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Prevention of contrast induced nephropathy after percutaneous transluminal interventions by inducing Renalguard™ controlled furosemide forced diuresis with matched hydration: study protocol for a randomized controlled trial

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List of abbreviations

ABI	Ankle Brachial Index
CIN	Contrast Induced Nephropathy
CRI	Chronic Renal Insufficiency
ICF	Informed Consent Form
KNF	Clinical Neurological Function laboratory
PSV	Peak Systolic Velocity
PTA	Percutaneous Transluminal Angioplasty
REC	Research Ethics Committee

Abstract

Introduction: Percutaneous transluminal interventions (PTA) are often complicated due to contrast-induced nephropathy (CIN) in patients diagnosed with chronic kidney disease (CKD). Hydration therapy is the cornerstone in the prevention of CIN. Furosemide forced diuresis with matched hydration using the Renalguard system™ enables a steady balance between diuresis and hydration. A randomized 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 CIN 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 CIN in an earlier stage compared to the golden standard, serum creatinine 48-72 hours post intervention.

Methods and analysis: a single centre randomized 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 pre- and post-hydration or furosemide forced diuresis with matched hydration periprocedural using the Renalguard system™. Four hours post intervention 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 post intervention. The primary endpoint is incidence of CIN post PTA. Secondary endpoint is the rise of urine biomarkers 4 hours post intervention.

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 chronic kidney disease receiving a PTA of the lower extremities.

Trial registration number: NTR6236

EudraCT number: 2016-005072-10

Strengths and limitations of this study

- The first study to evaluate the incidence of CIN in patients with PAD treated endovascularly while receiving furosemide forced diuresis using the Renalguard system.
- Study results might lead to a new preventive measurement in the prevention of CIN in patients with CKD requiring an endovascular procedure of the lower extremities.
- Study results might provide a method for early detection of CIN 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 CIN might differ.

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 PTA can cause contrast induced nephropathy (CIN).(1–3) CIN is defined as a decrease in estimated glomerular filtration rate (eGFR) of >25% compared to baseline values or a rise of >0.5 mg/dl serum creatinine within 72 hours after an iodine contrast mediated procedure (KDIGO guidelines).(4,5) Krasznai et al. described an 13% incidence of CIN in patients treated with a PTA, regardless of prior renal function.(6) The incidence of CIN can be as high as 50% in high-risk patients and is the cause of 10% acute in hospital renal failure.(1,7,8) Moreover, high-risk patients diagnosed with CKD are known to have an increased risk of developing CIN after administration of iodine contrast. CKD and iodine contrast are both independent risk factors in the development of CIN.(1) Furthermore, CKD is a global problem, affecting 10-16 percent of the general population.(8) Prevalence of CKD is increasing worldwide and is estimated to be as high as 45% in de population aged >70 years.(8) Moreover, incidence and prevalence of CIN are rising 5-8% annually.(1)

Contrast induced nephropathy is associated with a significant worse outcome due to increased risk of cardio-vascular events, acceleration to end stage renal failure requiring dialysis and extended hospitalization, causing increased morbidity and mortality.(6,9–12) Moreover, Ramaswami et al. showed a significant higher mortality rate in patients developing CIN after receiving a coronary angiography compared to patients without CIN (resp. 7.1% vs. 1.1%, n=1826).(3)

Extended hospitalization and additional care due to CIN is costly. Average cost of one year of dialysis in the Netherlands is estimated to be as high as 80.000 euro. The total annual medical costs for patients diagnosed with CIN in the united states are estimated 700 million to 1 billion dollar.(8,13,14) Relevant patient-related risk factors developing CIN are; chronic kidney disease, diabetes mellitus, heart failure, old age, anemia, and decreased function of the left ventricle.(6) The cause of contrast-induced nephropathy 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 hypoxemia.(15,16)

Prevention of CIN: Hydration therapy is the cornerstone in the prevention of CIN in high-risk patients.(15–17) Patients with an eGFR <45 ml/min/1.73m2 or an eGFR <60 ml/min/1.73m2 with one or more comorbidities (Diabetes Mellitus, Heart failure, PAD) will receive pre and post hydration. Per protocol it is customary in our clinic to administer 0.9% NaCl i.v. 3-4 ml/kg/h in uncomplicated high-risk patients for 4 hours pre- and 4 hours post intervention.

Complicated high-risk patients with heart- or renal failure (dyspnea d'efford, edema, eGFR <30 ml/min/1.73m2) receive 12 hours pre and post hydration with 0.9% NaCl i.v. 1 ml/kg/h.

Increased diuresis and prevention of dehydration is known to protect patients with CKD for possible CIN.(10,15–18) 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 edema.(18) Forced diuresis using furosemide in combination with intravenous NaCl 0,9% adjusted to diuresis prevents overhydration and provides a mild protection against developing CIN.(19) On the contrary, some studies show an increased incidence of CIN 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 in stead of dilution.(18–22)

Intervention: To achieve high volume diuresis without risking volume depletion or pulmonary edema in high-risk patients requires a delicate balance. Recent publications regarding the Renalguard system™ show promising results preventing CIN in patients receiving a coronary intervention.(17,23–27) The Renalguard system™ is an infusion system regulating volume of NaCl 0,9% administered based on the volume of urine produced. Pre procedure patients receive a 250ml NaCl 0.9% bolus in combination with a dose furosemide (0,5 mg/kg). The goal is to achieve diuresis of >300 ml/h 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.(17) The MYTHOS-trial demonstrated a reduction CIN in 74% of patients known with CKD, receiving iodine contrast for diagnostic purposes.(17) Moreover, Briguori et al. showed an optimal diuresis threshold of >450 ml/h with a minimum of >300 ml/h to achieve optimal protection against CIN.(26) Previous studies with the Renalguard™ did not report any life-threatening events and no serious electrolyte disturbances were mentioned.(26,27) Briguori et al. described an asymptomatic hypokalemia in 7,5% (400/30) of patients, in which only 4% (400/16) required potassium supplementation. No significant alterations of sodium levels were observed.(26,27) Nor was there a significant difference in incidence of pulmonary edema.(27) 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 CIN in patients with CKD receiving a PTA of the lower extremities.

Diagnosing CIN: Current diagnosis of CIN relies on rise of serum creatinine 48-72 hours post intervention. 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 post intervention, this is often dismissed. Early detection of acute kidney injury (AKI) or CIN is based on the slow rise in serum creatinine and therefore is an inadequate diagnostic tool.(28–30) In the past decade several studies tried to identify urine biomarkers for early detection of AKI.(30–32) Potential biomarkers are neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), cystatin C, liver fatty acid binding protein (L-FABP), N-acetyl-beta-D-glucosaminidase (NAG), pi-gluthathione-S-transferase (π-GST), and tissue inhibitor of metalloproteinase-2 (TIMP-2).(30,31) One of the more promising urine biomarkers to detect AKI is NGAL.(29) Rise in NGAL concentration is greatest 4-6 hours post intervention, with an increase up to 25 times compared to baseline value.(29)

Study hypothesis: Our primary hypothesis is that a significant reduction in the incidence of CIN can be established by increasing diuresis (>300 ml/h) 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 post intervention can predict CIN in an early stage in patients with CKD compared to rise in serum creatinine 72 hours post intervention.

Methods and analysis

Study design: This study (Protocol V.2.0, date 13 December 2016) is a non-blinded, single centre prospective randomized 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/1.73m2) 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 hospitalization or additional follow up compared to standard of care. Serum creatinine is obtained within 10 days prior to procedural and post procedure on day 1, 3 and 30 (Figure 1. Flow chart of the study). Obtaining these serum creatinine samples is standard of care. Estimated glomerular filtration rate (eGFR) is calculated using the adjusted formula by Levey et al.(33) Pre- and post hydration in the control group are 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 (0.5mg/kg) in the intervention group in conjunction with a bolus NaCl 0.9% (250ml) to increase diuresis. Use of furosemide is a

medicine registered to increase diuresis in treatment of edema associated with renal disease including nephrotoxic syndrome, congestive heart failure, and liver cirrhosis.

To observe reduction in CIN we compare patients treated with furosemide forced diuresis with matched hydration to a control group. Control group will receive standard of care pre and post hydration. This trial is registered with the Netherlands Trial Register.nl (NTR6236), registration date. The total study period is two years, from April 2018 to March 2020.

Outcome measurements:

Primary endpoints are defined as the incidence of CIN, after a successful endovascular procedure of the lower extremities, measured post intervention on day 1, 3 and 30. CIN is defined as a decrease in eGFR >25% or rise in serum creatinine of >0.5mg/dl compared to baseline values. Primary success is defined as a 50% reduction in the incidence of contrast induced nephropathy 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 AUC-ROC (area under the curve ROC) >0.7 sampled 4 hours after concluding endovascular procedure. Rise in urine biomarkers will be compared to rise in serum creatinine 72 hours post intervention to see if there is a correlation and early detection of CIN.

Secondary endpoints are complications due to CIN-prophylactic therapy (CIN requiring dialysis, electrolyte disturbances and/or acute pulmonary edema), post-operative in-hospital adverse events (acute myocardial infarct, death), length of hospitalization, post-operative complication at home requiring additional care (seroma, wound infection, pseudo aneurysm and re-occlusion or re-stenosis within 4 weeks after intervention). Complications will be registered in the days post intervention while hospitalized and evaluated 4 weeks after intervention in the outpatient clinic.

Other clinical study parameters

The following baseline parameters will be collected: age, gender, ethnicity, length, weight, diabetes mellitus (defined as receiving anti diabetic treatment), hypertension (defined as a systolic pressure >140 mmHg 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 or multi-level), OR-time, radiation dose, radiation time,

volume of contrast, volume of NaCl 0.9% administered (90 minutes pre till four hours post intervention). Table 1. schedule of enrolment.

Study population: Patients with chronic kidney disease (eGFR <60 ml/min/1.73m2) diagnosed with PAD requiring a PTA of the lower extremities.

Inclusion criteria

- Patients at least 18 years of age
- Diagnosed with occlusive or stenotic peripheral arterial disease requiring an endovascular intervention with contrast.
- eGFR <60 ml/min/1.73m2

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 randomized controlled trial comparing standard hydration therapy with Renalguard™ controlled furosemide forced diuresis with matched hydration in patients with CKD receiving a coronary procedure.(17) Incidence of CIN in the Renalguard™ group was 4.6% compared to 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.

Randomization and concealment

Randomization will be performed using a randomization program (http:/www.graphpad.com/quickcalcs/randomize2.cfm). Randomization will be performed prior to first inclusion. Patients will be assigned treatment in consecutive order as dictated by the randomization list. Included patients will be allocated a unique study number. Allocation

to a treatment group and study number will be registered in a password-protected document only accessible for the principle- and coordinating investigator. As patients in the intervention group will be treated with the Renalguard infusion system™ during and continuing 4 hours post intervention, concealment of treatment will not be possible.

Recruitment of participants

When referred by general practitioner patients will receive an ankle brachial index (ABI) 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 peripheral arterial disease (PAD) (non responders to SET and Rutherford IV-VI) with a new MRA will be discussed in a multi-disciplinary 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 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 randomization (Figure 1. Flow chart of the study). 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 will there be 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 IV 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 IV 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, metformin) are ceased on the day of intervention. Pre- and post hydration in the control group does not differ from current clinical treatment. On the day of intervention the patients will report on the pre operative ward at 7.30 am with an empty

stomach. Patients are prepped according to local protocol. An IV line and a Foley catheter are placed to administer fluids and monitor diuresis. Uncomplicated high-risk patients receive 4 hours pre- and 4 hours post hydration with 0.9% NaCl i.v. 3-4 ml/kg/h. Complicated high risk patients due to heart- or renal failure (dyspnea d'efford, edema, eGFR <30 ml/min/1.73m2) receive 12 hours pre an post hydration with 0.9% NaCl i.v. 1 ml/kg/h. 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 procedure the urimeter will be emptied, thereafter the urine produced in 15 minutes is collected for analysis. Once urine is collected the Foley catheter will be removed. Serum creatinine is obtained one-day post intervention. If there are no complications and spontaneous micturition is observed the patient will be discharged. Three days post-intervention the patient is instructed to have a blood sample taken to establish serum creatinine. Follow-up will be performed by one of the investigators. 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 four weeks post intervention.

Patients in the intervention group will be prepped in a similar fashion. However, after placing an IV line and Foley catheter the Renalguard system™ will be connected. 90 minutes prior to intervention the patients receive 250 ml NaCl 0.9% IV in 30 minutes. After NaCl is administered the patient will receive furosemide (0.5mg/kg) intra venous. If observed diuresis exceeds 300 ml/h the patient is ready for procedure. To maintain diuresis of >300 ml/h an additional dose furosemide can be administered up to a maximum dose of 2mg/kg. According to national guidelines the maximum dosage furosemide for adults (IV/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 minutes 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 minutes 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 analyzed using enzyme-linked immunosorbent assay (ELISA) kits to measure each individual urine biomarker.(23,33)

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 principle investigator (PI) and coordination investigator will be the only researchers with access to these files. Data will be summarized in an SPSS file for further analysis.

All included patients will receive an anonymized 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).(34) 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 analyzed 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 per operative characteristics are presented as means and standard deviations or median and interquartile ranges as is common for continues variables and as percentages for categorical variables.

