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Original Article

Statistical analysis plan for the biomarker-guided intervention to prevent acute kidney injury after major surgery (BigpAK-2) study: An international randomised controlled multicentre trial

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ABSTRACT

Objective: This article describes the statistical analysis plan for the Biomarker-guided intervention to prevent AKI after major surgery (BigpAK-2) trial.
Design: Adaptive trial design with an interim analysis after enrolment of 618 evaluable patients.
Setting: The BigpAK.-2 trial is an international, prospective, randomised controlled multicentre study.
Participants: The BigpAK-2 study enrols patients after major surgery who are admitted to the intensive care or high dependency unit and are at high-risk for postoperative AKI as identified by urinary biomarkers (tissue inhibitor of metalloproteinases-2 and insulin-like growth factor binding protein 7 ([TIMP-2]*[IGFBP7]) will be enrolled.
Intervention: Patients are randomly and evenly allocated to standard of care (control) group or the implementation of a nephroprotective care bundle (intervention group), as recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. The KDIGO care bundle recommends discontinuation of nephrotoxic agents if possible, ensuring adequate volume status and perfusion pressure, considering functional haemodynamic monitoring, regular monitoring of serum creatinine and urine output, avoiding hyperglycemia, and considering alternatives to radiocontrast procedures when possible.
Results: The BigpAK-2 study investigates whether the biomarker-gudied implementation of the KDIGO care bundle reduces the incidence of moderate or severe AKI (stage 2 or 3), according to the KDIGO 2012 criteria, within 72 h after surgery.
Conclusion: AKI is a common and often severe complication after major surgery. As no specific treatments exist, prevention of AKI is of high importance. The BigpAK-2 study investigates a promising approach to prevent AKI after major surgery.
Trial registration: The trial was registered prior to start at clinicaltrials.gov; NCT04647396.

Abbreviations: AKI, Acute Kidney Injury; AKI_0, Primary endpoint rate under standard care; AKI_1, Primary endpoint rate under the interventional treatment; CMH test, Cochrane Mantel Haenszel test; CONSORT, Consolidated Standards of Reporting Trials; DSMB, Data Safety Monitoring Board; GCP, Good Clinical Practice; ICH, International Conference on Harmonisation; ICU, Intensive Care Unit; ITT, Intention-To-Treat; KDIGO, Kidney Disease: Improving Global Outcomes Group; MAKE, Major adverse kidney events, including death, use of RRT and persistent renal dysfunction (defined as serum creatinine ≥2x to baseline value at hospital discharge); PCI, Principal Coordinating Investigator; SAP, Statistical Analysis Plan; RRT, Renal Replacement Therapy.

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1. Introduction

Acute kidney injury (AKI) is a common complication after major surgery and is associated with increased morbidity and mortality rates.[1] Major surgery is a key risk factor for the occurrence of acute kidney injury (AKI). The incidence of AKI after major surgery is highly variable depending on average age and comorbidities of the patient cohort, as well as the type of surgery performed.[2–5] Recently, the first prospective and international multicentre EPIS-AKI study reported an incidence of postoperative AKI of 18.4%.[6] If AKI occurs after major surgery, it is associated with postoperative complications, such as prolonged stay in the intensive care unit (ICU), development or progression of chronic kidney disease (CKD), and need for renal replacement therapy (RRT).[6,7] Given this significant impact on patient outcomes and a lack of causative therapy, prevention of AKI is of high relevance. For the prevention of AKI, the Kidney Disease: Improving Global Outcomes (KDIGO) group recommends the implementation of a nephroprotective care bundle in high risk patients.[8] This care bundle consists of the following recommendations: discontinue all nephrotoxic agents when possible, ensure volume status and perfusion pressure, consider functional haemodynamic monitoring, monitor serum creatinine and urine output, avoid hyperglycemia, and consider alternatives to radiocontrast procedures. However, research suggests that only a minority of critically ill patients is currently treated according to these guidelines.[9,10,11]

AKI is detected by a rise of serum creatinine or a reduction in urinary output (oliguria/anuria), according to KDIGO guidelines.[8] However, these two functional biomarkers currently used for detecting and staging AKI have several limitations.[11,12,13] Novel kidney biomarkers however identify patients at high risk for AKI, thereby extending the window of therapeutic interventions to a period before clinically manifest AKI occurs. Several studies demonstrated that the tubular stress and cell-cycle arrest biomarkers tissue inhibitor of metalloproteinases 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) have a good performance in predicting the development of AKI.[14,15,16,17] These biomarkers may thus allow a biomarker-guided implementation of the KDIGO care bundle and allow an intervention before a decline of kidney function occurs. Previous studies have successfully investigated this approach both in cardiac surgery and in a small cohort of abdominal surgery patients.[10,18,19,20]

