TRIAL PROTOCOL
AND STATISTICAL ANALYSIS PLAN
BIOMARKER GUIDED IMPLEMENTATION OF THE KDIGO GUIDELINES TO REDUCE THE OCCURRENCE OF AKI IN PATIENTS AFTER CARDIAC SURGERY
ACRONYM
PREVAKI - MULTICENTER

Funded by the European Society of Intensive Care Medicine (ESICM)

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on to third parties without the express agreement of the responsible institution or the Principal Coordinating Investigator (PCI).

Signatures

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II. Synopsis

Study-ID	07-AnIt-16
Title of the trial	Biomarker-guided implementation of the KDIGO guidelines to reduce the occurrence of AKI after cardiac surgery– Prevention of AKI
Acronym	PrevAKI – multicenter
Responsible institution	Department of Anesthesiology, Intensive Care and Pain Medicine Albert-Schweitzer-Campus 1, A1 48149 Muenster
Medical condition	Elective cardiac surgery with extracorporeal circulation
Trial type	Multicenter, prospective, randomized controlled, parallel group, clinical trial
Objective(s)	Acute kidney injury (AKI) is a well-recognized complication after cardiac surgery with cardiopulmonary bypass (CPB) with an important impact on short- and long-term morbidity and mortality. CPB is employed in most cardiac surgical procedures. Despite numerous clinical trials testing different pharmacological treatments, a mean to prevent cardiac surgery-associated AKI (CSA-AKI) remains elusive. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) workgroup published the KDIGO guidelines which recommend the implementation of a bundle of supportive measures to prevent AKI in patients with increased risk (discontinue all nephrotoxic agents when possible, discontinue angiotensin converting enzyme inhibitors(ACEi) and angiotensin receptor blockers (ARB) in the perioperative period to avoid severe hypotension, optimizing volume status and hemodynamic parameters, consider functional hemodynamic monitoring, close monitoring of serum creatinine and urine output, avoid hyperglycemia, consider alternatives to radiocontrast procedures). However, it is not clear whether this approach can prevent the occurrence of AKI in patients undergoing cardiac surgery. Moreover, it is not known how exactly to determinehigh risk. We hypothesize that the implementation of the KDIGO guidelines in high-risk cardiac surgery patients as identified by AKI biomarkers reduces the development of AKI.

Intervention	Patients at high risk of AKI will be identified by measuring NC [TIMP-2]*[IGFBP7] (NephroCheck® Test) 4h after CPB. Patients with NC ≥ 0.3 will be randomized. Validation group: Implementation of the KDIGO guidelines: Optimizing volume status and hemodynamic parameters (according to a hemodynamic algorithm, see **Figure 1.Hemodynamic** algorithm (validation arm), page 23), functional hemodynamic monitoring, discontinuation of all nephrotoxic agents when possible, discontinuation of angiotensin converting enzyme inhibitors(ACEi) and angiotensin receptor blockers (ARB) in the perioperative period to avoid severe hypotension, consideration of alternatives to radiocontrast agents, close monitoring of serum creatinine and urinary output, avoidance of hyperglycemia. Control group: The patients will receive standard of care. In these patients, cardiac output will be measured (e.g. by echocardiography, at initiation and then every 3h up to 12h) but the treating physician will not be informed about the values.
Key inclusion and exclusion criteria	Inclusion criteria: 1. Adult patients undergoing cardiac surgery with CPB 2. [TIMP-2]*[IGFBP7] ≥ 0.3 4h after CPB 3. Age between 18-90 years 4. Written informed consent Exclusion criteria: 1. Preexisting AKI 2. Patients with cardiac assist devices (ECMO, LVAD, RVAD, IABP) 3. Pregnancy 4. Known (Glomerulo-) Nephritis, interstitial nephritis or vasculitis 5. CKD with eGFR< 30 ml/min 6. Dialysis dependent CKD 7. Prior kidney transplant within the last 12 months 8. Participation in another intervention trial in the past 3 months 9. Persons with any kind of dependency on the investigator or employed by the institution responsible or investigator 10. Persons held in an institution by legal or official order
Primary trial objective	To investigate the adherence to the trial protocol in a multi-center

	multinational setting as a pilot project for a large randomized controlled trial (feasibility trial). Primary outcome: KDIGO recommendations fulfilled at all time
Study endpoints	Primary endpoint: • Compliance rate (proportion of patients who are treated according to the trial protocol): KDIGO recommendations fulfilled at all time Secondary endpoints: • Occurrence of AKI according to the KDIGO guidelines within 72 hours after cardiac surgery • Moderate and severe AKI (according to the KDIGO guidelines) • Severity of AKI (according to the KDIGO guidelines) • Renal recovery at days 30, 60 and 90 (renal recovery is defined as serum creatinine levels < 0.5 mg/dl higher than baseline serum creatinine) • 30-day, 60-day and 90-day mortality • Length of ICU stay • Length of hospital stay • Need and duration of renal replacement therapy • RRT at days 30, 60, 90 • $MAKE_{30}$, $MAKE_{60}$ and $MAKE_{90}$ (major adverse kidney events consisting of mortality, dialysis dependency, persistent renal dysfunction (defined as serum creatinine ≥ 2x compared to baseline value) • Determination of different biomarkers • Assessment of safety: complications in particular those related to the implementation of the KDIGO guidelines will be documented. No side effects have been reported.
Number of subjects	To be assessed for eligibility: n=1000 To be allocated to the trial: n=310 To be analyzed: n=280 (140/ treatment arm)
Time plan	First patient first visit (FPFV): 01/06/2017 Last patients first visit (LPFV): 31/05/2018 Last patient last visit (LPLV): 01/08/2018 Final study report: 01/11/2018

