Author's response to reviews

Title: Early postoperative serum cystatin C predicts severe acute kidney injury following cardiac surgery: a post-hoc analysis of a randomized controlled trial.

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Author's response to reviews: see over
Dear editor and reviewers,

many thanks for your critical remarks and suggestions to optimize the manuscript and to correct potential mistakes in the article sections. Following, we would like to comment on your remarks and described the changes we have made. The Tracking tool in Word is active and we report the lines in the paper.

Kind regards,
Arndt-H. Kiessling

**Major Revisions:**

**Reviewer 1:** The clinical data of the patients with renal replacement therapy were included. Line 142-146

"The main reason for an acute dialysis therapy was an anuresis in the first postoperative hours \((n=4)\) after the cardiac procedure. Renal replacement therapy was initiated after mean of 2.1±1.9 days and terminated after 22.5±21 days. Non of patients went into a chronic program. The other indications were potassium overload \((n=1)\) and respiratory failure due to lung congestions \((n=3)\)."

**Reviewer 2:**

1. NCT number delete line 75
2. Inclusion criteria’s adapted to primary study line 77-84
   - Inclusion criteria were a patient age of >75 years and/or a reduced left ventricular function of <40%.
   - Furthermore, informed consent and elective, planned surgery using the heart-lung machine were needed.
   - Patients with combined interventions on the aorta and/or carotid arteries and/or multiple valve operations were excluded.
   - Patients were similarly not included into the study if the following preoperative exclusion criteria were present: serum creatinine >1.8mg/dl, raised GOT/GPT values double the norm, haemoglobin (Hb) <11mg/dl, myocardial infarction within the last seven days before surgery and affiliation to the religious community of the Jehovah's Witnesses. [Error! Reference source not found.]
3. Exclusion criteria’s deleted line 84
4. Title changed Line 1
   - Early postoperative serum cystatin C predicts severe acute kidney injury following cardiac surgery: a post-hoc analysis of a randomized controlled trial.
5. Change to “urine output” Line 112
6. Oliguria line 109 and limitations changed:
   - An additional AKI criterion of the Acute Kidney Injury Network is oliguria (urine excretion <0.5mL/kg/h for 6 hours) [4]. This criterion is difficult to describe in the postoperative, cardiothoracic care. Due to intravenous fluid administration and diuretic application, the diagnosis of an AKI by oliguria could be masked by the individual ICU therapies. The urine output was nevertheless recorded at all measurement time points [9].
   - AKI was only defined by creatinine increase and not by the second criteria of a decreasing urine output.
7. Reference values CysC add
   - The mean reference serum cystatin C level is 0.84 mg/L in non-Hispanic adolescents and normal renal function [26].
8. Start RRT
   - "The main reason for an acute dialysis therapy was an anuresis in the first postoperative hours \((n=4)\) after the cardiac procedure. Renal replacement therapy was initiated after mean of 2.1±1.9 days and terminated after 22.5±21 days. Non of patients went into a chronic program. The other indications were potassium overload \((n=1)\) and respiratory failure due to lung congestions \((n=3)\)."
9. Creatinine
   - Table with Scr and ROC values were added. Creatinine is superior to Cys C in all timepoints.
10. Discussion extended:
But what are about patient's benefits in the development of new biomarkers in AKI patients? Patients who develop AKI have higher rates of mortality and resource utilization, with the worst values seen in dialyzed patients. Emerging evidence suggests that even small changes in creatinine after cardiac surgery are associated with significant effects on mortality. Whether AKI directly causes adverse outcomes is not entirely clear; however, an increase in infection and new-onset sepsis, congestive heart failure, and fluid overload may be contributory [1]. Traditional biomarkers of AKI (creatinine and urea) increase slowly in response to renal injury, are insensitive to mild degrees of AKI, and are influenced by nonrenal factors. There is considerable interest in novel biomarkers of AKI such as cystatin c that increase rapidly after renal injury, detect mild degrees of AKI, and are less subject to nonrenal factors. It has been postulated that the early diagnosis of cardiac surgery-associated AKI using novel biomarkers will result in improved outcomes. However, there is little evidence that interventions started early in the course of evolving AKI enhance renal recovery. Until effective therapies are developed that significantly improve the outcome from AKI, there is little benefit from early diagnosis using novel biomarkers [27].

11. Limitations switched
12. Fail to Failure
13. Rifle delete in Tables
14. Typo errors new re-linked

Minor Essential Revisions:

Inclusion/exclusion criteria are added from original publication. Line 77-84
Inclusion criteria were a patient age of >75 years and/or a reduced left ventricular function of <40%. Furthermore, informed consent and elective, planned surgery using the heart-lung machine were needed. Patients with combined interventions on the aorta and/or carotid arteries and/or multiple valve operations were excluded. Patients were similarly not included into the study if the following preoperative exclusion criteria were present: serum creatinine >1.8mg/dl, raised GOT/GPT values double the norm, haemoglobin (Hb) <11mg/dl, myocardial infarction within the last seven days before surgery and affiliation to the religious community of the Jehovah’s Witnesses. [Error! Reference source not found.]

Figure 1 in English

Age and sex deleted in introduction Line 60

EF and Age inclusion criterias from original article line 77-84

The definitions of “complex procedures” are explained by three examples. The terminus “complex” in the original article is unclear. Better should be “combination procedures”.

Journal style:
Conclusion header included line 228

Authors contribution included line 260-265
“Kiessling: Conceived and designed the study, analysis and interpretation of data and coordination and wrote the manuscript. Dietz: Participated in patient- and sample recruitment and data completion. Reyher has been involved in the intraoperative and ICU therapy interpretation and revising it critically for important intellectual content. Stock, Beiras-Fernandez and Moritz, conceived the study, coordination and revising it critically for important intellectual content and reviewed the manuscript. All authors read and approved the final manuscript.”