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Rational and design of the multicenter, randomized, triple-blind, placebo-controlled MERCURI-2 trial: proMoting Effective Renoprotection in Cardiac sURgery patients by Inhibition of sodium glucose cotransporter (SGLT)-2

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Short title

MERCURI-2 trial

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Abstract

Introduction

Acute kidney injury (AKI) is a major complication after cardiac surgery and is associated with postoperative morbidity and mortality. Currently, no effective therapy exists to reduce the incidence of postoperative AKI. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are effective in reducing AKI in outpatient settings for patients with chronic kidney disease. We hypothesized that perioperative SGLT2 inhibition will also reduce AKI incidence after cardiac surgery according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

Methods and analysis

We designed a multicenter randomized, placebo-controlled, triple-blinded, superiority trial. A total of 784 patients, aged 18 to 90 years, undergoing cardiac surgery will be included with stratification for sex and type 2 diabetes in a 1:1 ratio. Patients will receive either dapagliflozin 10mg or placebo from the day before until two days after surgery. Serum creatinine will be measured preoperatively and daily the first five days after the operation, and urine output will be measured until the urinary catheter is removed. The primary outcome is the incidence of postoperative AKI according to the KDIGO criteria.

Ethics and dissemination

The medical ethics committee of the Amsterdam UMC and the Dutch competent authority approved the study protocol (currently version 9 January 19 2024). This is an investigator-initiated study. The Amsterdam UMC, as sponsor, retains ownership of all data and publication rights. Results will be submitted for publication in a peer-reviewed international medical journal.

Trial registration number

Clinicaltrials.gov identifier: NCT05590143.

Keywords: acute kidney injury, cardiac surgery, dapagliflozin, SGLT2 inhibitor, randomized controlled trial

Article summary

Strengths and limitations of this study

- The first randomized controlled trial using SGLT2 inhibitors to prevent AKI after cardiac surgery
- Multicenter, randomized, triple-blind and placebo-controlled
- An easily clinically implementable intervention starting only one day prior to the operation
- Repurposing of a widely-used and safe anti-diabetic drug

Introduction

Annually, more than 2 million cardiac surgeries are performed worldwide, and the incidence of cardiac surgery-associated AKI (CSA-AKI) is reported up to 70%.(1) Currently no evidence-based preventive options are available.(2) The reported incidence varies considerably between countries and centers, which may depend on, standards of surgery as well as perioperative care, selected patient population, type of surgery and, perhaps most importantly, disparities in AKI definition and monitoring. The majority (71%) of diagnosed cases of CSA-AKI are classified as stage 1, according to Kidney Disease Improving Global Outcomes (KDIGO) criteria, which include an increase in serum creatinine of ≥ 0.3 mg/dl within 48 hours, ≥ 1.5 times baseline within 7 days, or urine output < 0.5 ml/kg/h for 6-12 hours, and resolve without treatment or medical intervention.(3) However, 12% of cases fall into stage 3, potentially necessitating renal replacement therapy for the management of AKI.(3) CSA-AKI is independently associated with higher postoperative mortality compared to patients without AKI: 3 times higher mortality for patients with stage 1 AKI and up to 37 times higher for patients requiring dialysis (stage 3 AKI). Patients with AKI also have enhanced length of stay in the intensive care unit (ICU) and hospital, and marked increments in cost of care, ranging from 1.21 times higher costs for stage 1 AKI to 2.74 for stage 3 AKI requiring dialysis.(2, 4) In addition, patients with only stage 1 AKI have a higher probability of developing chronic kidney disease (CKD) in the years following surgery, as compared to individuals without postoperative AKI.(5) The risk of death associated with AKI remains increased for up to 10 years after cardiac surgery, even for those with complete recovery of kidney function.(4, 6) It is evident from these data that CSA-AKI represents a major unmet medical need posing a burden on patients and society.

Despite several attempts with a variety of pharmacological interventions, including vasodilators, diuretics, analgesics, antioxidants, cholesterol-lowering and anti-inflammatory drugs, no successful interventions have been identified that prevent CSA-AKI.(7, 8) However, sodium-glucose cotransporter-2 (SGLT2) inhibitors are promising new drugs to prevent CSA-AKI. SGLT2 inhibitors were

initially developed for its glucose-lowering effects by inducing glucosuria.(4) In addition, they have obtained a prominent place in clinical practice as they reduced progression of kidney disease in patients with CKD with or without type 2 diabetes (T2D) in large outcome trials.(9) Moreover, in these trials, SGLT2 inhibitors reduced AKI incidence (HR 0.66, 95% confidence interval (CI) 0.54-0.80), even though it was assessed as a safety endpoint in most trials.(6) The mechanisms by which SGLT2 inhibitors prevent acute or chronic kidney injury are still the subject of research. SGLT2 inhibitors reduce estimated glomerular filtration rate (eGFR) and glomerular pressure, thereby preventing kidney damage.(10) Lowering glomerular hyperfiltration reduces kidney oxygen consumption and may thus ameliorate kidney hypoxia, and since oxygen deprivation is a major contributor to CSA-AKI this might protect against injury.(11) Furthermore, SGLT2 inhibitors improve hemodynamics and exhibit anti-inflammatory properties.(12, 13) Preclinical data has shown that SGLT2 inhibitors reduced renal ischemia-reperfusion injury.(14-16) An overview of the proposed advantages of SGLT2 inhibitors in reducing CSA-AKI is shown in Figure 1.

We conducted a pilot trial to test feasibility, safety and kidney protection of SGLT2 inhibitors in the context of cardiac surgery, the Metabolic and Renal outcomes in Cardiac sUrgery patients Receiving SGLT2 Inhibitors (MERCURI), at the Amsterdam University Medical Centre (UMC). This single-center, open label, randomized phase IV clinical trial, included 55 patients and showed a significant reduction in AKI incidence of 46.7% (95% CI -69.7 to -23.6, p =.001) comparing use of a SGLT2 inhibitor (empagliflozin) with the untreated control group.(17, 18)

The current MERCURI-2 trial investigates the effect of perioperative SGLT2 inhibition on the incidence of AKI in patients undergoing cardiac surgery.

Methods

The MERCURI-2 trial (clinicaltrials.gov identifier: NCT05590143) is a multicenter randomized triple-blind placebo-controlled (1:1) superiority trial in patients undergoing cardiac surgery. The trial is designed to evaluate the effect of dapagliflozin 10 mg once daily, compared to placebo, added to standard of care, on the incidence of CSA-AKI. This is an investigator-initiated study, with Amsterdam UMC as sponsor. The study protocol was approved by the Medical Ethics Committee of the Amsterdam UMC and by the Competent Authorities according to national and international regulations (METC 2022.0795 and EudraCT number 2022-002453-25).

Trial population

Our aim is to enroll 784 adult patients (age 18-90 years) scheduled to undergo elective cardiac surgery. Detailed exclusion criteria are listed (Table 1). Patients with type 1 diabetes (T1D) are excluded because of the risk of SGLT-2 inhibitor-associated euglycemic diabetic keto-acidosis (euDKA) in this patient population. For the same reason, patients with a history of DKA are excluded. Furthermore, patients with type 2 diabetes (T2D) with BMI < 25 kg/m^2 using multiple daily insulin injections are excluded as they phenotypically resemble T1D, placing them at higher risk for euDKA. Patients with a systolic blood pressure below 100 mmHg at time of inclusion are excluded due to the possible blood pressure lowering characteristics of dapagliflozin. Furthermore, patients currently treated with SGLT2 inhibitors or known or suspected allergy to dapagliflozin are excluded from participation.

Study Design

Potentially eligible patients who are scheduled for cardiac surgery will be contacted via telephone, during preoperative hospital admission or during a preoperative hospital visit. Patients will receive both written and oral information. After informed consent is obtained and signed, baseline characteristics such as age, sex, ethnicity, body mass index, blood pressure, American Society of Anesthesiologist (ASA) physical status, medical history and medication use will be collected. The most

recent serum creatinine and glycated hemoglobin A1c (HbA1c), if measured as part of standard medical care, before surgery will be recorded. Patients will subsequently be randomized to dapagliflozin or placebo. Patients will take the first dapagliflozin 10mg or placebo on the day before surgery, between 3 and 8 pm. The second dosage will be taken on the morning before surgery. The remainder dosages will be taken the first and second day after surgery. In case the surgery is postponed, an additional dose will be administered. Patients with T2D on glucose lowering therapy will be advised on how to adjust their current diabetes treatment to prevent potential hypoglycemia (Figure 2).

Serum creatinine will be measured daily until day seven or until discharge from hospital. We aim to collect an additional blood sample from 20% of the participants, both on the day before and after surgery, for potential future analyses. Urine output will be reported as measured during routine medical care, until the urinary catheter is removed. Complications (Supplementary Table 1) and ICU and hospital length of stay will be registered until 30 days after surgery. After 30 days, patients will receive a questionnaire measuring patient reported quality of life and disability with questions from the World Health Organization Disability Assessment Schedule 2.0 (WHO-DAS 2.0), Days at Home in first 30 days (DAH30) and 5-level EuroQol 5D (EQ5DL). Data will be collected using Castor EDC (Amsterdam, The Netherlands), a good clinical practice compliant data management system.(19) The study design is summarized in Figure 3.

Randomization

After inclusion, patients will be randomized by Castor EDC. Block randomization with computer generated blocks of 4, 6 or 8 patients will be used. The block size will be unknown to the researchers. Randomization is stratified for sex, presence of T2D and study site.

Allocation concealment and blinding

Investigators will register the patient in Castor EDC. The randomization outcome will be exclusively visible to the trial pharmacy. Treatment allocation of a patient will only be disclosed in case of a suspected unexpected serious adverse reaction. Study treatment is provided in identical boxes, each containing either six over-encapsulated tablets dapagliflozin or placebo. To ensure blinding, the original 10mg dapagliflozin (AstraZeneca, Södertälje, Sweden) tablets will be over-encapsulated by the GMP certified trial pharmacy at Amsterdam UMC. The capsules will be filled with microcrystalline cellulose PH102. The matching placebo capsules will solely contain microcrystalline cellulose PH102. Patients, healthcare providers and investigators will be blinded to group allocation until database lock.

Outcomes and outcome adjudication

The primary outcome of this study is the incidence of AKI according to the KDIGO criteria (Table 2) based on serum creatinine and urine output. Serum creatinine levels and urine output will be reviewed by a second investigator and the study monitor to ensure primary outcome adjudication. Other secondary outcome parameters include the difference in the primary outcome between males and females, incidence of individual AKI stages according to KDIGO criteria, the maximum change of creatinine postoperative compared to the baseline creatinine preoperative, the postoperative creatinine course, the incidence of de novo postoperative atrial fibrillation, registered on a 12-lead ECG and length of stay in the Intensive Care Unit and the hospital measured in days (Table 3). Complications within the first 30 days after surgery (Supplementary table 1) are retrieved from the electronic patient file and collected. The outcomes of the patient reported quality of life and disability measured with three questionnaires: DAH30(20), WHO-DAS 2.0(21) and EQ5D5L(22) will be evaluated across the treatment groups. Safety outcomes of SGLT2 inhibitors such as genital mycotic infections, diabetic keto-acidosis and hypoglycemia will be assembled and compared between the treatment groups.

Study oversight and organization

The core team of the MERCURI-2 investigator group consists of three principal investigators from the Amsterdam UMC and the trial coordinator. This team is responsible for the design of the study protocol and progress of the trial. The core team will draft the final report that will be approved by all MERCURI-2 investigators. The trial is conducted under supervision of an independent Data and Safety Monitoring Board (DSMB), consisting of two clinical experts and an epidemiologist. An independent statistician will present unblinded data to the DSMB. The DSMB reviews the incidence of AKI at two predefined intervals (after inclusion of 200 and 400 participants) to assess safety and efficacy outcomes. The DSMB can advise to stop the trial if patient safety is at risk or in case of overwhelming efficacy.

The study will be monitored by the Clinical Research Unit from the Amsterdam UMC. Each involved study site will receive a baseline and close out visit and additional visits after inclusion of 10 and 100 participants during the study. The monitor will approve informed consent papers, verify the serious adverse events and check data collection and quality of registration.

Sample size calculation

Sample size is based on Fisher's Exact Test, with an expected AKI incidence in the placebo group of 22%, based on previous cohorts,(2) taking a conservative estimation. A relative risk of 0.64 based on AKI reduction by SGLT2 inhibitors in previous trials(6) translates into an absolute risk reduction of 7.9% and incidence in the intervention group of 14.1%. The required total sample size to find such a difference with two-sided alpha 0.05 and 80% power is 784. We therefore aim to include 392 patients per arm.

Achieve sample size

Based on previous trials and the short trial duration per patient, we expect a low number of drop-outs. If a drop-out occurs, for example due to surgery cancellation or withdrawal of informed consent, dropouts will be replaced to maintain sufficient statistical power.