Statistics	**Power analysis** The required sample size is n=280 patients in total. This sample size is determined as follows: Patients will be randomized in a 1:1 ratio to one of the two treatment arms (intervention versus control). Randomization serves to estimate the incidence of AKI as secondary outcome to generate pre-information in terms of a pilot study for an upcoming confirmatory trial. The primary endpoint of the PrevAKI-multicenter trial is the compliance rate (Primary outcome: KDIGO recommendations fulfilled at all time), i.e. the proportion of patients who are treated according to the trial protocol. In order to estimate the compliance rate, the two treatment groups will be pooled together. In the primary analysis the compliance rate across all study patients will be estimated along with a two-sided 95% confidence interval (CI). As the compliance rate cannot be quantified in advance, we pursue a worst case approach and assume a compliance rate of 50%. In this case the CI has maximal width. Based on this assumption, with a sample size of n=280 patients the calculated 95% CI according to Clopper-Pearson (Fleiss 2003) ranges from 44% to 56%. Therefore, in case of any observed compliance rate apart from the worst-case scenario, the 95% CI is never wider than 56%-44%=12%. This corresponds to an estimation of the compliance rate with a precision of plus/minus 6%.
Trial Registration	The trial will be registered in a public register in accordance with the recommendations of the ICMJE.

III. Abbreviations

Abbreviation	Meaning
ACEi	Angiotensin converting enzyme inhibitor
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ALI	Acute lung injury
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARB	Angiotensin receptor blocker
ARDS	Acute respiratory distress syndrome
BMI	Body MassIndex
BUN	Blood urea nitrogen
CK	Creatine kinase
CKD	Chronic kidney disease
CK-MB	Muscle-Brain type CK
CPB	Cardiopulmonary bypass
CRF	Case report form
CRP	C-reactive protein
CSA-AKI	Cardiac surgery-associated acute kidney injury
CVP	Central venous pressure
ECMO	Extracorporeal membrane oxygenation
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
Hb	Hemoglobin
Hk	Hematocrit
IABP	Intra-aortic balloon pump
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IGFBP7	Insulin-like growth factor-binding protein 7
KDIGO	Kidney Disease: Improving Global Outcomes
LVAD	Left ventricular assist device
MAKE	Major adverse kidney event
MAP	Mean arterial pressure
PCI	Principal coordinating investigator
PTT	Partial thomboplastin time

RIFLE	Risk, Injury, Failure, Loss classification
RRT	Renal replacement therapy
RVAD	Right ventricular assist device
SAPS II	Simplified Acute Physiology Score
SOFA Score	Sequential Organ Failure Assessment Score
TIMP-2	Tissue inhibitor of metalloproteinases-2

1 Objective and specific aims

Acute kidney injury (AKI) is a well-recognized complication after cardiac surgery with an important impact on short- and long-term morbidity and mortality. Cardiopulmonary bypass (CPB) is employed in most cardiac surgical procedures. Despite numerous clinical trials testingdifferentpharmacologicaltreatments, a mean to prevent cardiac-surgery associated AKI (CSA-AKI) remains elusive. In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) workgroup published the KDIGO guidelines which recommend to implement a bundle of supportive measures in patients at high risk for AKI to prevent the development of AKI (discontinuationofall nephrotoxic agents when possible, optimization of volume status and hemodynamic parameters,discontinuation of angiotensin converting enzyme inhibitors(ACEi) and angiotensin receptor blockers (ARB) in the perioperative period to avoid severe hypotension,consideration of functional hemodynamic monitoring, close monitoring of serum creatinine and urine output, avoidance of hyperglycemia, consideration of alternatives to radiocontrast procedures). However, there is no evidence thatthis bundle of supportive measures actually prevents AKI.

Primary efficacy endpoint: The primary endpoint is the compliance rate (proportion of patients treated according to the trial protocol):KDIGO recommendations fulfilled at all time

Secondary endpoint(s): Occurrence of AKI within the first 72 hours after cardiac surgery (AKI is defined according to the KDIGO guidelines(1)); moderate and severe AKI (according to the KDIGO classification); severity of AKI; renal recovery at days 30, 60 and 90 (renal recovery is defined as serum creatinine levels < 0.5 mg/dl higher than baseline serum creatinine); 30-day, 60-day and 90-day mortality; length of ICU stay; length of hospital stay;need and duration of RRT; RRT at days 30, 60 and 90; $MAKE_{30}$, $MAKE_{60}$ and $MAKE_{90}$ (major adverse kidney events consisting of mortality, dialysis dependency persistent renal dysfunction (defined as serum creatinine ≥ 2x compared to baseline value).

Assessment of safety: No side effects are expected by implementing the KDIGO guidelines.

2 Background and significance

2.1 Background

AKI is defined as an acute loss of renal function developing over a period of hours to days and represents a common complication in patients undergoing cardiac surgery(2). Depending on how it is defined, AKI occurs in up to 45% of patients after cardiac surgery, and approximately 1 to 2% require renal replacement therapy (RRT) (3-5). It may occur in patients with preoperative normal kidney function as well as in patients with chronic kidney disease (CKD)(6). Several clinical conditions e.g. sepsis, hypovolemia, extended surgical procedures (cardiac surgery with CPB) and the use of nephrotoxic agents can result in the development of AKI. Complications associated with AKI, such as electrolyte imbalances, fluid overload and uremia can lead to life-threatening conditions and worsen patients' outcome.

CPB is employed in most cardiac surgical procedures, and although the mechanisms are not fully understood, ensuing ischemic and inflammatory injuries to renal tubular epithelial cells have been implicated in the cause of AKI(7). Despite numerous clinical trials of pharmacologicaltreatments, a mean to prevent CSA-AKI has remained elusive.

2.2 Evidence

Independent of the underlying disease, AKI is associated with an increased morbidity and mortality, especially in patients undergoing cardiac surgery with CPB (8, 9). Numerous studies demonstrate that 1/3 of patients undergoing cardiac surgery suffer from AKI in the postoperative period(7). Although most of the patients develop only a mild AKI, mortality rates are 5 times higher compared to patients without the development of AKI in the postoperative period(10). Minimal elevations of serum creatinine of 0.3 mg/dl are associated with higher mortality rates. Furthermore, patients surviving severe AKI are at high risk for the development of CKD and end-stage renal disease (ESRD) leading to worse long term outcome and a tremendous economic burden for the health care system. These facts give treatment strategies for the prevention of AKI a high priority(11).

