Preoperative sodium glucose cotransporter 2 inhibitors for prevention of postoperative acute kidney injury in cardiac surgery patients - a randomized, placebo-controlled, multi-centre, phase IV clinical trial

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This study has been transitioned to CTIS with ID 2024-515260-31-00 check the CTIS register for the current data. To investigate the potential of preoperative initiation and perioperative continuation until day 2 after surgery of the SGLT2 inhibitor...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional

Summary

ID

NL-OMON53593

Source
ToetsingOnline

Brief title
The MERCURI-2 trail

Condition

- Renal disorders (excl nephropathies)

Synonym
Cardiac Surgery-Associated Acute Kidney Injury; Kidney failure following cardiac surgery

Research involving

Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: ZonMw through Programme Goed gebruik geneesmiddelen Project number: 10140022010003

Intervention

Keyword: Acute Kidney Injury (AKI), Cardiac Surgery, Sodium-glucose co-transporter-2 inhibitors (SGLT2i)

Outcome measures

Primary outcome

Incidence of AKI occurring in 7 days after surgery, according to KDIGO

criteria, defined as an increase in serum creatinine by 0.3 mg/dl (26.5 mmol/l)

within 48 hours; or an increase in serum creatinine to 1.5 times baseline,

within 7 days; or a urine output <0.5 ml/kg/h for >6 hours.

Secondary outcome

1. Incidence of Stage 3 AKI according to KDIGO criteria, measured until day 7

postoperatively. 2. Postoperative change of eGFR compared to the baseline eGFR,

measured daily until day 7 postoperatively. 3. De novo postoperative atrial

fibrillation, registered on a 12-lead ECG. 4. Length of Stay in the Intensive

Care Unit, measured in days. 5. Length of Stay in hospital, measured in days.

6. MAKE: Major Adverse Kidney Events, within 30 postoperative days. Composite

endpoint of death, new dialysis, and worsened renal function.1 7. MACE: Major

Adverse Cardiovascular Events, within 30 postoperative days. Composite endpoint

of cardiovascular death, nonfatal myocardial infarction (MI), nonfatal

ischaemic cerebral vascular accident (iCVA) and hospitalization for heart

failure. 8. Patient reported quality of recovery measured at day 30 postoperatively, according to the following three questionnaires: o DAH30: Days at Home in first 30 days2 o WHO-DAS 2.0: World Health Organisation Disability Assessment Schedule 2.03 o EQ5D5L: 5 level EuroQol 5D questionnaire: a standardised measure of health status developed by the EuroQol Group to provide a simple, generic measure of health for clinical and economic appraisal 4 9. Safety outcomes: genital mycotic infections, diabetic keto-acidosis, and hypoglycaemia, in addition to incidence of postoperative complications and Serious Adverse Events (SAEs). 10. Healthcare and productivity costs will be objectified to weigh cost-effectiveness, using the following two questionnaires: o iPCQ: IMTA (Institute for Medical Technology Assessment) Productivity Cost Questionnaire. o IMCQ: IMTA (Institute for Medical Technology Assessment) Medical Consumption Questionnaire. 11. Peri-operative glucose measurements until day 3 postoperatively (routinely measured in clinical setting): average daily glucose, incidence of hypoglycaemia (blood glucose < 4 mmol/l) and hyperglycaemia (blood glucose > 10 mmol/l) 12. Peri-operative hemodynamic vital signs on day of surgery and during ICU admission (routinely measured in clinical setting). 13. Postoperative cardiac function (echocardiography and cardiac biomarkers) routinely carried out in clinical practice.14. In the AMC subpopulation, the urine oxygenation (during the days that a urinary catheter is placed), the correlation between urine oxygenation and current AKI markers and frequency and duration of measurement interruptions

Study description

Background summary

Acute kidney injury is one of the most common complications after cardiac surgery. The new glucose-lowering therapy, sodium glucose transport protein 2 inhibitors (SGLT2i) possess renoprotective properties in people with chronic kidney disease in the presence or absence of type 2 diabetes. Large cardiovascular outcome trials in patients with diabetes observed a lower incidence of acute kidney injury. However, these studies were not powered to investigate this nor did acute kidney injury concern an adjudicated endpoint.

Study objective

This study has been transitioned to CTIS with ID 2024-515260-31-00 check the CTIS register for the current data.

To investigate the potential of preoperative initiation and perioperative continuation until day 2 after surgery of the SGLT2 inhibitor dapagliflozin 10 mg once daily to prevent AKI according to the KDIGO criteria in patients undergoing cardiopulmonary bypass surgery.

Study design

Multi-centre, triple-blinded (patients, physicians, investigators), parallel-group, balanced (1:1), stratified (male-female 50-50), randomized, controlled (placebo), phase IV clinical trial.

Intervention

Participants receive 10 mg dapagliflozin once daily or matching placebo starting 1 day prior to surgery and continued until two days postoperatively (four doses).

Study burden and risks

General trial-related burden: We will withdraw 4.5 mL of blood at one day before surgery and one day postoperatively for biomarker analysis. No extra venepunctures are required, as these measurements coincide with routine clinical care. Intervention group related burden: Participants will be asked to take either 1 tablet of 10 mg dapagliflozin once daily from 7 days before surgery until 2 days postoperative (including the day of surgery) or a matching placebo regimen. Patients randomized to dapagliflozin will run a small a risk of treatable side effects related to the study drug. These are rare for short-term treatments. Participants will be informed about the following side

effects: 1. Genital mycotic infections: these usually only occur after longer-term use of SGLT2 inhibitors. In this study, patients will only receive this medication for up to 10 doses. Treatment of this side effect is straightforward with antifungal treatment. 2. Euglycemic ketoacidosis: a lowering of the pH in the blood through the build-up of ketones. This has been described in patients on long-term treatment and is ascribed to altered insulin sensitivity through increased glucose loss by SGLT2 inhibition. For this and other reasons, patients with type 1 diabetes mellitus and patients with type 2 diabetes mellitus and a body-mass-index <25 kg/m2 are excluded from this trail. We will monitor perioperative glucose and pH levels in all participants according to routine perioperative care. In addition, patients using insulin therapy will receive a perioperative glucose/insulin infusion, which suppresses the ketone production. Should keto acidosis occur in any other patient, treatment is straightforward with a glucose-insulin infusion. 3. Hypoglycemia: only patients with diabetes mellitus using sulfonylurea or insulin are at risk, according to previous research. To prevent this side effect: patients will receive an individualized adaptation of their glucose-lowering medication by investigator team. To treat this side-effect, blood glucose will be monitored in all patients according to standard perioperative cardiac surgery care and hypoglycaemia treatment protocols with urgent administration of intravenous glucose are in place. Risk-benefit: There is solid evidence to support that SGLT2 inhibitors offer kidney protection. Acute kidney injury is a common complication after cardiac surgery. Our hypothesis is therefore, that patients in the intervention group will receive protection against acute kidney injury. In addition, the results from this trial could lead to the improvement of care and protection of future patients undergoing cardiac surgery. The side-effect profile of dapagliflozin is mild, and participants will be intensively monitored in this study. Therefore, we estimate that the benefits outweigh the risks for participation in this trial.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. >18 years old 2. Undergoing elective cardiac surgery. 3. Providing informed consent

Exclusion criteria

1. Current treatment with SGLT2 inhibitors 2. Reduced kidney function at baseline with eGFR < 20 ml/min at time of inclusion 3. Diabetes Mellitus Type 1 4. History of diabetic keto acidosis 5. Diabetes Mellitus Type 2 with BMI<25 for people with type 2 diabetes who are using multiple daily insulin injections (both short and long-acting insulin) 6. Systolic blood pressure < 100 mmHg at time of inclusion 7. Emergency surgery, defined as in need of surgery for medical reasons < 7 days, i.e. *S1-4* according to the Amsterdam UMC classification 8. Female of child-bearing potential who is pregnant, breast-feeding or intend to become pregnant or is not using adequate contraceptive methods 9. Known or suspected allergy to trial products or other drugs in the same class

Study design

Design

Study phase:	4
Study type:	Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-06-2023
Enrollment:	784
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Forxiga
Generic name:	Dapagliflozin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	14-02-2023
Application type:	First submission
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Approved WMO

Date:	07-03-2023

Application type:	First submission
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	08-08-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-08-2023
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-02-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-515260-31-00
EudraCT	EUCTR2022-002453-25-NL
ClinicalTrials.gov	NCT05590143
CCMO	NL81190.018.22