1.1. Objectives of the trial

The primary objective of the BigpAK-2 trial is to determine the effectiveness of a biomarker-guided application of the KDIGO bundle in reducing the occurrence of post-operative moderate or/and severe AKI compared to standard of care. Patients at high risk for AKI are identified by the tubular stress biomarkers tissue inhibitor of metalloproteinases-2 and insulin like growth factor binding protein 7 ([TIMP-2]*[IGFBP7]). The study protocol has been previously published.[21]

2. Study design and participants

The BigpAK-2 trial is an international, prospective, randomised controlled multi-centre trial conducted at 32 study sites in Germany, Spain, Italy, France, the United Kingdom, Switzerland, Belgium and the Netherlands. A maximum number of 1418 evaluable patients will be enrolled during the recruitment period (including 618 patients in a first stage of recruitment and depending on the interim results up to 800 additional patients). The study enrols patients undergoing extended surgical procedures that require postoperative treatment in an intensive care or intermediate care unit. High-risk patients for postoperative AKI are identified by urinary biomarkers (tissue inhibitor of metalloproteinases-2 and insulin-like growth factor binding protein 7 ([TIMP-2]*[IGFBP7]) and additional pre-defined clinical risk factors (need for mechanical ventilation or vasopressors, preoperative CKD with an eGFR 30–60 ml/min/1.73m^2, intraoperative application of radiocontrast agents, or age >75 years). Eligible patients are randomly allocated to standard of care (control group) or the application of a nephroprotective care bundle (intervention group), as recommended by the KDIGO guidelines. The duration of the study intervention (KDIGO bundle or standard of care) is 72 h, with follow-up until 90 days after surgery. Co-enrolment in other studies is possible as long as they are observational or the intervention does not affect renal outcomes.

2.1. Sample size and power

Sample size and power calculations were performed based on a group sequential adaptive plan with one interim analysis and the primary endpoint occurrence of moderate or severe AKI (KDIGO stage 2 or 3) within 72 h after surgery. The expected AKI rate ($\geq$ stage 2), substantiated by published data of the BigpAK trial, in the control group and the intervention group is 20% and 14%, respectively. The target power was set to 80%. The interim analysis is performed when 309 evaluable patients have been recruited in each treatment group (2x309 = 618 patients in total). Using the results of the interim analysis, the sample size of the final analysis will be determined (see below).

The original power calculation was performed under the assumption that the final statistical analysis is performed when additional 309 evaluable patients have been recruited after the interim analysis in each treatment group (2x309+2x309 = 1236 evaluable patients in total). The resulting operating characteristics of the group sequential adaptive plan for the one-sided tests are shown in Table 2. Calculations were performed using the ADDPLAN software.

A number of up to 5% of recruited patients are expected to be lost to follow up and in the worst case have completely non-evaluable data. Therefore, an expected total number of 1302 patients have to be recruited in order to provide a number of 1236 evaluable patients. The final sample size adaptation rule (specified below) was designed to guard against deviations from the original planning assumptions. It will result in the possible total numbers of evaluable patients 618, 1118 or 1418. Although the above total number of 1236 evaluable patients therefore cannot occur, the original operating characteristics are maintained: under the expected AKI rates ($\geq$ stage 2) of 20% in the control group and 14% in the intervention group, the attained power is >80% (see below).

2.2. Randomisation

Treatment assignment will be accomplished using the RandIMI module for the electronic data capture system REDCap and randomisation will be performed centrally in a 1:1 proportion in blocks of a randomly chosen length of 4 or 6, stratified by center.[22–24] The study personnel involved in adjudication of endpoints or complications will be blinded to treatment assignment. Other study personnel and the patients cannot be blinded to treatment assignment due to the nature of the intervention.

3. Outcome measures

The primary outcome of the study is the occurrence of moderate or severe AKI (KDIGO stage 2 or 3) within 72 h after surgery. Secondary outcomes include adherence to the KDIGO bundle,

Table 1
Primary and secondary outcomes.

