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Prevention of postcontrast acute kidney injury after percutaneous transluminal angioplasty by inducing RenalGuard controlled furosemide forced diuresis with matched hydration: study protocol for a randomised controlled trial

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ABSTRACT

Introduction Percutaneous transluminal angioplasty (PTA) is often complicated due to postcontrast acute kidney injury (PC-AKI) in patients diagnosed with chronic kidney disease (CKD). Hydration therapy is the cornerstone in the prevention of PC-AKI. Furosemide forced diuresis with matched hydration using the RenalGuard system enables a steady balance between diuresis and hydration. A randomised controlled trial will be performed in order to investigate whether furosemide forced diuresis with matched hydration in combination with the RenalGuard system decreases incidence of PC-AKI in patients with CKD receiving a PTA of the lower extremities. Furthermore, we will investigate whether sampling of urine biomarkers 4 hours after intervention can detect PC-AKI in an earlier stage compared with the golden standard, serum creatinine 48–72 hours postintervention.

Methods and analysis A single-centre randomised controlled trial will be conducted. Patients >18 years in need of a PTA of the lower extremities and diagnosed with CKD will be randomly assigned to receive either standard of care prehydration and posthydration or furosemide forced diuresis with matched hydration periprocedural using the RenalGuard system. Four hours postintervention, a urine sample will be collected of all participating patients. Serum creatinine will be sampled within 10 days prior to intervention as well as 1, 3 and 30 days postintervention. The primary endpoint is incidence of PC-AKI post-PTA. Secondary endpoint is the rise of urine biomarkers 4 hours postintervention.

Ethics and dissemination Study protocol is approved by the research ethics committee and institutional review board (reference number 16T-201 and NL59809.096.16). Study results will be disseminated by oral presentation at conferences and will be submitted to a peer-reviewed journal. It is anticipated that study results will offer a solution to contrast-induced nephropathy in patients with CKD receiving a PTA of the lower extremities.

Trial registration number NTR6236; Pre-results.
EudraCT number 2016-005072-10

Strengths and limitations of this study

► The first study to evaluate the incidence of postcontrast acute kidney injury (PC-AKI) in patients with peripheral arterial disease treated endovascular while receiving furosemide forced diuresis using the RenalGuard system.
► Study results might lead to a new preventive measurement in the prevention of PC-AKI in patients with chronic kidney disease (CKD) requiring an endovascular procedure of the lower extremities.
► Study results might provide a method for early detection of PC-AKI in patients with CKD receiving an endovascular procedure of the lower extremities, using urine biomarkers.
► This is a single-centre study.
► The sample size is calculated based on study results in patients receiving a coronary procedure. Volume of contrast used and the incidence of PC-AKI might differ.
► This study is not powered to detect a significant difference in adverse events between the two treatment groups.

INTRODUCTION
Background

Endovascular treatment of stenotic or occlusive lesions in the management of peripheral arterial disease (PAD) requires the use of nephrotoxic iodine contrast. Iodine contrast in patients receiving a percutaneous transluminal angioplasty (PTA) can cause postcontrast acute kidney injury (PC-AKI).[1–3] Recent update of the European Society of Urogenital Radiology guidelines changed the definition of contrast-induced nephropathy (CIN) to PC-AKI as the preferred term for renal function deterioration after contrast medium.[4] This protocol will refer to CIN as PC-AKI.

PC-AKI is defined as a decrease in estimated glomerular filtration rate (eGFR) of >25% compared with baseline values or a rise of >0.5 mg/dL serum creatinine within 72 hours after an iodine contrast mediated procedure (KDIGO guidelines (Kidney Disease Improving Global Outcomes)).[5][6] Sigterman *et al* described an 13% incidence of PC-AKI in patients treated with a PTA, regardless of prior renal function.[7] The incidence of PC-AKI can be as high as 50% in high-risk patients and is the cause of 10% acute in hospital renal failure.[1][8][9] Moreover, high-risk patients diagnosed with chronic kidney disease (CKD) are known to have an increased risk of developing PC-AKI after administration of iodine contrast. CKD and iodine contrast are both independent risk factors in the development of PC-AKI.[1] Furthermore, CKD is a global problem, affecting 10%–16% of the general population.[9] Prevalence of CKD is increasing worldwide and is estimated to be as high as 45% in the population aged >70 years.[9] Moreover, incidence and prevalence of PC-AKI are rising 5%–8% annually.[1]

CIN is associated with a significant worse outcome due to increased risk of cardiovascular events, acceleration to end-stage renal failure requiring dialysis and extended hospitalisation, causing increased morbidity and mortality.[7][10–13] Moreover, Ramaswami *et al* showed a significant higher mortality rate in patients developing PC-AKI after receiving a coronary angiography compared with patients without PC-AKI (respectively, 7.1% vs 1.1%, n=1826).[3]

Extended hospitalisation and additional care due to PC-AKI is costly. Average cost of 1 year of dialysis in the Netherlands is estimated to be as high as €80 000. The total annual medical costs for patients diagnosed with PC-AKI in the USA are estimated US$700 million to US$1 billion.[9][14][15] Relevant patient-related risk factors developing PC-AKI are: CKD, diabetes mellitus, heart failure, old age, anaemia and decreased function of the left ventricle.[7] The cause of CIN is attributed by multiple mechanisms. Concisely, free radicals are activated in the kidneys due to hyperosmolar stress after contrast is administered, while vasoconstriction induces diminished blood supply to the kidneys, inducing hypoxaemia.[16][17]

Prevention of PC-AKI
Hydration therapy is the cornerstone in the prevention of PC-AKI in high-risk patients.[16–18] Patients with an eGFR <45 mL/min/1.73 m^2 or an eGFR <60 mL/min/1.73 m^2 with one or more comorbidities (diabetes mellitus, heart failure, PAD) will receive prehydration and posthydration. Per protocol it is customary in our clinic to administer 0.9% NaCl intravenous 3–4 mL/kg/hour in uncomplicated high-risk patients for 4 hours preintervention and 4 hours postintervention. Complicated high-risk patients with heart or renal failure (exercise-induced dyspnoea, oedema, eGFR <30 mL/min/1.73 m^2) receive 12 hours prehydration and posthydration with 0.9% NaCl intravenous 1 mL/kg/hour.

Increased diuresis and prevention of dehydration is known to protect patients with CKD for possible PC-AKI.[11][16–19] However, the volume of administered NaCl solution is often too low to warrant any form of renal protection. These low volumes are usually motivated by fear of overhydration and pulmonary oedema.[19] Forced diuresis using furosemide in combination with intravenous NaCl 0.9% adjusted to diuresis prevents overhydration and provides a mild protection against developing PC-AKI.[20] On the contrary, some studies show an increased incidence of PC-AKI after use of diuretics in combination with high-volume hydration. Mismatched diuretic forced diuresis can cause vasoconstriction due to intravascular volume depletion and thus concentration of contrast instead of dilution.[19–23]

Intervention
To achieve high-volume diuresis without risking volume depletion or pulmonary oedema in high-risk patients requires a delicate balance. Recent publications regarding the RenalGuard system show promising results preventing PC-AKI in patients receiving a coronary intervention.[18][24–28] The RenalGuard system is an infusion system regulating volume of NaCl 0.9% administered based on the volume of urine produced. Preprocedure patients receive a 250 mL NaCl 0.9% bolus in combination with a dose furosemide (0.5 mg/kg). The goal is to achieve diuresis of >300 mL/hour before commencing and maintaining output during the procedure. Marenzi *et al* proved RenalGuard controlled furosemide forced diuresis with matched hydration to be safe and effective in maintaining adequate intravenous volume.[18] The MYTHOS trial (Induced Diuresis With Matched Hydration Compared to Standard Hydration for Contrast Induced Nephropathy Prevention) demonstrated a reduction PC-AKI in 74% of patients known with CKD, receiving iodine contrast for diagnostic purposes.[18] Moreover, Briguori *et al* showed an optimal diuresis threshold of >450 mL/hour with a minimum of >300 mL/hour to achieve optimal protection against PC-AKI.[27] Previous studies with the RenalGuard did not report any life-threatening events and no serious electrolyte disturbances were mentioned.[27][28] Briguori *et al* described an asymptomatic hypokalaemia in 7.5% (30/400) of patients, in which only 4% (16/400) required potassium supplementation. No significant alterations of sodium levels were observed.[27][28] Nor was there a significant difference in incidence of pulmonary oedema.[28] However, all previous mentioned research is conducted in a population requiring cardiac diagnostic procedures and therapeutic interventions. No evidence is available using furosemide forced diuresis with matched hydration in combination with the RenalGuard infusion system to decrease incidence of PC-AKI in patients with CKD receiving a PTA of the lower extremities.

Diagnosing PC-AKI
Current diagnosis of PC-AKI relies on rise of serum creatinine 48–72 hours postintervention. However, patients

receiving a PTA are often discharged within 24 hours post-procedure. Although patients are instructed to return to the clinic for routine control of serum creatinine 3 days postintervention, this is often dismissed. Early detection of AKI or PC-AKI is based on the slow rise in serum creatinine and therefore is an inadequate diagnostic tool.[29–31] In the past decade, several studies tried to identify urine biomarkers for early detection of AKI.[31–33] Potential biomarkers are neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), cystatin C, liver-type fatty acid binding protein, N-acetyl-beta-D-glucosaminidase, pi-glutathione S-transferase and tissue inhibitor of metalloproteinase-2.[31 32] One of the more promising urine biomarkers to detect AKI is NGAL.[30] Rise in NGAL concentration is greatest 4–6 hours postintervention, with an increase up to 25 times compared with baseline value.[30]

Study hypothesis

Our primary hypothesis is that a significant reduction in the incidence of PC-AKI can be established by increasing diuresis (>300 mL/hour), using furosemide forced diuresis with matched hydration controlled with the RenalGuard system in patients with CKD receiving an endovascular intervention of the lower extremities.

Our second primary hypothesis is that sampling of urine biomarkers (NGAL, KIM-1 en IL-18) 4 hours postintervention can predict PC-AKI in an early stage in patients with CKD compared with rise in serum creatinine 72 hours postintervention.

METHODS AND ANALYSIS

Study design

This study (Protocol V.2.0, 13 December 2016) is a non-blinded, single-centre prospective randomised controlled trial. The patients will be included in the 'Zuyderland' Medical Centre, Heerlen, the Netherlands. Patients with a diminished renal function (eGFR <60 mL/min/1.73 m^2) diagnosed with PAD and in need of an endovascular intervention of the lower extremities will be included. Patients participating in this study will not require extended hospitalisation or additional follow-up compared with standard of care. Serum creatinine is obtained within 10 days prior to procedural and post-procedure on day 1, 3 and 30 (see figure 1). Obtaining these serum creatinine samples is standard of care. eGFR is calculated using the adjusted formula by Levey *et al*.[34] Prehydration and posthydration in the control group are
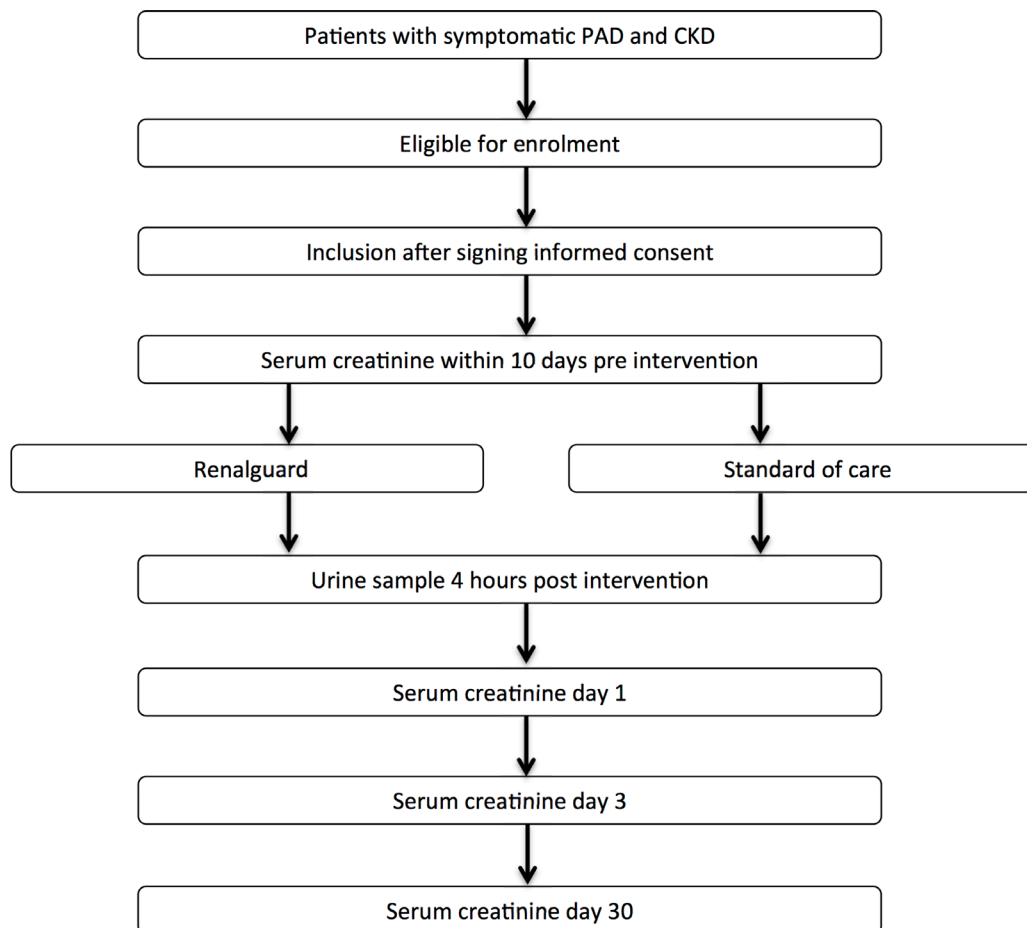

Figure 1 Flow chart of the study. Eligibility based on inclusion and exclusion criteria. Enrolment by random assignment. Serum creatinine for measurement of renal function preprocedure and postprocedure. Urine sampling to analyse biomarkers postprocedure. CKD, chronic kidney disease; PAD, peripheral arterial disease.

administered as dictated by hospital protocol. Patients will receive peripheral venous access for administration of NaCl 0.9%. Furthermore, a Foley catheter will be placed to monitor diuresis. Not within standard of care is administering furosemide (0.5 mg/kg) in the intervention group in conjunction with a bolus NaCl 0.9% (250 mL) to increase diuresis. Use of furosemide is a medicine registered to increase diuresis in treatment of oedema associated with renal disease including nephrotoxic syndrome, congestive heart failure and liver cirrhosis.

To observe reduction in PC-AKI, we compare patients treated with furosemide forced diuresis with matched hydration to a control group. Control group will receive standard of care prehydration and posthydration (described in intervention and comparison). The total study period is 2 years, from April 2018 to March 2020.

Patient and public involvement

Patient and public were not involved in the design, recruitment to and conduct of the study. The research question was not developed based on patients' priorities, experience or preferences. Results of the study will be disseminated to the study participant on request.

Outcome measurements

Primary endpoints are defined as the incidence of PC-AKI, 3 days after a successful endovascular procedure of the lower extremities. Serum creatinine is measured postintervention on day 1, 3 and 30. Patients are required to return to the hospital for blood samples at day 3 and day 30. PC-AKI is defined as a decrease in eGFR >25% or rise in serum creatinine of >0.5 mg/dL compared with baseline values. Primary success is defined as a 50% reduction in the incidence of CIN in the RenalGuard group using furosemide forced diuresis with matched hydration. Second primary endpoint is rise of urine biomarkers, after successful endovascular intervention of the lower extremities. Positive rise in urine biomarkers (NGAL, IL-18 and/or KIM-1) is defined as an (area under the curve-receiver operating characteristic, AUC-ROC) >0.7 sampled 4 hours after concluding endovascular procedure. Rise in urine biomarkers will be compared with rise in serum creatinine 72 hours postintervention to see if there is a correlation and early detection of PC-AKI.

Secondary endpoints are complications due to PC-AKI-prophylactic therapy (PC-AKI requiring dialysis (previously not requiring dialysis), serious electrolyte disturbances (requiring addition treatment) and/or acute pulmonary oedema (radiological confirmation and requiring diuretic medication)), postoperative in-hospital adverse events (AEs) (acute myocardial infarct (confirmed on ECG), death), length of hospitalisation, postoperative complication at home requiring additional care (seroma, wound infection, pseudo aneurysm and reocclusion or restenosis within 4 weeks after intervention). Complications will be registered in the days postintervention while hospitalised and evaluated 4 weeks after intervention in the outpatient clinic by a vascular

surgeon, unaware to allocated treatment. The follow-up data will be collected and processed by a member of the study team, not blinded to allocated treatment. It should be mentioned that this protocol is not powered to detect significant differences in the incidence of AEs between the two treatment groups.

Other clinical study parameters

The following baseline parameters will be collected: age, gender, ethnicity, height, weight, diabetes mellitus (defined as receiving anti diabetic treatment, not diet controlled), hypertension (defined as a systolic pressure >140 mm Hg (measured at the preoperative workup of the anaesthetist) or use of anti hypertensive medication), heart failure (defined as an ejection fraction <40%), baseline renal function (acquired at standard preoperative assessment, <10 days of intervention). The following operative data are collected: location of stenosis/occlusion (iliac, femoral, BTK (Below The Knee) or multilevel), OR-time, radiation dose, radiation time, volume of contrast, volume of NaCl 0.9% administered (90 min preintervention until 4 hours postintervention) see Table 1.

Study population

Patients with CKD (eGFR <60 mL/min/1.73 m^2) diagnosed with PAD requiring a PTA of the lower extremities.

Inclusion criteria

► Patients at least 18 years of age.
► Diagnosed with occlusive or stenotic PAD requiring an endovascular intervention with contrast.
► eGFR <60 mL/min/1.73 m^2.

Exclusion criteria

► Hypersensitivity to furosemide.
► Use of intravenous contrast within 10 days prior to qualifying intervention.
► Expected to receive intravenous contrast within 72 hours after qualifying intervention.
► Unable to receive a Foley catheter.

Sample size calculation

Sample size is based on a randomised controlled trial comparing standard hydration therapy with RenalGuard controlled furosemide forced diuresis with matched hydration in patients with CKD receiving a coronary procedure.[18] Incidence of PC-AKI in the RenalGuard group was 4.6% compared with 18% in the control group (standard of care hydration therapy). Based on these results, a sample size is calculated with a significance level of 5% and a power of 80%. Sample size is estimated to include 86 patients in each group, with a total sample size of 172 patients. Taking into account a possible lost to follow-up or early withdrawal of 5%, a total sample size of 180 patients is required.

Randomisation and concealment

Randomisation will be performed using a randomisation programme (http:/www.graphpad.com/quickcalcs/

Table 1 Schedule of enrolment, intervention and assessment

Process time point	Screening, enrolment and allocation	Preintervention (10 days)	Intervention	FU+4 hours	FU+1 day	FU+3 days	FU+30 days
Screening, enrolment and allocation							
Eligibility screen	X						
Informed consent	X						
Baseline parameters	X						
Vital signs	X		X	X	X	X	X
Intervention							
Operative data			X				
RenalGuard	X	X	X	X	X	X	X
Standard of care	X	X	X	X	X	X	X
Assessment							
Urine biomarkers				X			
Serum creatinine		X			X	X	X
Outcome measurements							
Primary				X	X	X	X
Secondary			X	X	X	X	X

FU, follow-up.

randomize2.cfm). Randomisation will be performed prior to first inclusion. Patients will be assigned treatment in consecutive order as dictated by the randomisation list. Included patients will be allocated a unique study number. When written consent is acquired, a second study member will be approached for the randomisation, unaware of patient characteristics to minimise selection bias. Allocation to a treatment group and study number will be registered in a password-protected document only accessible for the principal investigator (PI) and coordinating investigator. Blinding of patients and study members is not possible, as patients in the intervention group will be treated with the RenalGuard infusion system during and continuing 4 hours postintervention. The RenalGuard infusion system is installed prior to intervention. The control group will receive prehydration 4 hours prior to intervention and 4 hours postintervention.

Recruitment of participants
When referred by general practitioner, patients will receive an Ankle Brachial Index and duplex ultrasound of the lower extremities prior to first presentation in the outpatient clinic. Up to Rutherford classification III, patients will innately be treated with supervised exercise therapy (SET). When not responding to SET, an MRA is performed. All patients with PAD (non-responders to SET and Rutherford IV–VI) with a new MRA will be discussed in a multidisciplinary meeting of vascular surgeons and interventional radiologists. Treatment options are discussed and a plan of approach is formulated. If the patient qualifies for an endovascular intervention and is eligible to be included in this study, a member of the study

group will provide information regarding the study orally and on paper. A week after the information is provided by a member of the research group will call the patient and inquires whether the patient is willing to participate in the study. After oral confirmation, the patient is required to provide written consent at the outpatient clinic before randomisation (see figure 1). If the patient does not wish to participate in the study, he/she will be scheduled for a regular procedure according to standard of care. This decision will not influence quality of treatment nor there any resentment towards the patient.

RenalGuard system
The RenalGuard system is consists of a console and (disposable) RenalGuard set for infusion and urine collection. The disposable set contains a urine collection set that can be connected to a standard Foley catheter and an infusion set that can be connected to a standard intravenous catheter. The console weights the volume of urine produced in the collection set and administers an equal amount of hydration fluid (NaCl 0.9%) to match diuresis. The console relies on a patented software and electronic weight measurements to adjust velocity in which hydration fluid is administered as well as monitoring of diuresis. The console is mounted on an adjustable intravenous pole and is equipped with an internal battery enabling the console to keep functioning during transport from ward to operating theatre and vice versa.

Intervention and comparison
Nephrotoxic medications (NSAID (Non-Steroidal Anti-Inflammatory Drugs), metformin) are ceased on the day of

intervention. Prehydration and posthydration in the control group do not differ from current clinical treatment. On the day of intervention, the patients will report on the preoperative ward at 7:30 hours. Patients are instructed to stop oral intake after 00:00 hours the day before intervention. Oral fluids before 00:00 hours are permitted. Patients are prepped according to local protocol. An intravenous line and a Foley catheter are placed to administer fluids and monitor diuresis. Uncomplicated high-risk patients receive 4 hours prehydration and 4 hours posthydration with 0.9% NaCl intravenous 3–4 mL/kg/hour. Complicated high-risk patients due to heart or renal failure (exercise-induced dyspnoea, oedema, eGFR <30 mL/min/1.73 m^2) receive 12 hours prehydration and posthydration with 0.9% NaCl intravenous 1 mL/kg/hour. Hydration therapy in the control group is administered as dictated by hospital protocol. Endovascular intervention will be performed in a hybrid operating theatre by one of three vascular surgeons. After concluding the procedure, patients will be transported to the general ward. Regular controls will be performed according to hospital protocol. Four hours after the procedure, the urimeter will be emptied, thereafter the urine produced in 15 min is collected for analysis. Once urine is collected, the Foley catheter will be removed. Serum creatinine is obtained 1-day postintervention. If there are no complications and spontaneous micturition is observed, the patient will be discharged. Three days postintervention, the patient is instructed to have a blood sample taken (in the hospital) to establish serum creatinine. Follow-up will be performed by one of the vascular surgeons. Four weeks after intervention, patients will have a routine outpatient control. Prior to this follow-up moment, patients will receive a control duplex to evaluate treated lesion. Furthermore, serum creatinine is measured 4 weeks postintervention.

Patients in the intervention group will be prepped in a similar fashion. However, after placing an intravenous line and Foley catheter, the RenalGuard system will be connected. Ninety minutes prior to intervention, the patients receive 250 mL NaCl 0.9% intravenous in 30 min. After NaCl is administered, the patient will receive furosemide (0.5 mg/kg) intravenous. If observed diuresis exceeds 300 mL/hour, the patient is ready for procedure. To maintain diuresis of >300 mL/hour, an additional dose furosemide can be administered up to a maximum dose of 2 mg/kg. According to national guidelines, the maximum dosage furosemide for adults (intravenous/oral) should not exceed 1500 mg/day. The total dosage administered in the study is well below maximum. The RenalGuard will remain in situ up to 4 hours after the intervention is concluded. After removal of the RenalGuard, the urimeter will collect the urine production for 15 min for analysis. Thereafter, postoperative treatment is similar to the control group.

Urine samples collected for analysis will be stored at a temperature of 4°C till processing. Urine will be centrifuged for 10 min at a speed of 3000 rpm. The supernatant will be stored in 500 µL aliquots at a temperature of −80°C till further analysis. After completion of the study, all urine samples are thawed and analysed using ELISA kits to measure each individual urine biomarker.[24 34]

Data collection and monitoring

Baseline data and study results will be collected and reported on paper case report forms (CRFs). The CRFs are created prior to study initiation. The CRFs will be stored in a secure cabinet. The PI and coordination investigator will be the only researchers with access to these files. Data will be summarised in an SPSS file for further analysis.

All included patients will receive an anonymised study number. Coded data will be stored in a password-protected Excel file. This file will only be accessible to the PI and coordinating investigator. Healthcare inspectors, auditors, monitors and members of the medical ethical commission might be granted access to the source data on request as is prescribed by the law. Data and urine samples are treated as dictated by the 'code of conduct' for adequate use and secondary use of human tissue and use of data in healthcare research (Foundation Federation of Dutch Medical Scientific Societies).[35] Data will be stored for the duration of 15 years after conclusion of the study.

Statistical analysis

The results of this study will be collected and analysed in a secure database. Database will receive a periodical back up. Only members of the research group and licensed authorities will be able to access the database.

Baseline and perioperative characteristics are presented as means and SD or median and IQRs as is common for continues variables and as percentages for categorical variables.

Intention-to-treat analysis will be conducted on the final data. The primary outcome is based on the incidence of PC-AKI and will be presented in a contingency table. Statistical tests for significance will be performed using the χ^2 test for categorical variables. Continues variables are compared using the one-way analysis of variance or the Kruskal-Wallis test. Furthermore, proportion comparison (z-test) or calculations for ORs will be performed. Risk factors for PC-AKI, increased urine biomarker concentrations and fast renal decline are evaluated using multivariate logistic regression analysis.

ROC curves of the urine biomarkers for early detection of PC-AKI are calculated, as well as AUC ROC with correlating SE. Urine biomarkers are evaluated for their diagnostic accuracy for clinical use if lower 99% CI is >0.70. Patients with missing primary outcome data (complete case analysis) will be excluded. Whereas, sensitivity analysis with multiple imputations (mean of 5 imputations) will be performed for missing values other than primary outcome data. Optimal cut-off point for urine biomarker values for diagnosing PC-AKI and corresponding sensitivity and specificity are calculated assuming false positive and false negative result are of equal clinical importance using the following formula: Sensitivity $((1\text{Prevalence})/\text{Prevalence}) * (1 - \text{Specificity})$.

Clinical outcome of patients are compared with four categories (no PC-AKI and normal biomarkers, no PC-AKI and increased biomarkers, PC-AKI and normal biomarkers, PC-AKI and increased biomarkers). Statistical analysis will be performed by LJJB using SPSS V.21.0 (IBM).

Adverse events

All AE's observed by the study subject or by a member of the research group are noted and filed. Serious AEs (SAEs) are unexpected medical events or effect with potential risk of; death, life threatening, hospitalisation or extended hospitalisation, chronic impairment, or other important medical occurrences potentially harming the patient or requiring an intervention to advert one of the previously mentioned outcomes. SAEs occurring within 4 weeks after intervention are required to be reported to the research ethics committee (REC). The primary endpoint in this study is defined as PC-AKI 3 and 30 days postintervention and accounts for the limited period in which SAEs need to be reported. SAEs that occur within the 30 days postintervention are reported within 15 days. If a patient dies or a life-threatening situation unfolds, the REC needs to be notified within 7 days. If health of included patients is at risk, the study will be stopped and REC will be notified. In this period, the REC will investigate possible risks. SAEs will be followed until a stable situation is created or the SAE is resolved.

Ethics and dissemination

This trial will be conducted following the Good Clinical Practice Guidelines, the Declaration of Helsinki (seventh amendment, October 2013) and in accordance with national legislation (Medical Research Act). Substantial amendments to the study protocol will be resubmitted to the original research ethics committee. It is not required to submit a non-substantial amendment to the REC, however, a note to file is created and archived by the investigator. A substantial amendment is defined as an alteration to the originally submitted study protocol or supporting document with high probability to impact: safety or the physical or psychological integrity of the study subject, scientific value of the study, conducting or management of the study, quality or safety of one of the interventions in the study. All substantial amendments are submitted to the REC of initial approval of the study protocol.

Research findings will be submitted for publication in a PubMed-indexed medical journal within 1 year after inclusion of the last patient. If the study manuscript is not accepted for publication, the research findings will be made publicly available on the internet.

DISCUSSION

Total period of inclusion will be 2 years and is expected to finish by May 2020. Study results will clarify whether furosemide forced diuresis with matched hydration using the RenalGuard system is superior in the prevention of PC-AKI compared with standard of care hydration therapy in patients

with CKD. Furthermore, this study will define whether urine biomarkers, NGAL, IL-18 and KIM-1, are adequate biomarkers in detection of PC-AKI within 4 hours postintervention compared with serum creatinine after 72 hours.

Outcomes reported from a systematic review and meta-analysis of randomised controlled trials show furosemide forced diuresis with matched hydration using the RenalGuard system in patients undergoing interventional procedures to significantly decrease the need for renal replacement therapy.[28] However, all included trials performed coronary interventions or percutaneous aortic valve replacement. No literature is available using furosemide forced diuresis with matched hydration in patients treated with endovascular for symptomatic PAD. Nor is any previous research available using the RenalGuard system in patients with PAD. Safety evaluation of the RenalGuard system in the previous mentioned systematic review showed no increased risk of electrolyte imbalance or pulmonary oedema compared with conservative treatment.[28] However, the meta-analysis included only four trials with high risk for bias. Larger RCTs are needed to exemplify possible effectiveness in endovascular interventions other than coronary procedures.

PC-AKI is diagnosed by a gradual increase of serum creatinine concentration within the first days after endovascular procedure.[5 6] Delay in diagnosis due to slow increase in serum creatinine makes it an inadequate marker in the early detection of PC-AKI. As previously mentioned in this protocol, patients are often discharged before serum creatinine can be assessed 48–72 hours postintervention. Despite instructions to return for serum creatinine controls, patient often refrain from follow-up. Evaluating urine biomarkers 4 hours postintervention might possibly address this matter and enable us to detect PC-AKI in an early stage. Use of urine biomarkers depends on the diagnostic accuracy of the studied urine biomarkers and whether they are sufficiently high. Although PC-AKI rarely requires renal replacement therapy, early detection of PC-AKI increases awareness and provides an opportunity to closely monitor renal function and intervene immediately if necessary without delay.

In this RCT, we will include patients with CKD who qualify for an endovascular intervention of the lower extremities, regardless of anatomic location. Patients can be treated solely with angioplasty or with additional stenting. Consideration for additional stenting will transpire perioperative. The decision to include only patients with CKD was made based on previous literature proving renal replacement therapy is rarely needed in patients diagnosed with PC-AKI but without CKD.[36] PC-AKI requiring renal replacement therapy is prevalent in 1% of the patients without CKD, compared with 7% in patients with CKD.[37]

This trial is the first to investigate whether furosemide forced diuresis with matched hydration using the RenalGuard system can reduce the incidence of PC-AKI in patients with CKD and PAD receiving a PTA of the lower extremities. Furthermore, this study is the first study to establish the use of urine biomarkers in patients receiving a PTA in the detection of PC-AKI compared with serum creatinine.

It is anticipated that study results will provide a solution for early detection of CIN and offer a preventive measure in patients with CKD receiving a PTA of the lower extremities. Study results will be disseminated by oral presentation at conferences and will be submitted to a peer-reviewed journal.

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