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Randomised controlled trial to evaluate the effect of contrast material dilution on renal function in patients after endovascular aortic repair: rationale and design for the CULTURE trial

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ABSTRACT

Introduction Postoperative renal function decline is a major concern for thoracic endovascular aortic repair (TEVAR) and endovascular abdominal aortic repair (EVAR). Diluting contrast medium in the power injector may be helpful in reducing the risk of contrast-induced nephropathy, but it can also blur fluoroscopic vision during surgery. The quality of the current evidence is very low; thus, this study is designed to investigate the effect of contrast dilution in the power injector on renal function changes in patients after endovascular aortic repair.

Method and analysis The study is a prospective, single-blind, parallel, non-inferiority, randomised controlled trial with two independent cohorts: Cohort TEVAR and EVAR. Individuals will enter the appropriate cohort based on clinical interviews if they meet the eligibility criteria. Participants in Cohort TEVAR and EVAR will be randomly allocated to the intervention group (diluting contrast medium to 50% in the power injector) and control group (pure contrast medium in the power injector) separately in a 1:1 ratio. The primary study points consist of the proportion of patients who develop acute kidney injury within 48 hours after TEAVR or EVAR (first stage) and freedom of major adverse kidney events at 12 months after TEAVR or EVAR (second stage). The safety endpoint is freedom of all types of endoleaks at 30 days after TEVAR or EVAR. Follow-up will be conducted at 30 days and 12 months after intervention.

Ethics and dissemination The trial was approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University (approval number: 20201290). The results of the study will be disseminated through publications in peer-reviewed journals and presentations at academic conferences.

Trial registration number Chinese Clinical Trial Registry (ChiCTR2100042555).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The trial is a prospective, non-inferiority, randomised controlled trial to investigate the effect of contrast dilution on renal function changes in patients who underwent thoracic endovascular aortic repair (TEVAR) or endovascular abdominal aortic repair (EVAR).
⇒ This study uses acute kidney injury (AKI) and major adverse kidney events to describe the short-term and long-term changes in renal function, respectively.
⇒ Prespecified subgroup analyses will be performed for age, coronary intervention, degree of renal artery stenosis and chronic kidney disease stage to investigate the risk factors for AKI after TEVAR and EVAR.
⇒ The trial is conducted at a single centre, which may prevent the final conclusions from being applicable to other centres.
⇒ The surgeons cannot be blinded due to the nature of the intervention, which could lead to potential bias.

INTRODUCTION

With fast advances in fluoroscopic-guided intervention techniques, endovascular aortic repair has become the mainstream treatment for nearly all types of aortic pathologies with suitable anatomy. As demonstrated in the latest clinical practice guidelines from the European Society for Vascular Surgery and North American Society for Vascular Surgery, thoracic endovascular aortic repair (TEVAR) remains the first-line intervention for descending thoracic aortic aneurysm (DTAA) and type B aortic dissection (TBAD),[1 2] and endovascular abdominal aortic repair (EVAR) represents the preferred approach for the treatment of abdominal aortic aneurysm (AAA).[3 4] Despite various advantages of endovascular procedures, acute kidney injury (AKI) and renal function decline are common after aortic interventions.[5] Notably, postoperative AKI can increase the risk of mortality after all types of aortic repair[6]; thus, how to diminish the incidence of AKI after endovascular aortic repair is of great importance.