In 2012, the KDIGO group worked out some strategies for the prevention of AKI(12). These include the discontinuation of all nephrotoxic agents when possible, consideration of alternatives to radiocontrast agents, optimization of volume status and hemodynamic parameters,discontinuation of angiotensin converting enzyme inhibitors(ACEi) and angiotensin

receptor blockers (ARB) in the perioperative period to avoid severe hypotension, the consideration of a functional hemodynamic monitoring, close monitoring of serum creatinine and urinary output and the avoidance of hyperglycemia. Whether this bundle of supportive measures is effective to prevent AKI needs to be proven.

In theperioperativeperiod several classes of nephrotoxins are used, including antibiotics (e.g. vancomycin(13) and aminoglycosides(14)) and intravenous contrast agents(15). A number of studies have shown that these nephrotoxic agents may lead to a deterioration of renal function and consequently to AKI (13-16).

ACEi and ARBs are used to treat hypertension. A lot of patients undergoing cardiac surgery are on ACEi or ARBs which may cause severe and prolonged hypotension during anesthesia. These hypotensive episodes may lead to a reduced renal perfusion. Walsh et al. performed a cohort study on 33.330 patients undergoing non-cardiac surgery and demonstrated that intraoperative hypotensive episodes of less than 5 minutes with a MAP < 55 mmHg were associated with a significantly increased AKI rate (17). These datasupport the recommendation to discontinue ACEi and ARBs in the perioperative period and to consider functional hemodynamic monitoring to prevent the development of AKI.

Close monitoring of the classic biomarkers serumcreatinine and urinary output are important to detect functional damage early. The recommendation to avoid hyperglycemia stems from the landmark study by Van den Berghe et al. who showed a significant reduction of AKI in patients receiving strict glucose control(18). However, there are several trials showing that strict glucose control might not only be associated with higher AKI incidence but also with higher mortality rates(19, 20).

The severity of AKI is determined byvarious classification systems (RIFLE, AKIN, KDIGO) based on the degree of reduction of urinary output and/or increase of serum creatinine compared to baseline(1, 21). Both „classic biomarkers“ are not appropriate for the detection of kidney damage without a loss of function, because both are functional markers. Urinary output is influenced by the use of diuretics and fluid status (e.g. hypervolemia) and has a low specificity. Serum-creatinine elevations are not detectable until 50% of the glomerular filtration rate (GFR) is lost, showing that this parameter has a low sensitivity. However, the injury occurs at a much earlier timepoint. New biomarkers such as [TIMP-2]*[IGFBP7] are injury markers which indicate tubular injury before loss of kidney functionoccurs(22). We performed an observational trial demonstrating that urinary [TIMP-2]*[IGFBP7] levels 4h after cardiac surgery showed a good performance to predict AKIwithin the next 72h (NC 0.3: sensitivity 0.80, specificity 0.83, PPV

0.80, NPV 0.83)(23). In those patients with AKI, biomarker elevations were apparent two days before the increase of serum-creatinine.

Recently, we performed a single-center trial investigating the effect of the implementation of the KDIGO bundles to obtain preliminary data. We found a significant decrease in the occurrence of AKI within 72 hours in high risk patients (defined as TIMP-2*IGFBP7≥0.3) undergoing cardiac surgery (55.1% in the intervention versus 71.7% in the control group, p=0.004).

In this feasibility trial we will analyze the compliance rate to the trial protocol in a multicenter, multinational cohort in preparation for a large randomized controlled trial.

2.3 Rationale

CPB is frequently used in cardiac surgery and canlead to ischemic, inflammatory and oxidative damage of renal tubular epithelial cells. However, the exact mechanism of renal tubular epithelial cell damage is still unknown. Although numerous studies have investigated different pharmacological interventions to prevent AKI, effective strategies are missing. The KDIGO guidelines for AKI recommend various non-interventional strategies for the prevention of AKI:

- Discontinuation of all nephrotoxic agents when possible
- Optimization of volume status and hemodynamic parameters including perfusion pressure
- Consideration of functional hemodynamic monitoring
- Close monitoring of serum creatinine and urine output
- Avoidance of hyperglycemia
- Consideration of alternatives to radio contrast agents
- Discontinuation ofACEi and ARBs

Although the evidence for the different supportive measures is weak, the KDIGO guidelines recommend to implement them in patients at high risk for AKI.

Therefore, a randomized prospective multicenter trial is needed to investigate whether the implementation of the bundle of measures is effective to prevent AKI in high risk patients undergoing cardiac surgery.In this feasibility trial we will analyze the compliance rate to the trial protocol in a multicenter, multinational cohort in preparation for a large randomized controlled trial.

2.4 Benefit-risk assessment

Patients included in the trial have an increased risk for the development of AKI.

In the validation group,the bundle of supportive measures recommended by the KDIGO guidelines will be implemented, whereas patients in the control group receive standard of care therapy.Cardiacoutput (e.g. measured by echocardiography; at initiation and then every 3h up to 12h)will be measured in both groupswithout informing the treating physician about the values.The intervention may reduce the occurrence and severity of AKI.
The KDIGO guidelines include optimization of volume status and hemodynamic parameters, discontinuation of nephrotoxic agents when possible,discontinuation of ACEi and ARBs,close monitoring of serum creatinine and urinary output, and avoidance of hyperglycemia.To this date, the benefit of these simple and uncomplicated measures has not been proven. Patients assigned to the control group will not have any disadvantages compared to non-participation in the study.

All the patients included in this trial receive standard therapy according to the current clinical routine at each center.The patient's primary physicians will determine the remainder of patient management consistent with established best practice within the institution.