Statistical analyses

The baseline characteristics of all subjects, per treatment group, will be outlined in a table describing variables such as demographic variables, weight, length, relevant medical history and current medication use. Continuous data will be presented as mean with standard deviation (SD) or as median with interquartile range (IQR), depending on the distribution of the data. Distribution of data will be assessed with histograms, Q-Q plots and the Shapiro-Wilk test. We expect a small percentage of missing data due to the in-hospital setting and short duration of the study.

Primary study outcome

Statistical analyses will be based on an intention-to-treat approach. The main analysis will concern the comparison of the incidence of AKI between both groups. The disparity in AKI incidence will be evaluated using the Fisher's exact test. In addition, the risk difference of AKI between both groups along with the associated 95% confidence intervals (CIs) will be presented.

Secondary study outcomes

Heterogeneity of treatment effect between males and females will be studied for the primary outcome by examining a treatment-by-sex interaction effect in a logistic regression model with treatment and sex as main effects. Similarly, the heterogeneity of treatment effect in patients with and without T2D will be studied using the same approach. Treatment effect estimates, along with their corresponding 95% CIs, will be reported for each specific subgroup. Other secondary outcomes will be presented as number of events and analyzed with the Fisher's exact test. Continuous data will be presented as mean with SD and differences will be assessed employing the Student's t-test.

Generalized mixed-effect models will be constructed to examine potential differences in the repeated measurements. Predefined post hoc analysis will be conducted to estimate the influence of age, BMI, baseline kidney function and the presence of heart failure on the treatment effect and their possible interactions on the primary outcome. A 2-sided p-value <0.05 will be considered statistically significant. Statistical uncertainty will be expressed in 2-sided 95% confidence intervals.

Ethics and dissemination

All participants will receive a written patient information folder, accompanied by additional oral explanation from the study personnel. A subject screening and enrolment log will only be accessible to study personal and saved on a secure server. Whenever a patient is enrolled in the study, participation in the trial will be recorded in the electronic patient database, visible for all involved health care workers. A subjects' insurance has been taken out.

Planning

The first patient was included in June 2023. The trial has an estimated duration of three years. Whenever amendments to the protocol will be made, they will be subjected to the Ethics Committee of the Amsterdam UMC for approval and subsequently communicated to all involved study personnel. As sponsor, the Amsterdam UMC will remain owner of all data and rights to publication. The manuscript will be drafted by the core team and approved by the MERCURI-2 investigators.

Data statement

Full protocol, dataset and data management plan will be available upon reasonable request.

Patient involvement

The patient representatives of the Dutch patient societies for heart disease (Harteraad) and kidney disease (Nierpatienten Vereniging Nederland) were involved in in the design phase of the trial. Their insights were incorporated into the trial's planning and execution. They also reviewed the patient

information letter and provided advice on how to enhance clarity and comprehensibility. Throughout the trial, these representatives will receive updates on the progress of the trial.

Acknowledgements

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Author statement

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Competing interest

DHvR serves as a consultant and received honoraria from Boehringer Ingelheim and Lilly, Merck, Novo Nordisk, Sanofi, and AstraZeneca and has received research operating funds from Boehringer Ingelheim and Lilly Diabetes Alliance, AstraZeneca, and Novo Nordisk; all honoraria are paid to his employer (Amsterdam University Medical Centers, location VU University Medical Center).

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Tables and figures

Table 1. Inclusion and exclusion criteria of the MERCURI-2 trial.

Inclusion criteria	Exclusion criteria
Signed informed consent	T1D
Aged 18-90 years	T2D with a BMI < 25 and using multiple daily insulin injections (both short and long-acting insulin)
Scheduled for elective cardiac surgery	History of diabetic keto acidosis
	Systolic blood pressure < 100mmHg at time of inclusion
	Reduced kidney function at baseline with eGFR < 20ml/min at time of inclusion
	Current treatment with SGLT2 inhibitors
	Known or suspected allergy to trial products or other drugs in the same class
	Emergency surgery, defined as in need of surgery for medical reasons within 72 hours
	Woman of childbearing potential who is pregnant, breast feeding or intend to become pregnant or is not using adequate contraceptive methods

Abbreviations: BMI = Body Mass Index; eGFR = estimated glomerular filtration rate; SGTL2 = sodium-glucose cotransporter-2; T1D = Type 1 Diabetes; T2D = Type 2 Diabetes

Table 2. Definition and staging of Acute Kidney Injury according to Kidney Disease Improving Global Outcomes (KDIGO) criteria.

Stage	Acute Kidney Injury	Difference	Time frame
1	Serum Creatinine	≥0.3 mg/dl (26.5 mcmol/l) OR	Within 48 hours
		≥1.5 times baseline	Within 7 days
	Urine Output	<0.5 ml/kg/h	For 6-12 hours
2	Serum Creatinine	2.0 – 2.9 times baseline	
	Urine Output	<0.5 ml/kg/h	For >12 hours
3	Start Renal Replacement Therapy		
	Serum Creatinine	3.0 times baseline OR	Within 7 days
		≥4.0 mg/dl	
	Urine Output	<0.3 ml/kg/h OR	>24 hours
		Anuria	>12 hours

Table 3. Recorded secondary and exploratory outcomes

Outcome measures	Time Frame	Definition
Secondary outcomes		
Individual AKI stages	≤ 7 days postoperative	Incidence of stage 1, 2 and 3 AKI according to KDIGO criteria
Creatinine	≤ 7 days postoperative	Postoperative maximum change of creatinine compared to baseline creatinine
AF	≤ 7 days postoperative	Postoperative atrial fibrillation (AF) recorded with an electrocardiogram (ECG) or for which treatment is initiated
LoS-ICU	≤ 30 days postoperative	Length of Stay in the Intensive Care Unit (ICU), measured in days from transfer to ICU until discharge from ICU
LoS-Hos	≤ 30 days postoperative	Length of Stay in the Hospital, measured in days from surgery until discharge from the hospital
MAKE	≤ 30 days postoperative	Major Adverse Kidney Events (MAKE). Composite endpoint of death, new dialysis, and worsened renal function
MACE	≤ 30 days postoperative	Major Adverse Cardiovascular Events (MACE). Composite endpoint of cardiovascular death, nonfatal myocardial infarction, nonfatal ischaemic cerebral vascular accident (iCVA) and hospitalization for heart failure
Safety outcomes	≤ 30 days postoperative	Genital mycotic infections, diabetic keto-acidosis and hypoglycemia
Hypoglycemia	≤ 3 days postoperative	Incidence of hypoglycaemia (blood glucose < 4 mmol/l) detected during routine peri-operative glucose measurements
Hyperglycemia	≤ 3 days postoperative	Incidence of hyperglycaemia (blood glucose > 10 mmol/l) detected during routine peri-operative glucose measurements
Cardiac biomarker 1: troponin	From transfer to ICU until 48 hours postoperatively	Peak troponin concentration as routinely measured during clinical practice
Cardiac biomarker 2: CK-MB	From transfer to ICU until 48 hours postoperatively	Peak CK-MB concentration as routinely measured during clinical practice
Patient-reported quality of recovery 1	Recorded at 30 days postoperatively	According to DAH30: Days at Home in first 30 days
Patient-reported quality of recovery 2	Recorded at 30 days postoperatively	According to WHO-DAS2.0: World Health Organization Disability Assessment Schedule 2.0

Patient-reported quality of recovery 3	Recorded at 30 days postoperatively	According to EQ5D5L: 5 level EuroQol 5D questionnaire
Exploratory outcomes		
Systemic hemodynamics 1	From start of anaesthesia until discharge from the ICU, assessed up to 72 hours	Perioperative hourly average heart rate
Systemic hemodynamics 2	From start of anaesthesia until discharge from the ICU, assessed up to 72 hours	Perioperative hourly average mean arterial blood pressure
Systemic hemodynamics 3	From start of anaesthesia until discharge from the ICU, assessed up to 72 hours	Perioperative hourly average cardiac output (l/min)
Urinary oxygenation	From start of anaesthesia until discharge from the ICU, assessed up to 72 hours	Perioperative hourly average mean oxygen tension measured in the bladder
Postoperative LVF	≤ 30 days postoperative	Qualitative assessment (categorized as normal, or mildly, moderately or severely reduced function) of LVF as noted by the echocardiographer for routinely performed postoperative echocardiography performed during routine follow-up
Health care costs	Recorded at 30 days postoperatively	Using the iMCQ: IMTA (Institute for Medical Technology Assessment) Medical Consumption Questionnaire
Productivity costs	Recorded at 30 days postoperatively	Using the iPCQ: IMTA (Institute for Medical Technology Assessment) Productivity Cost Questionnaire

Abbreviations: AF = atrial fibrillation; AKI = acute kidney injury, ECG = electrocardiogram; ICU = Intensive Care Unit; KDIGO criteria = Kidney Disease Improving Global Outcomes; LoS-Hos = Length of Stay in the Hospital; LoS-ICU = Length of Stay in the Intensive Care Unit; LVF = Left Ventricle Function; MACE = Major Adverse Cardiovascular Events; MAKE = Major Adverse Kidney Events;

Supplementary Table 1. Recorded complications of the MERCURI-2 trial

Complications
Arrythmia
Myocardial infarction
Heart failure/ pleural effusion
Pericarditis/ pericardial effusion
Pneumothorax
Cerebrovascular stroke or haemorrhage
Sternal wound infections
Pneumonia
Sepsis/ bacteraemia
Urinary tract infections
Delirium
Coagulation disorders

Deep venous thrombosis/ pulmonary embolus
Re-operation
Complications already defined as secondary outcomes

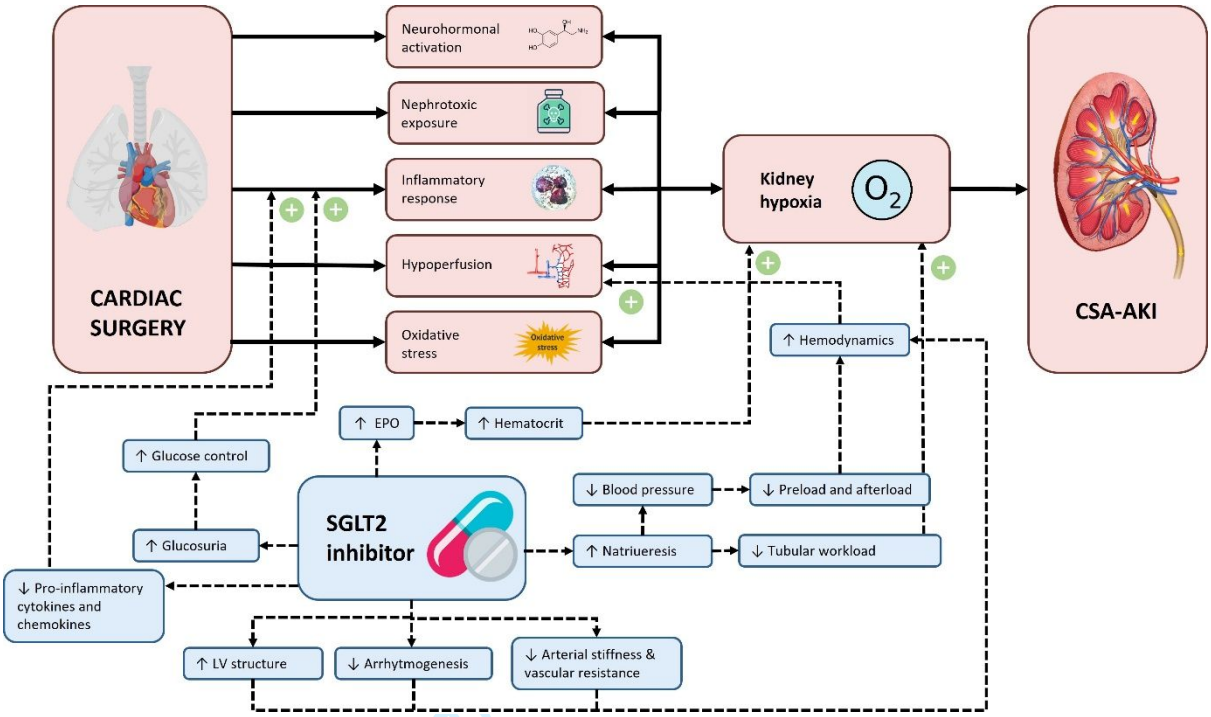

Figure 1: Overview of the proposed advantages of SGLT2 inhibitors in reducing CSA-AKI.