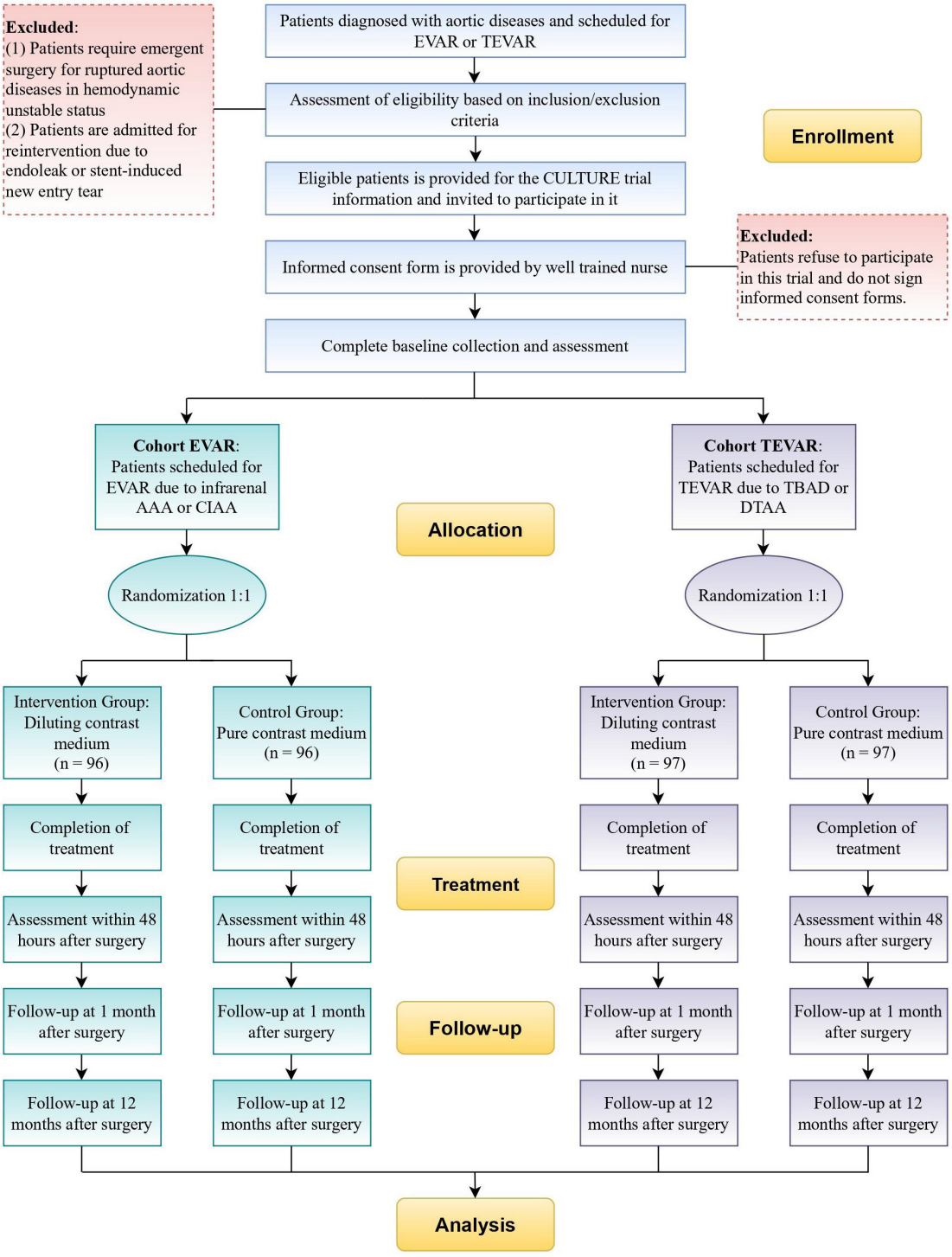

Figure 1 The participant timeline of the CULTURE trial. AAA, abdominal aortic aneurysm; CIAA, common iliac artery aneurysm; CULTURE, Contrast medium dilUtion on renaL funcTion in patients after endovascUlar aoRtic rEpair; DTAA, descending thoracic aortic aneurysm; EVAR, endovascular abdominal aortic repair; TBAD, type B aortic dissection; TEVAR, thoracic endovascular aortic repair.

Contrast-associated nephropathy is one of the major causes of AKI after fluoroscopic guided endovascular interventions. Iodin-based contrast material can help to locate important anatomical markers and indicate the blood flow area, which is almost inevitable during intraoperative planning and evaluation. However, contrast medium can also result in contrast associated AKI (CA-AKI) that may significantly affect the renal function of patients.[7] The potential mechanism may be associated with renal medullary hypoxia due to abnormal levels of oxidative stress and apoptosis under the direct toxicity of contrast agents.[8] As no specific therapy for CA-AKI is available to date, effective prevention of CA-AKI has become the top issue.

Current evidence indicates that proper use of contrast medium may reduce the risk of CA-AKI.[7 9] Recent guidelines of DTAA recommended diluting contrast medium in the power injector to a concentration of 50% or 70%, but the grade was weak, and the quality of evidence was low.[2] The level of recommendation may be impeded by the fact that the dilution of contrast medium may adversely affect the quality of fluoroscopy, which could increase the number of fluoroscopy attempts or result in a loss of sight of insidious intraoperative endoleak. Unfortunately, no related research can provide a high level of evidence for this recommendation.

