A preventive care strategy to reduce moderate or severe acute kidney injury after major surgery (BigpAK-2); a multinational, randomised clinical trial

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Summary

Background Acute kidney injury (AKI) is a common and important complication of major surgery, yet recommended preventive care is rarely administered. We used urinary biomarkers to identify patients at high risk of AKI and implemented a preventive care strategy to reduce AKI within 72 h after major surgery.

Methods BigpAK-2 was a multicentre randomised clinical trial done in 34 hospitals in Europe. Patients (aged ≥18 years) undergoing major surgery at high risk for AKI identified by predefined clinical risk factors and tubular stress biomarkers were randomly assigned to usual care or a preventive care strategy as per recommendations by the Kidney Disease Improving Global Outcome guidelines: advanced hemodynamic monitoring, optimisation of volume status and haemodynamics, avoidance of nephrotoxic drugs and radiocontrast agents, and prevention of hyperglycaemia. The primary outcome was the occurrence of moderate or severe AKI within 72 h after surgery, assessed in the intention-to-treat population. Safety was assessed by comparing rates of adverse events between groups. This trial is registered with ClinicalTrials.gov, NCT04647396.

Findings From Nov 25, 2020, to June 21, 2024, 7873 patients were screened and 1180 (15·0%) were randomly assigned (589 [49·9%] to the intervention group and 591 [50·1%] to the control group). Among the 1176 patients available for the primary endpoint analysis, moderate or severe AKI occurred in 84 (14·4%) patients in the intervention group and in 131 (22·3%) patients in the control group (odds ratio 0·57 [95% CI 0·40–0·79; p=0·0002; number needed to treat 12 [7–33]). There were no differences in adverse events. The most common adverse events were atrial fibrillation (50 [8·8%] in the intervention group *vs* 56 (9·7%) in the control group), hemodynamically relevant arrhythmias (41 [7·2%] in the intervention group *vs* 50 [8·6%] in the control group), significant bleeding or haemorrhage (34 [6·0%] in the intervention group *vs* 31 [5·3%] in the control group), and unplanned return to the operating room (29 [5·1%] in the intervention *vs* 38 [6·5%] in the control group).

Interpretation Among adults at high risk for AKI undergoing major surgery, a preventive care strategy consisting of supportive measures and avoidance of nephrotoxins significantly reduced the occurrence of moderate or severe AKI without increasing adverse events.

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Introduction

Acute kidney injury (AKI) is a common and important complication of major surgery.[1,2] The condition is independently associated with increased morbidity, mortality, and risk of chronic kidney disease (CKD).[3] The pathophysiology of surgery-associated AKI is complex. Haemodynamic changes, nephrotoxic exposures, and inflammation play key roles.[4,5] No specific treatment for AKI is available and guideline-recommended preventive strategies are not routinely implemented.[6] This strategy is in line with evidence from other fields of intensive care medicine, such as the sepsis care bundle, recommendations for low-tidal volume ventilation, or studies investigating adherence to several care bundles in the intensive care unit (ICU).[7] Research shows that implementation of care bundles is not feasible in all patients because of time and resource constraints, but implementation in selected patients at high risk is advisable. In this setting, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend implementing specific supportive measures to prevent AKI in patients at high risk.[8] These guidelines consist of optimisation of volume status and perfusion pressure, advanced haemodynamic monitoring, avoidance of potentially nephrotoxic agents and radiocontrast, and

Research in context

Evidence before this study

Before undertaking this study, there was insufficient evidence to establish the effectiveness of a preventive care strategy after major surgery to reduce occurrence of moderate or severe acute kidney injury (AKI). We searched PubMed, Scopus, Web of Science, and ClinicalTrials.gov for studies published from inception until June 30, 2020. Additionally, we reviewed reference lists from reviews, meta-analyses, and primary research articles on AKI prevention within the same time period. We included studies that focused on patients after major surgery, including clinical trials, studies published in peer-reviewed journals, and trials involving participants aged 18 years and older. Studies were excluded if they were not published in English or if a translation was not available, if they focused on non-surgical patients, or were not relevant to the prevention of AKI after surgery. Search terms used were combinations of the following keywords: "acute kidney injury", "prevention", "care bundle", "biomarker", and "surgery". Although we found several high-quality studies on this topic, there was no definitive, multicentre study testing this intervention in all forms of major surgery. Three studies investigating similar interventions were done before this trial: the PrevAKI and BigpAK studies were small single-centre trials restricted to cardiac and abdominal surgery, respectively, and the PrevAKI-2 trial was also restricted to cardiac surgery and, although multicentre, was done as a feasibility study.

Added value of this study

The BigpAK-2 study was a multinational randomised clinical trial including more than 1100 patients receiving major surgery from all surgical disciplines. BigpAK-2 was an adequately powered study showing the efficacy and safety of a preventive care strategy to significantly reduce rates of moderate or severe AKI after major surgery, which is a major public health concern worldwide.

Implications of all the available evidence

The investigated preventive care strategy offers an effective and safe tool to reduce rates of moderate or severe AKI in patients at high risk as identified by a urinary biomarker panel after major surgery. This study adds to the robust body of evidence supporting this approach. Further evidence is required to assess long-term implications and cost-effectiveness.

prevention of hyperglycaemia. Preliminary, single-centre, randomised trial evidence and a quality improvement initiative suggest that, in such patients, implementation of KDIGO-recommended protective strategies can significantly reduce the occurrence of AKI.[9–11] Finally, a 2021 trial found that this approach is feasible in a multicentre setting.[12]

AKI biomarkers, such as urinary TIMP-2 and IGFBP7, can be used to identify patients at high risk for moderate or severe AKI[13] and therefore most appropriate for interventions.[11,14] Multiple regulatory authorities around the world have approved these biomarkers for AKI prevention, and they are now widely available clinically. Biomarker-enabled prognostic enrichment is a cornerstone of precision medicine and is recommended in critical care nephrology.[15] This approach also maximises clinical trial efficiency by increasing effect size and thereby reducing trial size. For clinical practice, this approach avoids exposing patients to interventions that they cannot benefit from and improves cost-effectiveness. The combination of such biomarkers with clinical risk factors further improves such enrichment strategies. However, patients with advanced CKD might have non-modifiable risk and are therefore not appropriate for simultaneous recruitment with patients without CKD or less severe stages of CKD (stages 1–3).