Abbreviations: CSA-AKI = cardiac surgery-associated acute kidney injury; EPO = erythropoietin; LV = Left ventricle; SGTL2 = sodium-glucose cotransporter-2;

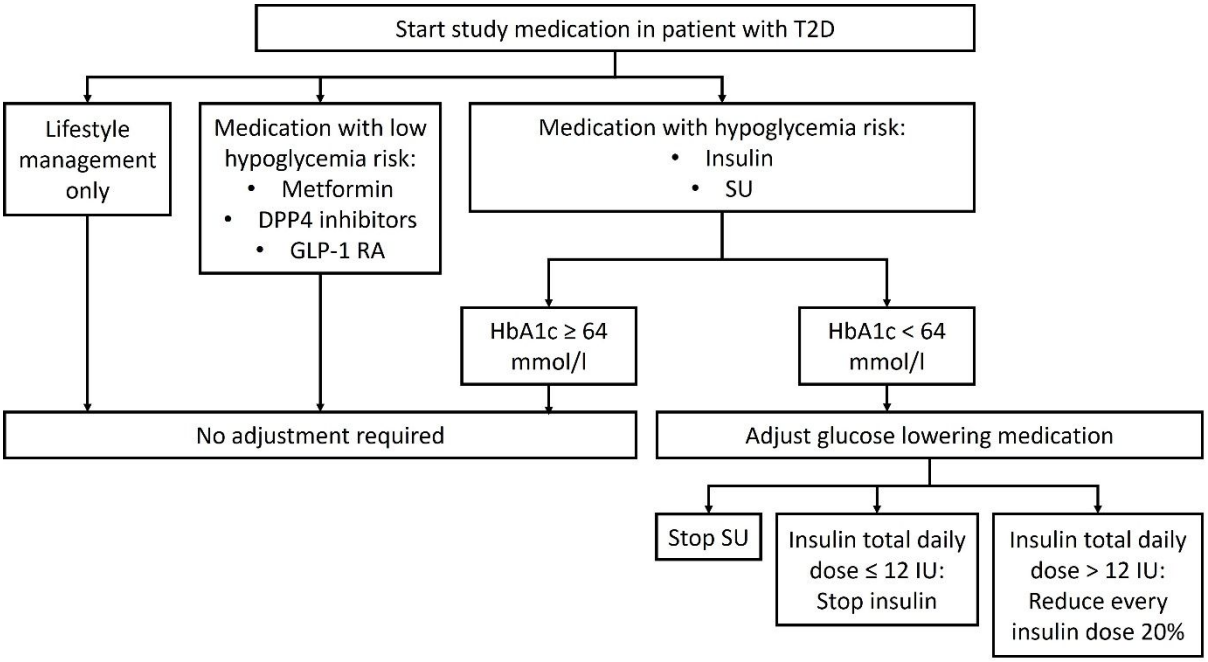

Figure 2: Treatment algorithm for adjustment of glucose lowering therapy in patients with T2D

Abbreviations: DPP4 = Dipeptidyl Peptidase IV; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA1c = hemoglobin A1c; IU = international unit; SU = sulfonylureas; T2D = Type 2 diabetes

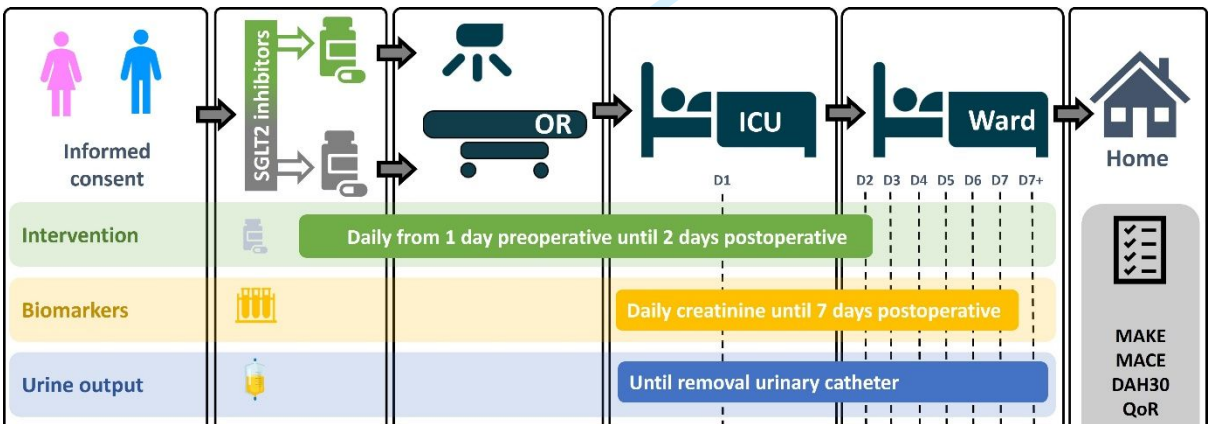

Figure 3: Summary of the study flow of the MERCURI-2 trial.

Abbreviations: AF = atrial fibrillation; DAH30 = Days at Home in first 30 days; ECG = electrocardiogram; ICU = Intensive Care Unit; MACE = Major Adverse Cardiovascular Events; MAKE = Major Adverse Kidney Events; OR = Operation Room; QoR = Quality of Recovery; SGLT2 =sodium-glucose cotransporter-2.

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Study protocol of the multicenter, randomized, triple-blind, placebo-controlled MERCURI-2 trial: proMoting Effective Renoprotection in Cardiac sURgery patients by Inhibition of sodium glucose cotransporter (SGLT)-2

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Study protocol of the multicenter, randomized, triple-blind, placebo-controlled MERCURI-2 trial: proMoting Effective Renoprotection in Cardiac sURgery patients by Inhibition of sodium glucose cotransporter (SGLT)-2

Short title

MERCURI-2 trial

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Abstract

Introduction

Acute kidney injury (AKI) is a major complication after cardiac surgery and is associated with postoperative morbidity and mortality. Currently, no effective therapy exists to reduce the incidence of postoperative AKI. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are effective in reducing AKI in outpatient settings for patients with chronic kidney disease. We hypothesized that perioperative SGLT2 inhibition will also reduce AKI incidence after cardiac surgery according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

Methods and analysis

We designed a multicenter randomized, placebo-controlled, triple-blinded, superiority trial. A total of 784 patients, aged above 18 years, undergoing cardiac surgery will be included with stratification for sex and type 2 diabetes in a 1:1 ratio. Patients will receive either dapagliflozin 10mg or placebo from the day before until two days after surgery. Serum creatinine will be measured preoperatively and daily the first seven days after the operation, and urine output will be measured until the urinary catheter is removed. The primary outcome is the incidence of postoperative AKI according to the KDIGO criteria.

Ethics and dissemination

The medical ethics committee of the Amsterdam UMC and the Dutch competent authority approved the study protocol (currently version 9 January 19 2024). This is an investigator-initiated study. The Amsterdam UMC, as sponsor, retains ownership of all data and publication rights. After completion of the trial, results will be disseminated to participants, patient societies and physicians via a network

meeting and digital newsletter. Results will be submitted for publication in a peer-reviewed international medical journal and presented on (inter)national congresses.

Trial registration number

Clinicaltrials.gov identifier: NCT05590143.

Keywords: acute kidney injury, cardiac surgery, dapagliflozin, SGLT2 inhibitor, randomized controlled trial

Article summary

Strengths and limitations of this study

- A randomized controlled trial using SGLT2 inhibitors to prevent AKI after cardiac surgery
- Multicenter, randomized, triple-blind and placebo-controlled
- An easily clinically implementable intervention starting only one day prior to the operation
- Repurposing of a widely-used and safe kidney protective drug
- As postoperative AKI is the primary outcome in this study, further research is required to investigate the longer term impact.

Introduction

Annually, more than 2 million cardiac surgeries are performed worldwide, and the incidence of cardiac surgery-associated AKI (CSA-AKI) is reported up to 70%.[1] Currently no evidence-based preventive options are available.[2] The reported incidence varies considerably between countries and centers, which may depend on, standards of surgery as well as perioperative care, selected patient population, type of surgery and, perhaps most importantly, disparities in AKI definition and monitoring. The majority (71%) of diagnosed cases of CSA-AKI are classified as stage 1, according to Kidney Disease Improving Global Outcomes (KDIGO) criteria, which include an increase in serum creatinine of ≥ 0.3 mg/dl within 48 hours, ≥ 1.5 times baseline within 7 days, or urine output < 0.5 ml/kg/h for 6-12 hours, and resolve without treatment or medical intervention.[3] However, 12% of cases fall into stage 3, potentially necessitating renal replacement therapy for the management of AKI.[3] CSA-AKI is independently associated with higher postoperative mortality compared to patients without AKI: 3 times higher mortality for patients with stage 1 AKI and up to 37 times higher for patients requiring dialysis (stage 3 AKI). Patients with AKI also have enhanced length of stay in the intensive care unit (ICU) and hospital, and marked increments in cost of care, ranging from 1.21 times higher costs for stage 1 AKI to 2.74 for stage 3 AKI requiring dialysis.[2, 4] In addition, patients with only stage 1 AKI have a higher probability of developing chronic kidney disease (CKD) in the years following surgery, as compared to individuals without postoperative AKI.[5] The risk of death associated with AKI remains increased for up to 10 years after cardiac surgery, even for those with complete recovery of kidney function.[4, 6] It is evident from these data that CSA-AKI represents a major unmet medical need posing a burden on patients and society.

Despite several attempts with a variety of pharmacological interventions, including vasodilators, diuretics, analgesics, antioxidants, cholesterol-lowering and anti-inflammatory drugs, no successful interventions have been identified that prevent CSA-AKI.[7, 8] However, sodium-glucose cotransporter-2 (SGLT2) inhibitors are promising new drugs to prevent CSA-AKI. SGLT2 inhibitors were initially

developed for its glucose-lowering effects by inducing glucosuria.[4] In addition, they have obtained a prominent place in clinical practice as they reduced progression of kidney disease in patients with CKD with or without type 2 diabetes (T2D) in large outcome trials.[9] Moreover, in these trials, SGLT2 inhibitors reduced AKI incidence (HR 0.66, 95% confidence interval (CI) 0.54-0.80), even though it was assessed as a safety endpoint in most trials.[6] The mechanisms by which SGLT2 inhibitors prevent acute or chronic kidney injury are still the subject of research. SGLT2 inhibitors reduce estimated glomerular filtration rate (eGFR) and glomerular pressure, thereby preventing kidney damage.[10] Lowering glomerular hyperfiltration reduces kidney oxygen consumption and may thus ameliorate kidney hypoxia, and since oxygen deprivation is a major contributor to CSA-AKI this might protect against injury.[11] Furthermore, SGLT2 inhibitors improve hemodynamics and exhibit anti-inflammatory properties.[12, 13] Preclinical data has shown that SGLT2 inhibitors reduced renal ischemia-reperfusion injury.[14-16] An overview of the proposed advantages of SGLT2 inhibitors in reducing CSA-AKI is shown in Figure 1.

We conducted a pilot trial to test feasibility and kidney protection of SGLT2 inhibitors in the context of cardiac surgery, the Metabolic and Renal outcomes in Cardiac sUrgery patients Receiving SGLT2 Inhibitors (MERCURI), at the Amsterdam University Medical Centre (UMC). This single-center, open label, randomized phase IV clinical trial, included 55 patients and showed a significant reduction in AKI incidence of 46.7% (95% CI -69.7 to -23.6, p =.001) comparing use of a SGLT2 inhibitor (empagliflozin) with the untreated control group.[17]

The current MERCURI-2 trial investigates the effect of perioperative SGLT2 inhibition on the incidence of AKI in patients undergoing cardiac surgery.

Methods

The MERCURI-2 trial (clinicaltrials.gov identifier: NCT05590143) is a multicenter randomized triple-blind placebo-controlled (1:1) superiority trial in patients undergoing cardiac surgery. The trial is designed to evaluate the effect of dapagliflozin 10 mg once daily, compared to placebo, added to standard of care, on the incidence of CSA-AKI. This is an investigator-initiated study, with Amsterdam UMC as sponsor. The study protocol was approved by the Medical Ethics Committee of the Amsterdam UMC and by the Competent Authorities according to national and international regulations (METC 2022.0795 and EudraCT number 2022-002453-25). The first patient was included in June 2023. The trial has an estimated duration of three years.

Trial population

Our aim is to enroll 784 adult patients (aged above 18years) scheduled to undergo elective cardiac surgery. Detailed exclusion criteria are listed (Table 1). Patients with type 1 diabetes (T1D) are excluded because of the risk of SGLT-2 inhibitor-associated euglycemic diabetic keto-acidosis (euDKA) in this patient population. For the same reason, patients with a history of DKA are excluded. Furthermore, patients with type 2 diabetes (T2D) with BMI < 25 kg/m^2 using multiple daily insulin injections are excluded as they phenotypically resemble T1D, placing them at higher risk for euDKA. Patients with a systolic blood pressure below 100 mmHg at time of inclusion are excluded due to the possible blood pressure lowering characteristics of dapagliflozin. Furthermore, patients currently treated with SGLT2 inhibitors or known or suspected allergy to dapagliflozin are excluded from participation.