Primary outcome
Occurrence of moderate or severe AKI (KDIGO stage 2 or 3) within 72 h after surgery
Secondary outcomes
1. Adherence to the KDIGO bundle[5]
2. Occurrence and severity of any stage of acute kidney injury within 3 days after surgery
3. Change in biomarker values during 12 h after initial measurement of [TIMP2]*[IGFBP7]
4. Free-days of mechanical organ support through to day 3
5. Free-days of vasopressors through day 3
6. Need of RRT at day 30 and 90
7. Duration of RRT at day 30 and 90
8. Renal recovery at day 90
9. 30-day and 90-day mortality
10. ICU length-of-stay and Hospital length-of-stay
11. Major adverse kidney events (MAKE90) (defined as the composite of death, use of RRT and persistent renal dysfunction (defined as serum creatinine ≥2x to baseline value at hospital discharge)) at day 90

occurrence of any stage of AKI, change in biomarker values during 12 h after initial measurement, free days of mechanical organ support through to day 3, free-days of vasopressors through day 3, need of RRT at day 30 and 90, duration of RRT at day 30 and 90, renal recovery at day 90, 30-day and 90-day mortality, ICU length-of-stay and Hospital length-of-stay, Major adverse kidney events (MAKE90) (defined as the composite of death, use of RRT and persistent renal dysfunction (defined as serum creatinine ≥2x to baseline value at hospital discharge)) at day 90. Table 1 shows the primary and secondary outcomes.

3.1. Data monitoring

Postoperative complications are recorded and reported as secondary outcomes. The safety population includes all patients who were randomised. Safety data are regularly monitored during the recruitment period by an external Data Safety Monitoring Board (DSMB).

Quality of the data and outcome measures is regularly monitored in every participating site. Data quality monitoring is performed after 10 patients recruited in any new study site and consecutively after further every 20 recruited patients. Sites with more than 40 recruited patients are monitored by additional on-site visits.

3.2. Statistical analysis

3.2.1. Primary statistical analysis: Basic concepts

3.2.1.1. Analysis populations. The full analysis population includes all patients who will be randomised. The per protocol population includes all patients without major protocol deviations.

Major protocol deviations that lead to exclusion from the per protocol population are.

1. Violation of inclusion/exclusion criteria
2. Noncompliance to the randomised intervention

The safety population includes all patients who were randomised.

3.2.1.2. Primary hypothesis and statistical approach. The null hypothesis H_0: $AKI_1 = AKI_0$ will be tested at a significance level of 5% against the two-sided alternative H_1: $AKI_1 \neq AKI_0$, where AKI_1 denotes the primary endpoint rate under the interventional treatment and AKI_0 under standard care. The primary statistical analysis provides confirmatory statistical evidence.

Formally, the two-sided test will be decomposed into two one-sided tests of the null hypotheses H_{0a}: $AKI_1 \geq AKI_0$ and H_{0b}: $AKI_1 \leq AKI_0$ against the respective alternatives. The significance level of each of the one-sided tests will be 2.5%. This is common practice for an adaptive design as difficulties in the interpretation of the two-sided testing procedures arise when results from different stages point in different directions.[25]

A group sequential adaptive plan with one interim analysis will be conducted. The statistical analysis will be performed applying the inverse normal method based on a group sequential plan with decision bounds determined by the O'Brien and Fleming type alpha spending function without futility stop.[25] Those bounds are based on one interim analysis conducted at information rate 0.5 and remain fixed as given in Table 2. The combination function of stage 1 and 2 will be constructed using fixed weights of both stages $w_1 = w_2 = \sqrt{0.5}$ (corresponding to half of the total number of patients, information rate 0.5). The primary statistical analysis will include all randomised patients (full analysis set) and will be performed according to the intention-to-treat principle (ITT) in order to prevent attrition bias. The randomised groups will be compared with a Cochrane Mantel Haenszel test[26] with stratification by center as "factors on which randomisation has been stratified should be accounted for later in the analysis" as stated by the ICH E9 Guideline. Stagewise p-values will be computed based on all patients recruited in the respective stage, including all strata with more than one patient. The results of the interim analysis will be compared to the final results in order to find out whether changes in practice may already have occurred during the study period. Missing values that may arise in effectiveness or safety parameters will not be replaced by any kind of statistical imputation. Statistical analyses will be performed using standard statistical software (SAS).

