Informed consent form

Dear Sir/Madam,

We would like to invite you to take part in a scientific study exploring how the medication empagliflozin affects oxidative stress in patients undergoing elective coronary angiography.

Title of the study: *The effect of a single dose of the SGLT2 inhibitor, empagliflozin, on oxidative stress in patients undergoing elective coronary angiography.*

The study is being conducted at the General Hospital Dr. Josip Bencevic, Andrije Stampara 42, 35000 Slavonski Brod.

Your participation in the study should be based on a clear understanding of the research objectives, the methods and procedures involved, and the potential benefits or risks to you as a participant. Therefore, before making a decision, please read and carefully review this information. If you encounter any unclear or unfamiliar terms or expressions, do not hesitate to ask the researchers or physicians involved in the study, who are obliged and willing to answer any questions you may have.

For any inquiries, please contact:
Principal Investigator:
Name and title: *Prim. Katica Cvitkušić Lukenda, specialist in internal medicine, subspecialist in cardiology*
Address: Department of Cardiology, General Hospital Dr. Josip Bencevic, Andrije Stampara 42, 35000 Slavonski Brod.
Phone number: +38535201 685, +38535201700

DESCRIPTION OF THE KEY ISSUE AND RESEARCH HYPOTHESIS

Coronary angiography is a diagnostic method that is inherently invasive and causes stress in patients, disrupting the body's balance, which may result in disorders of the cardiovascular system and kidney function. The procedure involves the use of a contrast agent that enables visualization of the coronary arteries to assess whether they are healthy or show atherosclerotic changes. In addition to the contrast, X-ray radiation is used to obtain images of the blood vessels. The duration of radiation exposure is associated with increased stress in patients. An increase in stress levels can worsen existing cardiovascular or kidney disease, or lead to new organ damage.

Drugs from the group of sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors) are a new class of medications used to lower blood glucose levels. Clinical studies investigating the effects of SGLT2 inhibitors, such as empagliflozin, in patients with and without diabetes have demonstrated beneficial effects on cardiovascular and renal outcomes.

One of the proposed mechanisms of action of this drug is the reduction of oxidative stress in the body. It is hypothesized that administration of a single dose of the SGLT2 inhibitor empagliflozin before coronary angiography will reduce stress in the body and promote a faster return to the natural physiological balance. In this way, the potential risks of adverse effects related to the procedure itself could be reduced.

OBJECTIVE AND PURPOSE OF THE STUDY

The aim of this study is to determine the effect of a single dose of the SGLT2 inhibitor, empagliflozin, administered before elective diagnostic coronary angiography, on oxidative stress during the procedure.

YOUR ROLE AS A PARTICIPANT IN THE STUDY

You have been referred for elective (planned) diagnostic coronary angiography to determine whether you have atherosclerotic coronary artery disease or progression of an already known coronary condition.

Coronary angiography is performed in the standard manner, through either the radial or femoral artery, which is punctured through the skin. Before the procedure, an intravenous line will be placed as part of standard medical care.

As a participant, you will be randomly assigned to either the study group or the control group. The study group will receive, in addition to standard care, a single 10 mg tablet of empagliflozin two hours before coronary angiography, under medical supervision.

Empagliflozin is a registered medication in the Republic of Croatia and is used for the treatment of diabetes mellitus and heart failure in patients with or without diabetes, in tablet form at a dose of 10 mg.

For the purpose of necessary measurements, a total of 12 ml of venous blood will be collected at three time points: upon admission (fasting), 4 hours after, and 24 hours after coronary angiography. From these blood samples, complete blood count, blood glucose, kidney and liver function, cardiac function and injury biomarkers, as well as an inflammatory biomarker, will be determined.

Additionally, separate samples will be analyzed to assess total antioxidant capacity, total plasma proteins and immunoglobulin G, and DNA damage, as indicators of stress and inflammation before and after coronary angiography.

All samples will be anonymized and labeled with a specific code. The persons performing the laboratory analyses will not know the participants' identities; they will only have access to the codes corresponding to each sample for data entry and analysis. Collected data will be used in aggregated form for scientific publications, and the identity of participants will not be disclosed at any point.