Significance

The occurrence of AKI after cardiac surgery is associated with an increased risk of morbidity and mortality. The KDIGO guidelines recommend to implementvarious measures in high risk patients to prevent AKI. However, it has not been proven whether the implementation of these measures reduces the occurrence of AKI after cardiac surgery. Patients at high risk for AKI will be identified by using the AKI biomarkers [TIMP-2]*[IGFBP7] which will be measured 4h after cardiac surgery.

Given the fact that more than 2 million patients are scheduled for cardiac surgery each year worldwide, reducing the occurrence of AKI by biomarker-guided implementation of the KDIGO guidelines would result in a remarkable positive effect for many patients, health care systems and health economics.

To plan a large randomized outcome study, in which we investigate whether biomarker-guided implementation of the KDIGO guidelines can reduce the occurrence of AKI after cardiac surgery, we have to know the adherence to the trial protocol. Once we have these data, we can perform the power analysis for the outcome study.

3 Organizational and administrative aspects of the trial

3.1 Responsible institution

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3.2 Principal Coordinating Investigator

Principal Coordinating

Investigator (PCI): **Univ.-Prof. Dr. med. A. Zarbock**

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3.3 Statistics

Statistician: Dr.rer. nat. J. Gerß
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3.4 Study laboratories and other technical services

Leukocyte Adhesion Laboratory
Univ.-Prof. Dr. med. A. Zarbock
Department of Anesthesiology, Intensive Care and Pain Medicine
University Hospital Muenster
Albert-Schweitzer-Campus 1, Building A1
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3.5 Investigators and trial sites

This clinical trial will be carried out as a multicenter trial with the University Hospital of Muenster as principal institution. The listing of trial sites, principal investigators, sub-investigators and further trial staff, will be kept and continuously updated in a separate list. The final version of this list will be attached to the final report of the clinical trial.

4 Trial conduct

4.1 General aspects of trial design

The clinical trial will be performed as a prospective, randomized controlled, blinded, parallelgroup,multicenter trial. Eligible patients will be randomized in a ratio of 1:1 to receive either interventional or standard treatment via an internet-based system.

Patients who are considered potential candidates for the study may only participate if signed written informed consent is provided or the specific process for unconscious patients in an emergency situation is followed before any study related procedures are initiated (see 4.3.1). Each consented patient will be assigned a unique patient number. This patient number will be used to identify the patient throughout the study. The patient's eligibility will be proven by checking the inclusion and exclusion criteria.

The randomization number allocates the patient to one of the treatment groups.

4.1.1 Time plan

The study comprises three main periods:

- Intervention period (from inclusion and randomization to 12 h)
- Observation period (during hospitalization)
- Follow-up period on day 90 after patient enrolment.

<u>End of the clinical trial</u>

The last patient's last visit (LPLV) is defined as the end of the clinical trial.

4.2 Discussion of trial design

All patients will receive standard perioperative care. In the validation group, patients will be strictly treated according to the KDIGO guidelines and according to a special algorithm to optimize

volume status and hemodynamic parameters. The KDIGO recommendations are safe and have no side effects. In the control group, patients will receive standard care.

AKI after cardiac surgery is associated with an increased morbidity and mortality. Numerous clinical trials tested differentpharmacologicaltreatments,however no agents have been demonstrated to be efficacious in clinical practice. In a preliminary study, we demonstrated that urinary [TIMP-2]*[IGFBP7] levels 4 hours after CPB showed good performance in predicting the development of AKI (AUC 0.81). Moreover, patients with a cut-off value ≥ 0.3 $((ng/ml)^2/1000)$ were identified to have a high risk for AKI (5-times higher than [TIMP-2]*[IGFBP7] < 0.3; p< 0.001). Thus, preventing AKI after cardiac surgery would have a great impact on morbidity and mortality.

4.2.1 Randomization

Prior to being randomized into the study, patients will have:

- Signed a written informed consent
- Completed screening
- Met all designated inclusion criteria and have no exclusion criteria

Randomization assignment (in a 1:1 ratio to the two treatment arms) will be given only to those patients fulfillingthe inclusion and none of the exclusion criteria and providing informed consent. Randomization will be performed by using a web-based randomization system. After identifying a high risk patient (urinary [TIMP2]*[IGFBP7] ≥ 0.3, NephroCheck® Test), patients will be assigned to control or intervention group, whereas the intervention will be provided by research staff not involved in the care of patient.

4.2.2 Blinding

Study intervention will be performed by research staff**not involved** in anesthesia, perioperative care, and endpoint assessment.In the control group, the independent research staff will carry out the hemodynamic evaluation so that the trial is still blinded. General anesthesia and perioperativecarewill be performed in all patients by an experienced anesthesia team. Thus, blinding concerns i) the individual patient, ii) investigators obtainingdata, follow-up visits and documentation, and iii) the endpoint committee. Group allocation will not be unfolded until final statistical analysis.

Intention-to-treat analysis will address attrition bias. To prevent publication bias in future meta-analyses, results are intended to be published irrespective of the outcome of the trial.

4.3 Selection of trial population

4.3.1 Consent and recruitment strategy

All adult patients fulfilling the inclusion criteria will be offered enrollment in the study. However, patients who enter the ICU after cardiac surgery are mostly sedated and mechanically ventilated. Biomarker elevations detect a potential renal damage at an early timepoint and interventions have to begin in this early phase to prevent the development of AKI. Therefore, the intervention cannot be delayed until patients regain consciousness. For this emergency situation, the informed consent process hasto follow the legal country-specific regulations. In Germany the informed consent process is defined on the basis ofthe German Civil Code (§ 1902 and § 1904) and on the basis ofthe German Drug Law (§40 and § 41)

The method of obtaining and documenting the informed consent and contents of the consent will complywithICH-GCP and all applicable regulatory requirement(s).

It is strongly recommended to consult a relative or an associated person as soon as possible and to enquire about the patient´s presumed wishes and any previous objections towards participation in clinical studies. The information has to be documented in the patient's medical record. Once the patient regains capacity togive informed consent he/ she needs to be asked for his/her informed consent to continue to participate in the study. The relevant forms to this effect are filed in the study folder.