4. Primary statistical analysis: Details of the interim analysis and sample size adaptation

The interim analysis will be performed using data of the first n_1: = 2x309 = 618 evaluable patients (309 patients per treatment group).

If the interim p-value $p_a^{interim}$ of the one-sided null hypothesis H_{0a}: $AKI_1 \geq AKI_0$ is at most 0.0015, the trial is finished. It will be concluded that the primary endpoint rate under the interventional treatment AKI_1 is lower than under standard care (AKI_0), and that the interventional treatment is superior to standard care.

If the interim p-value $p_b^{interim}$ of the one-sided null hypothesis H_{0b}: $AKI_1 \leq AKI_0$ is at most 0.0015, the trial is finished. It will be concluded that the primary endpoint rate under the interventional treatment AKI_1 is higher than under standard care (AKI_0), and that the interventional treatment is inferior to standard care.

Table 2
Decision bounds and operating characteristics of the original group sequential adaptive plan.

Stage	Infor-mation rate	Bounds accept H_0	Bounds reject H_0	Signifi-cance level (one-sided)	α spent	Power achieved	Sample size
1	0.5	–	2.963	0.0015	0.0015	0.1647	2x309
2	1.0	1.969	1.969	0.0245	0.0250	0.8010	2x309

If either $p_a^{interim} \leq 0.0015$ or $p_b^{interim} \leq 0.0015$, recruitment will stop as soon as possible. The primary final analysis will be performed with all patients who have been included in the interim analysis. Additional sensitivity analyses will be performed, additionally including "interim patients" who have been recruited between the data base lock of the interim analysis and the final recruitment stop.

If both p-values of the one-sided null hypotheses H_{0a}: $AKI_1 - \geq AKI_0$ and H_{0b}: $AKI_1 \leq AKI_0$ are >0.0015, the trial will be continued and the following procedure will be applied.

Based on $p_a^{interim}$ the number of additional evaluable patients n_2 (recruited after the interim analysis) will be determined as follows.

- If $p_a^{interim} \leq 0.0015$, the trial is finished after the interim analysis (see above).
- If $0.0015 < p_a^{interim} \leq \alpha_{interim}$,

an additional number of $n_2 = 2x250 = 500$ evaluable patients will be recruited.

The final statistical analysis will be performed using data of $n_2 = 2x250 = 500$ additional patients, who were recruited after the interim analysis.

The total number of evaluable patients is $n_1+n_2 = 618 + 500 = 1118$ (559 patients per treatment group).

- If $p_a^{interim} > \alpha_{interim}$ (or even >0.5),

an additional number of $n_2 = 2x400 = 800$ evaluable patients will be recruited.

The final statistical analysis will be performed using data of $n_2 = 2x400 = 800$ additional patients, who were recruited after the interim analysis.

The total number of evaluable patients is $n_1+n_2 = 618 + 800 = 1418$ (709 patients per treatment group). P-values in the range $p_a^{interim} > \alpha_{interim}$ include those with $p_a^{interim}$ >0.5. P-values $p_a^{interim}$ >0.5 occur if the pooled Odds Ratio comparing patients under the interventional treatment to those under standard of care is greater than 1, indicating that the interventional treatment may be inferior to standard care.

The parameter $\alpha_{interim}$ was specified at the time when the present Statistical Analysis Plan (SAP) was written (12 May 2023). Since then, its value is finally determined and will not be changed. The specified value of $\alpha_{interim}$ however is not included in the present SAP. It must be kept confidential until 500 additional patients that have not been included in the interim analysis have been recruited, in order to preserve the integrity of the trial. An appendix to the SAP was written at the same time as the present SAP (12 May 2023). The appendix to the SAP contains the specified value of $\alpha_{interim}$. The appendix to the SAP was sent to the DSMB. The DSMB deposits the appendix to the SAP until the end of the trial. It guarantees that the appendix to the SAP is not accessed by the Principal Coordinating lnvestigator (PCI) or any other study personnel. After the end of the trial, the DSMB will assess and confirm that the trial was conducted according to the previously specified value of $\alpha_{interim}$. If the trial is continued after the interim analysis, the information about the further recruitment will be reported to the Principal Coordinating Investigator (PCI) and all other study personnel in a stepwise way. Therefore, after the interim analysis, the PCI will be informed only, if the trial will be finished after the interim analysis ($n_2 = 0$), or if it will be continued. If the trial is continued, the PCI will not get to know the sample size n_2 yet. Whether the sample size n_2 is 500 or 800, will be reported to the PCI only in a second step, at the time when additional 500 evaluable patients have been recruited. At that time, the PCI will be informed, if the final sample size is reached ($n_2 = 500$), or if recruitment will be continued up to additional 300 evaluable patients (so that $n_2 = 500 + 300 = 800$).