POTENTIAL BENEFITS OF PARTICIPATION

The data obtained from this scientific research will be published in scientific journals, but your identity will remain completely anonymous.

You may not experience any direct personal benefit from participating in this study; however, the findings obtained may contribute to a better understanding of the processes involved in oxidative damage and the potential role of drugs with antioxidant effects.

You will be informed of any important new information obtained during the course of the study.

POTENTIAL RISKS OF PARTICIPATION

There is a potential risk of an allergic reaction after administration of a single dose of empagliflozin, as with all other medications, although this is very rare.

According to previous studies, the risk of hypoglycemia is comparable to that of placebo.

If you experience sweating, trembling, weakness, or shortness of breath, you should immediately inform the medical staff.

ARE YOU REQUIRED TO PARTICIPATE IN THE STUDY?

Your decision to participate in this study is entirely free and voluntary. You will decide independently whether or not you wish to take part. You may withdraw from the study at any time and for any reason, without any consequences.

CONFIDENTIALITY AND RIGHT OF ACCESS TO DOCUMENTATION

All your personal data will be stored and processed electronically. The principal investigator and their associates are required to fully adhere to the prescribed procedures for the protection of personal data.

You will be entered into our database under a unique code/identifier assigned after you have signed the informed consent form.

Your medical documentation will only be reviewed by the principal investigator and their associates, and your name will never be disclosed to third parties. Representatives of the Ethics Committee of the institution where the study is being conducted may also have access to your documentation.

USE OF DATA OBTAINED IN THIS SCIENTIFIC STUDY

The data obtained in this scientific research may be useful in clinical practice as well as for the further development and advancement of science. Therefore, it is expected that the results may be published in relevant scientific journals and publications. Your identity will remain completely anonymous and protected at all times.

WHO APPROVED THIS STUDY?

This study has been reviewed and approved by the Ethics Committee of the General Hospital Dr. Josip Benčević after a thorough evaluation of the submitted research proposal and accompanying documentation.

The research proposal has also been approved by the Ethics Committee of the Institute for Medical Research and Occupational Health in Zagreb and the Bioethics Committee of the Ruđer Bošković Institute in Zagreb.

The study will be conducted in accordance with all applicable guidelines, ensuring the proper conduct of research and the safety of participants, including the *Good Clinical Practice (GCP) Guidelines* and the *Declaration of Helsinki*.

WHO ELSE WILL BE INFORMED ABOUT THIS STUDY?

Your participation in this scientific study may also be communicated to your primary care physician.

YOUR WRITTEN CONSENT TO PARTICIPATE IN THIS STUDY

A copy of the document (signature page) that you will sign if you agree to participate in this study will be provided to both you and the principal investigator. The original document will be retained and securely stored by the principal investigator.

Thank you for reading this document and for considering participation in this scientific study.

This information sheet has been prepared in accordance with the provisions of the Health Care Act of the Republic of Croatia (NN 121/03) and the Patients' Rights Act of the Republic of Croatia (NN 169/04).

Consent for Participation of an Adult Subject in the Study

- I confirm that on the date _____ in _____ I have read the *Participant Information Sheet* for the above-mentioned scientific study and have had the opportunity to ask questions.
- I understand that my participation is voluntary and that I may withdraw from the study at any time, without providing a reason and without any consequences for my health or legal status.
- I understand that only authorized persons — the principal investigator and their associates, as well as members of the Ethics Committee of the institution conducting and approving this research — will have access to my medical documentation. I thereby grant permission for these individuals to access my medical records.

- I agree that my primary care physician (or a family member) may be informed of my participation in this scientific study.
- I wish and consent to participate in the above-mentioned scientific study.
- I consent to the collection of data through the use of a questionnaire.
- I consent to the collection and analysis of biological samples and parameters specified in the study.

Participant's full name (in block letters):

Signature:

Place and date:

Name and surname of the person who conducted the Participant Information and Consent procedure**:**

Signature:

Place and date: