-23-2

### Study design

Multi-centric randomized controlled trial

### Primary study design

Interventional

### Study type(s)

Treatment

### Health condition(s) or problem(s) studied

Effects of pulsatile cardiopulmonary bypass (CPB) in patients undergoing cardiac surgery with median sternotomy

## Interventions

Group allocation - institution-stratified permuted block randomization:

Patients will be randomly allocated in a 1:1 ratio in blocks of 6 patients within each institution (i.e., stratified by institution) to receive either pulsatile or non-pulsatile CPB. A random number generator software will be used. Each centre is expected to recruit 48 patients, making a total of 144 patients (see power calculations). Interim analysis for clinical outcomes is planned at the 50% of the target number of patients is reached within each institution.

### Pulsatile CPB:

For pulsatile CPB the roller pump must be used in all centres. CPB tubing systems should be used according to institutional standards, a hollow fiber oxygenator membrane (LivaNova F8 with a surface area of 1.8 m<sup>2</sup>), 1/2 or 3/8 inch pump boot, CPB tubing from the pump of 3/8 inch size and a straight 24 Fr aortic cannula (EOPA, Medtronic®). The pulsatile CPB starts at the time of aortic cross-clamp and finishes upon the cross-clamp release (i.e., continuously during the aortic cross-clamp time). Pulsatile CPB parameters should be set as:

1. Frequency (min<sup>-1</sup>) 75
2. Width (% of time at high speed) 60
3. Basic flow (%) 30

The target minimum pulse pressure on the arterial line (most commonly radial artery) should be 15 mmHg. Further adjustments will be performed according to the patient's pressure curve and pulse amplitude, for example, if the target pulse pressure is not achieved then the width should be reduced to 50% or 40% if needed. The mean arterial pressure during CPB should be maintained between 55 and 80 mmHg; for that purpose the cardiac index of 2.0-2.4 L/min/m<sup>2</sup> will be maintained for all patients in a balanced manner with the vasoactive agents (first-line noradrenaline, first-line vasodilator glyceryl trinitrate - as in the hemodynamics protocol).

Normothermic CPB should be used with the range of 35.0 - 37.0 C core body temperature.

### Non-pulsatile CPB (control group):

For non-pulsatile CPB the roller pump must be used in all centres. CPB tubing systems should be used according to institutional standards, CPB tubing systems should be used according to institutional standards, a hollow fiber oxygenator membrane a hollow fiber oxygenator membrane (LivaNova F8 with a surface area of 1.8 m<sup>2</sup>), 1/2 or 3/8 inch pump boot, CPB tubing from the pump of 3/8 inch size and a straight 24 Fr aortic cannula (EOPA, Medtronic®). The mean arterial pressure during CPB should be maintained between 55 and 80 mmHg; for that purpose the cardiac index of 2.0-2.4 L/min/m<sup>2</sup> will be maintained for all patients in a balanced manner with the vasoactive agents (first-line noradrenaline, first-line vasodilator: glyceryl trinitrate - as in the hemodynamics protocol). Normothermic CPB should be used with the range of 35.0 - 37.0 C core body temperature.

All parameters will be monitored until 66 hours after CPB; additionally, complications will be followed up to 7 days following surgery.

## Intervention Type

Device

## Phase

Not Applicable

## Drug/device/biological/vaccine name(s)

Cardiopulmonary bypass device settings: pulsatile or non-pulsatile flow

### **Primary outcome(s)**

1. Endothelial dysfunction: peak plasma syndecan-1 level measured with ELISA at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning following surgery), 42 hours after CPB and 66 hours after CPB.
2. Inflammation: peak plasma IL-6/IL-10 ratio measured with ELISA at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning following surgery), 42 hours after CPB and 66 hours after CPB.
3. Oxidative stress: peak plasma malondialdehyde (MDA) measured with ELISA at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning following surgery), 42 hours after CPB and 66 hours after CPB.
4. Microcirculation: perfused vessel density (variable of diffusive capacity) measured with GlycoCheck at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning following surgery), 42 hours after CPB and 66 hours after CPB.
5. Clinical outcomes: peak lactate levels measured at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning following surgery), 42 hours after CPB and 66 hours after CPB.