Therefore, we designed a prospective, single-blind, parallel, non-inferiority, randomised controlled trial in a 1:1 ratio to investigate the effect of contrast dilution in the power injector on the short-term and midterm renal function changes of patients who underwent TEVAR or EVAR. The short-term and midterm primary focus would be 30-day and 12-month major adverse kidney events (MAKE), respectively.

METHODS AND ANALYSIS

Study setting

The Contrast medium dilUtion on renaL funcTion in patients after endovascUlar aoRtic rEpair (CULTURE) trial was conducted in a tertiary academic hospital, West China Hospital of Sichuan University. This protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.[10] The SPIRIT checklist is presented in online supplemental table 1.

Participants and recruitment

The study population consists of two independent cohorts: Cohort TEVAR and EVAR. Participants will be screened for eligibility in Cohort TEVAR if they (1) plan TEVAR due to TBAD or DTAA and (2) sign informed consent. The inclusion criteria of individuals in Cohort EVAR are as follows: (1) patients schedule for EVAR due to infrarenal AAA or common iliac artery aneurysms (CIAA) and (2) patients who sign informed consent informs.

Both Cohort TEVAR and EVAR share the same exclusion criteria. Participants will be excluded if they meet one of the following criteria: (1) patients require emergent surgery for ruptured aortic diseases in haemodynamic unstable status, (2) patients are admitted for reintervention due to endoleak or stent-induced new entry tear, (3) patients refuse to participate in this trial.

After admission, the senior resident will inform the eligible individuals about the trial participation, and then a trained research nurse will provide consent 1 day prior to the surgery. After participation, withdrawal from the study is permitted at any time for any reason without any alteration to treatment plans. To achieve adequate enrolment, we will provide a fast-track channel for outpatient appointments and follow-up assessment.

Assignment of intervention

Participants in Cohort TEVAR and EVAR will be randomly allocated to the intervention group (diluting contrast medium to 50% in the power injector) and control group (pure contrast medium in the power injector) separately in a 1:1 ratio. Stratified randomisation based on age (<60, 60–80, ≥80 years) will be performed after collection of baseline data of participants. Permuted block randomisation with a block size of 4 is adopted within each stratum. A biostatistician will generate the allocation sequence and inform the surgeon by telephone before intervention. The surgeon will tell the fluoroscopic technician to dilute the contrast medium in the power injector. The trial participants, outcome assessors and data analysts will be blinded after assignment to interventions. The participant timeline is shown in figure 1.

During the perioperative period, all patients in the Cohort TEVAR and EVAR receive the same fluid management protocol. The intravenous crystalloid solution is Hartmann's solution, that is, Lactated Ringer's solution, and the amount of fluid will be based on individual's blood pressure and urine output. Intraoperatively, the patients' mean arterial pressure will be maintained within 80% of baseline for at least 90% of the operation time by intravenous fluids and vasopressor administration. Postoperatively, Hartmann's solution will be given intravenously at 2 mL/kg/hour for at least 6 hours, after which it will be adjusted for the patient's blood pressure and urine output. The target urine output is at least 0.5 mL/kg/hour. In addition, N-acetylcysteine, sodium bicarbonate administration, perioperative intravascular volume expansion or other renal protection strategies will not be used.

Iodixanol, an iso-osmolar contrast agent, is used for angiography in all patients in the Cohort TEVAR and EVAR. The volume of the power injector is 150 mL, and iodixanol is diluted to a concentration of 50% with normal saline in the intervention group, with 75 mL each in the injector reservoir. In the control group, the power injector will be filled with pure iodixanol. To ascertain adequate visibility of the aneurysm sac, the injection parameters of initial angiography in the intervention group will be adjusted if the aneurysm is larger than 65 mm, with a speed of 15 mL/s, a volume of 25 mL, and a pressure at 700 psi. By comparison, the injection parameters in the control group are as follows: (1) speed at 15 mL/s, (2) volume at 20 mL and (3) pressure at 600 psi.