In this study, we investigated the hypothesis that implementation of a preventive care strategy consisting of KDIGO-recommended nephroprotective measures would lead to a lower occurrence of moderate or severe postoperative AKI In surgical patients identified by biomarkers to be at high risk for AKI. This endpoint was selected because TIMP-2 and IGFBP7 are approved for risk stratification of moderate or severe (KDIGO stage 2–3) AKI and patients developing these endpoints are at increased risk of these complications. Furthermore, long-term outcomes such as death, dialysis, or persistent kidney dysfunction occur less commonly in patients without AKI compared with in patients with elevated urinary biomarkers [TIMP-2]×[IGFBP7] and a sufficiently powered clinical trial to detect differences in these endpoints would be more than ten times larger than a trial without biomarker enrichment.

Methods

Study design and participants

BigpAK-2 was an investigator-initiated, multinational, open-label, adaptive, randomised clinical trial. Patients were recruited at 34 academic and non-academic hospitals in eight European countries (appendix pp 4–6). The study was approved by the Ethics Committee of the Medical Faculty of the University of Münster (2020-601-f-S) and by the corresponding ethics committees of the participating sites, including procedural amendments (appendix pp 42–58). A study amendment extending the time period of biomarker measurement (from 0–4 h after surgery to 4–18 h after surgery) and allowing inclusion of up to 500 cardiac surgery patients was also approved (appendix pp 42–58). The inclusion period was extended to allow for inclusion of patients on the morning of the first day after admission to the postoperative ICU in the evening or night and

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See Online for appendix

because AKI events are common in the first 18 h following surgery.[16] Inclusion of up to 500 cardiac surgery patients was implemented to increase generalisability of study findings to all types of major surgery. In the UK, the trial was adopted as a National Institute for Health and Care Research portfolio study. All patients provided written informed consent. If local ethics approvals included the option of informed consent by legal guardians, such approval was obtained before study inclusion if patients were unable to provide informed consent themselves (eg, due to sedation or mechanical ventilation). When patients were able to provide informed consent again, consent was obtained again from the respective patients. Details of the rationale and design of the study have been published.[17] The trial used an adaptive study design with one interim analysis.[18]

Primary outcome adjudication was done by research staff masked to treatment allocation.

Patients admitted to an ICU or high dependency unit (HDU) following major surgery (defined as expected surgical duration >2 h and expected ICU or HDU admission; requirement for ICU or HDU care could be based on surgery-specific or patient-specific factors as assessed by the treating physicians) were screened for eligibility. Eligible patients were aged 18 years or older, with an indwelling urinary catheter, a central venous line, and at least one risk factor for AKI. Pre-defined risk factors for AKI included being age 75 years or older; ongoing requirement for postoperative vasopressor support or mechanical ventilation, or both; pre-existing CKD stage 3 (estimated glomerular filtration rate [eGFR] 30–59 mL/min per 1·73 m²), or intraoperative use of radiocontrast agents.

Patients were randomly assigned postoperatively to prevent kidney injury in patients with kidney stress. Our approach was to apply interventions within the soon after injury, when damage might still be reversible. Enrolled patients met all inclusion criteria, had at least one of four pre-defined clinical risk factors for AKI (appendix p 8), and had a urinary TIMP-2×IGFBP7 concentration of at least 0·3/1000 (ng/mL)² within 4–18 hours after surgery.[9,10,12] Repeated measurements of AKI biomarkers were permitted. Major exclusion criteria were pre-existing advanced CKD (eGFR <30 mL/min per 1·73 m²), kidney transplant within the past 12 months, pre-existing anuria, pre-existing AKI, and indication for renal replacement therapy (RRT) at the time of inclusion, or participation in another interventional trial (appendix p 8). Patients with advanced CKD (stage 4–5) were not included in the study as these patients have a substantially different and less modifiable risk profile for AKI compared with patients with normal kidney function or mild or moderate stages of CKD.[19]

Randomisation and masking

Patients were randomly assigned (1:1) to the intervention or control group, using a web-based system (RandIMI plug-in for RedCAP, Research Electronic Data Capture, version 10.6.22, Vanderbilt University, Nashville, TN, USA[20,21]) with the use of computer-generated, permuted-block sequences and stratification according to site. Because of the nature of the intervention, masking of participants or staff was not possible. However, outcome assessors were masked to treatment groups. To review safety data, the Data Safety Monitoring Board (DSMB) was not masked.

Procedures

All participants received usual preoperative and intraoperative care. Postoperatively, participants were randomly allocated to usual care (control group) or preventive KDIGO-recommended care (intervention group).[17] Each site received online training by the initiating site team during a site-specific initiation visit. The intervention in KDIGO-recommended nephroprotective care includes several aspects. First, hemodynamic optimisation was done for at least 12 h after randomisation. This contained three mandatory elements: (1) a passive leg raising manoeuvre at least every 3 h or more regularly dependent on clinical judgement, to assess fluid responsiveness—if this manoeuvre was positive (cardiac output increase >10%), patients received a fluid bolus (500–1000 mL) of balanced crystalloids— (2) targeting a mean arterial pressure of at least 65 mm Hg using norepinephrine, if necessary; and (3) advanced haemodynamic monitoring and targeting a cardiac index of at least 2·5 mL/min per m² using dobutamine or epinephrine, if necessary (appendix p 35). Advanced monitoring was implemented using different methods, such as transpulmonary thermodilution, pulse contour analysis, pulmonary artery catheter, transthoracic or transoesophageal echocardiography allowing measurement of the cardiac output and calculation of cardiac index. The method chosen was left to the discretion of the clinician.