The patient needs to be informed that all data are kept confidential and stored in pseudo-anonymized form. He/ she has the right to withdraw study participation at any timewithout giving a reason. A duplicate of the written informed consent needs tobe handed to the patient.

No patient will be excluded from the study on the basis of gender, race, ethnicity or sexual preference. Patients will be identified for recruitment by screening all patients receiving care in the critical care units.

4.3.2 Inclusion criteria

1. Patients undergoing cardiac surgery with CPB
2. Urinary [TIMP-2]*[IGFBP7] ≥ 0.3 4 h after CPB
3. Age between 18 and 90 years
4. Written informed consent

4.3.3 Exclusion criteria

None of the following conditions can be fulfilled:

1. Preexisting AKI
2. Patients with cardiac assist devices (ECMO, LVAD, RVAD, IABP)
3. Pregnancy
4. Known (Glomerulo-) Nephritis, interstitial nephritis or vasculitis
5. CKD with eGFR< 30 ml/min
6. Dialysis dependent CKD
7. Prior kidney transplant within the last 12 months
8. Participation in another clinical interventional trial in the last 3 months
9. Persons with any kind of dependency on the investigator or employed by the institution responsible or investigator
10. Persons held in an institution by legal or official order

4.4 Withdrawal of trial subjects after trial start

Once a patient has beenenrolled in the study the investigator will make every reasonable effort to keep the patient in the study. However, if the investigator has to withdraw a patient from the study or if the patient refuses further study participation, a final examination should be performed. For patients withdrawn from the study, the follow-up information should be obtained, if possible.

A patient may request to be withdrawn from the study at any time, for any reason, without prejudice. A patient may also be withdrawn from the study at the request of his/her legal representative or physician, for any reason.

4.4.1 Procedures for premature withdrawal from treatment during the trial

The active study participation stops with the end of the intervention period (12h after randomization). Patients who withdraw from active study participation earlier will be requested to permit continued data collection for the remainder of the follow-up period.

4.5 Closure of trial site/ premature termination of the clinical trial

4.5.1 Closure of trial site

The sponsor has the right to terminate the study at a specific study site. Reasons which may require termination are:

• Patient enrolment is too slow

• The investigator fails to comply with the study protocol or legal requirements
• Data recording is not accurate, e.g. CRFs are not completed or data entry is not legible.

4.5.2 Premature termination of the clinical trial

The PCI has the right to terminate the trial prematurely if there are any relevant medical or ethical concerns, or if completion of the trial is no longer practical. If such action is taken, the reasons for terminating the trial must be documented in detail. All trial subjects still under treatment at the time of termination must undergo a final examination which must be documented. The PCI must be informed without delay if any investigator has ethical concerns about continuation of the trial.

Premature termination of the trial will be considered if:

- The risk-benefit balance for the trial subject changes markedly
- It is no longer ethical to continue treatment
- The PCI considers that the trial must be discontinued for safety reasons
- Results of other research show that one of the components of the intervention is superior or inferior to another
- It is no longer practical to complete the trial

The PCI decides on whether to discontinue the trial in consultation with Advisory Board and/or statistician.

4.6 Treatment

All patients will receive standard of care therapy. In the validation group, functional hemodynamic monitoring (according to the standard of each center), optimization of fluid status and hemodynamic parameters according to a specific algorithm (see Figure 1), avoidance of hyperglycemia, discontinuation of nephrotoxic drugs if possible, consideration of alternatives to radio contrast agents, discontinuation of ACEiand ARBs, and close monitoring of serum creatinine and urine output will be performed. Further concomitant medication will not be restricted.

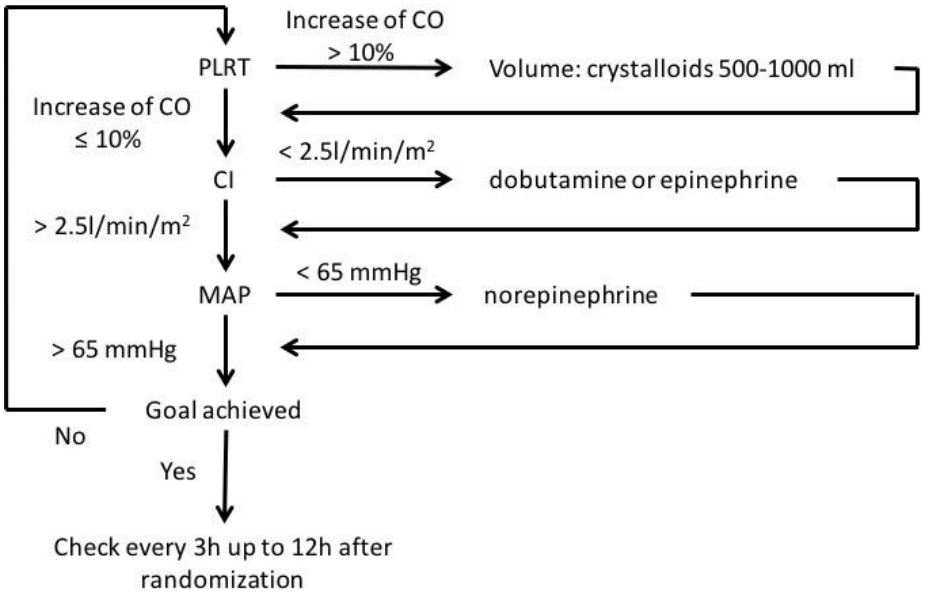
4.6.1 Experimental intervention

Four hours after terminating CPB in the context of a cardiac surgery procedure, urinary [TIMP-2]*[IGFBP7] will be measured to identify patients at high risk for AKI. Patients with a value ≥ 0.3 will be randomized as follows to one of the two treatment arms.