Study Design

Potentially eligible patients who are scheduled for cardiac surgery will be contacted via telephone, during preoperative hospital admission or during a preoperative hospital visit. Patients will receive both written and oral information (Supplementary File 1). After informed consent is obtained and

signed, baseline characteristics such as age, sex, ethnicity, body mass index, blood pressure, American Society of Anesthesiologist (ASA) physical status, medical history and medication use will be collected. The most recent serum creatinine and glycated hemoglobin A1c (HbA1c), if measured as part of standard medical care, before surgery will be recorded. Patients will subsequently be randomized to dapagliflozin or placebo. Patients will take the first dapagliflozin 10mg or placebo on the day before surgery, between 3 and 8 pm. The second dosage will be taken on the morning before surgery. The remainder dosages will be taken the first and second day after surgery. In case the surgery is postponed, an additional dose will be administered. Patients with T2D on glucose lowering therapy will be advised on how to adjust their current diabetes treatment to prevent potential hypoglycemia (Figure 2).

Serum creatinine will be measured daily until day seven or until discharge from hospital. We aim to collect an additional blood sample from 20% of the participants, both on the day before and after surgery, for potential future analyses. Urine output will be reported as measured during routine medical care, until the urinary catheter is removed. Complications (Supplementary Table 1) and ICU and hospital length of stay will be registered until 30 days after surgery. After 30 days, patients will receive a questionnaire measuring patient reported quality of life and disability with questions from the World Health Organization Disability Assessment Schedule 2.0 (WHO-DAS 2.0), Days at Home in first 30 days (DAH30) and 5-level EuroQol 5D (EQ5DL). Data will be collected using Castor EDC (Amsterdam, The Netherlands), a good clinical practice compliant data management system.[18] The study design is summarized in Figure 3.

Randomization

After inclusion, patients will be randomized by Castor EDC. Block randomization with computer generated blocks of 4, 6 or 8 patients will be used. The block size will be unknown to the researchers. Randomization is stratified for sex, presence of T2D and study site.

Allocation concealment and blinding

Investigators will register the patient in Castor EDC. The randomization outcome will be exclusively visible to the trial pharmacy. Treatment allocation of a patient will only be disclosed in case of a suspected unexpected serious adverse reaction. Study treatment is provided in identical boxes, each containing either six over-encapsulated tablets dapagliflozin or placebo. To ensure blinding, the original 10mg dapagliflozin (AstraZeneca, Södertälje, Sweden) tablets will be over-encapsulated by the GMP certified trial pharmacy at Amsterdam UMC. The capsules will be filled with microcrystalline cellulose PH102. The matching placebo capsules will solely contain microcrystalline cellulose PH102. Patients, healthcare providers and investigators will be blinded to group allocation until database lock.

Outcomes and outcome adjudication

The primary outcome of this study is the incidence of AKI according to the KDIGO criteria (Table 2) based on serum creatinine and urine output. Serum creatinine levels and urine output will be reviewed by a second investigator and the study monitor to ensure primary outcome adjudication. Other secondary kidney-related outcome parameters include the difference in the primary outcome between males and females, incidence of individual AKI stages according to KDIGO criteria, the maximum change of creatinine postoperative compared to the baseline creatinine preoperative, the postoperative creatinine course, the number of patients with a persistent kidney failure (defined as creatinine concentration ≥ 200% of baseline creatinine concentration after 30 days), the number of patients requiring dialysis, the number of patients who died due to a primary kidney-related cause. The cardiac-related secondary outcomes include the incidence of de novo postoperative atrial fibrillation, registered on a 12-lead ECG, the maximum postoperative creatine kinase (CK)-MB or troponine concentrations, the number of patients who developed new onset cardiac arrhythmia, new myocardial infarctions or cerebrovascular accident confirmed by computed tomography (CT)-scan wihtin the first 30 days postoperative, as well as the number of patients who required an extended hospital stay due to heart failure, needed readmission for heart failure, or died from a primary cardiac

cause. Furthermore, length of stay in the Intensive Care Unit and the hospital measured in days and all cause mortality were collected (Table 3). Complications within the first 30 days after surgery (Supplementary table 1) are retrieved from the electronic patient file and collected. The outcomes of the patient reported quality of life and disability measured with three questionnaires: DAH30[19], WHO-DAS 2.0[20] and EQ5D5L[21] will be evaluated across the treatment groups. Safety outcomes of SGLT2 inhibitors such as genital mycotic infections, diabetic keto-acidosis and hypoglycemia will be assembled and compared between the treatment groups.

Study oversight and organization

The core team of the MERCURI-2 investigator group consists of three principal investigators from the Amsterdam UMC and the trial coordinator. This team is responsible for the design of the study protocol and progress of the trial. The core team will draft the final report that will be approved by all MERCURI-2 investigators. The trial is conducted under supervision of an independent Data and Safety Monitoring Board (DSMB), consisting of two clinical experts and an epidemiologist. An independent statistician will present unblinded data to the DSMB. The DSMB reviews the incidence of AKI at two predefined intervals (after inclusion of 200 and 400 participants) to assess safety and efficacy outcomes. The DSMB can advise to stop the trial if patient safety is at risk or in case of overwhelming efficacy.

The study will be monitored by the Clinical Research Unit from the Amsterdam UMC. Each involved study site will receive a baseline and close out visit and additional visits after inclusion of 10 and 100 participants during the study. The monitor will approve informed consent papers, verify the serious adverse events and check data collection and quality of registration.

Regarding serious adverse events (SAE's), the sponsor will yearly present an overview of the SAE's via CTIS. Suspected unexpected serious adverse reactions (SUSARs) will be reported earlier via EudraVigilance depending on the seriousness of the reaction and will be as follows: In the case of fatal or life-threatening SUSARs, as soon as possible and in any event not later than seven days after

the sponsor became aware of the reaction, in the case of non-fatal or non-life-threatening SUSARs, not later than fifteen days after the sponsor became aware of the reaction and In the case of a SUSARs which was initially considered to be non-fatal or nonlife threatening but which turns out to be fatal or life-threatening, as soon as possible and in any event not later than seven days after the sponsor became aware of the reaction being fatal or life-threatening.

Sample size calculation

Sample size is based on Fisher's Exact Test, with an expected AKI incidence in the placebo group of 22%, based on previous cohorts,[2] taking a conservative estimation. A relative risk of 0.64 based on AKI reduction by SGLT2 inhibitors in previous trials[6] translates into an absolute risk reduction of 7.9% and incidence in the intervention group of 14.1%. The required total sample size to find such a difference with two-sided alpha 0.05 and 80% power is 784. We therefore aim to include 392 patients per arm.

Achieve sample size

Based on previous trials and the short trial duration per patient, we expect a low number of drop-outs. If a drop-out occurs, for example due to surgery cancellation or withdrawal of informed consent, dropouts will be replaced to maintain sufficient statistical power.

Statistical analyses

The baseline characteristics of all subjects, per treatment group, will be outlined in a table describing variables such as demographic variables, weight, length, relevant medical history and current medication use. Continuous data will be presented as mean with standard deviation (SD) or as median with interquartile range (IQR), depending on the distribution of the data. Distribution of data will be assessed with histograms, Q-Q plots and the Shapiro-Wilk test. We expect a small percentage of missing data due to the in-hospital setting and short duration of the study.

Primary study outcome

Statistical analyses will be based on an intention-to-treat approach. The main analysis will concern the comparison of the incidence of AKI between both groups. The disparity in AKI incidence will be evaluated using the Fisher's exact test. In addition, the risk difference of AKI between both groups along with the associated 95% confidence intervals (CIs) will be presented.

Secondary study outcomes

Heterogeneity of treatment effect between males and females will be studied for the primary outcome by examining a treatment-by-sex interaction effect in a logistic regression model with treatment and sex as main effects. Similarly, the heterogeneity of treatment effect in patients with and without T2D will be studied using the same approach. Treatment effect estimates, along with their corresponding 95% CIs, will be reported for each specific subgroup. Other secondary outcomes will be presented as number of events and analyzed with the Fisher's exact test. Continuous data will be presented as mean with SD and differences will be assessed employing the Student's t-test. Generalized mixed-effect models will be constructed to examine potential differences in the repeated measurements. Predefined post hoc analysis with regression analyses will be conducted to estimate the influence of age, BMI, baseline kidney function and the presence of heart failure on the treatment effect and their possible interactions on the primary outcome. A 2-sided p-value <0.05 will be considered statistically significant. Statistical uncertainty will be expressed in 2-sided 95% confidence intervals.

Ethics and dissemination

All participants will receive a written patient information folder, accompanied by additional oral explanation from the study personnel. A subject screening and enrolment log will only be accessible to study personal and saved on a secure server. Whenever a patient is enrolled in the study, participation in the trial will be recorded in the electronic patient database, visible for all involved

health care workers. A subjects' insurance has been taken out. The study protocol was approved by the Medical Ethics Committee of the Amsterdam UMC (METC 2022.0795). After completion of the trial, results will be disseminated to participants, patient societies and physicians via a network meeting and digital newsletter. Results will be submitted for publication in a peer-reviewed international medical journal and presented on (inter)national congresses.

Planning

The first patient was included in June 2023. The trial has an estimated duration of three years. Whenever amendments to the protocol will be made, they will be subjected to the Ethics Committee of the Amsterdam UMC for approval and subsequently communicated to all involved study personnel. As sponsor, the Amsterdam UMC will remain owner of all data and rights to publication. The manuscript will be drafted by the core team and approved by the MERCURI-2 investigators.

Data statement

Full protocol, dataset and data management plan will be available upon reasonable request.

Public and Patient involvement

The patient representatives of the Dutch patient societies for heart disease (Harteraad) and kidney disease (Nierpatienten Vereniging Nederland) were involved in in the design phase of the trial. Their insights were incorporated into the trial's planning and execution. They also reviewed the patient information letter and provided advice on how to enhance clarity and comprehensibility. Throughout the trial, these representatives will receive updates on the progress of the trial.

Acknowledgements

We extend our gratitude to the patient representatives of the Dutch patient societies for heart disease (Harteraad) and kidney disease (Nierpatienten Vereniging Nederland) who were involved in in the design phase of the trial.

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Competing interest

DHvR serves as a consultant and received honoraria from Boehringer Ingelheim and Lilly, Merck, Novo Nordisk, Sanofi, and AstraZeneca and has received research operating funds from Boehringer Ingelheim and Lilly Diabetes Alliance, AstraZeneca, and Novo Nordisk; all honoraria are paid to his employer (Amsterdam University Medical Centers, location VU University Medical Center). All other authors have no completing interest to declare.

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Tables and figures

Table 1. Inclusion and exclusion criteria of the MERCURI-2 trial.

Inclusion criteria	Exclusion criteria
Signed informed consent	T1D
Aged above 18 years	T2D with a BMI < 25 and using multiple daily insulin injections (both short and long-acting insulin)
Scheduled for elective cardiac surgery	History of diabetic keto acidosis
	Systolic blood pressure < 100mmHg at time of inclusion
	Reduced kidney function at baseline with eGFR < 20ml/min at time of inclusion
	Current treatment with SGLT2 inhibitors
	Known or suspected allergy to trial products or other drugs in the same class
	Emergency surgery, defined as in need of surgery for medical reasons within 72 hours
	Woman of childbearing potential who is pregnant, breast feeding or intend to become pregnant or is not using adequate contraceptive methods

Abbreviations: BMI = Body Mass Index; eGFR = estimated glomerular filtration rate; SGTL2 = sodium-glucose cotransporter-2; T1D = Type 1 Diabetes; T2D = Type 2 Diabetes

Table 2. Definition and staging of Acute Kidney Injury according to Kidney Disease Improving Global Outcomes (KDIGO) criteria.