The primary outcome is based on the incidence of CIN and will be presented in a contingency table. Statistical tests for significance will be performed using the Chi-square test for categorical variables. Continues variables are compared using the one-way ANOVA or the Kruskal-Wallis test. Furthermore, proportion comparison (z-test) or calculations for odds-ratios will be performed. Risk factors for CIN, increased urine biomarker concentrations and fast renal decline are evaluated using multivariate logistic regression analysis.

Receiver operating characteristic (ROC) curves of the urine biomarkers for early detection of CIN are calculated, as well as 'area under the curve' (AUC ROC) with correlating standard error. Urine biomarkers are evaluated for their diagnostic accuracy for clinical use if lower 99% confidence interval 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 CIN 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 – Prevalence) / Prevalence) * (1- Specificity).

Clinical outcome of patients are compared to four categories (no CIN and normal biomarkers, no CIN and increased biomarkers, CIN and normal biomarkers, CIN and increased biomarkers). Statistical analysis will be performed by L.J.J.B. using SPSS (IBM Corp, Armonk, New York, V.21.0).

Adverse Events

All adverse events (AE's) observed by the study subject or by a member of the research group are noted and filed. Serious adverse events (SAE's) are unexpected medical events or effect with potential risk of; death, life threatening, hospitalization or extended hospitalization, chronic impairment, or other important medical occurrences potentially harming the patient or requiring an intervention to advert one of the previously mentioned outcomes. SAE's 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 CIN 3 and 30 day post-intervention and accounts for the limited period in which SAE's need to be reported. SAE's that occur within the 30 days post intervention 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. (S)AE's will be followed until a stable situation is created or the SAE is resolved.

Ethics and dissemination:

The study protocol was submitted and approved by the research ethics committee (REC) and the institutional research board (Zuyderland Medical Centre, Heerlen). This trial will be conducted following the Good Clinical Practice Guidelines, the declaration of Helsinki (7th amendment, October 2013) and in accordance with national legislation (Medical Research Act). Substantial amendments to the study protocol will be re-submitted 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 one year after inclusion of the last patient. If the study manuscript is not accepted for publication the research findings will be made publically available on the Internet.

Discussion

Total period of inclusion will be two years and is expected to finish mid May 2020. Study results will clarify whether furosemide forced diuresis with matched hydration using the Renalguard system™ is superior in the prevention of CIN compared to 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 CIN within 4 hours post intervention compared to serum creatinine after 72 hours.

Outcomes reported from a systematic review and meta-analysis of randomized 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.(27) 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 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 edema compared to conservative treatment.(27) However, the meta-analysis included only four trials with high risk for bias. Larger RCT's are needed to exemplify possible effectiveness in endovascular interventions other than coronary procedures.

CIN is diagnosed by a gradual increase of serum creatinine concentration within the first days after endovascular procedure. (4,5) Delay in diagnosis due to slow increase in serum creatinine makes it an inadequate marker in the early detection of CIN. As previously mentioned in this protocol, patients are often discharged before serum creatinine can be assessed 48-72 hours post-intervention. Despite instructions to return for serum creatinine controls, patient often refrain from follow-up. Evaluating urine biomarkers 4 hours post intervention might possibly address this matter and enable us to detect CIN 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 CIN rarely requires renal replacement therapy, early detection of CIN 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 CIN

but without CKD.(35) CIN requiring renal replacement therapy is prevalent in 1% of the patients without CKD, compared to 7% in patients with CKD.(36)

This trial is the first to investigate whether furosemide forced diuresis with matched hydration using the Renalguard system™ can reduce the incidence of CIN in patients with CKD. Furthermore, this study is the first study to establish the use of urine biomarkers in patients receiving a PTA in the detection of CIN compared to serum creatinine.

It is anticipated that study results will provide a solution for early detection of contrast induced nephropathy and offer a preventive measure in patients with chronic kidney disease 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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Trial registration number: NTR6236
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Table 1 Schedule of enrolment, intervention and assessment

	Study Period						
Process Timepoint	Screening, enrolment and allocation	Pre intervention (10 days)	Intervention	FU + 4hour	FU + 1day	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

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Figure legend:

Figure 1. Flow chart of the study. Eligibility based on in- and exclusion criteria. Enrolment by random assignment. Serum creatinine for measurement of renal function pre- and post procedure. Urine sampling to analyse biomarkers post procedure.

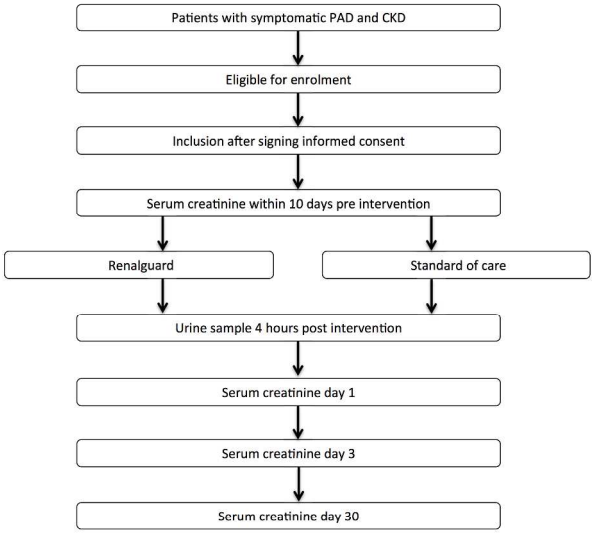

Figure 1. Flow chart of the study. Eligibility based on in- and exclusion criteria. Enrolment by random assignment. Serum creatinine for measurement of renal function pre- and post procedure. Urine sampling to analyse biomarkers post procedure.

297x209mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	x
Protocol version	3	Date and version identifier	7
Funding	4	Sources and types of financial, material, and other support	x
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	x
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	x
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	x

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	x
Objectives	7	Specific objectives or hypotheses	5-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7-13
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7-13
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-13
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7-13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	x
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	x
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-13

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____9_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____10_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____9-10_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____9-10____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____9-10____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____x_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____x_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____x_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____x_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7-13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	x
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	x
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11-12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11-12
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	x
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	x
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Prevention of contrast induced nephropathy after percutaneous transluminal interventions by inducing RenalguardTM controlled furosemide forced diuresis with matched hydration: study protocol for a randomized controlled trial

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Prevention of contrast induced nephropathy after percutaneous transluminal interventions by inducing Renalguard™ controlled furosemide forced diuresis with matched hydration: study protocol for a randomized controlled trial

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List of abbreviations

ABI	Ankle Brachial Index
CIN	Contrast Induced Nephropathy
CRI	Chronic Renal Insufficiency
ICF	Informed Consent Form
KNF	Clinical Neurological Function laboratory
PSV	Peak Systolic Velocity
PTA	Percutaneous Transluminal Angioplasty
REC	Research Ethics Committee

Abstract

Introduction: Percutaneous transluminal interventions (PTA) are often complicated due to contrast-induced nephropathy (CIN) in patients diagnosed with chronic kidney disease (CKD). Hydration therapy is the cornerstone in the prevention of CIN. Furosemide forced diuresis with matched hydration using the Renalguard system™ enables a steady balance between diuresis and hydration. A randomized 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 CIN 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 CIN in an earlier stage compared to the golden standard, serum creatinine 48-72 hours post intervention.