The KDIGO guidelines for prevention of acute kidney injury will be strictly implemented:

- Discontinuation of all nephrotoxic agents if possible
- Discontinuation of ACE inhibitors and ARBs forthe first 48 hours after surgery
- Close monitoring of serum creatinine and urinary output
- Avoidance of hyperglycemia by close monitoring for the first 72 hours after surgery
- Consideration of alternatives to radio contrast agents
- Functional hemodynamic monitoring (according to the standard of each center, e.g. PICCO, PAC, TOE)
- Hemodynamic monitoring and optimization according to a hemodynamic algorithm (see Fig. 1)

Figure 1. Hemodynamic algorithm (validation arm)



CI, cardiac index; CO, cardiac output; MAP, mean arterial pressure; PLRT, passive leg raising test

4.6.2 Control intervention

Patients in the control group will receive standard of care. In these patients, cardiac output will also be measured (e.g. via echocardiography; at initiation and then every 3h up to 12h) but the treating physician will not be informed about the values.

4.6.3 Additional treatments

The patient's primary physicians will determine the remainder of patient management consistent with established best practices with the management of critically ill patients. In patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), tidal volume for mechanical ventilation will be approximately 6 ml per kilogram of predicted body weight and adjusted to maintain a peak plateau pressure between 25 and 30 cm of water(24). Ventilator associated pneumonia will be evaluated and treated in accordance with published clinical practice guidelines and consensus statements(25). Sepsis will be diagnosed and treated in accordance with published guidelines(26). All medications will be dose adjusted for renal failure and RRT in accordance with standard dosing guidelines.

All patients will be prescribed a nutritional intake that will provide at least 25-30 kcal/kg/day, depending on mechanical ventilation and other factors. Protein intake will be at least 1.2 g/kg/day. In patients receiving parenteral nutrition, carbohydrate infusion rates will not exceed 5 mg/kg/min. Water-soluble vitamins will be supplemented to replace dialysis-related losses.

4.7 Efficacy and safety variables

4.7.1 Measurement of efficacy and safety variables

4.7.1.1 Primary target variable

- Compliance rate (proportion of patients who are treated according to the trial protocol): KDIGO recommendations fulfilled at all time

4.7.1.2 Secondaryand other target variables

- Occurrence of AKI within the first 72 hours after cardiac surgery (AKI will be defined according to the KDIGO guidelines)
- Moderate and severe AKI within 72 hrs (according to the KDIGO guidelines)
- Severity of AKI within 72 hrs
- Renal recovery

  Renal recovery at hospital discharge and at days 30, 60 and 90 will be defined asserum creatinine levels < 0.5 mg/dl higher than baseline.
- 30-day, 60.day and 90-day mortality
- Length of stay in intensive care unit and hospital

Information on ICU and hospital stays will be documented. From admission to ICU admission until follow-up (by phone) at day 90, the location of the patient within the hospital will be documented in the CRF. The following will be recorded for each patient

- Date and time of admission to ICU
- Date and time of discharge from ICU
- Date and time of discharge from hospital

- Need and duration of RRT during hospital stay
- RRT at days 30, 60 and 90
- $MAKE_{30}$, $MAKE_{60}$ and $MAKE_{90}$(major adverse kidney events consisting of mortality, dialysis dependency persistent renal dysfunction (defined as serum creatinine ≥ 2x compared to baseline value)
- Determination of different biomarkers

Blood and urine samples for biomarkers will be collected at the time of randomization and 12 hrs later

- Assessment of complications related to the implementation of the KDIGO guidelines will be documented.

4.7.1.3 Visits in detail

	T1 Base-line	T2[1] OD, interve ntion time	T3 POD 1	T4 POD 2	T5 POD 3	T6 Dis-charge	T7 Follow-up[2]
Inclusion and exclusion criteria	X						
Randomization	X						
Demographic Data (age, gender, BMI)	X						
Medical history(preexisting condition, premedication)	X						
Operation data (type of surgery, CPB time, X-clamp time, transfusion)	X						
Respiratory parameter	X	X					
Hemodynamic parameters (MAP, HR, CVP, CI, CO)		X					
Laboratory parameter (lactate, hemoglobin, electrolytes)	X	X	X	X	X		
Renal parameter (BUN, creatinine, GFR, urine volume [ml/h], urinary output, fluid balance)	X	X	X	X	X	X	X
Blood and urine samples	X	X					
AKI (severity, diagnosis by,		X	X	X	X		

[1] After randomization to end of intervention (12h)
[2] d30, d60, d90

transient/persistent, RRT dependency, RRT days)							
Scores (APACHE II, SOFA)		X	X	X	X		
Concomitant medication (vasopressors, radio contrast agents, diuretics, ACEi, ARBs)		X	X	X	X		
Renal recovery						X	X
Mortality							X
Length of ICU and hospital stay							X
Renal replacement therapy		X	X	X	X	X	X
MAKE							X
Complications (myocardial infarction, cerebral ischemia, ICB, bleeding >300ml/hour, re-operation)		X	X	X	X	X	X

4.8 Documentation

All data relevant to the trial are documented soon after measurement by the responsible investigator in the electronic case report form (eCRF) supplied. Entering data may be delegated to members of the trial team.

The information technology (IT) infrastructure and data management staff will be supplied by the ESICM Trials Group in cooperation with the Department of Anesthesiology, Intensive Care and Pain Medicine, University Hospital Muenster. The trial database will be developed and validated before data entry based on standard operating procedures (SOPs). The database that will be used is CLINFILE(© and is integrated into a general IT infrastructure and safety concept that complies with ICH E6 Standard, ISO 14155 standard, FDA 21 CRF Part 11 and Eudralex Annex 11.with a firewall and backup system. The data are backed up every hour in RAID 10 (disk cloning). After completion and cleaning of data, the database is locked and the data exported for statistical analysis.

4.8.1 Archiving

All CRFs, informed consent forms and other important trial materials will be archived for at least 10 years at each trial site.

5 Ethical and regulatory aspects

5.1 Independent ethics committee

The clinical trial will not be started before approval of the competent ethics committee. The principal investigator will inform the ethics committee about any changes in the study protocol.