4.1. Dataset analysed

The Consolidated Standards of Reporting Trials (CONSORT) will present all patients that were screened for the study. If consent is not obtained or withdrawn, data will be excluded from the analysis. Clinical data will be collected from the electronic healthcare record of each participating site and entered on an electronic CRF (RedCAP, Research Electronic Data Capture, Version 10.6.22, respectively up-to-date version, Vanderbilt University) in a pseudoanonymised form. Patient identifiable information will not be included in the data-analysis. Data transmission and storage of web-based information is encrypted and will be stored and backed up at the Westphalian Wilhelms University of Münster in Germany.

4.2. Trial profile and overview

The final statistical analysis will be conducted after the completion of the last follow-up of the last recruited patient, data cleaning and final hard locking of the database. The final study report will follow the guidelines of the Consolidated Standards of Reporting Trials (CONSORT) for reporting randomised controlled trials.[27] A flow diagram following the CONSORT guidelines will summarize the recruitment flow of the study. This diagram includes the number of screened patients, those meeting exclusion criteria and which exclusion criteria, eligible patients, informed consent, and those randomised into each of the study arms. The SAP has been written in accordance with the International Council for Harmonisation (ICH) guidelines (E9 Statistical Principles for Clinical Trials and E3 Structure and content of clinical study reports)[28,29].

5. Descriptive summary of study data

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), number of missing values, mean, standard deviation, median, first and third quartile, minimum, maximum.

For categorical variables the frequency and percentages of observed levels will be reported based on the non-missing sample size. All summary tables will be structured by treatment arms and annotated with the total population size relevant to that table/treatment, including any missing observations.

Censored variables will be summarised using Kaplan–Meier estimation.

5.1. Patient baseline characteristics

Baseline characteristics at time of randomisation will be reported for each of the two study arms. The randomisation success will be evaluated by comparing demographic and clinical characteristics between the randomised groups. Differences between treatment groups will be quantified as follows:

1. Normally distributed continuous variables: Student's two-sample t test, absolute mean difference between groups
2. Non-normally distributed continuous variables: Wilcoxon two-sample test (t approximation), Hodges-Lehmann estimator of location shift
3. Categorical variables: Chi squared test, Absolute difference of percentages, odds ratio
4. Censored variables: Log rank test, Absolute difference of percentages of observed events, hazard ratio

5.2. Outcome measure analysis

5.2.1. Primary statistical analysis: Final analysis

In the final statistical analysis, data of n_2 additional patients will be evaluated, who were recruited after the interim analysis ($n_2 = 500$ or $n_2 = 800$, see above).

The final overall p-value p_a^{final} of the one-sided null hypothesis H_{0a}: $AKI_1 \geq AKI_0$ is defined as the minimal possible one-sided significance level, that could have been specified, so that the final statistical analysis would result in rejection of the null hypothesis H_{0a}: $AKI_1 \geq AKI_0$ against the one-sided alternative H_{1a}: $AKI_1 < AKI_0$. This concept is known as a repeated p-value.[30] If the final overall p-value is $p_a^{final} \leq 0.025$, it will be concluded that the primary endpoint rate under the interventional treatment AKI_1 is lower than under standard care (AKI_0), and that the interventional treatment is superior to standard care. This is the case if and only if the combined p-value of the stagewise p-values for H_{0a} is smaller than the local significance level of the second stage (see Table 2).

The final overall p-value p_b^{final} of the one-sided null hypothesis H_{0b}: $AKI_1 \leq AKI_0$ is defined as the minimal possible one-sided significance level, that could have been specified, so that the final statistical analysis would result in rejection of the null hypothesis H_{0b}: $AKI_1 \leq AKI_0$ against the one-sided alternative H_{1b}: $AKI_1 > AKI_0$. If the final overall p-value is $p_b^{final} \leq 0.025$, it will be concluded that the primary endpoint rate under the interventional treatment AKI_1 is higher than under standard care (AKI_0), and that the interventional treatment is inferior to standard care. This is the case if and only if the combined p-value of the stagewise p-values for H_{0b} is smaller than or equal to the local significance level of the second stage (see Table 2).