Second, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs; all patients on treatment had stable heart function on the day of surgery) were discontinued for at least 48 h postoperatively, and other potentially nephrotoxic drugs (eg, hydroxyethyl starch, gelatin, vancomycin, aminoglycosides, chloride-rich solutions [except for drug infusions] and radiocontrast) were avoided for at least 72 h after surgery, if possible. Third, blood glucose concentrations were kept between 100 mg/dL and 150 mg/dL (5·5–8·3 mmol/L) with insulin infusion, if required. Treating physicians were expected to adhere to all study interventions unless an intervention was deemed inappropriate care for any individual patient.

Telephone follow-up was done at 30 days and 90 days after randomisation to assess vital status, need for renal replacement therapy, and to obtain a recent serum creatinine value. Follow-up at day 30 allowed for 5 days' difference of serum creatinine measurement to the

timepoint, and follow-up at day 90 allowed for 14 days' difference of serum creatinine measurement. If a patient could not be contacted directly, the investigator assessed vital status by contacting the patient's medical team, general practitioner, or the city register office, or by obtaining the patient's hospital electronic records, in accordance with local privacy and data protection regulations. Regular site monitoring visits were done by the principal investigator, deputy principal investigator, or by the trial coordinator. Online or on-site monitoring visits were done after five, ten, and 20 patients were recruited, and at study termination to monitor good clinical practice and perform source data verification for inclusion and exclusion data, biomarker data, primary outcome, bundle adherence, and random data verification. The DSMB was not involved in the design or conduct of the study, was independent of the study team, and without conflicts of interest. The DSMB met twice during the study to review data quality and safety data.

Outcomes

The primary outcome was moderate or severe AKI (KDIGO stage 2–3) within 72 h of surgery, defined using both serum creatinine and urine output (appendix p 9).[8] The preoperative serum creatinine value was used as a baseline serum creatinine to assess the primary and secondary outcomes. Stage 1 AKI was not included in the primary endpoint to account for transient fluctuations in serum creatinine or urine output—eh, on the basis of hemodynamic changes.

Prespecified secondary outcomes were adherence to study protocol, occurrence and severity of any stage AKI within 72 h of major surgery, persistent moderate or severe AKI (defined as AKI ≥48 h), change in biomarker values 12 h following initial measurement of TIMP-2×IGFBP7, number of days free of mechanical organ support and number of vasopressor-free days to day 3, RRT at day 30 and day 90, duration of RRT by day 30 and day 90, renal recovery at day 90 (defined as serum-creatinine ≤0·5 mg/dL higher than baseline and no need for RRT), 30-day and 90-day mortality, ICU and hospital length of stay, and major adverse kidney events until day 90 ($MAKE_{90}$), defined as the composite of death, use of RRT, and persistent renal dysfunction (defined as serum creatinine >2×serum creatinine at baseline before surgery[22]) at day 90.

Prespecified postoperative adverse events were collected and are listed in the appendix (p 10). Further sensitivity and subgroup analyses are exploratory and were done as post-hoc analyses.

Statistical analysis

On the basis of the previous BigpAK trial,[10] we hypothesised event rates of 20% in the control group and 14% in the intervention group. To adjust for deviations from these assumptions, we applied an adaptive plan with one interim analysis using O'Brien–Fleming boundaries and sample size recalculation to ensure power greater than 80%. We did an interim analysis after 618 evaluable patients. The study statistician did the interim analysis to decide how many more patients needed to be recruited to achieve sufficient power in accordance with the prespecified rule on the basis of the first-stage p value.[18] Per this analysis, we recruited the required 500 additional patients.

Following sequential study design methodology, one-sided p values were calculated in a stepwise manner (patients with primary endpoint) from a Cochrane–Mantel–Haenszel test stratified by study centres. We combined p values using the inverse normal combination function with equal weights. To account for the adaptive