5.2 Ethical basis for the clinical trial – Risk/benefit ratio

The present trial protocol and any amendments were and will be prepared in accordance with the Declaration of Helsinki in the version of October 2013 (64th General Assembly of the World Medical Association, Fortaleza, Brazil).

All patients will receive standard perioperative care. No side effects of the implementation of the KDIGO guidelinesare known. None of the patients in both groups will be exposed to additional risks.

AKI after cardiac surgery is associated with an increased morbidity and mortality. Despite numerous clinical trials of pharmacologic interventions, a mean to prevent AKI associated with cardiac surgery has remained elusive. In a preliminary study, we demonstrated that urinary [TIMP-2]*[IGFBP7] levels 4h after CPB showed a good performance in predicting the development of AKI (AUC 0.81). Moreover, patients with a cut-off value ≥ 0.3 $((ng/ml)^2/1000)$ were identified as patients with a high risk for AKI (5-times higher than [TIMP-2]*[IGFBP7] < 0.3; p< 0.001). Thus, preventing AKI after cardiac surgery would have a great impact on morbidity and mortality.

Participation in this study will be voluntary. Written informed consent will be obtained from patients.If the patient is unable to provide informed consent, local regulations provided by the competent, country-specific local ethics committee with respect to patients without capacity to consent, have to be followed. Independent of the opt-in process of the corresponding ethics committee, informed consent of the patient or legally authorized representative will be obtained as soon as the patient's condition allows it.

Data collection will be performed pseudo-anonymously and the patient's name will not appear on any CRF or in any other trial document submitted to the central data management. All collected data will be kept confidential.

The treating investigator will inform the patient or the legal representative in case the patient lacks capacity about the nature of the trial, its aims, expected advantages as well as possible risks. Each patient must consent in writing to participate in the study. The patientand legal

representative must be given enough time and opportunity to decide whether to participate and to ask questions before the beginning of documentation of the study.
The informed consent forms will be signed by both patient or legal representative and investigator. The original document is kept by the investigator and the patient receives a copy.

5.2.1 Legislation and guidelines used for preparation

The present clinical trial will be conducted in accordance with the published principles of the guidelines for Good Clinical Practice (ICH-GCP). These principles cover, amongst other aspects, ethics committee procedures, the obtaining of informed consent from trial subjects, adherence to the trial protocol, administrative documentation, data collection, trial subjects' medical records (source documents), documentation and reporting of complications related to the implementation of the KDIGO guidelines, preparation for inspections and audits, and the archiving of trial documentation. All investigators and other staff directly concerned with the study will be informed that domestic and foreign supervisory bodies, the competent federal authorities and authorised representatives of the responsible institution have the right to review trial documentation and the trial subjects' medical records at any time.

5.3 Registration

Before the trial is started, it will be registered under Current Controlled Trials (www.controlled-trials.com) or another trial register approved by the World Health Organisation (WHO) (http://www.who.int/ictrp/en/).

5.4 Data protection

The provisions of data protection legislation will be observed. It is assured by the responsible institution that all investigational materials and data will be pseudo-anonymised in accordance with the data protection legislation before scientific processing.

Trial subjects will be informed that their pseudo-anonymised data will be passed on in accordance with provisions for documentation and notification pursuant to § 12 and § 13 of the GCP Regulations to the recipients described there. Subjects who do not agree that the information may be passed on in this way will not be enrolled into the trial.

Laboratory data will be maintained in a separate, secure location with access limited only to laboratory personnel.

6 Statistics

6.1 Endpoints

The primary endpoint of this trial is the compliance rate, i.e. the proportion of patients who have been treated according to the trial protocol(KDIGO recommendations fulfilled at all time).
Secondary endpoints include occurrence of AKI within 72 hours after cardiac surgery, moderate and severe AKI, severity of AKI, renal recovery at days 30,60 and 90, 30-day, 60-day and 90-day mortality, length of ICU stay, length of hospital stay, need and duration of RRT, RRT at days 30, 60 and 90, $MAKE_{30}$, $MAKE_{60}$ and $MAKE_{90}$ (major adverse kidney events consisting of mortality, dialysis dependency persistent renal dysfunction (defined as serum creatinine ≥ 2x compared to baseline value).

The randomization ratio is 1:1.

6.2 Sample size

The required sample size is n=280 patients in total. This sample size is determined as follows.
Patients will be randomized in a 1:1 ratio to one of the two treatment arms (intervention versus control). Randomization serves to estimate the incidence of AKI as secondary outcome to generate pre-information in terms of a pilot study for an upcoming confirmatory trial.
The primary endpoint of the PrevAKI-multicenter trial is the compliance rate, i.e. the proportion of patients who have been treated according to the trial protocol (KDIGO recommendations fulfilled at all time). In order to estimate the compliance rate, the two treatment groups will be pooled together. In the primary analysis the compliance rate across all study patients will be estimated along with a two-sided 95% confidence interval (CI).
As the compliance rate cannot be quantified in advance, we pursue a worst case approach and assume a compliance rate of 50%. In this case the CI has maximal width. Based on this assumption, with a sample size of n=280 patients the calculated 95% CI according to Clopper-Pearson (Fleiss 2003) ranges from 44% to 56%. Therefore, in case of any observed compliance rate apart from the worst-case scenario, the 95% CI is never wider than 56%-44%=12%. This corresponds to an estimation of the compliance rate with a precision of plus/minus 6%.

6.3 Statistical analysis plan

The trial is designed to examine the feasibility of the trial protocol in a multicenter setting (as previously described).

The **descriptive analysis** of the data will include the calculation of means, standard deviations, and absolute and relative frequencies of the baseline and follow-up data. Randomization will be checked by suitable two-sided statistical tests (Chi-Square, or Fisher's exact test for categorical data, Students' t-Test or Mann-Whitney-U tests for continuous data). If normality of the data is not given non-parametric methods will be used.

In the primary statistical analysis the compliance rate across all recruited study patients will be estimated along with a two-sided 95% confidence interval (CI)according to Clopper-Pearson (Fleiss 2003).