Stage	Acute Kidney Injury	Difference	Time frame
1	Serum Creatinine	≥0.3 mg/dl (26.5 mcmol/l) OR	Within 48 hours
		≥1.5 times baseline	Within 7 days
	Urine Output	<0.5 ml/kg/h	For 6-12 hours
2	Serum Creatinine	2.0 – 2.9 times baseline	
	Urine Output	<0.5 ml/kg/h	For >12 hours
3	Start Renal Replacement Therapy		
	Serum Creatinine	3.0 times baseline OR	Within 7 days
		≥4.0 mg/dl	
	Urine Output	<0.3 ml/kg/h OR	>24 hours
		Anuria	>12 hours

Table 3. Recorded secondary and exploratory outcomes

Outcome measures	Time Frame	Definition
Secondary outcomes		
Individual AKI stages	≤ 7 days postoperative	Incidence of stage 1, 2 and 3 AKI according to KDIGO criteria
Creatinine	≤ 7 days postoperative	Postoperative maximum change of creatinine compared to baseline creatinine
AF	≤ 7 days postoperative	Postoperative atrial fibrillation (AF) recorded with an electrocardiogram (ECG) or for which treatment is initiated
LoS-ICU	≤ 30 days postoperative	Length of Stay in the Intensive Care Unit (ICU), measured in days from transfer to ICU until discharge from ICU
LoS-Hos	≤ 30 days postoperative	Length of Stay in the Hospital, measured in days from surgery until discharge from the hospital
MAKE	≤ 30 days postoperative	Major Adverse Kidney Events (MAKE). Composite endpoint of death, new dialysis, and worsened renal function
MACE	≤ 30 days postoperative	Major Adverse Cardiovascular Events (MACE). Composite endpoint of cardiovascular death, nonfatal myocardial infarction, nonfatal ischaemic cerebral vascular accident (iCVA) and hospitalization for heart failure
Safety outcomes	≤ 30 days postoperative	Genital mycotic infections, diabetic keto-acidosis and hypoglycemia
Hypoglycemia	≤ 3 days postoperative	Incidence of hypoglycaemia (blood glucose < 4 mmol/l) detected during routine peri-operative glucose measurements
Hyperglycemia	≤ 3 days postoperative	Incidence of hyperglycaemia (blood glucose > 10 mmol/l) detected during routine peri-operative glucose measurements
Cardiac biomarker 1: troponin	From transfer to ICU until 48 hours postoperatively	Peak troponin concentration as routinely measured during clinical practice
Cardiac biomarker 2: CK-MB	From transfer to ICU until 48 hours postoperatively	Peak CK-MB concentration as routinely measured during clinical practice
Patient-reported quality of recovery 1	Recorded at 30 days postoperatively	According to DAH30: Days at Home in first 30 days
Patient-reported quality of recovery 2	Recorded at 30 days postoperatively	According to WHO-DAS2.0: World Health Organization Disability Assessment Schedule 2.0

Patient-reported quality of recovery 3	Recorded at 30 days postoperatively	According to EQ5D5L: 5 level EuroQol 5D questionnaire
Exploratory outcomes		
Systemic hemodynamics 1	From start of anaesthesia until discharge from the ICU, assessed up to 72 hours	Perioperative hourly average heart rate
Systemic hemodynamics 2	From start of anaesthesia until discharge from the ICU, assessed up to 72 hours	Perioperative hourly average mean arterial blood pressure
Systemic hemodynamics 3	From start of anaesthesia until discharge from the ICU, assessed up to 72 hours	Perioperative hourly average cardiac output (l/min)
Urinary oxygenation	From start of anaesthesia until discharge from the ICU, assessed up to 72 hours	Perioperative hourly average mean oxygen tension measured in the bladder
Postoperative LVF	≤ 30 days postoperative	Qualitative assessment (categorized as normal, or mildly, moderately or severely reduced function) of LVF as noted by the echocardiographer for routinely performed postoperative echocardiography performed during routine follow-up
Health care costs	Recorded at 30 days postoperatively	Using the iMCQ: IMTA (Institute for Medical Technology Assessment) Medical Consumption Questionnaire
Productivity costs	Recorded at 30 days postoperatively	Using the iPCQ: IMTA (Institute for Medical Technology Assessment) Productivity Cost Questionnaire

Abbreviations: AF = atrial fibrillation; AKI = acute kidney injury, ECG = electrocardiogram; ICU = Intensive Care Unit; KDIGO criteria = Kidney Disease Improving Global Outcomes; LoS-Hos = Length of Stay in the Hospital; LoS-ICU = Length of Stay in the Intensive Care Unit; LVF = Left Ventricle Function; MACE = Major Adverse Cardiovascular Events; MAKE = Major Adverse Kidney Events;

Figure 1: Overview of the proposed advantages of SGLT2 inhibitors in reducing CSA-AKI.

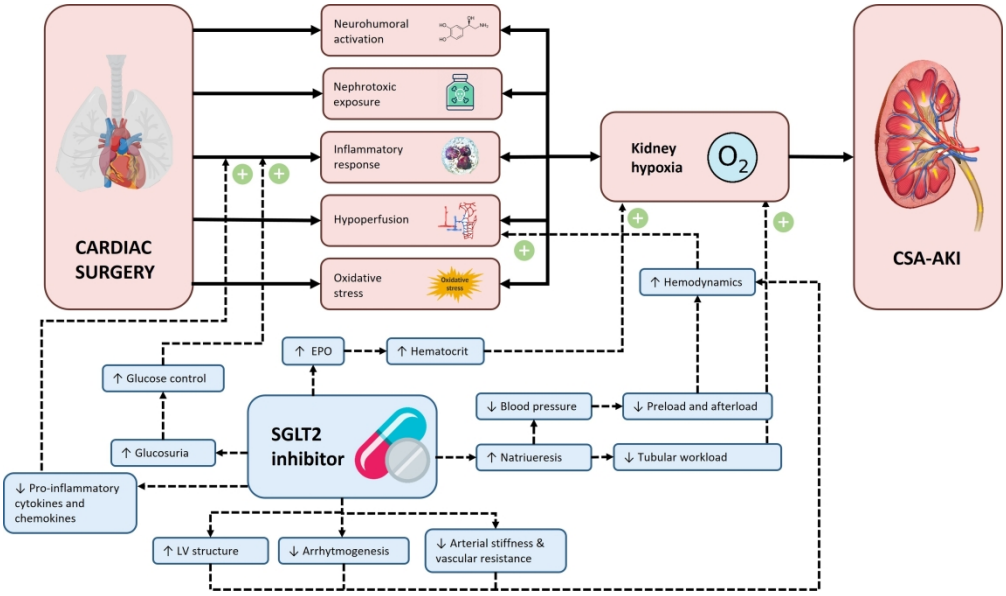
Abbreviations: CSA-AKI = cardiac surgery-associated acute kidney injury; EPO = erythropoietin; LV = Left ventricle; SGTL2 = sodium-glucose cotransporter-2;

Figure 2: Treatment algorithm for adjustment of glucose lowering therapy in patients with T2D

Abbreviations: DPP4 = Dipeptidyl Peptidase IV; GLP-1 RA = glucagon-like peptide-1 receptor agonist; HbA1c = hemoglobin A1c; IU = international unit; SU = sulfonylureas; T2D = Type 2 diabetes

Figure 3: Summary of the study flow of the MERCURI-2 trial.

Abbreviations: AF = atrial fibrillation; DAH30 = Days at Home in first 30 days; ECG = electrocardiogram; ICU = Intensive Care Unit; MACE = Major Adverse Cardiovascular Events; MAKE = Major Adverse Kidney Events; OR = Operation Room; QoR = Quality of Recovery; SGLT2 =sodium-glucose cotransporter-2.



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Abbreviations: CSA-AKI = cardiac surgery-associated acute kidney injury; EPO = erythropoietin; LV = Left ventricle; SGTL2 = sodium-glucose cotransporter-2;

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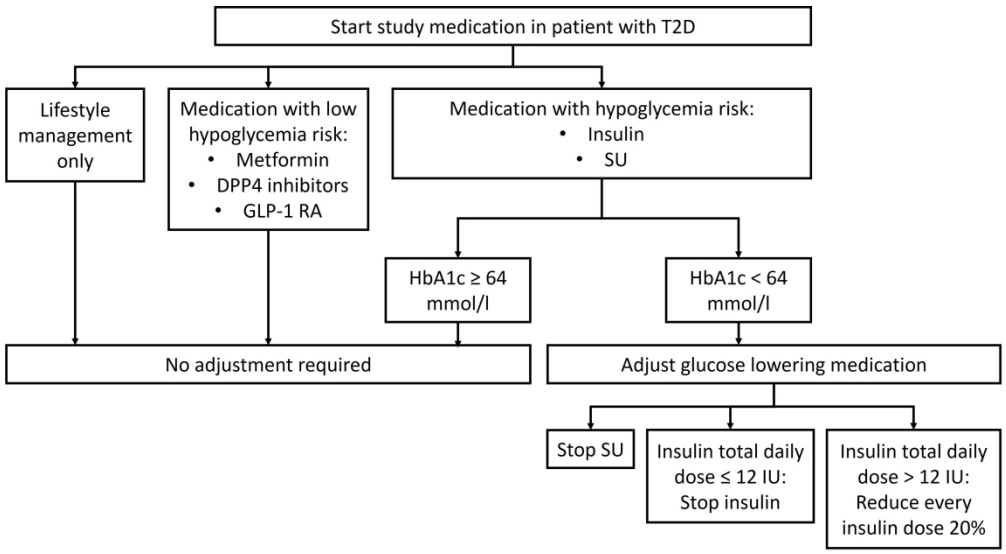

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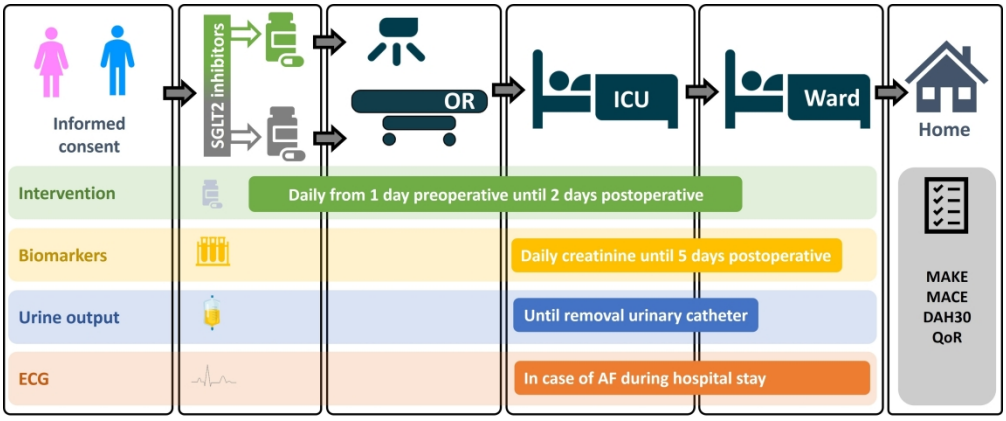

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Supplementary Table 1. Recorded complications of the MERCURI-2 trial

Complications
Arrythmia
Myocardial infarction
Heart failure/ pleural effusion
Pericarditis/ pericardial effusion
Pneumothorax
Cerebrovascular stroke or haemorrhage
Sternal wound infections
Pneumonia
Sepsis/ bacteraemia
Urinary tract infections
Delirium
Coagulation disorders
Deep venous thrombosis/ pulmonary embolus
Re-operation
Complications already defined as secondary outcomes

Proefpersoneninformatie voor deelname aan medisch-wetenschappelijk onderzoek

Dapagliflozine ter vermindering van acute nierschade na een hartoperatie - De MERCURI-2 studie

proMoting Effective Renoprotection in Cardiac sURgery patients by SGLT2- Inhibitors

Inleiding

Geachte heer/mevrouw,

Met deze informatiebrief willen we u vragen of u wilt meedoen aan medisch-wetenschappelijk onderzoek. Meedoen is vrijwillig. U krijgt deze brief omdat u binnenkort een hartoperatie ondergaat. U leest hier om wat voor onderzoek het gaat, wat het voor u betekent, en wat de voordelen en nadelen zijn. Het is veel informatie. Wilt u de informatie doorlezen en beslissen of u wilt meedoen? Als u wilt meedoen, kunt u het formulier invullen dat u vindt in bijlage D.

Stel uw vragen

U kunt uw beslissing nemen met de informatie die u in deze informatiebrief vindt. Daarnaast raden we u aan om dit te doen:

- Stel vragen aan de onderzoeker die u deze informatie geeft.
- Praat met uw partner, familie of vrienden over dit onderzoek.
- Stel vragen aan de onafhankelijk deskundige. Voor contactgegevens zie bijlage A
- Lees de informatie op www.rijksoverheid.nl/mensenonderzoek.

1. Algemene informatie

AMC heeft dit onderzoek opgezet. Hieronder noemen we het AMC steeds de ‘opdrachtgever’.
Onderzoekers, dit kunnen ook artsen en verpleegkundigen zijn, voeren het onderzoek uit in verschillende ziekenhuizen.
Deelnemers aan een medisch-wetenschappelijk onderzoek worden vaak proefpersonen genoemd.
Zowel patiënten als mensen die gezond zijn, kunnen proefpersoon zijn.
In Nederland zullen naar verwachting 784 meedoen.
De medisch-ethische toetsingscommissie van het AMC heeft dit onderzoek goedgekeurd.

2. Wat is het doel van het onderzoek?

In dit onderzoek bekijken we hoe veilig het nieuwe middel dapagliflozine is voor de behandeling van acuut nierfalen. En hoe goed het werkt.
We vergelijken de werking van dapagliflozine met de werking van een placebo. Een placebo is een middel zonder werkzame stof, een ‘nepmiddel’.

3. Wat is de achtergrond van het onderzoek?

Veel patiënten hebben tijdelijk een verminderde nierfunctie na een hartoperatie. Dit komt door schadelijke stoffen die in het bloed komen tijdens een hartoperatie. Zowel door het snijden van de chirurg, de verstoring van de bloedsomloop alsook de hartlongmachine die wordt gebruikt. In de meeste gevallen herstelt de nierfunctie in de dagen na de operatie, maar voor een kleine groep duurt deze verstoring langer en sommigen hebben zelfs een nierfunctie vervangende therapie (dialyse) nodig.