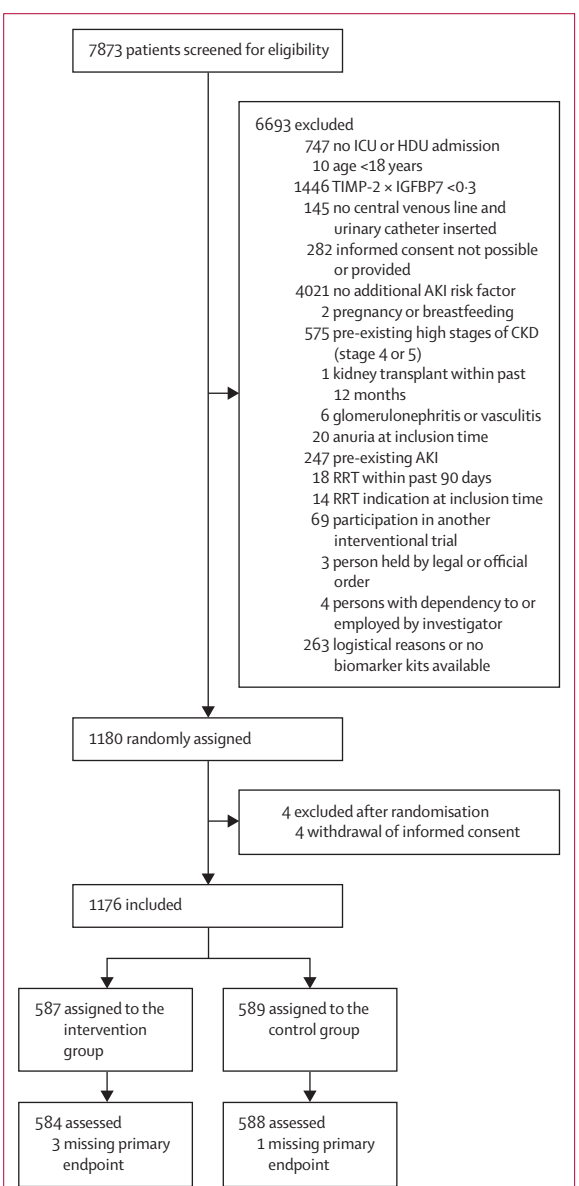

Figure 1: **Trial profile**

	Intervention (n=589)	Control (n=591)
Patient demographics		
Age, years	72·0 (63·0–78·0)	71·0 (63·0–77·0)
Sex		
Male	390 (66·2%)	394 (66·7%)
Female sex	199 (33·8%)	197 (33·7%)
Height, cm	172·0 (164·0–178·0)	172·0 (165·0–179·0)
Bodyweight, kg	79·0 (66·4–90·0)	79·0 (69·0–92·0)
BMI, kg/m²	26·3 (23·3–30·1)	26·4 (23·7–30·1)
Preoperative serum creatinine, mg/dL	0·90 (0·73–1·13)	0·91 (0·76–1·13)
Comorbidities		
ASA score*		
1 (healthy)	1 (0·2%)	8 (1·6%)
2 (mild or moderate illness)	107 (21·4%)	106 (20·7%)
3 (severe general illness)	323 (64·5%)	317 (61·9%)
4 (life-threatening general illness)	70 (14·0%)	81 (15·8%)
Hypertension	419 (73·0%)	402 (70·0%)
Congestive heart failure		
NYHA I	24 (5·4%)	20 (4·3%)
NYHA II	62 (14·1%)	51 (11·0%)
NYHA III	37 (8·4%)	40 (8·7%)
NYHA VI	3 (0·7%)	1 (0·2%)
APACHE II score†	14 (10–21)	15 (10–21)
Peripheral vascular disease	80 (13·9%)	79 (13·6%)
Diabetes of any type		
Non-insulin dependent	105 (18·3%)	91 (15·6%)
Insulin dependent	41 (7·1%)	48 (8·2%)
Previous stroke or transient ischemic attack	40 (7·0%)	45 (7·7%)
Chronic liver disease	52 (9·0%)	52 (8·9%)
Chronic kidney disease		
Stage 3a (eGFR 59–45 mL/min per 1·73 m²)	89 (15·5%)	72 (12·4%)
Stage 3b (eGFR 44–30 mL/min per 1·73 m²)	44 (7·6%)	47 (8·1%)
Chronic obstructive pulmonary disease	63 (11·0%)	75 (12·9%)
Previous myocardial infarction	72 (12·5%)	72 (12·4%)
Cancer	222 (38·6%)	226 (38·8%)
Medication		
Beta-blockers	263 (45·7%)	270 (46·4%)
ACE inhibitors	156 (27·2%)	147 (25·2%)
ARBs	139 (24·2%)	142 (24·4%)
Diuretics	212 (37·0%)	211 (36·2%)
Statins	281 (49·0%)	280 (48·0%)
Anticoagulation	174 (30·3%)	169 (29·0%)
NSAIDs	25 (4·4%)	36 (6·2%)

Data are n (%) or median (IQR). Numbers and percentages are provided where they are not missing. It is therefore possible that the figures do not add up to the total number of the cohort. SI conversion factor: to convert creatinine to µmol/L, multiply by 88·4. ACE=angiotensin-converting enzyme. APACHE=Acute Physiology And Chronic Health Evaluation. ARB=angiotensin II receptor blocker. ASA=American Society of Anesthesiology. eGFR=estimated glomerular filtration rate. ICU=intensive care unit. NSAID=non-steroidal anti-inflammatory drug. NYHA=New York Heart Association Functional Classification. *ASA classification are defined as: 3, a patient with severe systemic disease that limits physical activity; and 4, a patient with severe systemic disease that is a constant threat to life (patients with grade 1, 2 and 5 scores were not eligible for inclusion). †APACHE II is an ICU mortality prediction score with values ranging from 0 to 71. Higher values indicate higher probability of mortality (score 25–29: 55% mortality). The score is calculated on the basis of data collected within the first 24 h after ICU admission.

Table 1: **Baseline and ICU admission data**

design, repeated p values and repeated CIs for the odds ratios (Ors) were calculated for the primary endpoint. For subgroup analyses, the primary endpoint was analysed in a one-stage design using standard methods (see the published statistical analysis plan[18]). The statistical analyses included all randomly assigned patients and were done according to the intention-to-treat principle. Following standard adaptive study design methodology, the overall p value was calculated by combining the p value of the interim analysis and the consecutive study cohort. The adaptive design controlled the type I error rate at 5% overall. Additional sensitivity analyses included per-protocol and as-treated analyses and accounting for the modular nature of the KDIGO preventive strategy by including a separate factor for each individual component of the KDIGO preventive strategy on multivariable analyses. The definition of the per-protocol cohort is described in the appendix (p 41). For categorical variables, frequencies and percentages of observed counts are reported. Group comparisons were done using Cochrane–Mantel–Haenszel tests. Continuous variables are summarised by either medians (IQR) or means (SD), depending on their distribution. Accordingly, rank test procedures or a two-way ANOVA were used to compare groups. Right-censored event time data were analysed using the Kaplan–Meier method and compared using stratified log-rank tests. Effect measures were supplemented by two-sided 95% CIs. All statistical analyses were done using SAS (version 9.4).

This trial is registered with ClinicalTrials.gov, NCT04647396.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From Nov 25, 2020, to June 21, 2024, we screened 7873 patients for eligibility and randomly assigned 1180 (15·0%; figure 1). The most common reasons for non-eligibility were lack of a clinical risk factor (n=4021 [51·1%]) and low urinary TIMP-2×IGFBP7 (n=1446 [18·4%]). Thus, 589 (49·9%) patients were randomly assigned to the intervention group and 591 (50·1%) patients to the control group. Finally, 1176 (99·7%) patients were available for primary endpoint analysis because four (0·3%) randomly assigned patients withdrew informed consent (figure 1). Baseline and ICU admission characteristics (table 1) as well as surgical interventions and intraoperative management (table 2) were similar between the two groups. In the intervention group, 199 (33·8%) of 589 patients were women and 390 (66·2%) were men, and in the control group, 197 (33·3%) of 591 patients were women and 394 (66·7%) were men. Race or ethnicity data were not collected. Measures taken during the intervention period are described in the appendix (p 11–13) alongside frequency

of advanced haemodynamic monitoring during the intervention period (appendix p 14), showing substantially higher rates of cardiac index measurements and passive leg raising manoeuvres in the intervention group at all timepoints. Delivery of nephroprotective measures is summarised in the appendix (p 15), showing less exposure to nephrotoxins, less hypotension, and less hyperglycaemia with the intervention, as well as higher rates of advanced haemodynamic monitoring and assessment of fluid responsiveness in the intervention group.