Secondary endpoints will be analyzed in the ITT collective using Fisher's exact tests or chi-squared tests for categorical data, and Student's t-tests or Mann-Whitney-U tests for continuous data. Prognostic risk factors for AKI will be identified using a multivariable logistic regression analysis, accounting for confounding factors.In particular, based on a full model with potentially relevant covariates (e.g. sex, age, previous heart surgery, preoperative creatinine) the final model will be established applying a stepwise variable selection procedure.

7 Use of trial findings

7.1 Publication

It is planned to publish the trial results, in mutual agreement with the PCI, in a scientific journal and at international congresses. Publication of the results of the trial as a whole is intended. Any publication will take account of the International Committee of Medical Journal Editors(ICMJE).

The trial will also be registered in a public register in accordance with the recommendations of the ICMJE.

Any published data will observe data protection legislation covering the trial subject and investigators. Success rates or individual findings at individual trial sites are known only to the responsible institution.

Publications or lectures on the findings of the present clinical trial either as a whole or at individual investigation sites must be approved by the responsible institution in advance, and the

responsible institution reserves the right to review and comment on such documentation before publication.

8 Costs and payments

8.1 Research study costs

There will be no additional costs to subjects of this study. The additional study costs above what is considered to be standard hospital care are the costs for data management, statistical analysis, measurement of renal biomarkers and laboratory costs. These costs will be covered by the ESICM Trials Group Award given to Alexander Zarbock (Principal Coordinating Investigator). Subjects and their insurers and third party payers will be billed for routine care services, or services not connected with the study. These routine care services include services provided during this hospitalization and any ongoing services or medications required after leaving the hospital. Subjects will be responsible for any applicable copies, coinsurances, and deductibles.

8.2 Research subject costs

Research subjects will receive no payments or other remuneration for their participation in the study.

9 Amendments to the trial protocol

To ensure that comparable conditions are achieved as far as possible at individual trial sites and in the interests of a consistent and valid data analysis, changes to the provisions of this trial protocol are not planned. In exceptional cases, however, changes may be made to the trial protocol. Such changes can only be made if agreed by the responsible institution, the PCI and biometrician, and all authors of this trial protocol. Any changes to the trial procedures must be made in writing and must be documented with reasons and signed by all authors of the original trial protocol.

Amendments made in accordance with § 10 Secs. 1 and 4 GCP Regulations that require approval are submitted to the ethics committee and the supreme federal authority and will not be implemented until approved. Exceptions to this are amendments made to avoid immediate dangers.

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11 Appendices

11.1 Protocol Agreement Form

Study title: Biomarker-guided implementation of the KDIGO guidelines to reduce the occurrence of AKI after cardiac surgery – Prevention of AKI (PrevAKI-multicenter)

Study number: 07-AnIt-16

Date:

I confirm that I have read this protocol; I understand it and I will work according to this protocol and to the ethical principles stated in the latest version of the declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable laws and regulations of the country of the study centre for which I am responsible. I will accept the monitor's overseeing of the study.

Name and address:

Signature of Investigator: _____

Date: _____

11.2 Steering committee

	Name	Institution
1	Alexander Zarbock	Department of Anesthesiology, Intensive Care and Pain Medicine, University Hospital Muenster, University Muenster, Germany
2	Eric Hoste	Department of Intensive Care Medicine, University Hospital Gent, Belgium
3	John Kellum	Center for Critical Care Nephrology, Department of Critical Care Medicine, University of Pittsburgh, PA, USA.
4	Lui Forni	Department of Intensive Care Medicine, Royal Surrey County Hospital, Guildford, UK
5	Marlies Ostermann	Department of Critical Care, King's College London, Guy's & St Thomas' Foundation Hospital, Department of Critical, Care, London, UK

11.3 Scores

SOFA-Score

SOFA Score	0	1	2	3	4
Respiration PaO_2/FiO_2	>400	<400	<300	<200	<100
Platelet count ($10^3/\mu l$)	>150	<150	<100	<50	<20
Bilirubin (mg/dl)	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12
Cardiovascular	No hypotension	MAP <70 mmHg	Dobutamine (any dose)	Norepinephrine/ epinephrine ≤0.1µg/kg/min	Norepinephrine/ epinephrine > 0.1µg/kg/min
GCS	15	13-14	10-12	6-9	<6
Creatinine (mg/dl) or UO (ml/d)	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 ≤500	>5.0 <200

APACHE-Score

Points	+4	+3	+2	+1	0	+1	+2	+3	+4
Temp. °C	≥41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤29.9
MAP (mmHg)	≥160	130-159	110-129		70-109		50-69		≤49
HF/min	≥180	140-179	110-139		70-109		55-69	40-54	≤39
AF/min*1	≥50	35-49		25-34	12-24	10-11	6-9		≤5
Oxygenation	≥500	350-499	200-349		71-199	61-70		55-60	<55
pH	≥7.7	7.6-7.69		7.5-7.59	7.33-7.49		7.25-7.32	7.15-7.24	<7.15
Na^+ (mmol/L)	≥180	160-179	155-159	150-154	130-149		120-129	111-119	≤110
K^+ (mmol/L)	≥7	6.6-6.69		5.5-5.59	3.5-5.4	1.0-3.4	2.5-2.9		≤2.5
Creatinine (mg/dl) *2	≥3.5	2.0-3.4	1.5-1.9		0.6-1.4		<0.6		
Hematocrit (%)	≥60		50-59.9	46-49.9	30 -45.9		20-29.9		<20
Leukocytes (x1000)	≥40		20-39.9	15-19.9	3-14.9		1-2.9		<1
GCS	Points= 15-current GCS								

*1 spontaneous breathing or mechanical ventilation
*2 AKI receives double points

ASA-Score

ASA I	Normal healthy patients
ASA II	Patients with mild systemic disease
ASA III	Patients with severe systemic disease that is limiting but not incapacitating
ASA IV	Patients with incapacitating disease which is a constant threat to life
ASA V	Moribund patients not expected to live more than 24 hours
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes