

BMJ Open Biomarker-guided intervention to prevent acute kidney injury after major surgery (BigpAK-2 trial): study protocol for an international, prospective, randomised controlled multicentre trial

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ABSTRACT

Introduction Previous studies demonstrated that the implementation of the Kidney Disease Improving Global Outcomes (KDIGO) guideline-based bundle, consisting of different supportive measures in patients at high risk for acute kidney injury (AKI), might reduce rate and severity of AKI after surgery. However, the effects of the care bundle in broader population of patients undergoing surgery require confirmation.

Methods and analysis The BigpAK-2 trial is an international, randomised, controlled, multicentre trial. The trial aims to enrol 1302 patients undergoing major surgery who are subsequently admitted to the intensive care or high dependency unit and are at high-risk for postoperative AKI as identified by urinary biomarkers (tissue inhibitor of metalloproteinases 2*insulin like growth factor binding protein 7 (TIMP-2)*IGFBP7). Eligible patients will be randomised to receive either standard of care (control) or a KDIGO-based AKI care bundle (intervention). The primary endpoint is the incidence of moderate or severe AKI (stage 2 or 3) within 72 hours after surgery, according to the KDIGO 2012 criteria. Secondary endpoints include adherence to the KDIGO care bundle, occurrence and severity of any stage of AKI, change in biomarker values during 12 hours after initial measurement of (TIMP-2)*IGFBP7, number of free days of mechanical ventilation and vasopressors, need for renal replacement therapy (RRT), duration of RRT, renal recovery, 30-day and 60-day mortality, intensive care unit length-of-stay and hospital length-of-stay and major adverse kidney events. An add-on study will investigate blood and urine samples from recruited patients for immunological functions and kidney damage.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This trial is an international, prospective, multicentre, randomised study design in a large cohort of surgical patients.
- ⇒ Patients undergoing major surgery will be included to allow for an analysis of the effectiveness of a Kidney Disease Improving Global Outcomes care bundle to prevent acute kidney injury (AKI).
- ⇒ The trial will employ a personalised medicine approach by using AKI biomarkers (tissue inhibitor of metalloproteinases 2*insulin like growth factor binding protein 7 (TIMP-2)*IGFBP7) that identify patients at high risk for AKI after major surgery.
- ⇒ The trial will employ a biomarker ((TIMP-2)*IGFBP7) that detects kidney stress, hence providing opportunity to initiate preventive strategies before deterioration of renal function occurs.
- ⇒ The trial is limited by its intervention, which does not allow blinding of study personnel or patients. However, outcome assessors of the primary outcome are blinded to treatment group allocation.

Ethics and dissemination The BigpAK-2 trial was approved by the Ethics Committee of the Medical Faculty of the University of Münster and subsequently by the corresponding Ethics Committee of the participating sites. A study amendment was approved subsequently. In the UK, the trial was adopted as an NIHR portfolio study. Results will be disseminated widely and published in peer-

reviewed journals, presented at conferences and will guide patient care and further research.

Trial registration number NCT04647396.

INTRODUCTION

Acute kidney injury (AKI) is a common complication after major surgery. More than 2 million surgeries are performed each year and the incidence of AKI is between 12% and 45% depending on the comorbidities of the patients and the type of surgery resulting in a major impact on the healthcare system.^{1–5} AKI after surgery is an independent risk factor for adverse outcomes, such as prolonged stay in the intensive care unit (ICU), chronic kidney disease (CKD) and need for renal replacement therapy (RRT).⁶ As no specific treatment for AKI exists, prevention is therefore of utmost importance.

Using the currently available criteria of the Kidney Disease Improving Global Outcomes (KDIGO) criteria for AKI, interventions for AKI can only be started after a change in kidney function has already occurred, as both oliguria, as well as a rise of serum creatinine (SCr) indicate impaired kidney function. The KDIGO guidelines for AKI recommend to initiate different supportive measures (volume management, maintenance of adequate blood pressure and judicious avoidance of nephrotoxins, contrast agents and hyperglycaemia) in patients at high risk for AKI. However, the minority of patients at high risk is treated according to these guidelines.⁷ High risk patients can be identified by measuring renal biomarkers such as the two cell cycle arrest markers tissue inhibitor of metalloproteinases 2 (TIMP-2) and insulin like growth factor binding protein 7 (IGFBP7). A biomarker-guided implementation of the KDIGO bundle has been shown to be effective in reducing AKI in cardiac surgical patients.^{8–10} This could also be demonstrated in the previous single-centre BigpAK-1 trial of general surgical patients where this strategy significantly reduced the severity of AKI (27.1% in the intervention, 48.0% in the control group (p=0.03)) in patients with a positive biomarker result between 0.3 and 2.0 (ng/mL)²/1000.¹¹ However, this trial was limited by its small and single-centre design. The BigpAK-2 trial was designed to definitively answer the question whether a biomarker-guided implementation of the KDIGO bundle reduces the occurrence of AKI after major surgical procedures. If successful, this would strengthen the evidence for such a precision medicine approach to be implemented in clinical routine. A precision medicine approach to the care of patients at risk for AKI is a major opportunity to improve outcomes. To this effect, biomarkers play a critical role in clinical decision-making and may support streamlining treatment strategies. Given the heterogeneity of the AKI syndrome, such pragmatic improvements in the identification and management of patients at high risk for AKI appear more promising than the search for a single therapy for nephroprotection alone.

Objectives and aims

Aim 1

To investigate whether a biomarker-guided implementation of an AKI care bundle reduces the occurrence and/or severity of moderate or severe AKI (KDIGO stage 2 or 3) in high-risk patients within 72 hours after major surgery.

Aim 2

To understand whether the different strategies of prevention in patients undergoing surgery affect the mechanisms of illness and renal recovery.

METHODS AND ANALYSIS

Design and setting

The BigpAK-2 trial is an international, multicentre, randomised clinical trial, to be conducted in more than 30 centres across Europe (online supplemental table 1). The definitive list of the participating centres will be provided with the final report of the trial.

The protocol follows the principles of CONSORT and the conduct of the study follows the Declaration of Helsinki (version Fortaleza 2013).^{12 13} Figure 1 illustrates the study workflow, and figure 2 summarises study visits and assessments at each study visit.

Patient and public involvement

Patients and public were not involved in the research design of the study, but patient feedback was sought in individual countries. The study results will be published open access. If desired, patients or their representatives will be informed about the trial results distributed via the local investigators.

Participants

Adult patients (age≥18 years) with planned major surgery for at least 2 hours and planned admission to an ICU, postanaesthesia recovery unit or a high dependency unit postoperatively will be screened for eligibility. Patients will be randomised postoperatively, if they meet all inclusion criteria: (1) postmajor surgery and admitted to the ICU or high dependency unit, (2) age≥18 years, (3) kidney injury biomarker (TIMP-2)*(IGFBP7) ≥ 0.3 (ng/mL)²/1000 4–18 hours after surgery, (4) indwelling urinary catheter and jugular central venous line, (5) written informed consent and (6) presence of at least one additional risk factor for AKI. Risk factors include age≥75 years; signs of critical illness such as ongoing requirement of vasopressor support and/or mechanical ventilation postoperatively; pre-existing advanced CKD (estimated glomerular filtration rate (eGFR)<60 mL/min/1.73 m²); and/or intraoperative use of radio contrast agents. Patients are excluded if any of the following criteria is present: pregnancy or breastfeeding, pre-existing high stages of CKD (ie, ≥stage 4, ie, eGFR<30 mL/min/1.73 m²), kidney transplant within the last 12 months, known (glomerulo-)nephritis, interstitial nephritis or vasculitis, anuria at inclusion

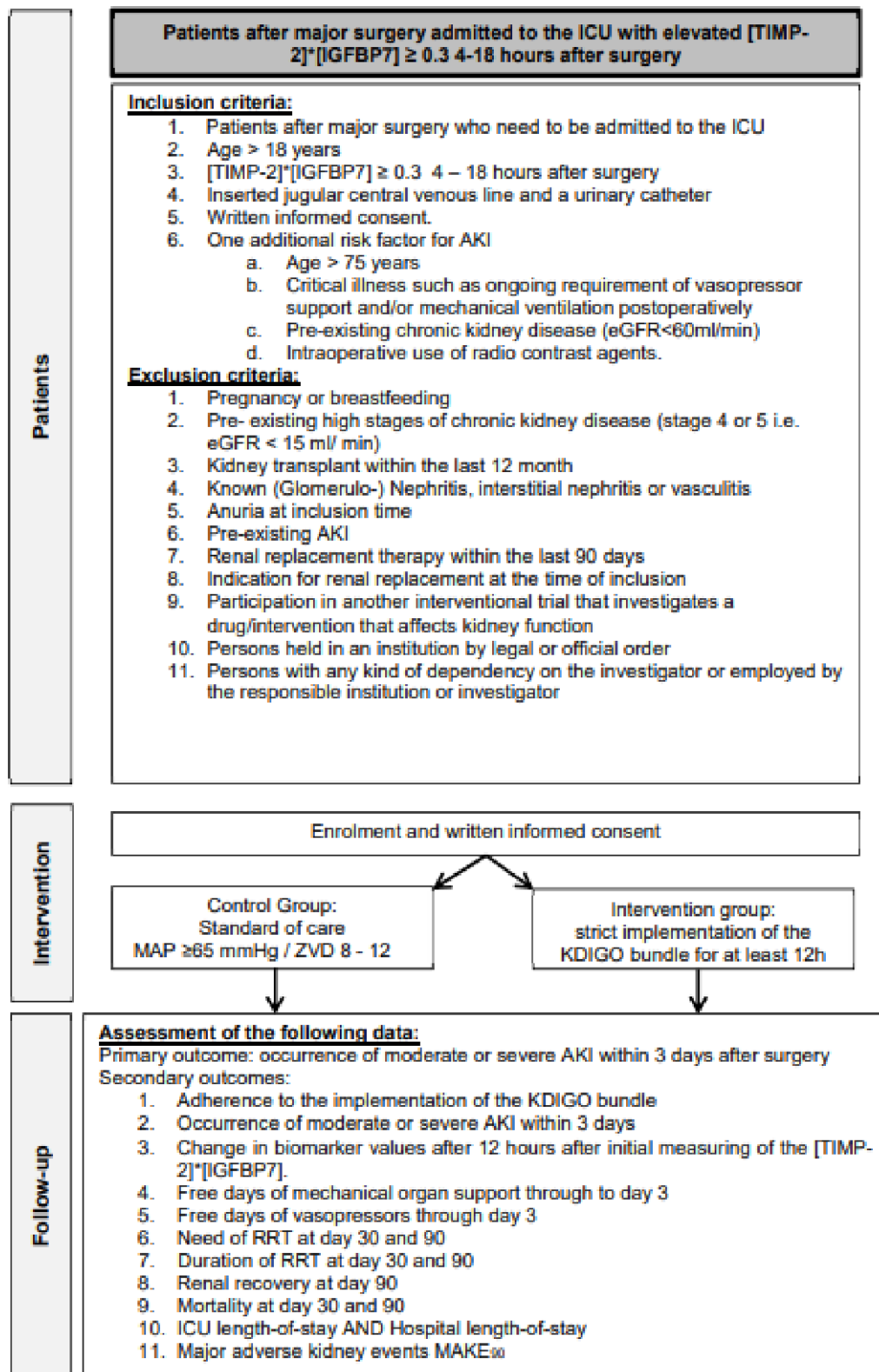


Figure 1 Trial workflow. AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; BUN, blood urea nitrogen; CVP, central venous pressure; ECMO, extracorporeal membrane-oxygenation; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IGFBP7, insulin like growth factor binding protein 7; KDIGO, Kidney Disease Improving Global Outcomes; MAKE, major adverse kidney events; NYHA, New York Heart Association; POD, post-operative day; RRT, renal replacement therapy; SOFA, sepsis-related organ failure assessment; TIMP-2, tissue inhibitor of metalloproteinases 2.

Visit	T1			T2	T3-T5	T6	T7	T8
	S ¹	R ²	B ³	OD	POD 1-3	Dis-charge /POD 7	POD 30	POD 90
Inclusion and Exclusion criteria	X							
Medical history (preexisting condition, premedication)	X							
Randomization		X						
Demographic data (Age, sex, BMI, comorbidities (hypertension, congestive heart failure, NYHA, peripheral vascular disease, diabetes, previous stroke or transient ischemic attack, chronic liver disease, chronic kidney disease, chronic obstructive pulmonary disease, cancer), medication (b-blockers, ACEI/ARBs, diuretics, anticoagulation))			X					
Admission diagnosis, Category of admission (elective, emergency)			X					
Surgical parameters (nature of surgical procedure, duration of surgical procedure, fluid input and output, intraoperative transfusion)				X				
APACHE II				X				
SOFA Score				X	X	X		
Blood and urine samples			X	X				
Hemodynamics (MAP, HR, CVP, CI (CVP, CI only on OD))				X	X			
Fluid input and output (balance)								
Laboratory parameters (sodium, potassium, lactate, bilirubin, glucose, hemoglobin, platelets)			X	X	X			
Renal parameters (BUN, creatinine, GFR, urine output, fluid balance)			X	X	X	X ⁴	X ⁴	X ⁴
Adherence to the KDIGO bundle			X	X	X			
Vasopressor use (begin and end vasopressors)				X	X	X	X	X
AKI (yes/no, severity, diagnosis by, transient/persistent, RRT dependency, type of RRT, RRT days)			X	X	X	X	X	X
Concomitant Medication (Pressors, N-acetylcysteine, amphotericin, aminoglycosides, cyclosporine, vancomycin, tacrolimus, radiocontrast agents, diuretics)			X	X	X			
Add-on study ⁵		X		X	X			
Mortality						X	X	X
Duration of mechanical organ support (Begin and end of RRT, ECMO, and mechanical ventilation)						X	X	X
Length of stay (ICU, Hospital)						X	X	X
Renal Recovery								X
Need of RRT						X	X	X
MAKE								X

¹ Screening

² Randomization

³ Baseline

⁴ Only creatinine

⁵ Blood and urine samples will be collected at time point of study inclusion and 12 hours later

Figure 2 Overview of study visits. AKI, acute kidney injury; ARB, angiotensin receptor blockers; BMI, body mass index; ICU, intensive care unit; GFR, glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes; MAKE, major adverse kidney events; MAP, map arterial pressure; RRT, renal replacement therapy.

time, pre-existing AKI, RRT within the last 90 days prior to inclusion, indication for RRT at the time of inclusion, participation in another interventional trial within the last

3 months, patients with any kind of relationship with the investigator/employed by the sponsor/investigator and patients held in an institution by legal or official order.

The initial study protocol only allowed inclusion of non-cardiac surgery patients and mandated measurement of the urinary biomarkers only up to 4 hours postoperatively. Subsequently, a study amendment was approved which allowed inclusion of cardiac surgery patients and extension of the timeframe for biomarker measurement from up to 18 hours after surgery.

Consent process

All patients will be approached and informed by a member of the research team about the trial, its aims, and expected advantages as well as possible risks before surgery (usually during the anaesthesia pre-evaluation visit) and will be invited to provide written informed consent. The informed consent form will be signed by both patient and treating investigator. The original document is kept in the medical notes, and a copy will be given to the patient.

Intervention period

All participants will receive standard preoperative and intraoperative care. Postoperatively, participants will either receive standard of care or standard of care plus the AKI care bundle according to randomisation. The control groups will receive standard of care as per local protocols. Patients in the intervention group will be managed according to the KDIGO care bundle, consisting of haemodynamic optimisation guided by functional haemodynamic monitoring, discontinuation of ACE inhibitors (ACEi) or angiotensin receptor blockers (ARBs), tight glycaemic control and avoidance of nephrotoxic drugs or radiocontrast agents, if possible. Haemodynamic optimisation will be performed for at least 12 hours after randomisation and includes three aspects: first, a passive-leg raising manoeuvre is performed to assess fluid responsiveness, and if positive (ie, rise in cardiac output of more than 10%), 500–1000 mL of balanced crystalloid fluid will be administered. Second, blood pressure will be measured and a mean arterial pressure of 65 mm Hg or higher will be targeted. If hypotension occurs, norepinephrine will be administered. Finally, cardiac output will be assessed and a cardiac index of 2.5 mL/min/m² will be targeted. If a patient presents with cardiac index less than 2.5 mL/min/m², dobutamine or epinephrine will be administered at the discretion of the treating clinicians. This haemodynamic algorithm will be performed at least five times (every 3 hours) during the 12 hour intervention period. The type of functional haemodynamic monitoring will not be mandated, but chosen according to the standards and availabilities at each centre. All available methods, such as transpulmonary thermodilution, cardiac ultrasound or non-invasive cardiac output monitors, may be used. Blood sugar levels will be kept between 100 and 150 mg/dL and nephrotoxic drugs, hydroxyethyl starch (HES), gelatin, chloride-rich solutions or radiocontrast will be avoided for at least 72 hours after surgery. Finally, ACEi and ARBs will be withheld for at least 48 hours postoperatively. SCr and urinary output (UO) will

be regularly assessed. Patients will be closely monitored for the first 72 hours after surgery and during ICU stay. Baseline demographics and data regarding routine clinical management, comorbidities, type of surgical procedure, complications and administered medication will be collected. Furthermore, AKI stages will be documented according to KDIGO criteria, based on SCr and UO. After removal of the indwelling urinary catheter, the urine criterion will no longer be used to diagnose and stage AKI. At 30 and 90 days, a follow-up will be performed by contacting the patient and/or the general practitioner.

Outcomes

The primary outcome of the trial is the development of moderate or severe AKI (stage 2 or stage 3) within the first 72 hours after surgery, according to the KDIGO criteria.

Secondary outcomes include the following:

- ▶ Adherence to the KDIGO bundle
- ▶ Occurrence and severity of any stage of AKI within 3 days after major surgery
- ▶ Change in biomarker values during 12 hours following initial measurement of (TIMP-2)*(IGFBP7).
- ▶ Number of free-days of mechanical organ support through day 3.
- ▶ Number of free-days of vasopressors through day 3
- ▶ Need for RRT at day 30 and 90
- ▶ Duration of RRT at day 30 and 90.
- ▶ Renal recovery at day 90
- ▶ 30-day and 90-day mortality
- ▶ ICU length-of-stay and hospital length-of-stay
- ▶ (Major adverse kidney events, MAKE₉₀ (defined as the composite of death, use of RRT and persistent renal dysfunction (defined as SCr₉₀ ≥ 2× to baseline value at hospital discharge)) at day 90.
- ▶ dd-on study: blood and urine samples will be collected and immunological functions and kidney damage will be investigated.

Data collection and randomisation process

Clinical data will be collected from the electronic health-care record of each participating site and entered on an electronic CRF (RedCAP, Research Electronic Data Capture, Version 10.6.22, respectively up-to-date version, Vanderbilt University) in a pseudoanonymised form. Patient identifiable information will not be included in the data-analysis. Investigators will be provided secure login credentials. Data transmission and storage of web-based information is encrypted and will be stored and backed up at the Westphalian Wilhelms University of Münster in Germany.

Treatment assignment will be accomplished using REDCap and randomisation will be performed centrally in a 1:1 random proportion. Participants will enter the observation period immediately after randomisation.

Data quality

Each study team will be trained in the study protocol and data entry prior to recruitment start at each site. This will

be facilitated during the study initiation meeting with each participating site. The AKI KDIGO criteria are also displayed in the eCRF to help the research team classifying AKI stages correctly.

Each site will be provided an emergency contact number and mail address to ask for help in case of medical, technical or protocol issues. The study organising team will offer rapid support throughout the entire study period. Furthermore, protocol and study materials are translated into common languages to facilitate processes and to avoid uncertainties. Regular contact will be made with national coordinators as well as each single study site with the aim to resolve potential uncertainties quickly. Regular monitoring visits will be conducted by the study sponsor with each study site. Monitoring visits will be performed after the first five recruited patients, after 10 recruited patients, after 20 recruited patients and at termination of recruitment with each study site. A Data Safety and Monitoring Board (DSMB) will meet regularly after enrolment of 400 patients and review data quality and rate and type of adverse events in both randomisation groups. The DSMB will thereby contribute to the scientific and ethical integrity of the study and patient safety. The members of the DSMB are independent of the study team and without any relevant conflicts of interest.

Sample size

Sample size and power calculations are based on a group sequential adaptive plan with one interim analysis (overall significance level 5%, power 80%, see below) and the primary endpoint occurrence of moderate or severe AKI (KDIGO stage 2 or 3) within 72 hours days after surgery. The expected AKI rate (\geq stage 2), substantiated by published data of the BigpAK trial, in the control group and the intervention group is 20% and 14%, respectively.¹¹ The interim analysis will be performed when 309 evaluable patients have been recruited in each treatment group ($2 \times 309 = 618$ patients in total). Using the results of the interim analysis, the sample size of the final analysis will be recalculated. If no sample size adjustment is found to be necessary, the final analysis will be performed when an additional 309 evaluable patients have been recruited in each treatment group after the interim analysis ($2 \times 309 + 2 \times 309 = 1236$ evaluable patients in total). We expect that up to 5% of participants will be lost to follow-up and in the worst case will have completely non-evaluable data. Therefore, a total number of 1302 patients will be recruited in order to have complete data of 1236 evaluable patients. Calculations were performed using the ADDPLAN software.

Statistical analysis

The following descriptive and inferential statistical methods will be applied. Normally distributed variables will be reported as mean and SD and will be compared between the randomised groups using Student's t test. For non-normally distributed variables, medians and lower and upper quartiles will be reported and the

non-parametric Mann-Whitney U test will be applied. Categorical variables will be reported as absolute frequencies and percentages and the χ^2 or Fisher's exact test will be applied. Point estimates of parameters of interest will generally be supplemented by 95% CIs.

Randomisation will be checked by comparing demographic and clinical baseline variables between the randomised groups.

In the primary statistical analysis, the primary endpoint occurrence of moderate or severe AKI (stage 2 or 3) within 72 hours after surgery will be evaluated. A group sequential adaptive plan with one interim analysis will be applied. The interim analysis will be performed using the inverse normal method based on a group sequential plan with O'Brien and Fleming type alpha spending function without futility stop. The primary statistical analysis will include all randomised patients (full analysis set) and will be performed according to the intention-to-treat (ITT) principle in order to prevent attrition bias. The randomised groups will be compared with a two-sided inverse normal Cochrane Mantel Haenszel test with stratification by centre (overall significance level 5%, power 80%). The interim analysis is planned to be conducted when half of the total number of patients have been recruited (information rate 0.5). The primary statistical analysis provides confirmatory statistical evidence.

Secondary outcomes will be evaluated in the full analysis set according to ITT. Secondary statistical analyses are intended to be exploratory (hypothesis generating) and will be interpreted accordingly. A two-sided p-value of ≤ 0.05 will be considered as noticeable ('significant') without adjustment for multiplicity. The results of the interim analysis will be compared with the final results in order to determine whether changes in practice may already have occurred during the study period.

Blinding

Neither the patient, nor the study personnel can be blinded to the treatment assignment. The individuals involved in adjudication of endpoints or complications will be blinded to treatment assignment.

Biomarker samples

The urinary biomarker (TIMP-2)*(IGFBP7) will be measured using the Nephrocheck test (bioMerieux, France), according to the manufacturer's protocol.

Treatment plan

Urinary (TIMP-2)*(IGFBP7) levels will be measured 4–18 hours after surgery to identify patients at high risk for AKI. Patients with a biomarker value ≥ 0.3 (ng/mL)²/1000 will be randomised if the inclusion criteria are met and no exclusion criterion exists.

Control group: standard of care as per centre.

Intervention group: the KDIGO AKI care bundle will be implemented.

The KDIGO AKI care bundle includes the following measures:

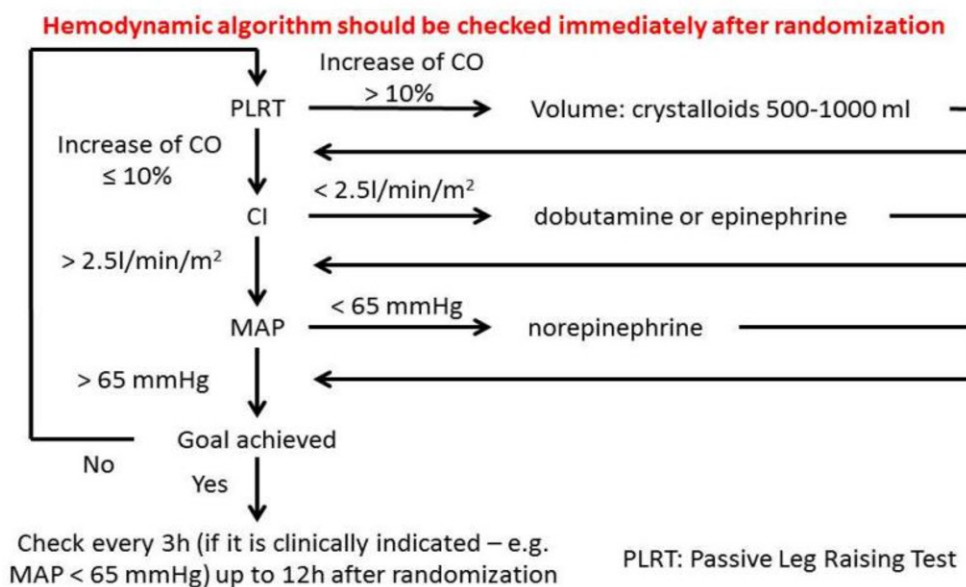


Figure 3 Haemodynamic algorithm of the intervention group which will be performed at least every 3 hours during the 12 hours following randomisation. CI, cardiac index; CO, cardiac output; MAP, mean arterial pressure.

- ▶ Discontinuation of all nephrotoxic agents, if possible.
- ▶ Haemodynamic monitoring and optimisation according to a predefined haemodynamic algorithm (figure 3).
- ▶ Close monitoring of SCr (twice a day), fluid balance (twice a day) and UO (every hour as long as the patient has a Foley catheter; if the patient does not have a Foley catheter, urine is collected for a certain time period and divided by the number of hours to calculate hourly urine volume).
- ▶ Avoidance of hyperglycaemia (defined as glucose levels >150 mg/dL for more than 3 hours) for the first 72 hours after surgery.
- ▶ Consideration of alternatives to radio contrast agents.
- ▶ Discontinuation of ACEi and ARBs for the first 48 hours after surgery.
- ▶ Avoidance of HES, gelatin and solutions with a chloride concentration >140 mEq/L.

At baseline and 12 hours after randomisation, blood and urine samples will be collected. All other therapies will be directed by the patient's clinical team. All medications will be dose adjusted according to renal function in accordance with standard dosing guidelines.

ETHICS AND DISSEMINATION

The BigpAK-2 Trial has been approved by the leading Ethics Committee of the University of Münster, including a non-substantial study amendment (2020-601 f-S), and by the corresponding Ethics Committee at each participating site (see Supplementary document for a list of ethics commissions that approved the study). The results will be presented at national, as well as international conferences. The final manuscript will be published in a peer-reviewed journal and results will be used to guide further research. To prevent publication bias in the future

meta-analyses, results will be published irrespective of the outcome of the trial.

Trial status

Recruitment started in November 2020. We estimate to complete the study by December 2024.

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