Methods and analysis: a single centre randomized 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 pre- and post-hydration or furosemide forced diuresis with matched hydration periprocedural using the Renalguard system™. Four hours post intervention 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 post intervention. The primary endpoint is incidence of CIN post PTA. Secondary endpoint is the rise of urine biomarkers 4 hours post intervention.

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 chronic kidney disease receiving a PTA of the lower extremities.

Trial registration number: NTR6236

EudraCT number: 2016-005072-10

Strengths and limitations of this study

- The first study to evaluate the incidence of CIN in patients with PAD treated endovascular while receiving furosemide forced diuresis using the Renalguard system.
- Study results might lead to a new preventive measurement in the prevention of CIN in patients with CKD requiring an endovascular procedure of the lower extremities.
- Study results might provide a method for early detection of CIN 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 CIN 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 PTA can cause contrast induced nephropathy (CIN).(1–3) CIN is defined as a decrease in estimated glomerular filtration rate (eGFR) of >25% compared to baseline values or a rise of >0.5 mg/dl serum creatinine within 72 hours after an iodine contrast mediated procedure (KDIGO guidelines).(4,5) Krasznai et al. described an 13% incidence of CIN in patients treated with a PTA, regardless of prior renal function.(6) The incidence of CIN can be as high as 50% in high-risk patients and is the cause of 10% acute in hospital renal failure.(1,7,8) Moreover, high-risk patients diagnosed with CKD are known to have an increased risk of developing CIN after administration of iodine contrast. CKD and iodine contrast are both independent risk factors in the development of CIN.(1) Furthermore, CKD is a global problem, affecting 10-16 percent of the general population.(8) Prevalence of CKD is increasing worldwide and is estimated to be as high as 45% in de population aged >70 years.(8) Moreover, incidence and prevalence of CIN are rising 5-8% annually.(1)

Contrast induced nephropathy is associated with a significant worse outcome due to increased risk of cardio-vascular events, acceleration to end stage renal failure requiring dialysis and extended hospitalization, causing increased morbidity and mortality.(6,9–12) Moreover, Ramaswami et al. showed a significant higher mortality rate in patients developing CIN after receiving a coronary angiography compared to patients without CIN (resp. 7.1% vs. 1.1%, n=1826).(3)

Extended hospitalization and additional care due to CIN is costly. Average cost of one year of dialysis in the Netherlands is estimated to be as high as 80.000 euro. The total annual medical costs for patients diagnosed with CIN in the United States are estimated 700 million to 1 billion dollars.(8,13,14) Relevant patient-related risk factors developing CIN are; chronic kidney disease, diabetes mellitus, heart failure, old age, anemia, and decreased function of the left ventricle.(6) The cause of contrast-induced nephropathy 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 hypoxemia.(15,16)

Prevention of CIN: Hydration therapy is the cornerstone in the prevention of CIN in high-risk patients.(15–17) Patients with an eGFR <45 ml/min/1.73m2 or an eGFR <60 ml/min/1.73m2 with one or more comorbidities (Diabetes Mellitus, Heart failure, PAD) will receive pre and post hydration. Per protocol it is customary in our clinic to administer 0.9% NaCl i.v. 3-4 ml/kg/h in uncomplicated high-risk patients for 4 hours pre- and 4 hours post intervention.

Complicated high-risk patients with heart- or renal failure (exercise-induced dyspnea, edema, eGFR <30 ml/min/1.73m2) receive 12 hours pre and post hydration with 0.9% NaCl i.v. 1 ml/kg/h.

Increased diuresis and prevention of dehydration is known to protect patients with CKD for possible CIN.(10,15–18) 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 edema.(18) Forced diuresis using furosemide in combination with intravenous NaCl 0.9% adjusted to diuresis prevents overhydration and provides a mild protection against developing CIN.(19) On the contrary, some studies show an increased incidence of CIN 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 in stead of dilution.(18–22)

Intervention: To achieve high volume diuresis without risking volume depletion or pulmonary edema in high-risk patients requires a delicate balance. Recent publications regarding the Renalguard system™ show promising results preventing CIN in patients receiving a coronary intervention.(17,23–27) The Renalguard system™ is an infusion system regulating volume of NaCl 0.9% administered based on the volume of urine produced. Pre procedure patients receive a 250ml NaCl 0.9% bolus in combination with a dose furosemide (0.5 mg/kg). The goal is to achieve diuresis of >300 ml/h 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.(17) The MYTHOS-trial demonstrated a reduction CIN in 74% of patients known with CKD, receiving iodine contrast for diagnostic purposes.(17) Moreover, Briguori et al. showed an optimal diuresis threshold of >450 ml/h with a minimum of >300 ml/h to achieve optimal protection against CIN.(26) Previous studies with the Renalguard™ did not report any life-threatening events and no serious electrolyte disturbances were mentioned.(26,27) Briguori et al. described an asymptomatic hypokalemia in 7.5% **(**30/400**)** of patients, in which only 4% **(**16/400**)** required potassium supplementation. No significant alterations of sodium levels were observed.(26,27) Nor was there a significant difference in incidence of pulmonary edema.(27) 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 CIN in patients with CKD receiving a PTA of the lower extremities.

Diagnosing CIN: Current diagnosis of CIN relies on rise of serum creatinine 48-72 hours post intervention. 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 post intervention, this is often dismissed. Early detection of acute kidney injury (AKI) or CIN is based on the slow rise in serum creatinine and therefore is an inadequate diagnostic tool.(28–30) In the past decade several studies tried to identify urine biomarkers for early detection of AKI.(30–32) Potential biomarkers are neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), cystatin C, liver fatty acid binding protein (L-FABP), N-acetyl-beta-D-glucosaminidase (NAG), pi-glutathione-S-transferase (π-GST), and tissue inhibitor of metalloproteinase-2 (TIMP-2).(30,31) One of the more promising urine biomarkers to detect AKI is NGAL.(29) Rise in NGAL concentration is greatest 4-6 hours post intervention, with an increase up to 25 times compared to baseline value.(29)

Study hypothesis: Our primary hypothesis is that a significant reduction in the incidence of CIN can be established by increasing diuresis (>300 ml/h), 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 post intervention can predict CIN in an early stage in patients with CKD compared to rise in serum creatinine 72 hours post intervention.