### **Key secondary outcome(s)**

1. Other markers of endothelial dysfunction, all measured with ELISA at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning following surgery), 42 hours after CPB and 66 hours after CPB:
  - 1.1. Heparan sulphate
  - 1.2. Angiopoietin Ang-1 and angiopoietin Ang-2 and Ang-2/Ang-1 ratio
  - 1.3. Endokan
  - 1.4. Syndecan-4
  - 1.5. Glypican-1
  - 1.6. Hyaluronic acid
  - 1.7. Orosomucoid
  - 1.8. Fractalkine
  - 1.9. Von Willebrand factor
  - 1.10. Vascular endothelial growth factor (VEGF)
2. Other markers of inflammation, all measured with ELISA at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning following surgery), 42 hours after CPB and 66 hours after CPB:
  - 2.1. IL-6/IL-10 patterns
  - 2.2. IL-10
  - 2.3. IL-6
  - 2.4. IL-5
  - 2.5. IL-16
  - 2.6. IL-8
  - 2.7. MMP-9
  - 2.8. MMP-13
  - 2.9. IL-1 $\beta$
  - 2.10. IL-7
  - 2.11. IL-17
  - 2.12. IL-18
  - 2.13. IL-18BP
3. Other markers of oxidative stress, all measured with ELISA at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning

following surgery), 42 hours after CPB and 66 hours after CPB:

3.1. Reactive oxygen species

3.2. Reactive nitrogen species

4. Other microcirculatory parameters, all measured with GlycoCheck at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning following surgery), 42 hours after CPB and 66 hours after CPB:

4.1. Convective blood flow: proportion of perfused vessels (proportion of perfused vessels = perfused vessel density/total vessel density)

4.2. Variables of diffusive capacity: Total vessel density and De Backer score

4.3. Variable of heterogeneity: Heterogeneity index

4.4. Variable of glycocalyx: Perfused boundary region

5. Clinical outcomes:

Vascular (extracted from patients' medical records for all):

1. Total dose of NA administered intraoperatively and in ICU until the first discharge or up to 66 h after the end of CPB (mcg/kg)

2. Total dose of V administered intraoperatively and in ICU (IE) until the first discharge or up to 66 h after the end of CPB

3. NA and V maximum rate intraoperatively and in ICU (mcg/kg/min // IE/h) until the first discharge or up to 66 h after the end of CPB

4. NA and V duration of treatment since the end of CPB until the first discharge from ICU or up to 66 h after the end of CPB

5. Frequency of vasoplegic syndrome: defined as MAP lower than 65 mmHg despite preload optimization requiring norepinephrine infusion for more than 4 hours after CPB

6. Fluid administration and fluid balance, defined as for ICU and HDU ([total fluid intake/24h] to blood loss + urine output/ 24h) (mL) and in OR ([total fluid intake anaesthesia + perfusionist/end of surgery] to blood loss + urine output/end of surgery) up to 66 h after the end of CPB

7. Incidence and extent of fluid overload defined as fluid balance > 5% = [fluid intake (L) - fluid output (L)]/body weight (kg) × 100%

8. Patients requiring vasodilator infusion intraoperatively and in ICU up to 66 h after the end of CPB (n, %)

9. NA equivalents intraoperatively and in ICU (mcg/kg/min) until the first discharge or up to 66 h after the end of CPB

Heart:

1. Patients requiring any inotropic support intraoperatively and in ICU until the first discharge or up to 66 hours after CPB (n, %) [extracted from patients' medical records]

2. Total dose of inotropes administered intraoperatively and in ICU (IE) until the first discharge or up to 66 h after the end of CPB [extracted from patients' medical records]

3. Peak hsTnI (ng/L), measured at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning following surgery), 42 hours after CPB and 66 hours after CPB

4. Peak heart-type fatty-acid binding protein, ELISA, measured at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning following surgery), 42 hours after CPB and 66 hours after CPB

5. Peak NT-proBNP (ng/L), measured at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning following surgery), 42 hours after CPB and 66 hours after CPB

6. New-onset atrial fibrillation (n, %) in ICU and in HDU up to 7 days after the end of CPB [extracted from patients' medical records]

7. Type 5 myocardial infarction : biomarker values above five times the 99th percentile of the

normal reference range during the initial 72 hrs following CABG + new pathological Q-waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium [extracted from patients' medical records]