The final overall two-sided p-value p_{final} is defined as the minimum of the doubled one-sided p-values p_a^{final} and p_b^{final}, i.e. $p_{final} = \min(2 \cdot p_a^{final}, 2 \cdot p_b^{final})$. The corresponding confidence interval of the Odds Ratio will be computed applying the repeated confidence interval approach. All reported numbers of patients refer to patients with evaluable primary endpoint data. The corresponding numbers of recruited patients may be increased in order to compensate for missing data.

5.2.1.1. Operating characteristics. The operating characteristics of the applied design and sample size adaptation are shown in Table 3, including the total numbers of patients, percent stops after stage 1, and overall power. The operating characteristics were determined with the R software (RPACT package) in 1.000.000 simulation runs[31,32]. Simulated data were generated assuming equal primary endpoint rates across all strata under standard care ($AKI_0 = 20\%$ in all strata), as well as under the interventional treatment ($AKI_1 = 10\%/14\%/15\%/20\%$ in all strata). The statistical analysis of simulated data was performed with Pearson's chi-squared tests.

Table 3
Operating characteristics.

Expected primary endpoint rate under standard care AKI_0	20%	20%	20%	20%
Expected primary endpoint rate under the interventional treatment AKI_1	10%	14%	15%	20%
Total number of patients:				
1. Minimum	618	618	618	618
2. Average	772.8	1145.1	1222.8	1400.8
3. Maximum	1418	1418	1418	1418
Percent stops after stage 1	70.8%	16.3%	9.1%	0.3%
Overall power (rejection of H_{0a})	99.9%	82.1%	66.0%	2.5%

6. Secondary statistical analyses

Secondary outcomes will be evaluated in the full analysis set according to ITT. Secondary statistical analyses are intended to be exploratory (hypothesis generating) and will be interpreted accordingly. A two-sided p-value of ≤ 0.05 will be considered as noticeable without adjustment for multiplicity.

Statistical analysis of the pre-specified secondary endpoints will be performed with descriptive and inferential statistical methods. In inferential statistical analyses two-sided significance tests will be applied with a local significance level alpha = 0.05. All point estimates of parameters of interest will be supplemented by 95% confidence intervals unless otherwise stated. Secondary outcomes will be evaluated and compared between the randomised treatment arms with stratification by center using the following methods. In case of normally or non-normally distributed metric outcomes, a two-way ANOVA or the van Elteren test will be applied, respectively. Categorical outcomes will be analysed using (generalized) Cochrane Mantel Haenszel tests. Survival data will be analysed using the Kaplan–Meier method and the stratified log-rank test. Hazard ratios will be estimated based on stratified Cox proportional hazards models after checking the proportional hazards assumption based on the Schoenfeld residuals.

6.1. Sensitivity analyses

Sensitivity analyses include per protocol population analyses of the primary outcome, excluding patients with major protocol deviations. In additional sensitivity analyses, the primary outcome will be evaluated with an amended stratification, combining strata that include fewer than 5 patients. In additional sensitivity analyses, we will investigate the effect of the actual implementation of individual components of the KDIGO bundle. The KDIGO bundle will be decomposed into its individual components. Multivariable statistical analyses will include a separate factor for every individual component of the KDIGO bundle. Each of these factors indicates if the respective component of the KDIGO bundle was actually implemented or not (as-treated approach).

6.2. Treatment of missing data

Missing data will not be imputed.

7. Deviation from analysis described in protocol

Not applicable.

8. Data availability statement

Individual patient data will not be made available with this publication because the BigpAK-2 trial is ongoing. Individual patient data will be accessible in anonymised form from the principal investigator after study completion upon reasonable request and in line with German data safety regulations.

9. Limitations

The most important feature of the developed adaptive trial design is the use of interim results to drive the further conduct of the trial, including the possible early completion of the trial after the interim analysis. The design and its application comes up with a few challenges and drawbacks that – even though they are outweighed by desirable properties – are worth to be mentioned. One important challenge is to keep the interim results strictly confidential in order to preserve the integrity of the trial. The stagewise results may deviate from each other too much and therefore may be difficult to interpret. A similar problem may arise when the interim analysis is repeated including “interim patients”, who have been

recruited between the data base lock of the interim analysis and the final recruitment stop. In the final statistical analysis, stagewise results are combined with pre-determined fixed weights. These weights do not completely agree with the optimal weights that would be adapted to the actual sample size of both stages. It is not possible however to pre-determine the stage 2 sample size and corresponding optimized weights. Pre-determination of stage 2 would contradict the desired possibility to flexibly adjust the further conduct of the trial after the interim analysis.