Methods and analysis

Study design: This study (Protocol V.2.0, date 13 December 2016) is a non-blinded, single centre prospective randomized 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/1.73m2) 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 hospitalization or additional follow up compared to standard of care. Serum creatinine is obtained within 10 days prior to procedural and post procedure on day 1, 3 and 30 (Figure 1. Flow chart of the study). Obtaining these serum creatinine samples is standard of care. Estimated glomerular filtration rate (eGFR) is calculated using the adjusted formula by Levey et al.(33) Pre- and post hydration in the control group are 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 (0.5mg/kg) in the intervention group in conjunction with a bolus NaCl 0.9% (250ml) to increase diuresis. Use of furosemide is a

medicine registered to increase diuresis in treatment of edema associated with renal disease including nephrotoxic syndrome, congestive heart failure, and liver cirrhosis.

To observe reduction in CIN we compare patients treated with furosemide forced diuresis with matched hydration to a control group. Control group will receive standard of care pre and post hydration (described in intervention and comparison). This trial is registered with the Netherlands Trial Register.nl (NTR6236), registration date. The total study period is two 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 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 upon request.

Outcome measurements:

Primary endpoints are defined as the incidence of CIN, 3 days after a successful endovascular procedure of the lower extremities. Serum creatinine is measured post intervention on day 1, 3 and 30. Patients are required to return to the hospital for blood samples at day 3 and day 30. CIN is defined as a decrease in eGFR >25% or rise in serum creatinine of >0.5mg/dl compared to baseline values. Primary success is defined as a 50% reduction in the incidence of contrast induced nephropathy 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 AUC-ROC (area under the curve ROC) >0.7 sampled 4 hours after concluding endovascular procedure. Rise in urine biomarkers will be compared to rise in serum creatinine 72 hours post intervention to see if there is a correlation and early detection of CIN.

Secondary endpoints are complications due to CIN-prophylactic therapy (CIN requiring dialysis (previously not requiring dialysis), electrolyte disturbances and/or acute pulmonary edema (radiologic confirmation and requiring diuretic medication)), post-operative in-hospital adverse events (acute myocardial infarct (confirmed on electrocardiogram), death), length of hospitalization, post-operative complication at home requiring additional care (seroma, wound infection, pseudo aneurysm and re-occlusion or re-stenosis within 4 weeks after intervention). Complications will be registered in the days post intervention while hospitalized 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 adverse events 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 mmHg (measured at the preoperative work up of the anesthetist) 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 or multi-level), OR-time, radiation dose, radiation time, volume of contrast, volume of NaCl 0.9% administered (90 minutes pre till four hours post intervention). Table 1. Schedule of enrolment.

Study population: Patients with chronic kidney disease (eGFR <60 ml/min/1.73m2) diagnosed with PAD requiring a PTA of the lower extremities.

Inclusion criteria

- Patients at least 18 years of age
- Diagnosed with occlusive or stenotic peripheral arterial disease requiring an endovascular intervention with contrast.
- eGFR <60 ml/min/1.73m2

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 randomized controlled trial comparing standard hydration therapy with Renalguard™ controlled furosemide forced diuresis with matched hydration in patients with CKD receiving a coronary procedure.(17) Incidence of CIN in the Renalguard™ group was 4.6% compared to 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.

Randomization and concealment

Randomization will be performed using a randomization program (http:/www.graphpad.com/quickcalcs/randomize2.cfm). Randomization will be performed prior to first inclusion. Patients will be assigned treatment in consecutive order as dictated by the randomization list. Included patients will be allocated a unique study number. Allocation to a treatment group and study number will be registered in a password-protected document only accessible for the principle- and coordinating investigator. Allocation concealment is not possible, as patients in the intervention group will be treated with the Renalguard infusion system™ during and continuing 4 hours post intervention. The Renalguard infusion system™ is installed prior to intervention. The control group will receive pre-hydration 4 hours prior to intervention and 4 hours post intervention.

Recruitment of participants

When referred by general practitioner patients will receive an ankle brachial index (ABI) 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 peripheral arterial disease (PAD) (non responders to SET and Rutherford IV-VI) with a new MRA will be discussed in a multi-disciplinary 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 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 randomization (Figure 1. Flow chart of the study). 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 will there be 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 IV 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 IV 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, metformin) are ceased on the day of intervention. Pre- and post hydration in the control group does not differ from current clinical treatment. On the day of intervention the patients will report on the pre operative ward at 7.30. Patients are instructed to stop oral intake after 24.00 the day before intervention. Oral fluids before 24.00 are permitted. Patients are prepped according to local protocol. An IV line and a Foley catheter are placed to administer fluids and monitor diuresis. Uncomplicated high-risk patients receive 4 hours pre- and 4 hours post hydration with 0.9% NaCl i.v. 3-4 ml/kg/h. Complicated high risk patients due to heart- or renal failure (exercise-induced dyspnea, edema, eGFR <30 ml/min/1.73m2) receive 12 hours pre an post hydration with 0.9% NaCl i.v. 1 ml/kg/h. 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 procedure the urimeter will be emptied, thereafter the urine produced in 15 minutes is collected for analysis. Once urine is collected the Foley catheter will be removed. Serum creatinine is obtained one-day post intervention. If there are no complications and spontaneous micturition is observed the patient will be discharged. Three days post-intervention 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 four weeks post intervention.

Patients in the intervention group will be prepped in a similar fashion. However, after placing an IV line and Foley catheter the Renalguard system™ will be connected. 90 minutes prior to intervention the patients receive 250 ml NaCl 0.9% IV in 30 minutes. After NaCl is administered the patient will receive furosemide (0.5mg/kg) intra venous. If observed diuresis exceeds 300 ml/h the patient is ready for procedure. To maintain diuresis of >300 ml/h an additional dose furosemide can be administered up to a maximum dose of 2mg/kg. According to national guidelines the maximum dosage furosemide for adults (IV/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 minutes 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 minutes 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 analyzed using enzyme-linked immunosorbent assay (ELISA) kits to measure each individual urine biomarker.(23,33)

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 principle investigator (PI) and coordination investigator will be the only researchers with access to these files. Data will be summarized in an SPSS file for further analysis.

All included patients will receive an anonymized 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).(34) 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 analyzed 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 per operative characteristics are presented as means and standard deviations

or median and interquartile ranges 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 CIN and will be presented in a contingency table. Statistical tests for significance will be performed using the Chi-square test for categorical variables. Continues variables are compared using the one-way ANOVA or the Kruskal-Wallis test. Furthermore, proportion comparison (z-test) or calculations for odds-ratios will be performed. Risk factors for CIN, increased urine biomarker concentrations and fast renal decline are evaluated using multivariate logistic regression analysis.

Receiver operating characteristic (ROC) curves of the urine biomarkers for early detection of CIN are calculated, as well as 'area under the curve' (AUC ROC) with correlating standard error. Urine biomarkers are evaluated for their diagnostic accuracy for clinical use if lower 99% confidence interval 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 CIN 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 – Prevalence) / Prevalence) * (1- Specificity).

Clinical outcome of patients are compared to four categories (no CIN and normal biomarkers, no CIN and increased biomarkers, CIN and normal biomarkers, CIN and increased biomarkers). Statistical analysis will be performed by L.J.J.B. using SPSS (IBM Corp, Armonk, New York, V.21.0).

Adverse Events

All adverse events (AE's) observed by the study subject or by a member of the research group are noted and filed. Serious adverse events (SAE's) are unexpected medical events or effect with potential risk of; death, life threatening, hospitalization or extended hospitalization, chronic impairment, or other important medical occurrences potentially harming the patient or requiring an intervention to advert one of the previously mentioned outcomes. SAE's 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 CIN 3 and 30 day post-intervention and accounts for the limited period in which SAE's need to be reported. SAE's that occur within the 30 days post intervention 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. (S)AE's will be followed until a stable situation is created or the SAE is resolved.

Ethics and dissemination:

The study protocol was submitted and approved by the research ethics committee (REC) and the institutional research board (Zuyderland Medical Centre, Heerlen). This trial will be conducted following the Good Clinical Practice Guidelines, the declaration of Helsinki (7th amendment, October 2013) and in accordance with national legislation (Medical Research Act). Substantial amendments to the study protocol will be re-submitted 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 one year after inclusion of the last patient. If the study manuscript is not accepted for publication the research findings will be made publically available on the Internet.

Discussion

Total period of inclusion will be two years and is expected to finish May 2020. Study results will clarify whether furosemide forced diuresis with matched hydration using the Renalguard system™ is superior in the prevention of CIN compared to 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 CIN within 4 hours post intervention compared to serum creatinine after 72 hours.

Outcomes reported from a systematic review and meta-analysis of randomized 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.(27) 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 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 edema

compared to conservative treatment.(27) However, the meta-analysis included only four trials with high risk for bias. Larger RCT's are needed to exemplify possible effectiveness in endovascular interventions other than coronary procedures.

CIN is diagnosed by a gradual increase of serum creatinine concentration within the first days after endovascular procedure. (4,5) Delay in diagnosis due to slow increase in serum creatinine makes it an inadequate marker in the early detection of CIN. As previously mentioned in this protocol, patients are often discharged before serum creatinine can be assessed 48-72 hours post-intervention. Despite instructions to return for serum creatinine controls, patient often refrain from follow-up. Evaluating urine biomarkers 4 hours post intervention might possibly address this matter and enable us to detect CIN 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 CIN rarely requires renal replacement therapy, early detection of CIN 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 CIN but without CKD.(35) CIN requiring renal replacement therapy is prevalent in 1% of the patients without CKD, compared to 7% in patients with CKD.(36)

This trial is the first to investigate whether furosemide forced diuresis with matched hydration using the Renalguard system™ can reduce the incidence of CIN in patients with CKD. Furthermore, this study is the first study to establish the use of urine biomarkers in patients receiving a PTA in the detection of CIN compared to serum creatinine.

It is anticipated that study results will provide a solution for early detection of contrast induced nephropathy and offer a preventive measure in patients with chronic kidney disease 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.

Funding statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Trial registration number: NTR6236
EudraCT number: 2016-005072-10

Table 1 Schedule of enrolment, intervention and assessment

	Study Period						
Process Time point	Screening, enrolment and allocation	Pre intervention (10 days)	Intervention	FU + 4hour	FU + 1day	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

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Figure legend:

Figure 1. Flow chart of the study. Eligibility based on in- and exclusion criteria. Enrolment by random assignment. Serum creatinine for measurement of renal function pre- and post procedure. Urine sampling to analyse biomarkers post procedure.

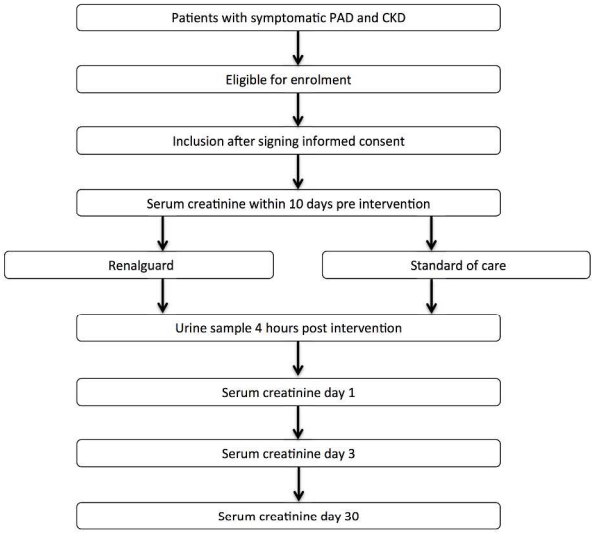

Figure 1. Flow chart of the study. Eligibility based on in- and exclusion criteria. Enrolment by random assignment. Serum creatinine for measurement of renal function pre- and post procedure. Urine sampling to analyse biomarkers post procedure.

297x209mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	x
Protocol version	3	Date and version identifier	7
Funding	4	Sources and types of financial, material, and other support	x
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	x
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	x
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	x

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	x
Objectives	7	Specific objectives or hypotheses	5-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7-13
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7-13
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-13
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7-13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	x
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	x
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-13

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____9_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____10_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____9-10_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____9-10____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____9-10____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____x_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____x_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____x_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____x_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7-13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	x
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	x
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11-12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11-12
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	x
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	x
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Prevention of post contrast acute kidney injury after percutaneous transluminal interventions by inducing RenalguardTM controlled furosemide forced diuresis with matched hydration: study protocol for a randomized controlled trial

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Prevention of post contrast acute kidney injury after percutaneous transluminal interventions by inducing Renalguard™ controlled furosemide forced diuresis with matched hydration: study protocol for a randomized controlled trial

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List of abbreviations

ABI	Ankle Brachial Index
CIN	Contrast Induced Nephropathy
CRI	Chronic Renal Insufficiency
ICF	Informed Consent Form
KNF	Clinical Neurological Function laboratory
PC-AKI	Post Contrast Acute Kidney Injury
PSV	Peak Systolic Velocity
PTA	Percutaneous Transluminal Angioplasty
REC	Research Ethics Committee

Abstract

Introduction: Percutaneous transluminal interventions (PTA) are often complicated due to post contrast 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 randomized 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 to the golden standard, serum creatinine 48-72 hours post intervention.

Methods and analysis: a single centre randomized 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 pre- and post-hydration or furosemide forced diuresis with matched hydration periprocedural using the Renalguard system™. Four hours post intervention 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 post intervention. The primary endpoint is incidence of PC-AKI post PTA. Secondary endpoint is the rise of urine biomarkers 4 hours post intervention.

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 chronic kidney disease receiving a PTA of the lower extremities.

Trial registration number: NTR6236

EudraCT number: 2016-005072-10

Strengths and limitations of this study

- The first study to evaluate the incidence of PC-AKI in patients with PAD 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 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 PTA can cause post contrast acute kidney injury.(1–3) Recent update of the ESUR (European Society of Urogenital Radiology) guidelines changed the definition of contrast induced nephropathy (CIN) to post contrast induced kidney injury (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 to baseline values or a rise of >0.5 mg/dl serum creatinine within 72 hours after an iodine contrast mediated procedure (KDIGO guidelines).(5,6) Krasznai 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 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 percent of the general population.(9) Prevalence of CKD is increasing worldwide and is estimated to be as high as 45% in de population aged >70 years.(9) Moreover, incidence and prevalence of PC-AKI are rising 5-8% annually.(1) Contrast induced nephropathy is associated with a significant worse outcome due to increased risk of cardio-vascular events, acceleration to end stage renal failure requiring dialysis and extended hospitalization, 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 to patients without PC-AKI (resp. 7.1% vs. 1.1%, n=1826).(3)

Extended hospitalization and additional care due to PC-AKI is costly. Average cost of one year of dialysis in the Netherlands is estimated to be as high as 80.000 euro. The total annual medical costs for patients diagnosed with PC-AKI in the United States are estimated 700 million to 1 billion dollars.(9,14,15) Relevant patient-related risk factors developing PC-AKI are; chronic kidney disease, diabetes mellitus, heart failure, old age, anemia, and decreased function of the left ventricle.(7) The cause of contrast-induced nephropathy 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 hypoxemia.(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/1.73m2 or an eGFR <60

ml/min/1.73m2 with one or more comorbidities (Diabetes Mellitus, Heart failure, PAD) will receive pre and post hydration. Per protocol it is customary in our clinic to administer 0.9% NaCl i.v. 3-4 ml/kg/h in uncomplicated high-risk patients for 4 hours pre- and 4 hours post intervention. Complicated high-risk patients with heart- or renal failure (exercise-induced dyspnea, edema, eGFR <30 ml/min/1.73m2) receive 12 hours pre and post hydration with 0.9% NaCl i.v. 1 ml/kg/h.

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 edema.(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 in stead of dilution.(19–23)

Intervention: To achieve high volume diuresis without risking volume depletion or pulmonary edema 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. Pre procedure patients receive a 250ml NaCl 0.9% bolus in combination with a dose furosemide (0.5 mg/kg). The goal is to achieve diuresis of >300 ml/h 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 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/h with a minimum of >300 ml/h 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 hypokalemia 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 edema.(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 post intervention. 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 post intervention, this is often dismissed. Early detection of acute kidney injury (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 fatty acid binding protein (L-FABP), N-acetyl-beta-D-glucosaminidase (NAG), pi-glutathione-S-transferase (π-GST), and tissue inhibitor of metalloproteinase-2 (TIMP-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 post intervention, with an increase up to 25 times compared to 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/h), 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 post intervention can predict PC-AKI in an early stage in patients with CKD compared to rise in serum creatinine 72 hours post intervention.

Methods and analysis

Study design: This study (Protocol V.2.0, date 13 December 2016) is a non-blinded, single centre prospective randomized 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/1.73m2) 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 hospitalization or additional follow up compared to standard of care. Serum creatinine is obtained within 10 days prior to procedural and post procedure on day 1, 3 and 30 (Figure 1. Flow chart of the study). Obtaining these serum creatinine samples is standard of care. Estimated glomerular filtration rate (eGFR) is calculated using the adjusted formula by Levey et al.(34) Pre- and post hydration in the control group are 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 (0.5mg/kg) in the intervention group in conjunction with a bolus NaCl 0.9% (250ml) to increase diuresis. Use of furosemide is a medicine registered to increase diuresis in treatment of edema 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 pre and post hydration (described in intervention and comparison). This trial is registered with the Netherlands Trial Register.nl (NTR6236), registration date. The total study period is two 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 upon 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 post intervention 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 >0.5mg/dl compared to baseline values. Primary success is defined as a 50% reduction in the incidence of contrast induced nephropathy 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 AUC-ROC (area under the curve ROC) >0.7 sampled 4 hours after concluding endovascular procedure. Rise in urine biomarkers will be compared to rise in serum creatinine 72 hours post intervention 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 edema (radiologic confirmation and requiring diuretic medication)), post-operative in-hospital adverse events (acute myocardial infarct (confirmed on electrocardiogram), death), length of hospitalization, post-operative complication at home requiring additional care (seroma, wound infection, pseudo aneurysm

and re-occlusion or re-stenosis within 4 weeks after intervention). Complications will be registered in the days post intervention while hospitalized 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 adverse events 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 mmHg (measured at the preoperative work up of the anesthetist) 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 or multi-level), OR-time, radiation dose, radiation time, volume of contrast, volume of NaCl 0.9% administered (90 minutes pre till four hours post intervention). Table 1. Schedule of enrolment.

Study population: Patients with chronic kidney disease (eGFR <60 ml/min/1.73m2) diagnosed with PAD requiring a PTA of the lower extremities.

Inclusion criteria

- Patients at least 18 years of age
- Diagnosed with occlusive or stenotic peripheral arterial disease requiring an endovascular intervention with contrast.
- eGFR <60 ml/min/1.73m2

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 randomized 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 to 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.

Randomization and concealment

Randomization will be performed using a randomization program (http:/www.graphpad.com/quickcalcs/randomize2.cfm). Randomization will be performed prior to first inclusion. Patients will be assigned treatment in consecutive order as dictated by the randomization list. Included patients will be allocated a unique study number. When written consent is acquired a second study member will be approached for the randomization, unaware of patient characteristics to minimize selection bias. Allocation to a treatment group and study number will be registered in a password-protected document only accessible for the principle- 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 post intervention. The Renalguard infusion system™ is installed prior to intervention. The control group will receive pre-hydration 4 hours prior to intervention and 4 hours post intervention.