#### Kidney:

1. Urine output intraoperatively (mL/kg/h), in ICU (mL/kg/h) and in HDU (mL/kg/h) [extracted from patients' medical records]
2. Peak creatinine and maximum change in creatinine from pre-operative ( $\mu\text{mol/L}$ ), measured at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning following surgery), 42 hours after CPB and 66 hours after CPB
3. Peak urea (mmol/L), measured at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning following surgery), 42 hours after CPB and 66 hours after CPB
4. Creatinine clearance (mL/min), measured at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning following surgery), 42 hours after CPB and 66 hours after CPB
5. Furosemide dose (mg) in ICU and in HDU up to 66 h after the end of CPB [extracted from patients' medical records]
6. Renal replacement therapy up to 66 h after the end of CPB (n, %) [extracted from patients' medical records]
7. AKI presence and stage by Kidney Disease Improving Global Outcomes (KDIGO) criteria: stage 1 is defined as an increase in serum creatinine (SCr) by  $\geq 26.5 \mu\text{mol/L}$  or an increase in SCr to  $\geq 1.5$  times baseline, or urine output  $< 0.5 \text{ mL/kg/h}$  for 6–12h. AKI stage 2 is defined as an increase in SCr to  $\geq 2.0$ – $2.9$  times the baseline, or urine output  $< 0.5 \text{ mL/kg/h}$  for  $\geq 12\text{h}$ . AKI stage 3 is defined as an SCr of up to 3.0 times the baseline or SCr increased to  $\geq 354 \mu\text{mol/L}$  or the initiation of renal replacement therapy or urine output  $< 0.3 \text{ mL/kg/h}$  for  $\geq 24\text{h}$  or anuria for  $\geq 12\text{h}$ .

#### Lungs:

1. Time of mechanical ventilation (intubation to extubation) until the first discharge from ICU or up to 66 h after the end of CPB (extracted from patients' medical records)
2. Time to extubation from the end of surgery until the first discharge from ICU or up to 66 h after the end of CPB (extracted from patients' medical records)
3. (Lowest)  $\text{PaO}_2/\text{FiO}_2$  level measured at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning following surgery), 42 hours after CPB and 66 hours after CPB

Liver (all measured at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB [i.e., the next morning following surgery], 42 hours after CPB and 66 hours after CPB):

1. Concentration of ALT ( $\mu\text{kat/L}$ )
2. Concentration of AST ( $\mu\text{kat/L}$ )
3. INR
4. Bilirubin  $\mu\text{mol/L}$
5. Concentration of GGT ( $\mu\text{kat/L}$ )

#### Other:

1. Peak CRP (mg/L) measured at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning following surgery), 42 hours after CPB and 66 hours after CPB
2. Peak PCT ( $\mu\text{g/L}$ ) measured at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning following surgery), 42 hours after CPB and 66 hours after CPB

3. Peak leucocytes count (10<sup>9</sup> cells per L) measured at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning following surgery), 42 hours after CPB and 66 hours after CPB
4. Lowest BE measured at baseline, 45 minutes after aortic cross-clamp, 2 hours after CPB, 6 hours after CPB, 18 hours after CPB (i.e., the next morning following surgery), 42 hours after CPB and 66 hours after CPB
5. Total heparin given during CPB (IE/kg)
6. Substitution of blood products intraoperatively and up to 66 hours after CPB (total number of packs and volume)
7. Chest tube drainage up to 66 hours after CPB
8. Hemostatic reoperation frequency within 7 days (n, %)
9. Duration of ICU stay
10. Duration of hospital stay

#### Major complications:

1. Occurrence of major adverse cardiovascular events (MACCE) within the 7 days following cardiac surgery. The criteria for MACCE required the occurrence of at least one outcome among the following: in-hospital mortality, successful resuscitated cardiac arrest, stroke, acute kidney injury, and mesenteric ischemia.
2. Stroke was defined as an embolic, thrombotic, or hemorrhagic cerebral event with persistent residual motor, sensory, or cognitive dysfunction (e.g., hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory) diagnosed by brain computed tomography scan
3. Additional complications: homeostatic revision surgery, deep sternal wound infection, superficial wound infection

#### Subgroup analyses:

1. The researchers will split the patients into two groups based on the duration of ACC: the shorter duration group will be compared to the longer duration (50:50 in each group)
2. They will split the patients into two groups based on the elevated AKI risk preoperatively: elevated AKI risk is defined by a score of  $\geq 1.5$  points using the following risk score: pre-operative haemoglobin  $< 130 \text{ g.l}^{-1}$  (2 points); pre-operative creatinine  $> 100 \text{ }\mu\text{mol.l}^{-1}$  (2 points); age  $> 70$  years (1.5 points), BMI  $> 30 \text{ kg.m}^{-2}$  (1.5 points) and New York Heart Association (NYHA) status 4 (1.5 points)

CORRELATIONS and ASSOCIATIONS (univariate and multivariable logistic regression analyses) between the collected variables.