In deze studie onderzoeken wij een middel dat mogelijk de nieren kan beschermen. Dapagliflozine is een middel dat al jaren veel wordt gebruikt in de behandeling van mensen met suikerziekte (diabetes mellitus). Deze ziekte veroorzaakt nierschade. Dit middel verhoogt de uitscheiding van suiker en natrium (zout) door de nieren. Uit eerder onderzoek blijkt dat bij mensen met suikerziekte die dit middel krijgen minder nierschade optreed. In ons onderzoek bekijken we of dapagliflozine ook een beschermend effect heeft op de nieren in mensen die een hartoperatie ondergaan. Dit willen we testen in zowel mensen met als zonder suikerziekte. Vervolgens vergelijken we een groep die dapagliflozine neemt in de periode voor en na hun operatie met een groep die een placebo (nepmiddel) neemt. We denken dat de mensen die dapagliflozine nemen minder vaak nierschade ontwikkelen na hun operatie.

4. Hoe verloopt het onderzoek?

Hoelang duurt het onderzoek?

Doet u mee met het onderzoek? Dan duurt dat in totaal ongeveer 1 maand.

Stap 1: bent u geschikt om mee te doen?

We willen eerst weten of u geschikt bent om mee te doen. Daarom stelt de onderzoeker een aantal vragen en bekijkt uw medisch dossier. De onderzoeker zal ook vragen naar uw etnische afkomst, omdat het risico op nierschade verschillend is voor mensen met verschillende genetische achtergronden.

Stap 2: de behandeling

We behandelen u 4 dagen met onderzoeksmiddelen.

Voor dit onderzoek maken we 2 groepen:

- Groep 1. De mensen in deze groep krijgen dapagliflozine.
- Groep 2. De mensen in deze groep krijgen placebo.

Loting bepaalt welke behandeling u krijgt. U en de onderzoeker weten niet in welke groep u zit. Als het voor uw gezondheid belangrijk is, kan dit wel worden opgezocht.

Stap 3: onderzoeken en metingen

Voor het onderzoek is het niet nodig dat u extra naar het ziekenhuis komt. Het onderzoek vindt plaats tijdens uw opname in het ziekenhuis. Dertig dagen na uw operatie bellen of e-mailen we nog een keer met een vragenlijst over uw ervaringen na de operatie.

We doen de volgende onderzoeken:

- Onderzoek van uw bloed. Daarvoor neemt de onderzoeker per keer 1 buisje bloed af. Alles bij elkaar nemen we 12 ml bloed bij u af. Met het bloedonderzoek testen we uw nierfunctie voor de en na de operatie. Verder gebruiken we de uitslagen van bloedonderzoek dat tijdens uw gewone zorg wordt afgenomen.
- Voor de operatie begint krijgt u standaard een katheter om de urine af te laten lopen tijdens en de eerste tijd na de operatie. Voor het onderzoek meten we met een extra sensor de zuurstofspanning in de urine.
- U vult een vragenlijst in. De vragen gaan over de kwaliteit van herstel na uw operatie en vraagt of er complicaties zijn opgetreden. Deze vragenlijst kunt u online invullen en kunt u via email toegestuurd krijgen invullen kost u ongeveer 30 minuten. Als u dat liever heeft, kan de onderzoeker u ook 1 keer opbellen. U krijgt dan de vragen uit de vragenlijst mondeling gesteld. Dit telefoongesprek duurt tevens ongeveer 30 minuten.

Wat is er anders dan bij gewone zorg?

Er is bij dit onderzoek niet zoveel anders dan bij gewone zorg. Deelname aan dit onderzoek heeft verder geen invloed op de gewone zorg en de operatie die u ondergaat, en zal bijvoorbeeld niet tot vertraging of uitstel leiden.

5. Welke afspraken maken we met u?

We willen graag dat het onderzoek goed verloopt. Daarom maken we de volgende afspraken met u

- U neemt het medicijn op de manier die de onderzoeker u heeft uitgelegd.
- U doet tijdens dit onderzoek niet mee aan een ander medisch-wetenschappelijk onderzoek.
- U neemt contact op met de onderzoeker in deze situaties:
  - U wilt andere medicijnen gaan gebruiken. Ook als dit homeopathische middelen, natuurgeneesmiddelen, vitaminen of geneesmiddelen van de drogist zijn.
  - U wordt in een ziekenhuis opgenomen of behandeld.
  - U krijgt plotseling problemen met uw gezondheid.
  - U wilt niet meer meedoen met het onderzoek.
  - Uw telefoonnummer of e-mailadres verandert.

Mag u of uw partner zwanger worden tijdens het onderzoek?

Vrouwen die zwanger zijn of borstvoeding geven, kunnen niet meedoen aan dit onderzoek.

Vrouwen mogen ook niet zwanger worden tijdens het onderzoek.

Dit onderzoek kan namelijk gevolgen hebben voor een ongeboren kind. De onderzoeker vertelt u hoe u het beste een zwangerschap voorkomt. Praat hierover met uw partner.

Toch zwanger?

Wordt u toch zwanger tijdens het onderzoek? Laat dit dan meteen weten aan de onderzoeker. U moet dan in overleg met de onderzoeker zo snel mogelijk stoppen met dit onderzoek. Wordt uw partner zwanger van u tijdens het onderzoek? Vraag haar dan toestemming om dit aan de onderzoeker te laten weten. Dan kan de zwangerschap extra gecontroleerd worden en kan informatie over het verloop en de uitkomst van de zwangerschap bij andere hulpverleners worden opgevraagd. Maar alleen als u/ uw zwangere partner daar toestemming voor geeft.'*Zwanger worden na het onderzoek*?'

De onderzoeker zal met u bespreken of deelname aan het onderzoek gevolgen kan hebben als u later zwanger wilt worden.

6. Van welke bijwerkingen kunt u last krijgen?

Dapagliflozine kan bijwerkingen geven. Bijwerkingen zijn zeldzaam en in principe mild en goed te behandelen.

De volgende bijwerkingen komen soms voor:

- Dorst, duizeligheid, lage bloeddruk.
- Urineweginfecties
- Lager bloedsuiker als u andere bloedsuikerverlagende therapie gebruikt.

Het onderzoeksmiddel kan ook bijwerkingen hebben die nog onbekend zijn, als deze aan het licht komen tijdens de looptijd van deze studie stellen wij u hiervan op de hoogte.

Meer informatie over dapagliflozine staat in de bijsluiter. Doet u mee aan het onderzoek? Dan krijgt u de bijsluiter mee bij het middel.

Wat zijn de mogelijke ongemakken van metingen tijdens het onderzoek?

Bloedafname kan wat pijn doen. Of u kunt daardoor een bloeduitstorting krijgen. De meeste bloedafnames zullen we echter doen uit het infuus dat u toch al krijgt tijdens uw opname. U zult daarom zo min mogelijk geprikt worden voor dit onderzoek.

7. Wat zijn de voordelen en de nadelen als u meedoet aan het onderzoek?

Meedoen aan het onderzoek kan voordelen en nadelen hebben. Hieronder zetten we ze op een rij. Denk hier goed over na, en praat erover met anderen.

Dapagliflozine kan het waarschijnlijk risico op nierfalen na uw operatie verminderen, maar zeker is dat nog niet. Daarom doen we dit onderzoek.

Meedoen aan het onderzoek kan deze nadelen of gevolgen hebben:

- U kunt last krijgen van de bijwerkingen of nadelige effecten van dapagliflozine. U kunt last hebben van de metingen tijdens het onderzoek.
- Meedoen aan het onderzoek kost u extra tijd.
- U moet zich houden aan de afspraken die horen bij het onderzoek.

Wilt u niet meedoen?

U beslist zelf of u meedoet aan het onderzoek. Wilt u niet meedoen? Dan krijgt u de gewone behandeling indien toch acuut nierfalen optreedt, meestal betekent dit afwachten of het overgaat, en als deze ernstig is nierfunctie vervangende therapie door middel van een dialyse machine. Uw arts kan u meer vertellen over de behandelingsmogelijkheden die er zijn. En over de voor- en nadelen daarvan.

8. Wanneer stopt het onderzoek?

De onderzoeker laat het u weten als er nieuwe informatie over het onderzoek komt die belangrijk voor u is. De onderzoeker vraagt u daarna of u blijft meedoen.

In deze situaties stopt voor u het onderzoek:

- Alle onderzoeken volgens het schema zijn voorbij.
- U bent zwanger geworden.
- U wilt zelf stoppen met het onderzoek. Dat mag op ieder moment. Meld dit dan meteen bij de onderzoeker. U hoeft er niet bij te vertellen waarom u stopt. U krijgt dan weer de gewone behandeling en operatie. De onderzoeker zal u nog wel uitnodigen voor een nacontrole als u dat wenst.
- De onderzoeker vindt het beter voor u om te stoppen. De onderzoeker zal u ook dan nog wel uitnodigen voor een nacontrole.
- Een van de volgende instanties besluit dat het onderzoek moet stoppen:
  - Het AMC,
  - de overheid, of
  - de medisch-ethische commissie die het onderzoek beoordeelt.

Wat gebeurt er als u stopt met het onderzoek?

De onderzoekers gebruiken de gegevens en het lichaamsmateriaal zoals uw bloed die tot het moment van stoppen zijn verzameld. Als u wilt, kan verzameld lichaamsmateriaal worden vernietigd. Geef dit door aan de onderzoeker.
Het hele onderzoek is afgelopen als alle 784 deelnemers het onderzoek hebben doorlopen.

9. Wat gebeurt er na het onderzoek?

Kunt u de medicatie blijven gebruiken?

De medicatie die u tijdens dit onderzoek krijgt beschermen uw nieren tijdens een operatie. Er is dus geen reden om na de operatie deze medicatie te blijven gebruiken. Het zou wel kunnen dat u van uw huisarts of medisch specialist dezelfde medicatie krijgt voorgeschreven met een andere reden.

Krijgt u de resultaten van het onderzoek?

Ongeveer 12 maanden nadat het hele onderzoek is afgerond kan de onderzoeker u laten weten wat de belangrijkste uitkomsten zijn van het onderzoek. De onderzoeker kan u dan ook vertellen in welke groep u zat. Als u dit op prijs stelt kunt u dit aangeven en uw e-mailadres met ons te delen aan het einde van dit formulier.

10. Wat doen we met uw gegevens en lichaamsmateriaal?

Doet u mee met het onderzoek? Dan geeft u ook toestemming om uw gegevens en lichaamsmateriaal te verzamelen, gebruiken en bewaren.

Welke gegevens bewaren we?

We bewaren deze gegevens:

- uw naam
- uw geslacht
- uw geboortedatum
- uw etniciteit
- gegevens over uw gezondheid
- (medische) gegevens die we tijdens het onderzoek verzamelen

Welk lichaamsmateriaal bewaren we?

We verzamelen, gebruiken en bewaren buisjes bloed.

Waarom verzamelen, gebruiken en bewaren we uw gegevens en lichaamsmateriaal?

We verzamelen, gebruiken en bewaren uw gegevens en uw lichaamsmateriaal om de vragen van dit onderzoek te kunnen beantwoorden. En om de resultaten te kunnen publiceren. Gegevens en/of lichaamsmateriaal kunnen worden gebruikt door de opdrachtgever bij het analyseren van onderzoeksgegevens.

Hoe beschermen we uw privacy?

Om uw privacy te beschermen geven wij uw gegevens en uw lichaamsmateriaal een code. Op al uw gegevens en lichaamsmateriaal zetten we alleen deze code. De sleutel van de code bewaren we op een beveiligde plek in het ziekenhuis. Als we uw gegevens en lichaamsmateriaal verwerken, gebruiken we steeds alleen die code. Ook in rapporten en publicaties over het onderzoek kan niemand terughalen dat het over u ging.

Wie kunnen uw gegevens zien?

Sommige personen kunnen wel uw naam en andere persoonlijke gegevens zonder code inzien. Dit kunnen gegevens zijn die speciaal voor dit onderzoek zijn verzameld, maar ook gegevens uit uw medisch dossier.
Dit zijn mensen die controleren of de onderzoekers het onderzoek goed en betrouwbaar uitvoeren.
Deze personen kunnen bij uw gegevens komen:

- Leden van de commissie die de veiligheid van het onderzoek in de gaten houdt.
- Een controleur die voor de opdrachtgever werkt.
- Nationale en internationale toezichthoudende autoriteiten.

Deze personen houden uw gegevens geheim. Voor inzage door deze personen vragen wij u toestemming te geven. De Inspectie Gezondheidszorg en Jeugd kan zonder uw toestemming uw gegevens inzien.

Hoelang bewaren we uw gegevens en lichaamsmateriaal?