Recruitment of participants

When referred by general practitioner patients will receive an ankle brachial index (ABI) 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 peripheral arterial disease (PAD) (non responders to SET and Rutherford IV-VI) with a new MRA will be discussed in a multi-disciplinary 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 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 randomization (Figure 1. Flow chart of the study). 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 will there be 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 IV 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 IV 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, metformin) are ceased on the day of intervention. Pre- and post hydration in the control group does not differ from current clinical treatment. On the day of intervention the patients will report on the pre operative ward at 7.30. Patients are instructed to stop oral intake after 24.00 the day before intervention. Oral fluids before 24.00 are permitted. Patients are prepped according to local protocol. An IV line and a Foley catheter are placed to administer fluids and monitor diuresis. Uncomplicated high-risk patients receive 4 hours pre- and 4 hours post hydration with 0.9% NaCl i.v. 3-4 ml/kg/h. Complicated high risk patients due to heart- or renal failure (exercise-induced dyspnea, edema, eGFR <30 ml/min/1.73m2) receive 12 hours pre an post hydration with 0.9% NaCl i.v. 1 ml/kg/h. 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 procedure the urimeter will be emptied, thereafter the urine produced in 15 minutes is collected for analysis. Once urine is collected the Foley catheter will be removed. Serum creatinine is obtained one-day post intervention. If there are no complications and spontaneous micturition is observed the patient will be discharged. Three days post-intervention 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 four weeks post intervention.

Patients in the intervention group will be prepped in a similar fashion. However, after placing an IV line and Foley catheter the Renalguard system™ will be connected. 90 minutes prior to intervention the patients receive 250 ml NaCl 0.9% IV in 30 minutes. After NaCl is administered the patient will receive furosemide (0.5mg/kg) intra venous. If observed diuresis exceeds 300 ml/h the patient is ready for procedure. To maintain diuresis of >300 ml/h an additional dose furosemide can be administered up to a maximum dose of 2mg/kg. According to national guidelines the maximum dosage furosemide for adults (IV/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 minutes 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 minutes 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 analyzed using enzyme-linked immunosorbent assay (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 principle investigator (PI) and coordination investigator will be the only researchers with access to these files. Data will be summarized in an SPSS file for further analysis.

All included patients will receive an anonymized 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 analyzed 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 per operative characteristics are presented as means and standard deviations or median and interquartile ranges 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 Chi-square test for categorical variables. Continues variables are compared using the one-way ANOVA or the Kruskal-Wallis test. Furthermore, proportion comparison (z-test) or calculations for odds-ratios will be performed. Risk factors for PC-AKI, increased urine biomarker concentrations and fast renal decline are evaluated using multivariate logistic regression analysis.

Receiver operating characteristic (ROC) curves of the urine biomarkers for early detection of PC-AKI are calculated, as well as 'area under the curve' (AUC ROC) with correlating standard error. Urine biomarkers are evaluated for their diagnostic accuracy for clinical use if lower 99% confidence interval 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 – Prevalence) / Prevalence) * (1- Specificity).

Clinical outcome of patients are compared to 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 L.J.J.B. using SPSS (IBM Corp, Armonk, New York, V.21.0).

Adverse Events

All adverse events (AE's) observed by the study subject or by a member of the research group are noted and filed. Serious adverse events (SAE's) are unexpected medical events or effect with potential risk of; death, life threatening, hospitalization or extended hospitalization, chronic impairment, or other important medical occurrences potentially harming the patient or requiring an intervention to advert one of the previously mentioned outcomes. SAE's 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 day post-intervention and accounts for the limited period in which SAE's need to be reported. SAE's that occur within the 30 days post intervention 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. (S)AE's will be followed until a stable situation is created or the SAE is resolved.

Ethics and dissemination:

The study protocol was submitted and approved by the research ethics committee (REC) and the institutional research board (Zuyderland Medical Centre, Heerlen). This trial will be conducted following the Good Clinical Practice Guidelines, the declaration of Helsinki (7th amendment, October 2013) and in accordance with national legislation (Medical Research Act). Substantial amendments to the study protocol will be re-submitted 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 one year after inclusion of the last patient. If the study manuscript is not accepted for publication the research findings will be made publically available on the Internet.

Discussion

Total period of inclusion will be two years and is expected to finish 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 to 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 post intervention compared to serum creatinine after 72 hours.

Outcomes reported from a systematic review and meta-analysis of randomized 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 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 edema compared to conservative treatment.(28) However, the meta-analysis included only four trials with high risk for bias. Larger RCT's 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 post-intervention. Despite instructions to return for serum creatinine controls, patient often refrain from follow-up. Evaluating urine biomarkers 4 hours post intervention 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 to 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 to serum creatinine.

It is anticipated that study results will provide a solution for early detection of contrast induced nephropathy and offer a preventive measure in patients with chronic kidney disease 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.

Funding statement

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Trial registration number: NTR6236
EudraCT number: 2016-005072-10

Table 1 Schedule of enrolment, intervention and assessment

	Study Period						
Process Time point	Screening, enrolment and allocation	Pre intervention (10 days)	Intervention	FU + 4hour	FU + 1day	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

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Figure legend:

Figure 1. Flow chart of the study. Eligibility based on in- and exclusion criteria. Enrolment by random assignment. Serum creatinine for measurement of renal function pre- and post procedure. Urine sampling to analyse biomarkers post procedure.

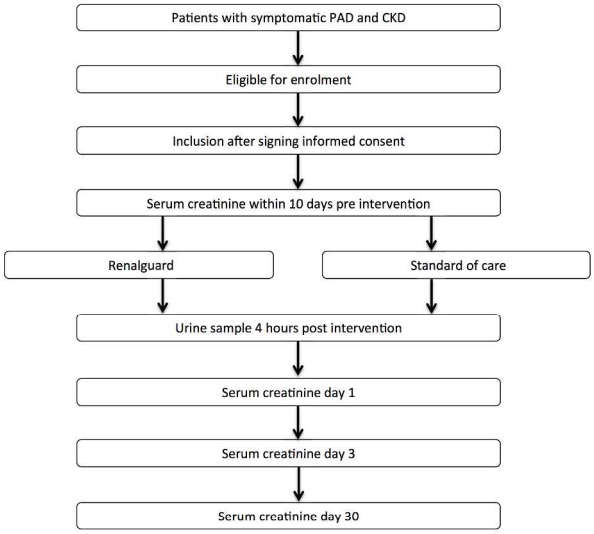

Figure 1. Flow chart of the study. Eligibility based on in- and exclusion criteria. Enrolment by random assignment. Serum creatinine for measurement of renal function pre- and post procedure. Urine sampling to analyse biomarkers post procedure.

297x209mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	x
Protocol version	3	Date and version identifier	7
Funding	4	Sources and types of financial, material, and other support	x
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2
	5b	Name and contact information for the trial sponsor	x
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	x
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	x

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	x
Objectives	7	Specific objectives or hypotheses	5-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7-13
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7-13
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-13
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7-13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	x
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	x
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7-13

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____9_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____10_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____9-10_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____9-10____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____9-10____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____x_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____x_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____x_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____x_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7-13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	x
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	x
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11-12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11-12
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	x
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	13
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	13
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	x
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.