Within 72 h of surgery, moderate or severe AKI occurred in 84 patients (14·4%) in the intervention group and in 131 (22·3%) patients in the control group (OR 0·57 [95% CI 0·40–0·79]; p=0·0002; number needed to treat 12 [7–33]; figure 2).

Implementation of all components of the KDIGO-recommended nephroprotective strategy occurred in 268 (46·9%) participants in the intervention group (353 [62·7%] after excluding tight glycaemic control), compared with 29 (5·0%) in the control group (30 [6·8%] after excluding tight glycaemic control). Any stage of AKI occurred in 213 (36·7%) patients randomly assigned to the intervention compared with 240 (40·9%) patients in the control group (OR 0·78 [95% CI 0·60–1·01]; table 3). Persistent moderate or severe AKI occurred in 32 (39·0%) patients in the intervention group compared with 57 (44·5%) patients in the control group (OR 0·71 [0·38–1·34]). There were no differences in other secondary outcomes, biomarker differences within 12 h after randomisation, or $MAKE_{90}$ rate (61 [11·0%] patients in the intervention group *vs* 60 [10·6%] patients in the control group; OR 1·03 [0·69–1·52]). Multivariable analysis of all patients with complete data on nephroprotective strategy measures (1114 [94·4%] of 1180 patients) including a separate factor for each individual component of the preventive care strategy is summarised in the appendix (p 16). Our findings show that the prevention of hypotension and discontinuation of ACE inhibitors and ARBs had the strongest association with the primary outcome (appendix p 16).

The intervention reduced moderate and severe AKI both when assessed by oliguria or serum creatinine AKI criteria (appendix p 17). As shown in a post hoc analysis, the preventive effect of the study intervention was directionally consistent for all surgical, sex, CKD, and early biomarker measurement (within 9 h after surgery) subgroups (appendix p 36–38). Furthermore, we performed a competing-risk analysis to investigate a potential bias of death on AKI rates (appendix p 18) and found no effect of death, given only one patient died within the period until the primary endpoint (72 h) without reaching the primary endpoint first. Further analyses showed differences between groups during the intervention period regarding methods of advanced hemodynamic monitoring used (appendix p 19), rates of patients receiving vasoactive or inotropic drugs at different timepoints (appendix p 20), nephrotoxic drugs (appendix p 21), and postoperative blood glucose concentrations and antihyperglycaemic interventions (appendix p 22). We found similar rates of types of methods used for advanced hemodynamic monitoring used between groups. Although cumulative doses of vasopressors did not differ substantially between groups, we found higher rates of dobutamine use in the intervention group than in the control group at different time points (appendix p 20). Use of nephrotoxic drugs did not differ between groups, apart from a reduced use of non-steroidal anti-inflammatory drugs in the intervention group (appendix p 21). Analyses investigating differences in blood glucose concentrations showed lower serum glucose concentrations in the intervention group than in the control group (appendix p 22). Adverse events were similar between groups (appendix p 23). Rates of loss to follow-up were similar

	Intervention (n=589)	Control (n=591)
Surgical category		
Elective	513 (89·2%)	531 (91·2%)
Emergency	62 (10·8%)	51 (8·8%)
Surgical discipline		
General or abdominal	194 (33·5%)	208 (35·5%)
Cardiac	197 (34·0%)	185 (31·6%)
Vascular	87 (15·0%)	93 (15·9%)
Thoracic	25 (4·3%)	27 (4·6%)
Urological	25 (4·3%)	25 (3·4%)
Orthopaedic or trauma	10 (1·7%)	13 (2·2%)
Gynaecological	10 (1·7%)	14 (2·4%)
Other (eg, neurosurgery, plastics, or oral or maxillofacial)	31 (5·4%)	26 (4·4%)
Intraoperative clinical data, fluid, and vasopressor management		
Fluid administration, mL		
Crystalloids	2243 (1224–5012)	2366 (1316–5239)
Colloids (hydroxyethyl starch, gelatin, or albumin)	500 (100–1000)	500 (200–1000)
Blood products, mL		
Red blood cell concentration	600 (350–1000)	680 (463–1200)
Platelet concentratation	400 (250–500)	400 (250–600)
Fresh frozen plasma	1000 (750–1450)	1200 (750–2000)
Fluid balance, mL		
Urine output	450 (250–800)	500 (250–1000)
Blood loss	200 (0–600)	300 (0–700)
Total fluid balance	1920 (1002–3497)	1998 (1000–3500)
Vasopressors (cumulative intraoperative dose until ICU admission)		
Norepinephrine, µg	1720 (802–3705)	1590 (720–3000)
Adrenaline, µg	491 (285–1320)	592 (204–1590)
Vasopressin, IU	9·8 (3·0–16·5)	4·8 (3·2–11·7)
Dobutamine, mg	27·7 (16·2–59·0)	28·2 (15·3–47·4)
Baseline TIMP-2 × IGFBP7 $(ng/mL)^2/1000$	0·65 (0·43–1·20)	0·66 (0·44–1·26)

Data are n (%) or median (IQR). Numbers and percentages are provided where they are not missing. It is therefore possible that the figures do not add up to the total number of the cohort. ICU=intensive care unit.