We bewaren uw gegevens 25 jaar in het ziekenhuis. Uw lichaamsmateriaal bewaren we in het ziekenhuis. Het wordt 2 jaar bewaard om daarop in de loop van dit onderzoek nog nieuwe bepalingen te kunnen doen die te maken hebben met dit onderzoek. Zodra dit niet meer nodig is, vernietigen we uw lichaamsmateriaal.

Mogen we uw gegevens en lichaamsmateriaal gebruiken voor ander onderzoek?

Uw verzamelde gegevens en uw (overgebleven) lichaamsmateriaal kunnen ook van belang zijn voor ander wetenschappelijk onderzoek op het gebied van nierfalen na hartoperaties. Daarvoor zullen uw gegevens en lichaamsmateriaal 2 jaar worden bewaard in het ziekenhuis. In het toestemmingformulier geeft u aan of u dit goed vindt. Geeft u geen toestemming? Dan kunt u nog steeds meedoen met dit onderzoek. U krijgt dezelfde zorg.

Kunt u uw toestemming voor het gebruik van uw gegevens weer intrekken?

U kunt uw toestemming voor het gebruik van uw gegevens op ieder moment intrekken. Zeg dat dan tegen de onderzoeker. Dit geldt voor het gebruik in dit onderzoek en voor het gebruik in ander onderzoek. Maar let op: trekt u uw toestemming in, en hebben onderzoekers dan al gegevens verzameld voor een onderzoek? Dan mogen zij deze gegevens nog wel gebruiken. Voor uw lichaamsmateriaal geldt dat de onderzoekers dit vernietigen nadat u uw toestemming intrekt. Maar zijn er dan al metingen gedaan met uw lichaamsmateriaal? Dan mag de onderzoeker de resultaten daarvan blijven gebruiken.

Wilt u meer weten over uw privacy?

- Wilt u meer weten over uw rechten bij de verwerking van persoonsgegevens? Kijk dan op www.autoriteitpersoonsgegevens.nl.
- Heeft u vragen over uw rechten? Of heeft u een klacht over de verwerking van uw persoonsgegevens? Neem dan contact op met degene die verantwoordelijk is voor de verwerking van uw persoonsgegevens. Voor uw onderzoek is dat: Het AMC. Zie bijlage A voor contactgegevens, en website.
- Als u klachten heeft over de verwerking van uw persoonsgegevens, raden we u aan om deze eerst te bespreken met het onderzoeksteam. U kunt ook naar de Functionaris Gegevensbescherming van het AMC gaan. Of u dient een klacht in bij de Autoriteit Persoonsgegevens.

Waar vindt u meer informatie over het onderzoek?

Op de volgende website(s) vindt u meer informatie over het onderzoek. www.ClinicalTrials.gov. Na het onderzoek kan de website een samenvatting van de resultaten van dit onderzoek tonen. U vindt het onderzoek door te zoeken op 'NCT05590143'

11. Krijgt u een vergoeding als u meedoet aan het onderzoek?

De onderzoeksmiddelen, en extra testen voor het onderzoek kosten u niets. U krijgt ook geen vergoeding als u meedoet aan dit onderzoek.

12. Bent u verzekerd tijdens het onderzoek?

Voor iedereen die meedoet aan dit onderzoek is een verzekering afgesloten. De verzekering betaalt voor schade door het onderzoek. Maar niet voor alle schade. In **bijlage B** vindt u meer informatie over de verzekering en de uitzonderingen. Daar staat ook aan wie u schade kunt melden.

13. We informeren uw behandelend specialist en apotheker.

De onderzoeker stuurt uw behandelend specialist en apotheker een bericht om te laten weten dat u meedoet aan het onderzoek. Dit is voor uw eigen veiligheid.

14. Heeft u vragen?

Vragen over het onderzoek kunt u stellen aan de onderzoeker. Wilt u advies van iemand die er geen belang bij heeft? Ga dan naar de onafhankelijk deskundige, voor contactgegevens zie bijlage A. Hij weet veel over het onderzoek, maar werkt niet mee aan dit onderzoek.
Heeft u een klacht? Bespreek dit dan met de onderzoeker of de arts die u behandelt. Wilt u dit liever niet? Ga dan naar de klachtenfunctionaris van uw ziekenhuis. In bijlage A staat waar u die kunt vinden.

15. Hoe geeft u toestemming voor het onderzoek?

U kunt eerst rustig nadenken over dit onderzoek. Daarna vertelt u de onderzoeker of u de informatie begrijpt en of u wel of niet wilt meedoen. Wilt u meedoen? Dan vult u het toestemmingsformulier in dat u bij deze informatiebrief vindt. U en de onderzoeker krijgen allebei een getekende versie van deze toestemmingsverklaring.

Dank voor uw tijd.

16. Bijlage A: contactgegevens onderzoek

X

Bijlage B:
INFORMATIE OVER DE VERZEKERING

X

18. Bijlage C: Schema onderzoekshandelingen

Vóór de opname in het ziekenhuis:
U krijgt mondeling en schriftelijke informatie.
U tekent schriftelijk voor toestemming met deelname aan dit onderzoek.
We verzamelen enkele medische gegevens.

Tijdens de opname voor uw operatie:
Op de dag vóór uw operatie krijgt u de studiemedicatie. Deze neemt u voor het eerst op de dag vóór uw operatie, daarna dagelijks, in de ochtend voor de drie dagen daarna. Dat wil zeggen, 1 keer op de ochtend van uw operatie, en op de twee dagen na de operatie.

Rond uw operatie verzamelen de onderzoekers medische gegevens, wat u hier van merkt is dat er voor de operatie en in de eerste 7 dagen na uw operatie iedere dag een buisje bloed wordt afgenomen voor het meten van uw nierfunctie.

Ná de opname voor uw operatie.
Dertig dagen na uw operatie, sturen we u een vragenlijst, die vraagt naar uw ervaringen tijdens de opname en de weken na uw operatie. Wij vragen naar eventuele bijwerkingen, kwaliteit van herstel na de operatie en eventuele complicaties.

19. Bijlage D: toestemmingsformulier proefpersoon

Behorende bij

Dapagliflozine ter vermindering van acute nierschade na een hartoperatie - De MERCURI-2 studie

proMoting Effective Renoprotection in Cardiac sURgery patients by SGLT2- Inhibitors

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn goed genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen met het onderzoek. Of om ermee te stoppen. Ik hoef dan niet te zeggen waarom ik wil stoppen.
- Ik geef de onderzoeker toestemming om mijn behandelend medisch specialist en apotheker te laten weten dat ik meedoe aan dit onderzoek.
- Ik geef de onderzoeker toestemming om medische informatie op te vragen bij mijn huisarts en het ziekenhuis waar ik opgenomen ben vóór of ná mijn hartoperatie.
- Ik geef de onderzoeker toestemming om mijn huisarts of behandelend specialist informatie te geven over onverwachte bevindingen uit het onderzoek die van belang zijn voor mijn gezondheid.
- Ik geef de onderzoekers toestemming om mijn gegevens en lichaamsmateriaal te verzamelen en gebruiken. De onderzoekers doen dit alleen om de onderzoeksvraag van dit onderzoek te beantwoorden.
- Ik weet dat voor de controle van het onderzoek sommige mensen al mijn gegevens kunnen inzien. Die mensen staan in deze informatiebrief. Ik geef deze mensen toestemming om mijn gegevens in te zien voor deze controle.
- Ik weet dat ik niet zwanger mag worden tijdens het onderzoek.
- Indien van toepassing heeft de onderzoeker met mij besproken hoe ik het beste voorkom dat ik zwanger word.

Wilt u in de tabel hieronder ja of nee aankruisen?

Ik geef toestemming om mijn gegevens te bewaren om dit te gebruiken voor ander onderzoek, zoals in de informatiebrief staat.	Ja ☐	Nee ☐
Ik geef toestemming om mijn (overgebleven) lichaamsmateriaal (bloed) te bewaren om dit te gebruiken voor ander onderzoek, zoals in de informatiebrief staat. Het lichaamsmateriaal wordt daarvoor nog 2 jaar bewaard.	Ja ☐	Nee ☐
Ik geef toestemming om mij eventueel na dit onderzoek te vragen of ik wil meedoen met een vervolgonderzoek.	Ja ☐	Nee ☐
Ik geef toestemming om de zuurstofspanning in de urine te meten	Ja ☐	Nee ☐
Ik geef de onderzoekers toestemming om na het onderzoek te laten weten welke behandeling ik heb gehad/ in welke groep ik zat.	Ja ☐	Nee ☐

Ik wil meedoen aan dit onderzoek.

Mijn naam is (proefpersoon): ……..

Handtekening: …… Datum : __ / __ / __

Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek. Wordt er tijdens het onderzoek informatie bekend die die de toestemming van de proefpersoon kan beïnvloeden? Dan laat ik dit op tijd weten aan deze proefpersoon.

Naam onderzoeker (of diens vertegenwoordiger): ……

Handtekening: …… Datum: __ / __ / __

Als u na afloop van het onderzoek graag te weten komt in welke groep u viel en de resultaten van ons onderzoek ontvangt vul dan hier uw email adres in:

……@……

De proefpersoon krijgt een volledige informatiebrief mee, samen met een door beide partijen getekende versie van het toestemmingsformulier.

English translation

Participant Information for Participation in Medical-Scientific Research

Dapagliflozin for Reducing Acute Kidney Injury After Heart Surgery – The MERCURI-2 Study

proMoting Effective Renoprotection in Cardiac sURgery patients by SGLT2 Inhibitors

Introduction

Geachte heer/mevrouw,

Dear Sir/Madam,

With this information letter, we would like to ask if you would be willing to participate in medical-scientific research. Participation is voluntary. You are receiving this letter because you will soon be undergoing heart surgery.

In this document, you will find details about the study, what participation entails, and the potential benefits and risks. It contains a lot of information. Please take the time to read it carefully and decide whether you would like to participate. If you choose to participate, you can fill out the form found in **Appendix D**.

Ask Questions

You can make your decision based on the information provided in this letter. Additionally, we recommend that you:

- Ask questions to the researcher providing you with this information.
- Discuss the study with your partner, family, or friends.
- Consult an independent expert. Contact details can be found in Appendix A.
- Read more at www.rijksoverheid.nl/mensenonderzoek.

General Information

The AMC has initiated this study. Throughout this document, we will refer to AMC as the 'sponsor.' Researchers—including doctors and nurses—will conduct the study in various hospitals.

Participants in medical-scientific research are often referred to as study subjects. Both patients and healthy individuals can participate as study subjects.

In the Netherlands, approximately 784 participants are expected to take part in this study.

The Medical Ethics Review Committee of AMC has approved this study.

What is the Purpose of the Study?

This study aims to assess the safety and effectiveness of the new drug dapagliflozin for the treatment of acute kidney injury (AKI).
We will compare the effect of dapagliflozin with a placebo. A placebo is an inactive substance, often referred to as a 'dummy drug,' which contains no active ingredients.

What is the Background of the Study?

Many patients experience temporary reduced kidney function after heart surgery. This occurs due to harmful substances that enter the bloodstream during the procedure. Factors contributing to this include:

- The surgical incision,
- Disruptions in blood circulation, and
- The use of the heart-lung machine during surgery.

In most cases, kidney function recovers within a few days after surgery. However, for a small group of patients, this impairment lasts longer, and some may even require kidney replacement therapy (dialysis).
This study aims to investigate a drug that may protect the kidneys. Dapagliflozin has been widely used for years in the treatment of diabetes mellitus (diabetes). Diabetes is known to cause kidney damage. This medication increases the excretion of sugar and sodium (salt) through the kidneys. Previous research has shown that patients with diabetes who take dapagliflozin experience less kidney damage. In this study, we aim to determine whether dapagliflozin also has a protective effect on the kidneys of patients undergoing heart surgery. We will test this in both patients with and without diabetes.
To assess this, we will compare:

- A group of patients taking dapagliflozin before and after surgery, and
- A group taking a placebo (inactive drug).

We hypothesize that patients taking dapagliflozin will be less likely to develop kidney damage after surgery.

How is the Study Conducted?

How Long Does the Study Last?
If you participate, the study will last approximately one month.
Step 1: Are You Eligible to Participate?
To determine your eligibility, the researcher will:

- Ask you a few questions,
- Review your medical records, and
- Inquire about your ethnic background (since the risk of kidney damage varies across genetic backgrounds).