#### Completion date

01/01/2027

## Eligibility

#### Key inclusion criteria

1. Adult patients undergoing elective cardiac surgery with cardiopulmonary bypass (CPB)
2. Expected aortic cross-clamp (ACC) time of  $> 45$  minutes
3. Full or partial median sternotomy with central cannulation (mini-CPB should not be used)
4. surgery starting in the morning:
  - 4.1. Cardiac valve surgery
  - 4.2. Isolated coronary artery bypass grafting (CABG)

- 4.3. Combination of valvular and CABG surgery
- 4.4. Any of the above combined with ascending aorta surgery  
(NO concomitant radio-frequency ablations, NO concomitant carotid artery surgery)

**Participant type(s)**

Patient

**Healthy volunteers allowed**

No

**Age group**

Adult

**Lower age limit**

18 years

**Sex**

All

**Key exclusion criteria**

Exclusion criteria:

1. Refusal to participate in the study
2. Pregnant women
3. Patients with previous cardiac surgery (i.e., redo surgery)
4. Patients with left ventricular ejection fraction <30%
5. Patients on chemo/immunosuppressive therapy (including inhaled corticosteroids, antileukocyte drugs or TNF- $\alpha$  blockers)
6. Patients with body mass index, >35 kg·m<sup>-2</sup> or <18 kg·m<sup>-2</sup>
7. Patients with a body surface area (BSA - duBois formula) >2.20 m<sup>2</sup> (as it would be impossible to achieve pulsatile pump flow equivalent to a cardiac index of 2.0-2.4, without exceeding maximum safe line pressure in the extracorporeal circuit)
8. Patients with any autoimmune diseases, immunocompromised patients (e.g., with AIDS) or with leucopenia (<3.5·10<sup>9</sup> cells·L<sup>-1</sup>)
9. Clinical and/or laboratory signs of infection
10. Patients with advanced chronic lung disease with pO<sub>2</sub> on air: <9.8 kPa
11. Patients with known liver disease (albumin <30 g/L; bilirubin >34.2 $\mu$ mol·L<sup>-1</sup>)
12. Patients with renal failure (serum creatinine >176  $\mu$ mol·L<sup>-1</sup>)
13. Patients with malignant diseases within the last 5 years (i.e., remission or cure 5 years or longer)
14. Patients with ischemic stroke or myocardial infarction (STEMI) within the last 3 months
15. Patients with known epilepsy
16. Patients with known allergy to any drugs used in the study protocol

Exclusion criteria - after enrolment:

Two analyses will be performed, one based on the treatment received and the second one with the additional exclusion criteria which could have an additional effect on the measured outcomes of endothelial dysfunction, inflammation, and/or oxidative stress; for example, patients who received systemic glucocorticoid medication before the last blood sampling.

**Date of first enrolment**

28/05/2024

**Date of final enrolment**

31/12/2025

**Locations****Countries of recruitment**

Croatia

Slovenia

**Study participating centre****University Medical Centre Maribor**

Ljubljanska ulica 5

Maribor

Slovenia

2000

**Study participating centre****University Medical Centre Ljubljana**

Zaloska 2

Ljubljana

Slovenia

1000

**Study participating centre****Klinicki bolnicki centar Rijeka**

Kresimirova 42

Rijeka

Croatia

51000

**Sponsor information****Organisation**

Slovenian Research and Innovation Agency

**Organisation**

Croatian Science Foundation

**ROR**

<https://ror.org/03n51vw80>

## **Funder(s)**

### **Funder type**

Government

### **Funder Name**

Slovenian Research and Innovation Agency

### **Funder Name**

Hrvatska Zaklada za Znanost

### **Alternative Name(s)**

Croatian Science Foundation, The Croatian Science Foundation, HRZZ

### **Funding Body Type**

Government organisation

### **Funding Body Subtype**

Trusts, charities, foundations (both public and private)

### **Location**

Croatia

## **Results and Publications**

### **Individual participant data (IPD) sharing plan**

The datasets generated and/or analysed during the current study will be available upon request from Marko Zdravkovic ([marko.zdravkovic@ukc-mb.si](mailto:marko.zdravkovic@ukc-mb.si)).

### **IPD sharing plan summary**

Available on request