10. Conclusion

The BigpAK-2 study will provide definitive evidence for the hypothesis that a biomarker-guided implementation of the KDIGO bundle reduces the occurrence of moderate or severe AKI after major surgery. Using an adaptive trial design with interim analyses, a pragmatic and efficient determination of required sample size will be achieved.

Ethics approval

The study was approved by the Ethics Committee Westfalen-Lippe and subsequently by the corresponding Ethics Committee of the participating sites. A study amendment was approved subsequently. In the UK, the trial was adopted as an NIHR portfolio study. Clinicaltrials.gov registration number NCT04647396.

Authorship contribution statement

Conceptualization: AZ, MM, TvG, JG.
Methodology: AZ, JG, MFD.
Formal analysis: AZ, TvG, JG, MFD.
Investigation: AZ, TvG, JG, MFD, BigpAK-2 study group.
Writing - original draft: TvG, JG.
Writing: Review & Editing: AZ, MM, MFD, BigpAK-2 study group.
Supervision: AZ.
Project administration: AZ, MM, TvG, JG.

Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Alexander Zarbock reports financial support was provided by bioMérieux Inc. Alexander Zarbock reports a relationship with AM Pharma, Baxter, Bayer, bioMerieux, Fresenius Medical Care, Guard Therapeutics, Novartis, Paion. that includes: funding grants and speaking and lecture fees. Melanie Meersch reports a relationship with Biomériux, Baxter and Fresenius Medical Care that includes: funding grants and speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ccrj.2024.03.001.