Step 2: The Treatment
The study treatment lasts four days. Participants are divided into two groups:

- Group 1: Receives dapagliflozin
- Group 2: Receives a placebo (inactive drug)

Random assignment (lottery) determines which group you are in.
Neither you nor the researcher will know which treatment you receive. However, if it becomes medically necessary, this information can be accessed.
Step 3: Examinations and Measurements

You do not need to visit the hospital extra times for this study. The study will take place during your hospital stay. Thirty days after surgery, we will contact you via phone or email with a questionnaire about your recovery.
We will conduct the following tests:

- Blood Tests:
  - A small blood sample (1 tube) will be taken per test, totaling 12 mL.
  - These tests will evaluate your kidney function before and after surgery.
  - We will also use results from routine blood tests conducted as part of your standard care.
- Urine Tests:
  - Before surgery, a catheter will be placed (as part of standard care) to drain urine during and after the procedure.
  - During the study, an additional sensor will be used to measure oxygen levels in the urine.
- Questionnaire:
  - You will be asked about your recovery quality and whether you experienced any complications.
  - The questionnaire takes about 30 minutes to complete and can be filled out online via email.
  - If preferred, a researcher can call you to go through the questions over the phone (also around 30 minutes).

What is Different from Standard Care?
This study does not significantly alter your standard medical care.

- Participation will not affect your scheduled surgery.
- There will be no delays or changes in your treatment due to the study.

We doen de volgende onderzoeken:

- Onderzoek van uw bloed. Daarvoor neemt de onderzoeker per keer 1 buisje bloed af. Alles bij elkaar nemen we 12 ml bloed bij u af. Met het bloedonderzoek testen we uw nierfunctie voor de en na de operatie. Verder gebruiken we de uitslagen van bloedonderzoek dat tijdens uw gewone zorg wordt afgenomen.
- Voor de operatie begint krijgt u standaard een katheter om de urine af te laten lopen tijdens en de eerste tijd na de operatie. Voor het onderzoek meten we met een extra sensor de zuurstofspanning in de urine.
- U vult een vragenlijst in. De vragen gaan over de kwaliteit van herstel na uw operatie en vraagt of er complicaties zijn opgetreden. Deze vragenlijst kunt u online invullen en kunt u via email toegestuurd krijgen invullen kost u ongeveer 30 minuten. Als u dat liever heeft, kan de onderzoeker u ook 1 keer opbellen. U krijgt dan de vragen uit de vragenlijst mondeling gesteld. Dit telefoongesprek duurt tevens ongeveer 30 minuten.

Wat is er anders dan bij gewone zorg?

Er is bij dit onderzoek niet zoveel anders dan bij gewone zorg. Deelname aan dit onderzoek heeft verder geen invloed op de gewone zorg en de operatie die u ondergaat, en zal bijvoorbeeld niet tot vertraging of uitstel leiden.

What Agreements Do We Make With You?

We want the study to proceed smoothly. Therefore, we ask you to agree to the following:

- You take the medication exactly as instructed by the researcher.
- You do not participate in any other medical-scientific research during this study.
- You contact the researcher in the following situations:
    - If you plan to take other medications, including homeopathic remedies, herbal supplements, vitamins, or over-the-counter drugs.
    - If you are hospitalized or receive medical treatment.
    - If you experience sudden health problems.
    - If you wish to withdraw from the study.
    - If your phone number or email address changes.

Can You or Your Partner Become Pregnant During the Study?

Women who are pregnant or breastfeeding cannot participate in this study. Additionally, women must not become pregnant during the study, as the medication could potentially affect an unborn child. The researcher will explain how to prevent pregnancy during the study. We recommend discussing this with your partner.

What If You Become Pregnant?

If you become pregnant during the study, inform the researcher immediately. You will need to stop participation as soon as possible, in consultation with the researcher.

If your partner becomes pregnant during the study, we ask you to request her permission to inform the researcher. This will allow for additional monitoring of the pregnancy. With your partner's

consent, the researcher may also gather information from other healthcare providers about the pregnancy's progress and outcome.

What About Pregnancy After the Study?

The researcher will discuss whether participation in the study could have any future effects on pregnancy.

What Side Effects Might You Experience?

Dapagliflozin can cause side effects. These are rare, usually mild, and treatable.

Some possible side effects include:

- Thirst, dizziness, low blood pressure.
- Urinary tract infections.
- Lower blood sugar levels (especially if you are taking other blood sugar-lowering medications).

There may also be unknown side effects that are discovered during this study. If any new side effects become known, we will inform you.

For more information about dapagliflozin, please refer to the medication leaflet. If you participate, you will receive this leaflet along with the medication.

What Are the Possible Discomforts From the Study Measurements?

- Blood draws may cause mild pain or bruising.
- However, most blood samples will be taken from the IV line already placed during your hospital stay, so you will be pricked as little as possible.

What Are the Benefits and Risks of Participating in the Study?

Participating in this study may have both benefits and drawbacks. Please consider these carefully and discuss them with others.

Potential Benefits

- Dapagliflozin may reduce the risk of kidney failure after surgery, but this is not yet certain—that is why we are conducting this study.

Potential Risks or Drawbacks

- You may experience side effects or discomfort from the study medication.
- You may experience mild discomfort from the measurements conducted during the study.
- Participation will require extra time.
- You must adhere to study-related agreements and procedures.

What If You Choose Not to Participate?

Participation is entirely your decision. If you choose not to participate:

- You will receive standard treatment in case of acute kidney injury.
- This usually involves monitoring and waiting to see if kidney function recovers.
- If the kidney injury is severe, kidney replacement therapy (dialysis) may be required.

Your doctor can provide more details about the available treatment options, including their advantages and disadvantages.

When Does the Study End?

The researcher will inform you if new information becomes available that is important for you. At that point, you can decide whether you wish to continue participating.

Your participation in the study will end in the following cases:

- You have completed all study-related procedures as scheduled.
- You become pregnant during the study.
- You decide to withdraw from the study at any time. If you wish to stop, please inform the researcher immediately. You do not need to provide a reason. After withdrawing, you will receive the standard treatment and surgery. If you wish, the researcher may invite you for a final follow-up appointment.
- The researcher determines that it is better for you to stop. In this case, you may also be invited for a follow-up.
- The study is terminated by one of the following:
    - Amsterdam UMC (AMC)
    - The government
    - The medical ethics committee reviewing the study

What Happens If You Stop Participating?

- Any data and biological samples (such as blood) collected before you stopped will still be used in the study.
- If you wish to have your collected samples destroyed, please inform the researcher.
- The study will officially end once all 784 participants have completed the research.

What Happens After the Study?

Can You Continue Using the Medication?
The study medication is designed to protect your kidneys during surgery, but there is no reason to continue taking it after surgery. However, your general practitioner or specialist may prescribe this medication in the future for other medical reasons.
Will You Receive the Study Results?
Approximately 12 months after the study is completed, the researcher can inform you about the key findings of the research. You may also be told which study group you were in.
If you wish to receive these results, please provide your email address at the end of the consent form.

What Happens to Your Data and Biological Samples?

If you participate in the study, you consent to the collection, use, and storage of your data and biological samples.

What Data Do We Store?

We store the following information:

- Your name
- Your gender
- Your date of birth
- Your ethnicity
- Your health-related information
- Medical data collected during the study

What Biological Samples Do We Store?

We collect, use, and store blood samples for the study.

Why Do We Collect, Use, and Store Your Data and Samples?

- To answer the research questions of this study.
- To publish the study results.
- The study sponsor may analyze the research data.

How Do We Protect Your Privacy?

- Your data and biological samples are coded to protect your privacy.
- This code replaces your personal information, and only a secure key stored at the hospital can link the code back to you.
- Any study reports or publications will ensure that you cannot be identified.

Who Can Access Your Data?

Certain individuals may access your uncoded personal data, including:

- Study safety monitoring committee members
- Auditors working for the study sponsor
- National and international regulatory authorities

These individuals must keep your data confidential.

The Dutch Health and Youth Care Inspectorate (IGJ) can access your data without requiring your consent.

How Long Are Your Data and Samples Stored?

- Your data will be stored for 25 years at the hospital.
- Your blood samples will be stored for 2 years and will be destroyed once they are no longer needed.

Can Your Data and Samples Be Used for Other Research?

Your data and unused blood samples may also be useful for future research on kidney failure after heart surgery.

- If you agree, your data and samples will be stored for 2 years for potential future research.
- If you do not agree, you can still participate in this study and receive the same care.

Can You Withdraw Your Consent for Data Use?

Yes. You can withdraw your consent for data and sample use at any time. However:

- Previously collected data may still be used for the study.
- If your samples have already been analyzed, the results cannot be deleted but will not be used for future research.

Want to Know More About Your Privacy?

- More information on your rights: www.autoriteitpersoonsgegevens.nl
- If you have questions or complaints about your data, contact Amsterdam UMC (AMC) (see Appendix A).
- You may also file a complaint with the Data Protection Officer at AMC or the Dutch Data Protection Authority (Autoriteit Persoonsgegevens).

Where Can You Find More Information About the Study?

- Study details are available at www.ClinicalTrials.gov.
- After the study ends, a summary of the results may be posted under study ID: NCT05590143.

Will You Receive Compensation for Participation?

No, participation in this study is voluntary and unpaid.

However, the study medication and additional tests are provided at no cost to you.

Are You Insured During the Study?

Yes. A special insurance policy has been arranged for all study participants.

- This insurance covers damages resulting from the study.
- However, not all damages are covered.
- See Appendix B for details on insurance coverage and how to report damages.

Will Your Doctor and Pharmacist Be Notified?

Yes.

The researcher will inform your doctor and pharmacist that you are participating in this study.

This is done for your safety.

Do You Have Questions?

If you have questions about the study, contact the researcher.

Would you like advice from someone independent who is not involved in the study?

- Contact the independent expert listed in Appendix A.

Do you have a complaint?

- Discuss it with the researcher or your doctor.
- If you prefer, you can contact the hospital's complaints officer (see Appendix A).

How Do You Give Your Consent?

You will have time to think about whether you want to participate.

If you decide to participate:

- Inform the researcher that you understand the information.
- Sign the consent form provided with this information sheet.
- Both you and the researcher will keep a signed copy of the form.

Thank You for Your Time.

Appendix A: Contact Information for the Study

X

Appendix B: Information About the Insurance

X

Appendix C: Study Procedure Schedule

Before Hospital Admission:

- You will receive oral and written information.
- You will provide written consent to participate in this study.
- We will collect some medical data.

During Hospital Admission for Your Surgery:

- On the day before your surgery, you will receive the study medication.
- You will take the medication for the first time on the day before your surgery and then daily in the morning for the next three days. This means:
  - Once on the morning of your surgery
  - Once on each of the two days after surgery
- Around the time of your surgery, researchers will collect medical data. The only thing you will notice is that a blood sample will be taken once a day before the surgery and for seven days after the surgery to monitor your kidney function.

After Hospital Admission for Your Surgery:

- Thirty days after your surgery, we will send you a questionnaire.
- This questionnaire will ask about your experience during hospitalization and the weeks following your surgery.
- We will inquire about any side effects, quality of recovery, and possible complications.

Appendix D: Informed Consent Form for Participants

Behorende bij

Related to:

Dapagliflozin for the Reduction of Acute Kidney Injury After Heart Surgery – The MERCURI-2 Study

proMoting Effective Renoprotection in Cardiac sURgery patients by SGLT2-Inhibitors

- I have read the information letter. I had the opportunity to ask questions, and my questions have been answered sufficiently. I had enough time to decide whether I want to participate.
- I understand that participation is voluntary. I also understand that I can decide at any time to withdraw from the study without providing a reason.
- I give the researcher permission to inform my treating medical specialist and pharmacist that I am participating in this study.
- I give the researcher permission to request medical information from my general practitioner and the hospital where I was admitted before or after my heart surgery.
- I give the researcher permission to provide my general practitioner or treating specialist with any unexpected findings from the study that are relevant to my health.
- I give the researchers permission to collect and use my data and biological material solely to answer the research question of this study.
- I understand that, for the purpose of study oversight, certain individuals may access my full medical records. These individuals are listed in the information letter. I consent to them reviewing my data for this purpose.
- I understand that I must not become pregnant during the study.
- If applicable, the researcher has discussed with me the best ways to prevent pregnancy during the study.

De MERCURI-2 study NL81190.018.22

proMoting Effective Renoprotection in Cardiac sURgery patients by SGLT2- Inhibitors

Would you please mark "Yes" or "No" in the table below?

I give permission to store my data for use in other research, as described in the information letter.	Yes ☐	No ☐
I give permission to store my remaining biological material (blood) for use in other research, as described in the information letter. The biological material will be stored for 2 more years.	Yes ☐	No ☐
I give permission to be asked after this study if I would like to participate in follow-up research.	Yes ☐	No ☐
I give permission for the oxygen levels in my urine to be measured.	Yes ☐	No ☐
I give the researchers permission to inform me after the study regarding the treatment I received and which group I was in.	Yes ☐	No ☐

I want to participate in this research.

My name is (participant): ……..

Signature: …… Date : __ / __ / __

I declare that I have fully informed the participant about the research mentioned. If any information arises during the study that could affect the participant's consent, I will inform them in time.

Name researcher (or representative): ……

Signature: …… Date: __ / __ / __

If you would like to know which group you were in and receive the results of the study after its completion, please fill in your email address here:

……@……