Outcomes of interest

A blinded outcome assessment team consisting of two residents will be in charge of evaluating all outcomes. A schedule of the outcome assessment based on the SPIRIT recommendations is presented in table 1. The CULTURE trial involves two stages: the first stage (30 days postintervention) is to assess the short-term changes in renal function, and the second stage (12 months postintervention) is to focus on the midterm status of renal function. The primary and secondary study endpoints are as follows:

Table 1 Standard Protocol Items: Recommendations for Interventional Trials schedule for the Contrast medium dilUtion on renaL funcTion in patients after endovascUlar aoRtic rEpair trial

	Prestudy		Study visit		Follow-up	
	Enrolment	Baseline/allocation	Treatment	Within 48 hours after surgery	30 days after surgery	12 months after surgery
Timepoint	–T1	0	T1	T2	T3	T4
Enrolment						
Eligibility screen and informed consent	×					
Clinical interviews		×				
Allocation		×				
Interventions			×			
Assessments						
Primary study endpoint						
The proportion of patients who develop AKI				×		
Freedom of MAKE						×
Secondary study endpoint						
The proportion of patients who develop MAKE					×	
Freedom of all types of endoleaks					×	
Other outcomes of interest						
The change in eGFR					×	×
The change in serum creatine (SCr)					×	×
The proportion of patients who need RRT					×	×
The stenosis of renal arteries					×	×
All-cause mortality					×	×
Freedom of major adverse aortic MAAE						×
Other systematic complications					×	×

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; MAAE, major adverse aortic events; MAKE, major adverse kidney events; RRT, renal replacement therapy.

Primary study endpoint

- First stage: the proportion of patients who develop AKI within 48 hours after TEVAR or EVAR.
- Second stage: freedom of MAKE at 12 months after TEVAR or EVAR.

Secondary study endpoint

- Efficacy endpoint: the proportion of patients who develop MAKE at 30 days after TEVAR or EVAR.
- Safety endpoint: freedom of all types of endoleaks at 30 days after TEVAR or EVAR.

Other outcomes of interest

- The change in eGFR at 30 days and 12 months after intervention.
- The change in serum creatine (SCr) at 30 days and 12 months after intervention.
- The proportion of patients who need renal replacement therapy at 30 days and 12 months after intervention.
- Stenosis of renal arteries assessed by duplex ultrasound at 30 days and 12 months after intervention.
- All-cause mortality at 30 days and 12 months after intervention.
- Freedom of major adverse aortic events (MAAE) at 12 months after intervention.
- Other systematic complications at 30 days and 12 months after intervention.

MAKE is defined as a composite endpoint consisting of death, new dialysis, and a >25% decline in the estimated glomerular filtration rate (eGFR). And eGFR will be calculated by the Chronic Kidney Disease Epidemiology Collaboration equation based on SCr, which is the most precise formula in populations with cardiovascular diseases and has been validated and widely used in the Chinese population.[11 12] The definition of AKI is based on the Kidney Disease Improving Global Outcomes (KDIGO) criteria, meeting one of the following standards: (1) increase in SCr ≥26.5 mmol/L within 48 hours compared with baseline; (2) increase in SCr more than 1.5 times within 48 hours compared with baseline; (3) decrease in urine output ≤0.5 mL/kg/hour for ≥6 hours. MAAE is defined as a composite endpoint comprising endoleaks, graft thrombosis, reintervention and death. Endoleak, stent migration, false lumen perfusion, aneurysm diameter will be measured at 12 months after intervention and will be used to assess reintervention.

Data collection and management

Demographics including age, sex, body mass index, comorbidities, types of aortic diseases (TBAD, DTAA, AAA, CIAA, etc), will be recorded before assignment to facilitate stratified randomisation. The levels of baseline SCr and eGFR will be collected a few days before aortic intervention. Anatomic characteristics of aortic pathologies will be collected according to measurements on CT angiography. In Cohort TEVAR, the following anatomical parameters will be collected: the diameter of the aneurysm/true lumen/false lumen, the origin of renal arteries (from true lumen or false lumen), the extension of aortic pathology based on the latest reporting standard of SVS,[13] etc. In Cohort EVAR, the neck parameters (diameter, length, angles), stenotic degree of bilateral renal arteries (percentage), aneurysm sac diameter, intraluminal thrombus load, parameters of iliac arteries (tortuosity, diameter, length, etc) will be measured. In addition, intraoperative details will be also recorded, including the following items: (1) the volume of contrast medium and the ratio of contrast medium to eGFR (CV/eGFR); (2) fluoroscopic time and operative time; (3) stent graft sizes, configuration and types; and (4) technical success or not. Moreover, vital signs such as heart rate, blood pressure, respiration and blood oxygen will be recorded postoperatively. Total amount of fluid input and urine output especially for the first 24 hours will be recorded, too. All data that need to be collected are shown in online supplemental table 2.