References

[1] Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman CR, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015;41(8):1411–23. https://doi.org/10.1007/s00134-015-3934-7.
[2] O'Connor ME, Kirwan CJ, Pearse RM, Prowle JR. Incidence and associations of acute kidney injury after major abdominal surgery. Intensive Care Med 2016;42:521–30.
[3] Romagnoli S, Zagli G, Tuccinardi G, Tofani L, Chelazzi C, Villa G, et al. Postoperative acute kidney injury in high-risk patients undergoing major abdominal surgery. J Crit Care 2016;35:120–5.
[4] Hobson CE, Yavas S, Segal MS, Schold JD, Tribble CG, Layon AJ, et al. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. Circulation 2009;119:2444–53.
[5] Hobson C, Lysak N, Huber M, Scali S, Bihorac A. Epidemiology, outcomes, and management of acute kidney injury in the vascular surgery patient. J Vasc Surg 2018;68:916–28.
[6] Zarbock A, Weiss R, Albert F, Rutledge K, Kellum JA, Bellomo R, et al. Epidemiology of surgery associated acute kidney injury (EPIS-AKI): a prospective international observational multi-center clinical study [published online ahead of print, 2023 Jul 28]. Intensive Care Med 2023. https://doi.org/10.1007/s00134-023-07169-7.
[7] Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med 2014;371:58–66.
[8] Kidney Disease. Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO Clinical Practical Guideline for Acute Kidney Injury in Kidney Inter; 2012. p. 1–138.
[9] Küllmar M, Weiß R, Ostermann M, Campos S, Novellas NG, Thomson G, et al. A multinational observational study exploring adherence with the kidney disease: improving global outcomes recommendations for prevention of acute kidney injury after cardiac surgery. Anesth Analg 2020;130:910–6.
[10] Zarbock A, Küllmar M, Ostermann M, Lucchese G, Baig K, Cennamo A, et al. Prevention of cardiac surgery-associated acute kidney injury by implementing the KDIGO guidelines in high-risk patients identified by biomarkers: the PrevAKI-multicenter randomized controlled trial. Anesth Analg 2021;133(2):292–302. https://doi.org/10.1213/ANE.0000000000005458.
[11] Massoth C, Küllmar M, Pajares Moncho A, Susana G-S, Ivkin EGA, von Dossow V, et al. Implementation of the Kidney Disease Improving Global Outcomes guidelines for the prevention of acute kidney injury after cardiac surgery: an international cohort survey. Eur J Anaesthesiol 2023;40(6):418–24. https://doi.org/10.1097/EJA.0000000000001837.
[12] Schetz M, Schortgen F. Ten shortcomings of the current definition of AKI. Intensive Care Med 2017;43(6):911–3.
[13] Md Ralib A, Pickering JW, Shaw GM, Endre ZH. The urine output definition of acute kidney injury is too liberal. Crit Care 2013;17(3):R112. https://doi.org/10.1186/cc12784. 2013 Jun 20.
[14] Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care 2013;17(1):R25. https://doi.org/10.1186/cc12503.
[15] Bihorac A, Chawla LS, Shaw AD, Al-Khafaji A, Davison DL, Demuth GE, et al. Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. Am J Respir Crit Care Med 2014;189(8):932–9. https://doi.org/10.1164/rccm.201401-0077OC.
[16] Hoste EA, McCullough PA, Kashani K, Chawla LS, Joannidis M, Shaw AD, et al. Derivation and validation of cutoffs for clinical use of cell cycle arrest biomarkers. Nephrol Dial Transplant 2014;29(11):2054–61. https://doi.org/10.1093/ndt/gfu292.
[17] Meersch M, Schmidt C, Van Aken H, Martens S, Rossaint J, Singbartl K, et al. Urinary TIMP-2 and IGFBP7 as early biomarkers of acute kidney injury and renal recovery following cardiac surgery. PLoS One 2014;9(3):e93460. https://doi.org/10.1371/journal.pone.0093460.
[18] Engelman DT, Crisafi C, Germain M, Greco B, Nathanson BH, Engelman RM, et al. Using urinary biomarkers to reduce acute kidney injury following cardiac surgery. J Thorac Cardiovasc Surg 2020;160:1235–46.
[19] Meersch M, Schmidt C, Hoffmeier A, van Aken H, Wempe C, Gerss J, et al. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the prevaki randomized controlled trial. Intensive Care Med 2017;43:1551–61.
[20] Göcze I, Jauch D, Götz M, Kennedy P, Jung B, Zeman F, et al. Biomarker-Guided intervention to prevent acute kidney injury after major surgery: the prospective randomized bigpak study. Ann Surg 2018;267:1013–20.
[21] von Groote T, Meersch M, Romagnoli S, Ostermann M, Ripollés-Melchor J, Schneider AG, et al. Biomarker-guided intervention to prevent acute kidney injury after major surgery (BigpAK-2 trial): study protocol for an international, prospective, randomised controlled multicentre trial. BMJ Open 2023;13(3):e070240. https://doi.org/10.1136/bmjopen-2022-070240. Published 2023 Mar 27.
[22] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inf 2009;42(2):377–81. https://doi.org/10.1016/j.jbi.2008.08.010.
[23] Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inf 2019;95:103208. https://doi.org/10.1016/j.jbi.2019.103208.
[24] Greulich L, Brix TJ, Storck M, Dugas M. A seamless pseudonymization and randomization workflow for REDCap. Stud Health Technol Inf 2021 May 27;281:952–6. https://doi.org/10.3233/SHTI210319. PMID: 34042814.
[25] Wassmer G, Brannath W. Group sequential and confirmatory adaptive designs in clinical trials. Springer; 2016.

[26] A one-sided version of the Cochrane Mantel Haenszel test (CMH) is constructed, using the fact that the CMH test statistic – if it is not squared – follows a standard normal distribution under the null hypothesis H_0: $AKI_1 = AKI_0$ (in all strata).
[27] Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Trials 2010;11(1):1–8.
[28] Statistical Principles for Clinical Trials E9 Version 4 International Conference on Harmonisation. https://database.ich.org/sites/default/files/E9_Guideline.pdf. Accessed 07 February 2022.
[29] Structure and Content of Clinical Study Reports E3: International Council for Harmonisation. https://database.ich.org/sites/default/files/E3_Guideline.pdf. Accessed 07 February 2022.
[30] Wassmer G, Brannath W. Group sequential and confirmatory adaptive designs in clinical trials. Springer; 2016.
[31] R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2023. URL, https://www.R-project.org/.
[32] Wassmer G, Pahlke F. _rpact: confirmatory adaptive clinical trial design and analysis_. 2023. R package version 3.3.4, https://CRAN.R-project.org/package=rpact.