Table 2: **Surgical and clinical data up to randomisation**

between groups at approximately 5% (appendix p 24). $MAKE_{90}$ rates were also assessed on the basis of AKI status in an exploratory manner and we found higher $MAKE_{90}$ rates in patients who developed AKI within 72 h, compared with patients without AKI. Finally, $MAKE_{90}$ rates were higher in patients with higher AKI stages (appendix p 25). Results for the per-protocol population (appendix p 26–29) and as-treated population (appendix p 30–34) indicate larger treatment effects compared with the intention-to-treat analysis.

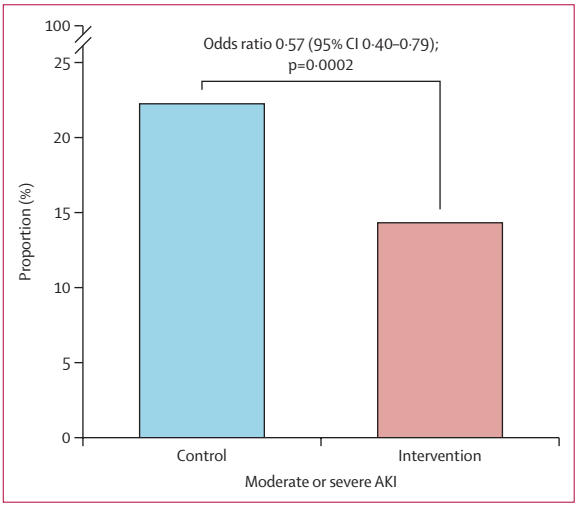

Figure 2: **Rates of moderate or severe AKI**
AKI=acute kidney injury. CKD=chronic kidney disease. HDU=high dependency unit. ICU=intensive care unit.

Discussion

This multinational, adaptive, open-label, randomised clinical trial included adult patients undergoing major surgery who were deemed at high risk of AKI by clinical features and biomarker results. Implementation of an AKI preventive care strategy that was based on KDIGO guidelines was compared with usual care. The trial intervention significantly decreased the occurrence of moderate or severe AKI within 72 h of surgery defined by full KDIGO criteria or by urine output or creatinine criteria alone. This effect was consistent both in the intention-to-treat and per-protocol and as-treated analyses.

We included patients at high risk for AKI using a biomarker-based enrichment strategy in addition to clinical risk factors.[15] This approach selected a group of patients at high risk (approximately 45% of patients fulfilling all other inclusion criteria were biomarker

	Intervention (n=589)	Control (n=591)	Effect estimate (95% CI)	p value
Moderate or severe AKI within 72 h	84/584 (14·4)	131/588 (22·3)	OR 0·57 (0·40 to 0·79)	0·0002
Secondary outcomes: renal endpoints				
Any AKI within 72 h	213/584 (36·5%); 584 non-missing	240/588 (40·8%); 588 non-missing	OR 0·78 (0·60 to 1·01)	..
Stage 1	129/213 (60·6%); 584 non-missing	109/240 (45·4%); 588 non-missing	AD 15·2 (6·1 to 24·2)	..
Stage 2	50/213 (23·%5); 584 non-missing	93/240 (38·8%); 588 non-missing	AD –15·3 (–23·7 to –6·9)	..
Stage 3	34/213 (16·0%); 584 non-missing	38/240 (15·8%); 588 non-missing	AD 0·1 (–6·6 to 6·9)	..
Duration of moderate or severe AKI				
Transient (≤48 h)	50/82 (61·0%); 582 non-missing	71/128 (55·5%); 585 non-missing	AD 5·5 (–8·1 to 19·1)	..
Persistent (>48 h)	32/82 (39·0%); 582 non-missing	57/128 (44·5%); 585 non-missing	AD –5·5 (–19·1 to 8·1)	
Secondary outcomes: clinical endpoints				
Full KDIGO adherence	268 (46·9%); 572 non-missing	29 (5·0%); 577 non-missing	OR 11·58 (7·16 to 18·73)	..
Change in biomarker values during 12 h following initial measurement	–0·24 (–0·71 to 0·10); 447 non-missing	–0·26 (–0·70 to 0·09); 439 non-missing	AD 0·02 (–0·07 to 0·11)	..
RRT up to day 30	30 (5·1%); 587 non-missing	34 (5·8%); 589 non-missing	OR 0·881 (0·517 to 1·501)	..
RRT up to day 90	30 (5·1%); 587 non-missing	35 (5·9%); 589 non-missing	OR 0·861 (0·509 to 1·456)	..
Deaths until day 30	30 (5·1%); 587 non-missing	27 (4·6%); 589 non-missing	..	..
Deaths until day 90,	41 (7·0%); 587 non-missing	41 (7·0%); 589 non-missing	..	..
Survival rate	0·93 (0·91 to 0·95); 587 non-missing	0·93 (0·90 to 0·95); 589 non-missing	HR 1·063 (0·692 to 1·634)	..
Days without mechanical organ support until day 3	3 (3 to 3); 452 non-missing	3 (2 to 3); 437 non-missing	HL 0 (0 to 0)	..
Days without vasopressors until day 3	2 (0 to 3); 587 non-missing	2 (0 to 3); 589 non-missing	HL 0 (0 to 0)	..
ICU length of stay, days	2·94 (1·14 to 6·93); 577 non-missing	2·82 (1·04 to 6·13); 584 non-missing	HL –0·08 (–0·29 to 0·06)	..
Hospital length of stay, days	15·67 (9·65 to 30·50); 577 non-missing	15·70 (9·70 to 28·71); 584 non-missing	HL –0·01 (–1·11 to 1·08)	..
Renal recovery at day 90	206 (35·1%); 587 non-missing	195 (33·1%); 589 non-missing	OR 1·107 (0·852 to 1·438)	..
Major adverse kidney event until day 30	51 (9·0%); 565 non-missing	50 (8·8%); 567 non-missing	OR 1·009 (0·658 to 1·545)	..
Major adverse kidney event until day 90	61 (11·0%); 555 non-missing	60 (10·6%); 564 non-missing	OR 1·026 (0·692 to 1·522)	..

Data are n (%) or median (IQR), unless otherwise indicated. Numbers and percentages are provided where they are not missing; it is therefore possible that the figures do not add up to the total number of the cohort. AD=absolute difference. HL=Hodges–Lehman estimator. HR=hazard ratio. ICU=intensive care unit. OR=odds ratio.

Table 3: **Primary and secondary outcomes**

positive) and was feasible. As AKI is a heterogeneous syndrome, the combination of risk factors with biomarker identification represents an individualised selection approach, justifying targeted treatment algorithms. Although the rate of moderate or severe AKI is unknown for our biomarker-negative (TIMP-2×IGFBP7 ≤0·3 [ng/mL]²/1000) patients, results from previous trials indicate a low incidence of any stage of AKI in an unenriched cohort of cardiac surgery patients of 24·2%,[6] and incidence of moderate or severe postoperative AKI was even lower in a general postsurgical cohort at 6·7%.[1] Therefore, a similar rate of postoperative AKI was expected in our cohort, by contrast with the postoperative AKI rate of 38·7% in our biomarker-positive cohort. Indeed, the negative predictive value of urinary TIMP-2×IGFBP7 concentration of 0·3 (ng/mL)²/1000 or less is 96·3%, so we would predict a low rate of AKI in patients excluded for low test results.[24] Importantly, our enrichment strategy allowed us achieve a power of greater than 80% with our sample size. Had we applied the intervention to all patients, we would have needed to enrol nearly three times the number of patients (assuming the same relative risk reduction that we observed). The innovative study design, using an adaptive approach, allowed for prespecified interim assessment of the optimal sample size required.

Kidney injury and AKI phenotype varies considerably by type of surgery and whether cardiopulmonary bypass was used. We investigated such possible influences in a post-hoc subgroup analysis, which showed coherence for the primary endpoint across surgical, sex, CKD, and early biomarker measurement subgroups. The elements of the preventive care strategy were chosen because evidence of benefit exists for each intervention[24] (advanced hemodynamic monitoring, optimisation of volume status and haemodynamics, avoidance of nephrotoxic drugs and radiocontrast agents, discontinuation of ACE inhibitors and ARBs, and prevention of hyperglycaemia). Therefore, a synergistic protective effect appeared logical. Recommended periods to implement the components were based on KDIGO recommendations and clinical applicability. Because many patients are discharged from ICU and moved to a normal ward on the first postoperative day, advanced haemodynamic monitoring and the haemodynamic optimisation algorithm were only mandated for the first 12 h after randomisation but could be extended if deemed appropriate.

This trial adds robust evidence to a body of evidence from smaller randomised clinical trials.[9,10,12] The demographic and clinical characteristics of the study cohort, surgical interventions, and intraoperative management were well balanced, supporting internal validity. The study was done both at academic and non-academic hospitals in eight countries, which provides a degree of generalisability. Additionally, the intervention had been successfully applied in previous smaller trials, showing reproducibility.[9,10,12] The primary outcome included both serum creatinine and oliguria as recommended by the KDIGO AKI definition. Although AKI is less frequently diagnosed on the basis of serum creatinine than oliguria, evidence shows that both criteria are associated with worse outcomes (especially stage 2–3) and should therefore both be incorporated in clinical care and trials.[25] We incorporated both criteria in the primary endpoint to align with KDIGO recommendations and because stage 2–3 AKI with increased TIMP-2×IGFBP7 carries a higher risk of death or dialysis than biomarker-negative AKI.[3] Most AKI diagnoses in our cohort were based on the oliguria criterion and fewer AKI diagnoses were based on serum creatinine. Notably, our intervention reduced both serum creatinine-based and oliguria-based AKI. Nevertheless, the number needed to treat should be interpreted with caution. Fluid balance and applied intravenous fluid resuscitation did not differ substantially between groups, thus making any effects of haemodilution on serum creatinine measurement unlikely.

We acknowledge several limitations. First, because of the nature of the intervention, masking was not possible. However, data collection and analysis were independent of allocation. Second, the implementation of some of the recommended interventions might already be part of postoperative management in some centres. However, as seen in other fields of medicine, compliance with guidelines is low.[7] Aligned with such findings, full postoperative compliance with KDIGO preventive measures was only 5·3% in a cohort of cardiac surgery patients.[6] Third, although patients were representative of those undergoing major surgery in Europe, the study population might not be representative of patients in low-income and middle-income countries or jurisdictions with different ethnic distributions or background care. Furthermore, patients with CKD stage 4–5 were not included because their risk might not be modifiable. Future studies should investigate whether the preventive strategy can reduce AKI rates in patients with stage 4–5 CKD. Fourth, we did not collect AKI data in biomarker-negative patients, limiting assessment of enrichment-effectiveness using biomarkers. However, this analysis was not the aim of our study and it is already known that patients with a positive TIMP-2×IGFBP7 value are at an increased risk to develop AKI compared with biomarker-negative patients.[25] Fifth, investigating multiple secondary outcomes without adjustment for multiplicity increases the risk of false-positive findings. Acknowledging this limitation, all secondary outcome and sensitivity analyses must be interpreted with caution and should be considered exploratory analyses. Moreover, implementation of all components of the preventive strategy proved to be challenging in multiple ways: (1) achieving clinical targets was not always possible despite best efforts; (2) conflicting clinical targets (eg avoidance of nephrotoxic antibiotics *vs* requirement of antibiotic treatment in the absence of non-nephrotoxic alternatives) had to be balanced against each other and nephroprotection could not be prioritised under all circumstances; and (3) human

factors including staffing, shift patterns, emergency situations, and training with regard to implementation of the preventive strategy might have influenced adherence and effectiveness of the intervention. Although the overall cumulative dose of applied vasopressors or fluids did not differ between groups, implementation of the preventive strategy resulted in more individualised haemodynamic management, driven by increased monitoring and functional testing in the intervention group. This finding is highlighted by high rates of advanced haemodynamic monitoring implemented in the intervention group compared with the control group (78·6% *vs* 8·8%) and regular performance of a passive leg raising manoeuvre in the intervention group compared with controls (80·6% *vs* 10·5%). This difference also resulted in improved clinical management of intervention patients, as shown for example by hypotension occurring only half as often in intervention patients compared with controls (7·6% *vs* 15·3%). Application of nephrotoxic drugs did not differ between groups, except for non-steroidal anti-inflammatory drugs that were less frequently applied in the intervention group than in the control group (6·42% *vs* 9·55%). Of the strategy components, tight glycaemic control proved especially difficult to achieve and maintain for the complete intervention period; however, tight glycaemic control is a component with strongly conflicting evidence.[24,26–28] We acknowledge the limitation that tight glycaemic control is not viewed as standard of care and our sensitivity analysis also suggests no benefit of tight glycaemic control to prevent moderate or severe AKI. Excluding tight glycaemic control from the preventive strategy shows a high rate of full preventive strategy implementation of 62·7% in the intervention group compared with 6·8% in the control group. This finding is similar to other trials finding no effect of the intervention when differences in adherence were only marginally different between groups.[29] To increase adherence in real-world clinical settings, we suggest to focus on patients at high risk for AKI, training caregivers in applying the protocol, and to consider the proposed measures in these patients. Some components of the preventive strategy might not be appropriate for some patients, so we allowed local clinicians to withhold certain interventions if deemed inappropriate for a specific patient. The preventive strategy consists of interventions that are not resource intensive and can be easily implemented in patients at high risk in lower-resource hospitals. Further research is required to investigate implementation of preventive strategies in different settings. Finally, the event rate of secondary outcomes was low (except for any AKI). Thus, the study was not powered to detect changes in long-term outcomes. Importantly, clinical outcomes such as death or RRT are rare in this patient population. Even the composite MAKE, which also includes persistent kidney dysfunction, only occurred in 10% of control patients. These endpoints are not recommended for AKI prevention trials.[15] Our sample size only provided adequate power to detect a relative risk reduction (RRR) of at least 40% in $MAKE_{90}$. Therefore, much larger trials would be required to assess the effect of our intervention on $MAKE_{90}$. To further illustrate this, given that $MAKE_{90}$ occurs in about 5% of patients without AKI, and AKI increases the risk to 19% (appendix p 25), our intervention has an expected effect size (RRR) of approximately 35% (on stage 2–3 AKI), so our expected effect would be to reduce $MAKE_{90}$ from 10·5% to 8·7%. To see this effect would require randomly assigning more than 8000 patients.

In conclusion, compared with usual care, in major surgery patients at high risk for AKI, as identified by urinary TIMP-2×IGFBP7 together with clinical risk factors, a KDIGO-recommended preventive care strategy significantly decreased the occurrence of moderate or severe AKI within 72 h of surgery.

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Contributors
AZ and JK conceptualised the study. AZ, CW, and TvG coordinated the study. AZ, MO, LF, CB, LW, CP, DPR, ELM, CA, TR, SdR, CM, AGS, AG, MJK, SR, JG, NL, JGH, JRM, SS, AS, EF, LA, IRB, RGA, AB, PR, MS, MM, and TvG were study investigators. CW was the study coordinator. KF conducted the statistical analysis. All authors participated in the interpretation of data outputs and study results, and in the drafting, critical revision, and approval of the final version of the manuscript. All authors had access to all the included data and permission to access the raw data. AZ, TvG, MD, JG, and KF directly accessed and verified the data. The statistical analyses and results were further verified by an independent member of the Institute for Biometry and Clinical Research of the University of Münster. Safety data were monitored by the Data Safety Monitoring Board (appendix p 7). AZ, LF, RB, JK, and TvG drafted the manuscript. The manuscript was critically revised by MO, AS, EF, and MS. All authors accept final responsibility for the decision to submit for publication.

Data sharing
De-identified datasets of the data supporting the results in the manuscript and statistical code will be available upon reasonable request, 12 months following publication of the study results. Requests should be

sent to the Principal Investigator, AZ (zarbock@uni-muenster.de), stating the variables required and purpose of the request (objective or objectives and research plan). The study protocol and data dictionary will also be made available via the Principal Investigator's email. Requests will be considered on a case-by-case basis, and requestors will be asked to complete a data sharing agreement with the sponsor before data transfer.

Declaration of interests

AZ has received consulting fees from Astute-Biomerieux, Baxter, Bayer, Novartis, Guard Therapeutics, AM Pharma, Paion, Fresenius, research funding from Astute-Biomerieux, Fresenius, and Baxter, and speakers fees from Astute-Biomerieux, Fresenius, and Baxter. MO received funding from Baxter and Biomerieux, which was paid to the institution. LF received funding and honoraria from Baxter and consulting fees from Astra Zeneca, Baxter, and SphingoTec. CB received research support from SphingoTec. CP and CA received consulting fees from SphingoTec. TR received funding and honoraria from bioMéríeux. SdR received honoraria from Baxter, Fresenius, and Toray Industries. CM received honoraria from Fresenius, bioMérieux, and Baxter. AGS received funding and honoraria from bioMéríeux. SR received honoraria and travel funding from Medtronic, Masimo, Baxter, BBraun, Fresenius, Vygon, and Viatris. JGH and JR-M received honoraria from Edwards Lifesciences, Fresenius Kabi, and Baxter. EF received honoraria from Draeger Medical and GE Healthcare. RGA received honoraria from AOP Orphan. MM received funding from Baxter and honoraria from Fresenius, Baxter, and Franz Köhler Chemie. JAK holds royalties or licenses from CytoSorbents, Klotho, bioMérieux, and J3RM; holds stock options of and is contracted by Spectral Medical; received honoraria from AstraZeneca, Bayer, Novartis, bioMéríeux, Mitsubishi Tenabe, and Chugai Pharma; and holds patents with CytoSorbents, bioMéríeux, J3RM, and Klotho. TvG was supported by a rotational position funded by the Deutsche Forschungsgemeinschaft (493624047). All other authors declare no competing interests.

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