In this trial, all data involving participant personnel information will be kept in the form of a cryptographic web spreadsheet, which can only be accessed and edited with specific permissions. Individuals' information will not be disclosed without their written consent.

Sample size calculation

As shown in figure 1, the CULTURE trial contains two cohorts: Cohort TEVAR and Cohort EVAR. As there were no previous data revealing the incidence of AKI after contrast dilution, the range of AKI incidence (10%–15%) after TEVAR reported in the current guideline was adopted,[2 14 15] presumed as the proportions of AKI in the two groups. In Cohort TEVAR, 87 patients are required in each group to prove non-inferiority with a non-inferiority margin of 0.075, with a beta of 0.20 and an alpha of 0.05. Counting for a 10% dropout rate, a total of 194 patients (97 patients in each group) are needed in Cohort TEVAR.

For the incidence of AKI after infrarenal EVAR, we adopted the proportion (18%) reported in a prospective multicentre cohort study (MARI study) as the estimated proportion in the control group.[5] Due to limited evidence of prospective data, we expect a one-third decrease in AKI incidence in the intervention group as in the Cohort TEVAR, that is, 12% in the dilution group. Thus, 86 patients are required in each group to prove non-inferiority with a non-inferiority margin of 0.075 (beta at 0.20 and alpha at 0.05). To allow for a 10% dropout rate, a total of 192 patients are required in Cohort EVAR. The calculation process of the sample size is shown in online supplemental files 1 and 2.

Statistical analysis

The statistical analysis of Cohort TEVAR and EVAR will be reported separately. Both intention-to-treat (ITT) and per-protocol (PP) populations are analysed in the CULTURE trial, and ITT analysis is set as the main summary of outcomes of interest, while PP analysis serves as sensitivity analysis. The non-inferiority test will be evaluated as a two-sided test with an alpha of 0.05 and a beta of 0.20, with a non-inferiority margin of 0.075. When non-inferiority is reached, ITT analysis is further tested for superiority.

A generalised linear model (GLM) is adopted to compare short-term outcomes of interest in the two groups. Adjustment for covariates, for example, age, sex, renal artery stenosis and preoperative stage of chronic kidney disease (CKD), is addressed by multivariate GLM analysis. Univariate and multivariate logistic regressions using generalised estimating equations are applied to compare categorical short-term endpoints. Differences in the midterm outcomes will be evaluated graphically using Kaplan-Meier curves and compared by log-rank test. Based on the proportionality of the time-to-event data, multivariate Cox proportional hazard regression analysis is used to assess adjusted HRs and corresponding 95% CI for midterm outcomes. If the proportionality assumption is not met, we will adopt risk ratios and their corresponding 95% CIs. Missing data for covariates will be refilled by multiple imputations.

Prespecified subgroup analyses will be performed in the following populations: (1) prior percutaneous coronary interventions versus no previous interventions, (2) octogenarians versus younger patients, (3) severe renal artery stenosis (>70%) versus lesser or no stenosis in renal arteries and (4) CKD stage >3 versus CKD stage ≤2 or none.

Monitoring

The data review and interim analysis will be performed by the Data Monitoring Committee (DMC) independent of the study team. When 50% of the participants have been randomly assigned and followed up for 12 months, an independent statistician within the DMC will conduct the interim analysis based on the primary, efficacy and safety endpoints. After that, the DMC will decide whether to continue the trial or adjust the sample size according to the results of the interim analysis.

Adverse events, any untoward medical occurrence in a participant, will also be monitored by investigators. Severe adverse events that result in death, disability, permanent impairment and prolonged hospital stay, should be reported promptly to the ethics committee. Details of all adverse events will be recorded by the study team.

Ethics and dissemination

The study was approved by the Ethics Committee on Biomedical Research of the hospital (approval number: 2020-1290) on 16 December 2020. The trial was registered in the Chinese Clinical Trial Registry on 23 January 2021. The study is scheduled to be conducted from 30 January 2021 to 28 February 2023. The results of the study will be disseminated through publications in peer-reviewed journals and presentations in academic conferences.

Patients and public involvement

The patients and members of public were not involved in the design, conduct, reporting or dissemination plans of our study.

DISCUSSION

Although endovascular aortic repair has become the mainstream treatment for the vast majority of aortic diseases due to various advantages, postoperative AKI is still a common and intractable complication. The incidence of AKI after EVAR was as high as 18% and even higher after fenestrated or branched EVAR based on multiple retrospective and prospective cohort studies using KDIGO criteria.[5 16 17] In particular, developing AKI is associated with increased mortality, cardiovascular morbidity and long-term renal function decline.[17 18] Therefore, how to protect renal function after endovascular aortic intervention has become a topical issue in recent years.

