Intravenous versus oral hydration to reduce the risk of postcontrast acute kidney injury after intravenous contrast-enhanced CT in patients with severe chronic kidney disease (ENRICH): a study protocol for a single-centre, parallel-group, open-labelled non-inferiority randomised controlled trial in Denmark

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ABSTRACT

Introduction Contrast-enhanced CT (CECT) is widely used for diagnostic purposes. The use of contrast medium carries a risk for postcontrast acute kidney injury (PC-AKI), especially in patients with AKI or chronic kidney disease (CKD). Current guidelines recommend prophylactic intravenous hydration to prevent PC-AKI in high-risk patients. Oral hydration is non-inferior to intravenous hydration in patients with moderate CKD, but it has not been evaluated in high-risk patients.

Methods and analysis The ENRICH trial will enrol 254 patients with estimated glomerular filtration rate <30 mL/min/1.73 m² undergoing intravenous CECT, who are block randomised (2:4:2) with stratification for CKD stage, diabetes status, and indication for referral to prophylactic treatment with oral or intravenous hydration. PC-AKI is defined as an absolute increase in SCR of >0.3 mg/dL or >1.5 from baseline at 2–5 days. Renal function will also be evaluated <90 days, <7 days and 1–3 days before intravenous CECT, and 25–40 days after intravenous CECT. Secondary outcomes include dialysis, renal adverse events, hospitalisation due to hydration-related or contrast-related sequelae, and all-cause mortality ≤30 days postcontrast. Pre- and postcontrast plasma and urinary biomarkers will be evaluated for diagnostic and prognostic accuracy of the primary and secondary outcomes.

Ethics and dissemination Oral hydration is patient-friendly and less costly compared with intravenous hydration. If oral hydration is non-inferior to intravenous hydration in high-risk patients, it could be implemented as new hydration strategy, which will facilitate the clinical diagnosing of elective patients with severe CKD without unnecessary resource utilisation. The protocol is approved by the Regional Scientific Ethical Committee for Southern Denmark (S-20210126), and the Da ta Protection Agency (21/66779). The study is conducted in accordance with the Declaration of Helsinki. Positive as well as negative findings will be reported in international peer-reviewed journals.

Trial registration number NCT05283512.

STRENGTHS AND LIMITATIONS OF THIS STUDY

Strengths include the investigator-initiated, stratified block randomisation, non-inferiority design with blinded outcome assessment.

Other strengths are multiple control blood samples prior to contrast medium exposure along with multiple plasma and urinary biomarkers for evaluation of postcontrast acute kidney injury.

The hydration protocols are highly reproducible in a clinical setting.

The results will also be highly generalisable due to broad inclusion criteria and few exclusion criteria.

Limitations include lack of blinding among care providers and lead investigators, no invasive intravascular contrast procedures, and single-centre trial design.

BACKGROUND

Contrast-enhanced CT (CECT) is widely used for diagnostic purposes. More than 75 million CECTs were conducted on a worldwide basis...
in 2022, which is expected to increase in the future with the growing patient burden and advances in techniques and applicability.1 2 The use of contrast medium (CM) poses a risk of postcontrast acute kidney injury (PC-AKI) and contrast-induced AKI (CI-AKI).3–8 PC-AKI is a correlative diagnosis, which is defined as a sudden increase in serum creatinine (SCr) that may occur because of CM exposure, whereas CI-AKI is a causative diagnosis defined as a sudden increase in SCr directly caused by CM exposure.9 CI-AKI is a rare event, while PC-AKI occurs more often and is characterised by a transient, asymptomatic and self-limiting elevation in SCr.9 The risk of PC-AKI is additively correlated to comorbidities and health factors such as age, cardiovascular disease (CVD), diabetes mellitus (DM), chronic kidney disease (CKD), anaemia, and CM osmolality, volume, infusion rate, and route of administration.6 9 10 The most critical patient-related risk factor is pre-existing CKD,3 4 6 11 12 of which the global prevalence was estimated to be 10%–16% in 2013.13 14 Taking the global prevalence of CKD into account, an estimated 6–12 million annual CECTs are performed in risk patients. Recognising CKD as a critical health issue with poor short-term and long-term outcomes, The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines have classified CKD in clinical stages of I–V according to the estimated glomerular filtration rate (eGFR) and provided the current definition of PC-AKI.6

Most of the studies on PC-AKI are derived from invasive intraarterial CM procedures, which have reported incidences of 19%–20%.5 7 15 16 and a twofold increase in PC-AKI related to the stage of CKD.5 Futhermore, AKI has been associated with a sevenfold increase in mortality along with increased length of stay and hospital costs.17 These findings have been translated into an overall cautious attitude towards CM administration in patients with CKD. However, intraarterial CM differs from intra-venous CM in major ways. The most important differences are the risk of dislodging atheroemboli during the catheter-based injection and the first pass renal exposure.3 9 These risk-associated differences imply that incidences from invasive intraarterial CM procedures cannot be extrapolated to intravenous CM procedures. Furthermore, the indication for invasive intraarterial CM procedures may also account for prerenal and systemic conditions, which are confounders for AKI. Despite procedure- and risk-related differences, the remaining consensus is that hydration with intravenous isotonic 0.9% NaCl for 3–4 hours pre- and postcontrast is recommended as prophylactic treatment to prevent PC-AKI in high-risk patients.5 13

Recent studies have challenged the consensus regarding increased risk of PC-AKI following intravenous CECT6 9 18–26 among patients with pre-existing CKD. Meta-analyses found no significant difference on the incidence of AKI, death and dialysis between patients exposed to intravenous CM and unexposed patients in controlled studies.25 26 27 Intravenous CECT was not a significant risk factor in terms of hard endpoints such as PC-AKI, dialysis treatment and death, which also included subgroup analyses of moderate-risk and high-risk patients with DM, CKD stage III and IV–V and heart failure.26–28 However, the design and methods of these studies emphasise the lack of randomised controlled trials (RCT) and that our current knowledge of the causality between PC-AKI and intravenous CECT is still limited.20–23 Although the risk of PC-AKI after intravenous CECT seems to be overestimated, the incidence generally increases with the clinical stage of CKD,22 28 29 which suggest that the risk of PC-AKI is dependent on the procedure, patient setting and the number of risk factors. Therefore, the current guidelines recommend clinicians to perform individual risk assessment based on kidney function and health status to undertake targeted prophylactic treatment.5 10

The evaluation of kidney function and the diagnosis of PC-AKI is based on measurements of SCr and eGFR. PC-AKI has not been properly defined, but the most common definition is a relative increase in SCr of >25% from baseline or an absolute increase in SCr of >0.5 mg/dL measured 2–3 days after CM exposure.6 9 10 The recently published KDIGO-guidelines refer to PC-AKI under the same definition of AKI, which is a relative increase of SCr >1.5 or an absolute increase of SCr >0.3 mg/dL from baseline measured 2–3 days after CM exposure.6 Apart from varying definitions of PC-AKI, another issue is that SCr is an unreliable indicator of kidney injury because of its sensitivity to external factors (eg, hydration status, age, sex, muscle mass, physical activity, nutritional status and medications).9 SCr can demonstrate increments consistent with PC-AKI independent of CM exposure and has limited sensitivity to detect the minor tubular injury caused by CM.6 30 31 The timing of blood sampling is also crucial in high-risk patients because the rate of increasing SCr from decreasing creatinine clearance caused by nephron damage is slower in patients with severe CKD compared with patients with normal renal function.32 Thus, the timing of SCr-measurements may be crucial for the detection of PC-AKI.6 32

Neutrophil gelatinase-associated lipocalin (NGAL) has demonstrated promising diagnostic and prognostic accuracy for PC-AKI in settings with intravenous and intraarterial CM procedures.33–39 Elevated serum levels of cell-free DNA (cfDNA) have also been associated with AKI, mortality and dialysis treatment in different settings.40 41 Low NGAL/SCr concentrations (<56.4 µg/mg) precluded PC-AKI with a 96.5% probability,42 while cfDNA has demonstrated significant elevations in patients with AKI after intraarterial CM procedures.42 Significant cfDNA-elevations has also been demonstrated in rat models, in which AKI was induced by nephrotoxic drugs.43 44 Another benefit is also that the plasma and urine concentration of NGAL and cfDNA increase significantly 3–6 hours in the presence of kidney injury.34 39–45 These findings suggest that NGAL and cfDNA could be novel biomarkers with early and specific diagnostic and prognostic accuracy for PC-AKI and major adverse events after intravenous CECT compared with SCr.
The search for a less resource-demanding and patient-friendly hydration protocol as well as early and precise biomarkers of PC-AKI is ongoing. Prophylactic treatment with intravenous hydration is resource-demanding in all aspects of patient care and may not always be feasible in a universal healthcare system with an increasing patient burden and financial cutbacks. Oral hydration is a patient-friendly and easily feasible hydration method, which have been reported to be non-inferior to intravenous hydration in patients with mild to moderate CKD. However, the clinical evidence of these studies is limited by lack of statistical power, few time points for evaluation of renal function, no control groups, and few high-risk patients. These issues, especially the latter, have halted the implementation of oral hydration as prophylactic treatment to prevent PC-AKI in high-risk patients. RCTs with high-risk patients are therefore needed to verify oral hydration as a safe prophylactic strategy and to evaluate the true risk of PC-AKI and Cl-AKI after intravenous CECT.

The aim of the ENRICH trial is to evaluate if oral hydration with bottled tap water is non-inferior to intravenous hydration with isotonic 0.9% NaCl as prophylactic treatment for prevention of PC-AKI in patients with eGFR<30 mL/min/1.73 m² referred for an elective intravenous CECT. Furthermore, the ENRICH trial will evaluate the diagnostic and prognostic accuracy of NGAL and cfDNA for the occurrence of PC-AKI, dialysis treatment, renal adverse events, hospitalisation, and all-cause mortality.

**Research hypothesis**
1. Oral hydration with bottled tap water is non-inferior to intravenous hydration with isotonic 0.9% NaCl as prophylactic treatment to prevent PC-AKI in patients with severe CKD referred for an elective intravenous CECT.
2. NGAL and cfDNA are early and precise plasma and urinary biomarkers of PC-AKI with satisfying diagnostic and prognostic accuracy for PC-AKI, dialysis treatment, renal adverse events, hospitalisation and all-cause mortality.

**METHODS**

**Trial design**
The ENRICH trial is a pragmatic investigator-initiated, single-centre, open-labelled, parallel-group non-inferiority RCT with two parallel arms. Patients will be allocated to either oral hydration or intravenous hydration as prophylactic treatment to prevent PC-AKI after intravenous CECT. The Inclusion and exclusion criteria are listed in table 1.

**Participants and study setting**
The ENRICH trial is conducted at Odense University Hospital (OUH), which is a tertiary healthcare centre. The referral area covers the region of Southern Denmark, which corresponds to 1.25 million citizens in 22 municipalities of both urban and rural environment. The trial enrols high-risk patients with an eGFR<30 mL/min/1.73 m² scheduled for intravenous CECT using approximately 50–150 mL of CM (GE Healthcare, Omnipaque, osmolality 350 mg I/mL). Indications for referral for intravenous CECT comprise the following: Workup for treatment of CVD (eg, transaortic valve implantation, ablation, endocarditis) or suspected CVD (eg, angina), suspected cancer, thoracic/abdominal/urogenital diseases or cardiovascular workup before kidney transplantation (KTx). Patients referred for an acute or subacute intravenous CECT with competing etiologies for PC-AKI (eg, sepsis, acute tubular necrosis, cardiogenic shock) are not eligible for inclusion.

**Intervention hydration protocol**
The intravenous hydration protocol is based on the guidelines on contrast agents from European Society of Urogenital Radiology and the American College of Radiology. Specific hydration protocols for oral hydration are not well established in patients with eGFR<30 mL/min/1.73 m² undergoing elective intravenous CECT. Furthermore, the ideal infusion rate and volume has not been established for intravenous hydration. The participants are allocated to a pragmatic and easily feasible hydration protocol with a fixed volume of 500 mL pre- and postcontrast in both groups. The fixed volume is reduced to 250 mL in patients with heart failure. In this trial, oral hydration with bottled water is chosen because it is easy, feasible, pragmatic, and patient-friendly compared to other oral hydration methods (eg, oral NaCl or oral NaHCO₃) while being highly generalisable to clinical settings across the world. In addition, the hydration status prior to elective intravenous CECT may also be an important factor. Thus, the fluid intake within 24 hours of the intravenous CECT will be registered for all participant.

**Open access**

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**Table 1** Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
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<tr>
<td>eGFR&lt;30 mL/min/1.73 m²</td>
<td>Allergy to iodine</td>
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<tr>
<td>Scheduled for elective intravenous CECT</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Age ≥18</td>
<td>Active dialysis treatment</td>
</tr>
<tr>
<td>Signed informed consent</td>
<td>Active preterial and/or postrenal kidney failure</td>
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<td></td>
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CECT, contrast-enhanced CT; eGFR, estimated glomerular filtration rate.
immediately after intravenous CECT. In patients with heart failure (left ventricular ejection fraction (LVEF) ≤40%), the pre- and postcontrast volumes are reduced to 250 mL.

**Intravenous hydration group (standard of care)**

The intravenous hydration with isotonic 0.9% NaCl will be initiated 3 hours prior to and completed 4 hours after intravenous CECT (infusion rate of 1–3 mL/kg/hour). Patients are prescribed a fixed volume of approximately 500 mL before and 500 mL after intravenous CECT. In patients with heart failure (LVEF≤40%), the pre- and postcontrast volumes are reduced to 250 mL.

**Control group**

The trial does not have an actual control group, who are exposed to CM without preventive measures. However, each patient is required to have multiple blood samples drawn for evaluation of renal function prior to CM exposure within the same time frame as the diagnostic criteria for PC-AKI, which will illustrate the variation in renal function among high-risk patients without CM exposure. The physiological variation in renal function will be evaluated from blood samples at <90 days, <7 days and 1–3 days prior to the scheduled intravenous CECT. Furthermore, the renal function will be evaluated at baseline before initiation of the hydration protocol and CM exposure, hereby defining the baseline renal function. The purpose of the control group is to establish the physiological variation of SCr in patients with severe CKD and support the evidence of causality between CM exposure and deterioration in renal function.

**Participant timeline and recruitment**

Eligible patients are identified from recent test results for evaluation of renal function prior to scheduling the intravenous CECT. Eligible patients will be informed about the guideline-recommended prophylactic treatment with intravenous hydration. A brief introduction of the study is then given. The patient will be contacted by the lead investigators upon approval and a thorough presentation of the trial is provided, after which a verbal consent to participate in the study is sought. The guideline-required blood sampling for evaluation of renal function <7 days prior to their intravenous CECT will be planned along with an additional blood sample 1–3 days prior to their intravenous CECT. Additionally, blood samples to evaluate renal function will be planned at 2–3 days, 4–5 days and 30 days after intravenous CECT along with a follow-up consultation by telephone 4–5 days and 30 days after intravenous CECT. If PC-AKI is present 4–5 days after intravenous CECT, additional blood samples will be planned 7 days and 14–21 days after intravenous CECT to continuously evaluate renal function depending on the SCr trend. The informed consent is obtained at baseline, after which the medical interview is conducted along with blood and urine sampling for baseline renal function and baseline plasma and urine biomarkers. The hydration protocol will be initiated after the blood and urine sampling is completed approximately 3 hours before the scheduled intravenous CECT. An echocardiography will also be performed prior to the initiation of the hydration protocol if the patient has CVD without a recent echocardiography to evaluate LVEF. The participant timeline is illustrated in table 2.

### Outcomes

**Primary outcome**

The primary outcome is defined as the incidence of PC-AKI in each arm of the trial. The common definition of PC-AKI prescribes measurements of SCr 2–3 days after CM exposure to diagnose PC-AKI. In the present trial, SCr is measured 2–3 days and/or 4–5 days after intravenous CECT. This initiative will minimise the risk of missing changes in SCr consistent with PC-AKI since the

<p>| Table 2 | Participant timeline and applied tests (for further details, please see the variables and applied tests section) |</p>
<table>
<thead>
<tr>
<th>Days from baseline</th>
<th>&gt; -90</th>
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<th>+2 to 3</th>
<th>+4 to 5</th>
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<th>(+14 to +21)</th>
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<td>X</td>
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</tbody>
</table>

*Evaluation of baseline renal function includes blood and urine samples for analyses of biomarkers for PC-AKI.
†Baseline echocardiography will be performed in all cardiological and nephrological patients prior to the scheduled intravenous CT-scan as part of their clinical work-up. Other patients will only have an extraordinary echocardiography performed for left ventricular ejection fraction (LVEF) estimation if cardiovascular disease with clinical significance for the administered hydration volume is suspected.
‡Non-contrast CT-scan will only be performed in some cases depending on the indication for intravenous CECT according to the department’s predefined CT-protocols.

CECT, contrast-enhanced CT; PC-AKI, post-contrast acute kidney injury.
rate of SCr increasements are slower in patients with CKD compared with patients with normal renal function. In addition, evaluation of renal function 2–3 days after intravenous CECT may be difficult due to logistics constraints (eg, weekends, holidays, availability for blood-sampling). By allowing a larger time frame to evaluate renal function, the primary outcome will realistically reflect the clinical setting and its limitations to evaluate renal function exactly 2–3 days post-contrast.

The peak SCr at 2–5 days will be used to define PC-AKI in accordance with the KDIGO guidelines. PC-AKI is defined as a relative increase of SCr$>1.5$ or an absolute increase of SCr$>0.3$ mg/dL from baseline. The primary endpoint will also be evaluated in prespecified subgroups based on risk factors for PC-AKI:

- **Age $\geq 75$ years, gender, DM status, CVD, CKD stage, nephrogenic anaemia (haemoglobin $<6.5$ g/L and/or active erythropoietin treatment), high contrast-volumes ($\geq 75$ mL), smoking, and indication for referral.

**Key secondary outcomes**

The key secondary objectives in the ENRICH trial are to determine the outcome of the following safety endpoints. The outcomes will be analysed both as individual endpoints and as a composite endpoint:

- Need for dialysis $\leq 30$ days after intravenous CECT.
- Renal adverse events defined as a relative increase in SCr$>15\%$ and/or a decrease in eGFR$>15\%$ and/or progression in CKD-stage from CKD-stage IV to CKD-stage V from baseline within 25–40 days after intravenous CECT.
- Hospitalisation due to symptomatic heart failure $\leq 30$ days after intravenous CECT.
- All-cause mortality $\leq 30$ days after intravenous CECT.

**Other secondary outcomes**

- The incidence of PC-AKI within the population and the two arms defined as a relative increase in SCr$>25\%$ from baseline or an absolute increase $>0.5$ mg/dL.
- The difference in PC-AKI diagnosed 2–3 days after intravenous CECT and 4–5 days after intravenous CECT within the population and the two arms.
- Progression in CKD-symptoms $\leq 30$ days after intravenous CECT defined as an increase in number of uraemic symptoms compared with number of uraemic at baseline within the two arms (see definition of ‘uraemic symptoms’ under ‘Variables’).
- Hospitalisation due to suspected hydration- or contrast-related sequelae (eg, arrhythmias, renal insufficiency, hyponatraemia or hypernatraemia) $\leq 30$ days after intravenous CECT.
- Number of participants with normalisation of PC-AKI at the different time points for evaluation of renal function after intravenous CECT within study population and the two arms. Normalisation of PC-AKI is defined as the event of SCr returning to a level below the diagnostic criteria for PC-AKI.

- Mean changes in SCr and eGFR from baseline at different time points (days from baseline): $-89$ to $-7$ days, $-6$ to $-4$ days, $-3$ to $-1$ days, $0$ days (baseline), $+2$ to $3$ days, $+4$ to $5$ days and $+25$ to $+40$ days.
- Mean changes in standard blood parameters at $+2$ to $3$ days, $+4$ to $5$ days and $+30$ days from baseline.
- Mean values in plasma and urinary biomarkers from baseline (0 hours) and 4 hours after intravenous CECT.
- Delta-values in plasma and urinary biomarkers from baseline (0 hours) to 4 hours after intravenous CECT.
- Prognostic and diagnostic accuracy of plasma and urinary biomarkers for PC-AKI, dialysis treatment, renal adverse events, hospitalisation and all-cause mortality.
- Kidney size indexed to the body size as a risk factor for the occurrence of PC-AKI.
- The use of resources for hydration, length of admission and complications during hospitalisation.

**Sample size**

Limited RCT data exist comparing different hydration protocols for their ability to prevent PC-AKI in patients exposed to intravenous CECT. 

- No RCTs have evaluated the efficacy of oral hydration versus intravenous hydration for the incidence of PC-AKI in patients exposed to intravenous CECT. Data from meta-analyses on RCTs, which compare oral hydration to intravenous hydration for prevention of PC-AKI in outpatients, have reported incidences of PC-AKI around 7.7%–9.5%. However, these incidences cannot easily be extrapolated to our study population due to low inclusion of high-risk patients. Data on the incidence of PC-AKI after intravenous CECT among outpatients with severe CKD has been reported as 12.1%–20.5%. However, no RCTs have evaluated the efficacy of oral hydration versus intravenous hydration for the incidence of PC-AKI after intravenous CECT in the setting of high-risk patients. This trial will evaluate whether oral hydration is non-inferior to intravenous hydration to prevent PC-AKI among high-risk patients under the assumption that both hydration methods will prevent PC-AKI successfully in approximately 80% cases equivalent to an incidence of 20% in each arm. Based on the expected incidences in each arm, a sample size of 254 patients will have a power of 80% with a one-sided alpha level of 5% aiming to detect an absolute difference in PC-AKI between the two groups of more than 12.5%. A non-inferiority limit of 12.5% may seem high, but this is for the primary outcome, which is based on changes in SCr and not dialysis or mortality. The chosen non-inferiority limit is based on the clinical assumption that a higher incidence of PC-AKI may not result in an increase of major adverse events (ie, dialysis, renal adverse events, hospitalisation or all-cause mortality). PC-AKI often resolves within few days weeks and major adverse clinical events have been reported to be $<1\%$. Thus, it is expected that the high incidence of PC-AKI among high-risk patients will not lead to increased incidence of major adverse events. Taking this clinical assumption into consideration, an absolute difference $<12.5\%$ between the two arms is reasoned to be
acceptable in the absence of an increase in major adverse events between the two arms.

**Stratified randomisation**
The randomised allocation to prophylactic treatment with oral hydration or intravenous hydration will be performed in Research Electronic Data Capture (REDCap), which is computer-based tool provided by OPEN. The unique block randomisation list was generated using software provided by Sealed Envelope Ltd. 2022 and implemented in our database, which was provided and monitored by our data manager at Open Patient data Explorative Network (OPEN). The block randomisation list will remain unknown throughout the study period.

The randomisation will be performed as block randomisation (2-4-2) with stratification for DM status (yes vs. no), CKD stage (eGFR<15 mL/min/1.73 m² vs. 15–29 mL/min/1.73 m²) and the basis of referral for intravenous CECT (diagnostic work-up for KTx vs. all other). Participants are then followed for a 30-day period with standard blood testing for kidney function 2–5 days after CECT and a 30-day follow-up for the key secondary outcomes (see figure 1 and table 2).

**Blinding**
In this study, laboratory personnel processing the blood samples for renal evaluation will be blinded along with outcome-assessors and data-analysers. Caretakers and the lead investigators cannot be blinded due to the obvious differences between the two prophylactic treatments. However, patients and medical staff will remain masked for the intervention until signed informed consent is collected.

**Adherence**
The study includes an adherence reminder session, which will take place at the question-and-answer session prior to the signing of the declaration of consent. This session will include:

- Instructions about the purpose, design, method and use of the study.
Information about the hydration protocol and fluid balance chart.

Instructions about the appointments for blood samples, including information about the timing of the blood samples, the parameters measured, the importance of complying to the appointments, and what to do in the event of a missed blood sample.

The importance of following study guidelines for adherence.

**Participant retention, follow-up and withdrawal**

Once a patient is enrolled and randomised, the research group will make every reasonable effort to follow the patient for the entire study period. If the patient fails to attend their appointment for blood sampling to evaluate renal function, the patient will be contacted by telephone, and a new appointment for blood sampling is scheduled within the next 24 hours. The patient will only be excluded from the study after randomisation if the patient is not hydrated according to the hydration protocol or if the intravenous CECT is cancelled after randomisation and interventional hydration. The rate of lost to follow-up for the primary and secondary outcomes is expected to be <10%.

**Variables**

Standard blood parameters for evaluation of renal function will be obtained at <90 days, <7 days, 1–3 days before intravenous CECT, and at baseline before prophylactic hydration and CM exposure. Furthermore, a urine sample for albumin/creatinine ratio (mg/g) will be obtained at baseline. The standard blood parameters for evaluation of renal function will also be obtained 2–3 days and/or 4–5 days and 25–40 days after intravenous CECT. Additional blood sampling to evaluate renal function will be performed at 7 days and/or 14–21 days after intravenous CECT among patients with increasing SCr 4–5 days after intravenous CECT consistent with PC-AKI. The standard blood parameters for patients referred for intravenous CECT consist of the following: haemoglobin (mM), erythrocytes (count/L), SCr (µmol/L), eGFR (mL/min/1.73 m²), albumine (µmol/L), sodium (mM) and potassium (mM).

The prospective cohort will be followed over a 30-day period for events of dialysis treatment, renal adverse events, hospitalisation due to hydration-related or contrast-related sequelae (ie, symptomatic heart failure, arrhythmias, renal insufficiency, hyponatraemia or hypernatraemia), and all-cause mortality. Furthermore, progression in CKD symptoms will be obtained from registration of uraemic symptoms through a medical interview at baseline and ≤30 days after intravenous CECT. A trained interviewer will identify any clinical signs of progression in CKD within the 30-day follow-up. Progression in CKD is defined as progression in uraemic symptoms, which consist of the following:

- Weight loss, loss of appetite, cramps, nausea, vomiting, pruritus, bruising, fatigue, peripheral oedema, impaired consciousness and changes in sense of taste.

The medical history and medicine use of the participants will be obtained at baseline before initiation of the hydration protocol along with the echocardiography. The patient will then tend to their scheduled intravenous CECT. Blood and urine samples for biomarkers of PC-AKI will be collected before initiation of the hydration protocol and 3–4 hours after intravenous CECT. The admission time of the participants is defined as the timespan between the start and the completion of the hydration regimen (see table 2), which is registered as ‘date-month-year-hours-minutes’. Dates and reasons for hospital admission <90 days before intravenous CECT will also be registered along with additional contrast exposure within the 30-day follow-up period after the scheduled intravenous CECT.

The following parameters will also be obtained for the subgroup of participants, who are referred for a scheduled cardiac intravenous CECT:

- Estimated Coronary Artery Calcification score.
- Stenosis >50% of the left main coronary artery (LM).
- The grade of stenosis will be assessed if present in the coronary arteries; LM, left anterior descending artery, left circumflex artery and right coronary artery (see figure 2).
- Aortic valve calcification and mitral annulus calcification.
- Calcification (Agatson score) of the aorta (aorta ascendens, archus aorta and aorta descendens), the suprarenal and infrarenal aorta, and the renal arteries.

**Statistics**

All analyses will be performed on an intention-to-treat basis if missing data exceeds 10% for our follow-up on PC-AKI 2–5 days after intravenous CECT and the key secondary outcomes ≤30 days after intravenous CECT. In this case, the analyses of our primary outcome and key secondary outcomes will be adjusted for drop-outs. Data will be analysed as per-protocol if the drop-out rates are <10%. P values <0.05 are considered statistically significant. Baseline characteristics are presented as frequencies, mean SD, median IQR as appropriate. The balance of the baseline characteristics is compared in the two arms using Fisher’s exact test or the Wilcoxon rank sum test as appropriate.

For the primary outcome, the incidences of PC-AKI will be presented as overall incidence and incidences within the two arms. Furthermore, PC-AKI will be characterised by normalisation of SCr below the criteria of PC-AKI 4–5 days, 7 days, 14–21 days and/or 30 days after intravenous CECT in each arm. The upper bound of the 90% CI for the difference of the PC-AKI rates will be determined to align with our one-sided alpha rate of 0.05 (type-I error rate). Similar stratified analyses will be performed in our prespecified subgroups, and multivariable logistic regression analyses will be performed to assess the association between PC-AKI risk factors and the incidences of PC-AKI. The risk factors will also be evaluated as independent risk factors for PC-AKI after controlling for eGFR.
values for interaction will be derived from multivariable logistic regression to test for differences across the two arms and the prespecified subgroups. The risk of PC-AKI is estimated from a generalised linear model adjusting for potential confounders, which is presented as OR.

For the secondary outcomes, χ² test will be used to test for statistic differences in categorical variables. Mean values of continuous variables (renal function, data from CECT, admission time, etc) are estimated and tested for statistical differences between the two arms and subgroups by Student’s t-test for independent samples. We expect that the incidences of each key secondary outcomes (ie, dialysis, renal adverse events, hydration-related sequelae or AKI and all-cause mortality) to be markedly low, which is why they will be analysed and described as for common descriptive statistics. If the incidences exceed our expectations, the individual risk of each key secondary outcome will be examined using a competing risk analysis for estimating 30 days cumulative incidence and a Cox proportional hazard model to estimate HR.

Analysis of pre- and postcontrast NGAL and cfDNA from blood and urine samples is performed by an unpaired Mann-Whitney U test. Receiver operating curves adjusted for sex, BMI, and area under curve will be calculated to determine the diagnostic accuracy of the biomarkers. Furthermore, the baseline and 3–4 hours levels of the biomarkers will also be evaluated for their prognostic accuracy for the key secondary outcomes. Cut-off values are calculated by the Youden’s index. Positive predictive values and negative predictive values are calculated from the sensitivities and specificities of the respective biomarkers along with the positive and negative likelihood ratios. Univariate and multivariate logistic regression adjusted for PC-AKI and risk factors (as appropriate) are performed to evaluate NGAL’s and cfDNA’s individual ability to detect PC-AKI. The calculations will be based on a derivation cohort and a validation cohort, which will comprise the first 127 included patients and the last 127 included patients, respectively. The same analyses will also be performed on the full study population.

Safety
An interim analysis will be performed after inclusion of 127 patients to evaluate the primary outcomes and the key secondary outcomes. The steering committee (SC) will consider terminating the study preliminary if the analyses conclude a significant difference in the incidence of the primary and/or the key secondary outcomes between the two groups.

Harms
The participants are clinical patients, who are treated and followed according to the usual clinical care, except for the intervention with oral hydration or intravenous...
hydration. We do not expect any serious unexpected suspected adverse events (SUSAE) based on the nature of the two prophylactic interventions, but all patients are followed closely by the lead investigators to make sure that any SUSAE will be noticed and reported if necessary. The patients are advised to communicate with the trial management committee (TMC) if they notice any suspicious side effects or symptoms, but the lead investigators will specifically ask about any SUSAE following prophylactic hydration and CM administration at the 4–5 day and 30 day follow-up consultation. If any SUSAE occur, the TMC will assess the seriousness of the SUSAE and report the SUSAE. Furthermore, the TMC will also report the SUSAE to the referring physician, who is responsible for the diagnosing and treatment of the patient. The lead investigators will then take steps to initiate the necessary treatment and management of the SUSAE.

Extraction, storage and analysis of biomaterial

The total amount of blood and urine samples equals to a standard of 14 samples equivalent to 68 mL and 4 urine samples equivalent to 23 mL. Twelve standard blood samples of 4 mL and one urine sample of 4 mL are analysed for the standard blood parameters at different time points and albumin/creatinine ratio at baseline, respectively (see participant timeline). If SCr has increased significantly consistent with PC-AKI within 2–5 days after intravenous CECT, additional standard blood samples of 4 mL will be acquired to evaluate SCr and eGFR at 7 days and 14–21 days from baseline depending on the SCr trend. At baseline, two blood-samples of 10.0 mL and two urine samples of 10.0 mL will also be obtained before intravenous CECT and 3–4 hours after intravenous CECT. Plasma EDTA and urine will be obtained by centrifugation at 3700 g for 10 min at room temperature immediately after sampling. The samples will then be stored in a biobank at −70°C afterwards. Blood and urine cfDNA is analysed in OPEN lab, OUH. In the declaration of consent, we formally ask the patient for consent to transfer their blood and urine samples from our biobank to a new biobank intended for future research in clinical biomarkers of PC-AKI (see online supplemental material). We emphasise that the process of transferring the patient biological material will comply with the rules and regulations of the Danish Data Protection Act.

Neutrophil gelatinase-associated lipocalin

EDTA-plasma and urine levels of NGAL will be determined in duplicates using an in-house sandwich ELISA based on anti-NGAL antibodies and recombinant NGAL. (DY1757, R&D Systems, Minneapolis, USA). This test-kit has demonstrated high performance for precision, parallelism, recovery, selectivity, limit of quantitation, vulnerability to interference, hook effect and interassay agreement.58 59 Measurements will be performed using a VICTOR Nivo microplate reader (PerkinElmer) and by an individual blinded to the sample IDs. Low-quality and high-quality control samples will be analysed in each analytical run. Assay range is 0.078–5 ng/mL, and the assay behaves linearly within the analytical range. In previous analyses, the limit of detection was <0.1 ng/mL based on NSB+3SD. The within-assay coefficient of variation (CV) of standards, controls and unknown samples averaged less than 10%, and between-assay CV of standards and control samples averaged <15%.

Cell-free DNA

cfDNA will be purified from one mL EDTA plasma using the Maxwell RSC cfDNA plasma kit (Promega) on a Maxwell RSC (Promega) according to the manufactures standard protocol. The concentration of cfDNA is determined using Quant-iT PicoGreen dsDNA Assay Kits (Invitrogen) according to the manufacturers’ instruction. The analysis of cfDNA from plasma EDTA was compared with plasma from cfDNA BCT (golden standard), which showed no significant difference in test results.

Data management

Data entry is managed in REDCap. REDCap is an online database connected to Open Patient data Explorative Network’s (OPEN) server, which is issued by the Region of Southern Denmark. The database is developed specifically to non-commercial clinical research and will be used to register, code and save data online. All data are encrypted in agreement with the rules and regulations of the Danish Data Protection Act and Good Clinical Practice for data entry and modifications. The quality of the data obtained (ie, hydration and CT data) will continuously be promoted through double data entry from paper charts. The REDCap database will be supervised by the data manager, who is financed by OPEN and serves as an independent monitoring unit. The data entry and modifications will be documented in the REDCap database through logging with time and date stamps. Data quality reports will regularly be compiled and sent to the data manager to maintain a high standard of data quality and prohibit inconsistencies and errors. Furthermore, data in REDCap is available for the Danish Data Protection Agency and the Research Ethics Committee during the whole study period. Data concerning the medical history and medicine use of the patients will be typed manually during the medical interview and double-checked against their medical charts. Numeral values in the REDCap database are encoded with a standard range check, which notifies the data collector if any of the typed values exceed the predefined reference range.

ETHICS

Patient and public involvement

Patients and the public were not involved in the design of the study. Independent board members of the Regional Scientific Ethical Committee for Southern Denmark, who
represent the public, have approved participant information and the declaration of consent.

Consent and dissemination of amendments
Participation in the trial is permitted after a signed informed consent (see ‘patient consent form’ and ‘patient consent form future research’ attached as online supplemental material). The declaration of consent will be collected by the lead investigators. Study participants will have participated in a thorough question and answer session with the possibility of subsequent deliberation time of minimum 24 hours before signing the declaration of consent. Access to the patient data will only be available for the clinical researchers and the hospital staff, who are involved in the clinical care for the participants. All protocol modifications and major amendments will be communicated to the competent authorities: The Research Ethics Committee, The Danish Data Protection Agency and the trial registry of Clinical Trials through additional protocols. Both positive and negative findings will be published in international peer-reviewed journals. A layman description of the study results and conclusions will be sent to study participants, who has requested it.

Provision and compensation
All patients can file a complaint or seek recompense for any harm from trial participation within boundaries of relevant legislations. Before signing the declaration of consent, all patients will be provided with a brochure from The National Research Ethics Committee. The brochure elaborates each step of the process.

Organisation
Principal investigators: Emil Johannes Ravn, Claus Bistrup and Kristian A. Øvrehus
The principal investigators are responsible for the design and conduct of ENRICH, preparation of protocol, protocol revisions, investigators brochure (IB) and CRFs (Case Report Forms) along with publication of study reports.

SC: Emil Johannes Ravn, Selma Hasific, Axel Diederichsen, Claus Bistrup and Kristian A. Øvrehus
The SC is responsible of the agreement on the final protocol and reviewing progress of study. If necessary, the SC will be responsible for adjusting the protocol and/or IB to facilitate the running of the study.

TMC: Emil Johannes Ravn, Kristian A. Øvrehus and Claus Bistrup
The TMC will handle all practical issues concerning study planning, reporting of SUSAE, the trial master file, budget administration and contractual issues, and collection of serum samples.

Data manager: OPEN, OUH, Allan Lind-Thomsen
The data manager will handle the maintenance of trial IT-systems and data verification along with promotion of data quality.

Lead Investigators: Kristian A. Øvrehus, Emil Johannes Ravn, Viktor Poulsen and Selma Hasific
The lead investigators are responsible for identification and inclusion of patients, data collection and data entry, follow-up of study patients and completion of CRFs.

Feasibility
The facilitation of the study is based on a cooperation between the Department of Cardiology, the Department of Radiology, the Department of Vascular Surgery and the Department of Nephrology at OUH. The lead investigators conducted a historical review of referral rates for intravenous CECT among high-risk patients prior to the initiation of the trial. The expected inclusion rate was estimated to approximately 50–100 yearly patients. We expect low drop-out rates, because the participants are treated according to the standard of care.

Rationale
The effect of intravenous hydration with NaCl have been demonstrated in several larger studies in different settings.5 8 60 The true incidence and severity of PC-AKI and CI-AKI is still unknown, but PC-AKI studies from different clinical settings with varying procedures have demonstrated a discrepancy in the incidence and clinical severity of PC-AKI5 7 15–18 24 26–29 55 Several studies have suggested that oral hydration is non-inferior to intravenous hydration for the prevention PC-AKI 46 47 50–52 61–63 while reducing the costs of patient care significantly.46 Oral hydration is more patient-friendly and will improve the facilitation of the work-up for future patients. Furthermore, the costs associated with intravenous hydration may not be feasible in a universal healthcare system, which demands rational resource utilisation due to an increasing patient-burden and financial cutbacks. The current studies and meta-analyses comparing oral hydration to intravenous hydration as prophylactic strategies to prevent PC-AKI are limited by small study populations, few high-risk patients, heterogenicity, lack of hard clinical outcomes. These limitations have been considered in the design ENRICH trial in order to obtain solid data with reliable results.

Clinical perspective
Our study is the first to evaluate the effectiveness oral hydration versus intravenous hydration to prevent PC-AKI in high-risk patients with eGFR<30 mL/min/1.73 m², of which the vast majority are patients with predialytic CKD (stage 5a). Furthermore, the trial will be the first larger RCT to evaluate NGAL and cfDNA as biomarkers for the diagnosing and prognosis of PC-AKI and major adverse events in an outpatient-setting after intravenous CECT. The results from this trial will bring solid data and reliable results to clarify an important clinical issue, which can impact the guidelines on contrast agents. Oral hydration is undeniably more time- and cost-effective as well as patient-friendly, which will benefit the clinical diagnosing of patients with severe CKD. Earlier detection of PC-AKI...
from NGAL and cfDNA may improve the diagnosing, treatment and prognosis of the patients as the effectiveness of the treatment rely on early detection, improvement of haemodynamic status and controlling of the underlying comorbidities.5 7 8 12 64

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Underlying comorbidities.5 7 8 12 64

treatment and prognosis of the patients as the effective-
is non-

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Supplemental material

Ejnar Bjørnows Foundation (Grant/journal number: 2022-A5201).

This is an open access artic

Patient and public involvement

None declared.

Patient consent for publication

Consent obtained directly from patient(s).

Provenance and peer review

Not commissioned; externally peer reviewed.

Contributors

KAØ, CB and EJR conceived the study. EJR, SH, MT, RH, KBL, AD, CB and KAØ initiated the study design. EJR wrote the protocol and is the principal investigator along with KAØ. EJR is grant holder. KAØ is responsible for the Cardiac CT protocol, and SH will assist EJR in analysing data from CT and echocardiography. MT and RH are responsible for analysis of the speci-

fied biomarkers and will assist EJR, SH, AD, CB and KAØ in the interpretation of the results. EJR, SH, AD, KAØ and CB contributed with statistical expertise and improvement of the clinical trial design, and EJR will draft the articles. All authors contributed to refinement of the study protocol and approved the final manuscript.

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Competing interests

None declared.

Patient consent for publication

Consent obtained directly from patient(s).

Supplemental material

This content has been supplied by the author(s).

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Samtykkeerklæring til fremtidig forskning

Forskningsprojektets titel: Risk of intravenous contrast-induced acute kidney injury in high-risk patients undergoing cardiac CT - a randomized controlled trial

Som led I deltagelse af ovenstående projekt tages et sæt blod- og urinprøver hhv. før din CT-scanning og ca. 4 timer efter din CT-scanning. Disse blod- og urinprøver bruges i projektsammenhæng til at undersøge, om både en række klinisk etablerede biomarkører og en række nye biomarkører kan bruges til at erkende kontrastforårsaget akut nyreskade tidligere.

På nuværende tidspunkt har projektet til formål at undersøge følgende klinisk etablerede biomarkører for kontrastforårsaget akut nyreskade: NGAL, KIM-1, FGF23, TNFR1, TNFR2, trombomodulin og suPAR

Følgende nye biomarkører, som ikke er blevet undersøgt før, vil også blive undersøgt i dette studie: cirkulerende cellefrit DNA og miRNA specifikt for nyreceller.

Det understreges på det kraftigste, at der ikke er tale om genetisk forskning, hvad angår cirkulerende cellefrit DNA og miRNA specifikt for nyreceller. Disse biomarkører undersøges, fordi mindre studier har tydet på, at man kan finde en stigning af cirkulerende cellefrit DNA og miRNA specifikt for nyreceller, hvis nyrerne tager skade af kontrastmaterialet.

Eftersom flere biomarkører identificeres undervejs som forskningen inden for feltet udvikler sig, vil vi spørge Dem, om vi må bruge dine blod- og urinprøver til yderligere forskning inden for kontrastforårsaget akut nyreskade ude i fremtiden, hvis dette viser sig at kunne være relevant. Desuden om vi må flytte dine blod- og urinprøver fra biobanken oprettet til dette studie til en fremtidig biobank oprettet til den forskning, som potentielt kan blive relevant ude i fremtiden.

Deltagerens navn: _______________________________________________________________

Dato: ______________   Underskrift: _____________________________________

Information givet af: _______________________________________________________________

Dato: ______________   Underskrift: _____________________________________
DET VIDENSKABSETISKE KOMITESYSTEM

Informert samtykke til deltagelse i et sundhedsvidenskabeligt forskningsprojekt

Forskningsprojektets titel: Intravenous vs. oral hydration to reduce the risk of post-contrast acute kidney injury after intravenous contrast-enhanced computed tomography in patients with severe chronic kidney disease (ENRICH): A randomized controlled trial

Erklæring fra forsøgspersonen:
Jeg har fået skriftlig og mundtlig information, og jeg ved nok om formal, metode, fordele og ulemper til at sige ja til at deltage.
Jeg ved, at det er frivilligt at deltage, og at jeg altid kan trække mit samtykke tilbage uden at miste mine nuværende eller fremtidige rettigheder til behandling.
Jeg giver samtykke til at deltage i forskningsprojektet og til at mit biologiske materiale må udtages med henblik på opbevaring i en forskningsbiobank. Jeg har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Forsøgspersonens navn: __________________________________________________________
Dato: ___________________ Underskrift: _____________________________________

Hvis der kommer nye væsentlige helbredsoplysninger frem om dig i forskningsprojektet, vil du blive informeret. Vil du frabede dig information om nye væsentlige helbredsoplysninger, som kommer frem i forskningsprojektet, bedes du markere her: _________ (sæt x).

Ønsker du at blive informeret om forskningsprojektets resultater samt eventuelle konsekvenser for dig?:
Ja: _______ (sæt x)  Nej: _______ (sæt x)

Erklæring fra den, der afgiver information:
Jeg erklærer, at forsøgspersonen har modtaget mundtligt og skriftligt information om forsøget.
Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes en beslutning om deltagelse i forsøget.
Navn på den, der har afgivet information: __________________________

Dato: ___________________ Underskrift: _____________________________________

Projektidentifikation: Projekt-IDS-20210126