Among the factors of postoperative AKI, contrast associated nephropathy is a major cause and a systematic review of six studies involving 862 patients indicated that the overall frequency of CA-AKI was 9.2% during vascular surgery.[19] Previous strategies to prevent CA-AKI during endovascular aortic repair included intravenous fluid hydration with oral N-acetylcysteine[20] or with intravenous sodium bicarbonates,[21 22] targeted renal therapy by renal arterial infusion of fenoldopam,[23] remote ischaemic preconditioning using sequential lower limb ischaemia,[24] infusion of dexmedetomidine after anaesthetic induction,[25] etc. Unfortunately, the studies that have explored those prevention strategies, although randomised controlled trials, have used inconsistent reporting standards for renal function change, and their sample size is inadequate.[18] Moreover, some researchers reported that the administration of statins or antioxidants helps to prevent CA-AKI, but these results have not been verified in prospective studies related to endovascular aortic intervention.[26 27] Carbon dioxide appears to be a promising alternative to nephrotoxic iodinated contrast, and its effectiveness has been demonstrated in patients at high risk for CA-AKI during EVAR.[28] However, its disadvantages, such as inconvenience, poor imaging quality, potential embolism, and risk of neurotoxicity, are also prominent.[29] In brief, solid evidence to support those prevention strategies is still lacking and relevant research is continually envovling.[7 9]

The above options are not always available due to the complexity or significant cost of the operating procedures. In contrast, the dilution of contrast medium seems to be a more feasible method, and it significantly reduces the incidence of CA-AKI in fistula angiography during dialysis fistula angiography and venous mapping.[30 31] However, some investigators have pointed out that dilute contrast may impede optimal image quality, especially in the thoracic or abdominal aorta.[29] Whether this will prolong the time of angiography or lead to missed diagnoses of insidious intraoperative endoleak during endovascular aortic intervention remains uncertain, since the study on this aspect is still lacking. Perhaps that was why contrast dilution was weakly recommended to protect renal function by related guidelines in 2020.[2]

Our trial aims to fill this gap and provide high-level evidence. To the best of our knowledge, the CULTURE trial is the first randomised controlled trial to investigate the effect of contrast dilution on renal function changes in patients who underwent TEVAR or EVAR. We used the KDIGO criteria to define AKI, which was consistent with current mainstream research. The planned sample sizes in Cohort TEVAR and EVAR were 194 and 192, respectively. In addition, MAKE, as the primary outcome of interest in this study, is more representative in terms of midterm and long-term renal function change. Other outcomes, such as freedom of all types of endoleaks and MAAE, could well explain the safety of diluting contrast medium during TEVAR and EVAR. Furthermore, prespecified subgroup analyses of age, coronary intervention, degree of renal artery stenosis and CKD stage will be performed to investigate the risk factors for AKI after TEVAR and EVAR. Based on the results of the subgroup analyses, we hope to identify the population at risk for CA-AKI who would benefit from contrast dilution.

Simultaneously, the trial has some limitations. First, the CULTURE trial is conducted at a single centre, and differences in the number of the surgeries and perioperative care experience may prevent the final conclusions from being applicable to other centres. Second, urine output recording after catheter removal is not precise, which may hinder the diagnosis of AKI. Finally, the 1-year follow-up is still slightly insufficient to evaluate the long-term mortality and the long-term morbidity of related complications.

Contrast medium dilution in the power injector may reduce the risk of AKI after TEAVR or EVAR, while it can also adversely affect the image resolution of angiography and blur visions of potential intraoperative endoleaks. Recent clinical guidelines recommend diluting contrast medium in the power injector to a concentration of 50% or 70%, but high-quality evidence is lacking to support this. In consideration of the low grade of recommendation and the paucity of related studies, comparison of the diluting contrast medium versus pure contrast medium during TEVAR or EVAR is of great importance for improving the prognosis of patients at high risk of postoperative AKI.

Contributors YZ and JW contributed to the conception and design of the trial. JZ and DY will recruit and screen the participants. YZ, JW and TW will participate in data collection and analysis. YZ and JW drafted the manuscript. JZ, TW and BH provided supervision support. All authors contributed to the critical revisions and final approval of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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