The role of Goal Directed Therapy in the prevention of Acute Kidney Injury after Major Gastrointestinal Surgery: Sub-study of the OPTIMISE Trial

Macdonald, Neil*; Pearse, Rupert M.; Murray, Patrick T.; Inzitari, Rosanna; Doran, Peter; and Prowle, John R.

Correspondence and requests for re-prints to:
N. MacDonald
Department of Perioperative Medicine and Pain
Royal London Hospital
London
E1 1BB
United Kingdom
e-mail: n.macdonald2@nhs.net
Tel: +44 20 3594 0346

Keywords: Goal Directed Therapy, Fluid therapy, Haemodynamic therapy, Acute kidney injury, renal injury biomarkers, high risk surgery

Main Text: 2272 **Abstract: 299**

Summary

Background: Acute Kidney Injury (AKI) is an important adverse outcome after major surgery. Perioperative goal directed haemodynamic therapy (GDT) may improve outcomes by reducing complications such as AKI.

Objective: To determine if GDT was associated with a reduced incidence of postoperative AKI according to specific renal biomarkers.

Design: Prospective sub-study of the OPTIMISE trial, a multi-centre randomised controlled trial comparing perioperative GDT to usual patient care (UC).

Setting: Four UK National Health Service hospitals.

Patients: 287 high-risk patients aged ≥50 years undergoing major gastrointestinal surgery.

Outcome measures: The primary outcome measure was AKI defined as urinary neutrophil gelatinase-associated lipase (NGAL) ≥150ng/ml at either 24 or 72 hours after surgery. Secondary outcomes were between-group differences in NGAL measurements and NGAL:creatinine ratios at 24 and 72 hours after surgery, AKI of stage 2 or greater according to Kidney Disease Improving Global Outcomes (KDIGO) criteria within 30 days of surgery.

Results: In total, 20/287 patients (7%) experienced post-operative AKI of KDIGO grade 2 or 3 within 30 days. The proportion of patients with urinary NGAL ≥150ng/ml at either 24 or 72h after surgery was similar in the two groups (GDT 31/144 [21.5%] patients vs. UC 28/143 [19.6%] patients; p=0.88). Absolute values of urinary NGAL were also similar at 24 hours (GDT 53.5 vs. UC 44.1 ng/ml; p=0.38) and 72 hours (GDT 45.1 vs. UC 41.1 ng/ml; p=0.50) as were urinary NGAL:creatinine ratios at 24 hours (GDT 45 vs. UC 43 ng/mg; p=0.63) and 72 hours (GDT 66 vs. UC 63 ng/mg; p=0.62). The incidence of KDIGO defined AKI was also similar between the groups (GDT 9/144 [6%] patients vs UC 11/143 [8%] patients; p=0.80).

Conclusion: In this trial, GDT did not reduce the incidence of AKI amongst high-risk patients undergoing major gastrointestinal surgery. This may reflect improving standards in usual patient care.

Introduction

While the mortality and morbidity associated with surgery appears to be decreasing (1), the increasing volume of surgical procedures in an aging population means that complications following major surgery continue to be major health burden (2), particularly in high risk surgical populations (3). Investigation of post-operative complications shows the development of perioperative acute kidney injury (AKI) (4, 5) has been associated with a greater 30-day mortality, prolonged hospital stay and the development of chronic kidney disease (4, 6, 7). The incidence of AKI varies with surgical setting and patient population but affects around 13% of patients following major abdominal surgery (4, 5).

Goal Directed Haemodynamic Therapy (GDT) algorithms utilise intravenous fluids and low dose inotropic drugs to optimise cardiac output in the high-risk surgical patients(8-10). The findings of several randomised trials have suggested this intervention may reduce the number of complications, including AKI, in the high-risk patient population (11-14). A meta-analysis of the effects of GDT algorithms on post-operative AKI has also suggested a beneficial effect (15). However, the findings of the largest trial to date (OPTIMISE) did not indicate any reduction in AKI rates (GDT 17/368 patients vs Usual care 17/365 patients) (16).

The introduction of the Kidney Disease Improving Global Outcomes (KDIGO) consensus definition of AKI using urine output and changes in serum creatinine has revolutionised the field of AKI research (17). Standardised definitions between studies have emphasised the wider consequences of AKI, not simply renal replacement therapy. However, diagnosis of post-operative AKI using serum creatinine is complicated by the physiological response to surgery which reduces both urine output and creatinine release by skeletal muscle (18, 19). Use of more sensitive biomarkers may improve our identification of AKI. Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) is a biomarker of renal tubular cell injury that has been used in a number of clinical settings as a more sensitive measure of AKI (20-28). In a sub-set of patients recruited to the OPTIMISE trial, we measured urinary NGAL and urinary NGAL:creatinine ratio at 24 and 72 hours following major gastrointestinal surgery. We report the rates of AKI according to these more sensitive biomarkers and compare them to those defined according to the KDIGO criteria (29).

Methods

The OPTIMISE trial was approved by the East London and City Research Ethics Committee (09/H0703/23) and the Medical and Healthcare Products Regulatory Agency (ISRCTN04386758). Approval was also given for the collection and storage of blood and urine for further analysis. The trial was sponsored by Queen Mary University of London and the urinary biomarker analysis was carried out at the University of Dublin.

Data Collection

The OPTIMISE trial recruited patients over 65 and those patients over 50 with a specified co-morbidity undergoing major gastrointestinal surgery lasting more than ninety minutes. Patients were randomised into receiving a GDT algorithm or usual care using a computer-generated dynamic procedure (minimisation) with a random component. To ensure consistent care across both groups certain perioperative parameters were predefined. These were keeping the heart rate between 60-100 beats per minute, a mean arterial pressure of between 60-100 mmHg, oxygen saturations greater than 94% and haemoglobin greater than 80g dl^{-1}. The algorithm used cardiac output monitoring (LiDCO) to optimise left ventricular stroke volume and a low dose dopexamine infusion (0.5mcg/kg/min) for the duration of surgery and six hours post-operatively. All patients in the OPTIMISE trial were followed up during their hospital stay and until 30 days post-operatively. The development of any complication was decided by the follow up narrative given to the principal investigator or nominated deputy if aware of the allocation. Four of the seventeen sites involved in recruiting patients for OPTIMISE recruited into the biomarker sub-study.

Outcome measures

The primary outcome measure was AKI defined as urinary neutrophil gelatinase-associated lipase (NGAL) ≥150ng/ml at either 24 or 72 hours after surgery. Secondary outcomes were between-group differences in NGAL measurements and NGAL:creatinine ratios at 24 and 72 hours after surgery , AKI of stage 2 or greater according to Kidney Disease Improving Global Outcomes (KDIGO) criteria within 30 days of surgery i.e. a doubling of serum creatinine relative to pre-operative baseline or reduction in urine output (when a catheter was available) up to thirty days after surgery.

Sample collection

Urine samples were collected preoperatively and at 24 and 72 hours after surgery. The urine samples were from a sample provided by the patient or withdrawn from an indwelling urinary catheter. These were placed into three separate microcentrifuge tubes for each time point and frozen at -80^{o}C. Urine samples were stored prior to being sent to a central laboratory for batched analysis.

Measurement of urinary biomarkers

Urinary NGAL and urinary creatinine were measured in all samples. The Creatinine (CRENZu) enzymatic assay was performed on Abbott Architect ci4100 Clinical Analyser and the NGAL assay was performed on Abbott Architect I4100SR Clinical Analyser (30). The two analysers are located in the UCD CRC Biomarker Core Lab, SVUH Dublin. Prior to testing instrument calibration was performed, followed by imprecision testing (four duplicates of each control per day for 3 days). In addition, duplicates of each control were run each day. A total coefficient of variation (CV) of <10% was considered acceptable for NGAL, while CV of <3.6% was considered acceptable for CRENZu. NGAL was analysed using a two-step immunoassay for the quantitative determination of NGAL in human urine using CMIA technology with flexible assay protocols (Chemiflex). Results are presented as NGAL concentration and NGAL:Creatinine ratio to standardise for differences in urinary concentration. As the validity for standardisation for urinary concentration has been questioned (31), our primary analysis was based on absolute urinary NGAL concentration.

Statistical analysis

Statistical analysis was performed in R v3.3.3 (R Foundation for Statistical Computing, Vienna, Austria) using RStudio v1.0.136 (RStudio Inc, Boston, MA, USA). Continuous data are presented median with interquartile range (IQR) and compared with the Wilcoxon rank sum, categorical data were compared using Fisher's exact test. Predictive accuracy of the biomarker level for AKI outcome was assessed by calculation of the receiver operating characteristic area under the curve (ROC-AUC) with 95% confidence intervals computed with 2000 stratified bootstrap replicates (32).

Results

287 of the 734 patients enrolled in the OPTMISE trial were included in this biomarker sub-study analysis. Of the 287 patients 144 were in the GDT group and 143 were in the UC group. As in the main OPTMISE trial the patients in the UC group were older but there was no other significant difference in co-morbidities or in surgical procedure or type (Table 1).

Incidence of AKI

There was no difference in the incidence of AKI between the GDT and UC groups as measured by urinary NGAL (31/144 vs 28/143; p=0.88) and no difference in the urinary NGAL between the groups at 24 hours (GDT 53.5 ng/ml vs usual care 44.1 ng/ml; p=0.38) or at 72 hours (GDT 45.1 ng/ml vs usual care 41.2 ng/ml; p=0.50) after surgery (Figure 1). Using the NGAL:creatinine ratio demonstrated no difference in the incidence of AKI between the two groups at 24 hours (GDT 45ng/mg vs UC 43 ng/mg) or 72 hours (GDT 66 ng/mg vs UC 63 ng/mg) after surgery (Figure two). Similarly, there was no difference in the rate of AKI as diagnosed by the KDIGO criteria (GDT 9/144 vs usual care 11/143; p=0.80) (Table 2).

Relationship between post-operative NGAL and KDIGO defined diagnosis of AKI

Urinary NGAL was significantly higher in patients who developed AKI at both 24 hours (No AKI 45.7 vs AKI 78.0; p=0.01) and at 72 hours after surgery (No AKI 40.1 vs AKI 129.6; p<0.001) (Figure 3, Table 3). This was reflected in the urinary NGAL:creatinine ratio which was higher at 24 hours (No AKI 0.43 vs AKI 0.82 p=0.015) and 72 hours (No AKI 0.60 vs AKI 4.0; p=0.001) in those who developed AKI (Figure 4, Table S4). In contrast to post-operative measurement pre-operative urinary NGAL and NGAL:Creatinine ratio did not significantly differ between those who did and did not develop AKI (Table 3).

Discussion

This sub-study of the OPTIMISE trial did not show any difference in rates of biomarker-defined AKI between high-risk surgical patients randomised to receive either a GDT algorithm or usual care. There was no difference in urinary NGAL concentrations or urinary NGAL:creatinine ratio at discrete time points of 24 or 72 hours after surgery. These results suggest there is no effect of the GDT intervention on post-operative AKI either using serum creatinine based definitions or a more sensitive urinary biomarkers which capture sub-clinical AKI.

Our findings in this sub-study are in contrast to previous studies of perioperative GDT which have demonstrated a reduction in post-operative AKI (11-14, 33, 34) However more recent studies have also suggested no AKI reduction from a GDT algorithm in major abdominal surgery(35, 36). Improvements in usual care including routine use of haemodynamic targets haemodynamic targets and better intra-operative fluid management may explain the loss of effect of GDT in some more recent trials.

We are not aware of any larger studies that have used renal biomarkers to assess post-operative AKI after GDT in the high risk non-cardiac surgical patient. The importance of post-operative AKI and the difficulty in identifying it using a combination of creatinine rise and urine output has increased the interest in the ability of a renal specific biomarker to identify post-operative AKI. There are, however, some limitations to this analysis. We recruited as many patients as possible into this sub-study, but it may be underpowered to detect any difference in the groups, although, no difference in AKI 2-3 was shown in the main OPTIMISE study group in line with these findings. Only KDIGO stage 2 and stage 3 were recorded as a significant renal complication in OPTIMISE and therefore stage 1 AKI was not assessed. The incidence of AKI stage 2-3 in OPTIMISE was 5%, however the incidence of urinary NGAL≥150ng/ml at 24 or 72h was 13.4% similar to that reported for all AKI in a number of studies in major abdominal surgery suggesting our biomarker measurement was capturing the expected incidence of AKI in this population (37). Importantly, this sub-study did not aim to assess NGAL as a predictive biomarker preceding diagnosis of AKI, in this study AKI-criteria may have been present before, at the same time or after biomarker measurement thus we cannot make any conclusions regarding utility of NGAL in anticipating AKI. However, our intention was to use NGAL as a marker of renal injury that was mechanistically distinct from a measure of filtration (such as creatinine) that would be sensitive for mild, ‘sub-clinical’ AKI to better confirm or refute a renal-protective effect of the GDT intervention, not to test the utility of NGAL, which has been examined in many studies.

There is no universally agreed biomarker-definition of kidney injury and non-specific rises in plasma NGAL may occur in inflammatory states. Furthermore, heterogeneity of NGAL as a predictive biomarker for AKI in varying clinical settings has led to expressions of doubt of the clinical usefulness of NGAL. However, while prediction of AKI in individual patients may be inaccurate, this may be related to the inadequacy of creatinine as a gold standard, while analysis of NGAL differences across groups of individuals should be more robust. There have been many different cut off values used to determine the optimal cut off urinary NGAL in predicting AKI with values been between 20-460 ng/ml(38, 39) quoted in literature mostly related to cardiac surgery. This study pre-specified a value of 150ng/ml that has been used previously (40), though a more recent review suggests a cut off 80ng/ml may be optimal (41).

The time that the samples is a feature of the design of sample collection for OPTIMISE sub-studies. Previous studies have measured either urinary or plasma NGAL up to 24 hours after surgery, however we measured urinary NGAL at 24 and 72 hours after surgery. Interestingly 72h urinary NGAL and urinary NGAL:creatinine better correlated with post-operative AKI than samples obtained at 24 hours post-operatively. This suggests that in patients with AKI stage 2 or 3 occurring in the post-operative period renal tubular injury is still occurring or ongoing three days after surgery, implying that some cases of AKI may be associated with post-operative events. Lack of effect of peri- and immediately post-operative GDT in preventing AKI is understandable if the majority of renal injury occurring post-operatively. In this context, a promising approach for the clinical use of renal biomarkers is to identify patients with evolving AKI after major surgery and target an AKI prevention/mitigation strategy at these individuals in the post-operative period. Such an approach requires the correct choice of biomarker and agreement on appropriate treatments to for patients with early post-operative renal injury. Two recent small studies in the context of cardiac and abdominal study have employed this approach with the urinary TIMP2xIGFBP7 biomarker of renal tubular cell cycle arrest with favourable preliminary results (42, 43). Thus, in the context of major surgery it may be that renal biomarkers are less useful as a read-out of the effect of intervention on renal injury than a method of targeting high-risk patients to specific interventions that may improve renal outcomes.

Conclusions

In this biomarker sub-study we did not observe any difference in urinary NGAL concentration, or any other biochemical marker of AKI, between the patients having a GDT intervention and those patients receiving usual care. This is in keeping with the findings from the overall OPTIMISE trial and may reflect high standards of patient care in the control group. Future trials of GDT may measure AKI biomarkers

to assess the impact of GDT on the incidence of AKI but further research should also focus on the predictive ability of kidney injury biomarkers to identify early perioperative kidney injury.

Conflict of interest statement

RP holds research grants, has given lectures and/or performed consultancy work for BBraun, GlaxoSmithkline, Medtronic, Intersurgical and Edwards Lifesciences. JP has consultancy agreements with Medibeacon Inc, Quark Pharmaceuticals Inc, GE Healthcare and Nikkiso Europe GmbH and has received speakers fees and/or hospitality from Baxter Inc, Nikksio Europe GmbH and Fresenius Medical Care AG. All other authors declare they have no conflicts of interest.

Acknowledgements

This was an investigator initiated study funded by the National Institute for Health Research (UK). The authors had full data access and were solely responsible for data interpretation, drafting and critical revision of the manuscript and the decision to submit for publication. The authors would like to thank Abbott for the donation of the urinary NGAL assays.

References

1. Abbott TEF, Fowler AJ, Dobbs TD, Harrison EM, Gillies MA, Pearse RM. Frequency of surgical treatment and related hospital procedures in the UK: a national ecological study using hospital episode statistics. Br J Anaesth. 2017;119(2):249-57.
2. deaths. Nciip. Knowing the Risk: A review of peri-operative care of surgical patients. 2011.
3. Pearse RM, Harrison DA, James P, Watson D, Hinds C, Rhodes A, et al. Identification and characterisation of the high-risk surgical population in the United Kingdom. Crit Care. 2006;10(3):R81.
4. O'Connor ME, Hewson RW, Kirwan CJ, Ackland GL, Pearse RM, Prowle JR. Acute kidney injury and mortality 1 year after major non-cardiac surgery. Br J Surg. 2017;104(7):868-76.
5. Grams ME, Sang Y, Coresh J, Ballew S, Matsushita K, Molnar MZ, et al. Acute Kidney Injury After Major Surgery: A Retrospective Analysis of Veterans Health Administration Data. Am J Kidney Dis. 2016;67(6):872-80.
6. Bihorac A, Yavas S, Subbiah S, Hobson CE, Schold JD, Gabrielli A, et al. Long-term risk of mortality and acute kidney injury during hospitalization after major surgery. Ann Surg. 2009;249(5):851-8.
7. Kork F, Balzer F, Spies CD, Wernecke KD, Ginde AA, Jankowski J, et al. Minor Postoperative Increases of Creatinine Are Associated with Higher Mortality and Longer Hospital Length of Stay in Surgical Patients. Anesthesiology. 2015;123(6):1301-11.
8. Jhanji S, Dawson J, Pearse RM. Cardiac output monitoring: basic science and clinical application. Anaesthesia. 2008;63(2):172-81.
9. Pearse RM, Belsey JD, Cole JN, Bennett ED. Effect of dopexamine infusion on mortality following major surgery: individual patient data meta-regression analysis of published clinical trials. Crit Care Med. 2008;36(4):1323-9.
10. Ackland GL, Iqbal S, Paredes LG, Toner A, Lyness C, Jenkins N, et al. Individualised oxygen delivery targeted haemodynamic therapy in high-risk surgical patients: a multicentre, randomised, double-blind, controlled, mechanistic trial. Lancet Respir Med. 2015;3(1):33-41.
11. Som A, Maitra S, Bhattacharjee S, Baidya DK. Goal directed fluid therapy decreases postoperative morbidity but not mortality in major non-cardiac surgery: a meta-analysis and trial sequential analysis of randomized controlled trials. J Anesth. 2017;31(1):66-81.
12. Giglio M, Manca F, Dalfino L, Brienza N. Perioperative hemodynamic goal-directed therapy and mortality: a systematic review and meta-analysis with meta-regression. Minerva Anestesiol. 2016;82(11):1199-213.
13. Sun Y, Chai F, Pan C, Romeiser JL, Gan TJ. Effect of perioperative goal-directed hemodynamic therapy on postoperative recovery following major abdominal surgery-a systematic review and meta-analysis of randomized controlled trials. Crit Care. 2017;21(1):141.
14. Prowle JR, Chua HR, Bagshaw SM, Bellomo R. Clinical review: Volume of fluid resuscitation and the incidence of acute kidney injury - a systematic review. Crit Care. 2012;16(4):230.
15. Chong MA, Wang Y, Berbenetz NM, McConachie I. Does goal-directed haemodynamic and fluid therapy improve peri-operative outcomes?: A systematic review and meta-analysis. Eur J Anaesthesiol. 2018;35(7):469-83.
16. Pearse RM, Harrison DA, MacDonald N, Gillies MA, Blunt M, Ackland G, et al. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. JAMA. 2014;311(21):2181-90.
17. (KDIGO). KDIGO. Section 2: AKI Definition. Kidney Int Suppl. (2011) 2012(2):19-36.

18. Prowle JR, Kolic I, Purdell-Lewis J, Taylor R, Pearse RM, Kirwan CJ. Serum creatinine changes associated with critical illness and detection of persistent renal dysfunction after AKI. Clin J Am Soc Nephrol. 2014;9(6):1015-23.
19. Puckett JR, Pickering JW, Palmer SC, McCall JL, Kluger MT, De Zoysa J, et al. Low Versus Standard Urine Output Targets in Patients Undergoing Major Abdominal Surgery: A Randomized Noninferiority Trial. Ann Surg. 2017;265(5):874-81.
20. Bennett M, Dent CL, Ma Q, Dastrala S, Grenier F, Workman R, et al. Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. Clin J Am Soc Nephrol. 2008;3(3):665-73.
21. de Geus HR, Ronco C, Haase M, Jacob L, Lewington A, Vincent JL. The cardiac surgery-associated neutrophil gelatinase-associated lipocalin (CSA-NGAL) score: A potential tool to monitor acute tubular damage. J Thorac Cardiovasc Surg. 2016;151(6):1476-81.
22. Liebetrau C, Dorr O, Baumgarten H, Gaede L, Szardien S, Blumenstein J, et al. Neutrophil gelatinase-associated lipocalin (NGAL) for the early detection of cardiac surgery associated acute kidney injury. Scand J Clin Lab Invest. 2013;73(5):392-9.
23. Thanakitcharu P, Jirajan B. Determination of urinary neutrophil gelatinase-associated lipocalin (NGAL) cut-off level for early detection of acute kidney injury in Thai adult patients undergoing open cardiac surgery. J Med Assoc Thai. 2014;97 Suppl 11:S48-55.
24. Au V, Feit J, Barasch J, Sladen RN, Wagener G. Urinary neutrophil gelatinase-associated lipocalin (NGAL) distinguishes sustained from transient acute kidney injury after general surgery. Kidney Int Rep. 2016;1(1):3-9.
25. Singer E, Schrezenmeier EV, Elger A, Seelow ER, Krannich A, Luft FC, et al. Urinary NGAL-Positive Acute Kidney Injury and Poor Long-term Outcomes in Hospitalized Patients. Kidney Int Rep. 2016;1(3):114-24.
26. Hunsicker O, Feldheiser A, Weimann A, Liehre D, Sehouli J, Wernecke KD, et al. Diagnostic value of plasma NGAL and intraoperative diuresis for AKI after major gynecological surgery in patients treated within an intraoperative goal-directed hemodynamic algorithm: A substudy of a randomized controlled trial. Medicine (Baltimore). 2017;96(28):e7357.
27. Hjortrup PB, Haase N, Treschow F, Moller MH, Perner A. Predictive value of NGAL for use of renal replacement therapy in patients with severe sepsis. Acta Anaesthesiol Scand. 2015;59(1):25-34.
28. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A, Group NM-aI. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis. 2009;54(6):1012-24.
29. Helmersson-Karlqvist J, Arnlov J, Larsson A. Day-to-day variation of urinary NGAL and rational for creatinine correction. Clin Biochem. 2013;46(1-2):70-2.
30. Kume T, Saglam B, Ergon C, Sisman AR. Evaluation and comparison of Abbott Jaffe and enzymatic creatinine methods: Could the old method meet the new requirements? J Clin Lab Anal. 2018;32(1).
31. Waikar SS, Sabbisetti VS, Bonventre JV. Normalization of urinary biomarkers to creatinine during changes in glomerular filtration rate. Kidney Int. 2010;78(5):486-94.
32. Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez JC, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinformatics. 2011;12:77.
33. Calvo-Vecino JM, Ripolles-Melchor J, Mythen MG, Casans-Frances R, Balik A, Artacho JP, et al. Effect of goal-directed haemodynamic therapy on postoperative complications in low-moderate risk surgical patients: a multicentre randomised controlled trial (FEDORA trial). Br J Anaesth. 2018;120(4):734-44.
34. Massari C, Brienza S, Rotarski M, Gastiaburu J, Misset JL, Cupissol D, et al. Pharmacokinetics of oxaliplatin in patients with normal versus impaired renal function. Cancer Chemother Pharmacol. 2000;45(2):157-64.

35. Schmid S, Kapfer B, Heim M, Bogdanski R, Anetsberger A, Blobner M, et al. Algorithm-guided goal-directed haemodynamic therapy does not improve renal function after major abdominal surgery compared to good standard clinical care: a prospective randomised trial. Crit Care. 2016;20:50.
36. Patel A, Prowle JR, Ackland GL, Investigators P-OS. Postoperative goal-directed therapy and development of acute kidney injury following major elective noncardiac surgery: post-hoc analysis of POM-O randomized controlled trial. Clin Kidney J. 2017;10(3):348-56.
37. 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(4):521-30.
38. Heise D, Rentsch K, Braeuer A, Friedrich M, Quintel M. Comparison of urinary neutrophil glucosaminidase-associated lipocalin, cystatin C, and alpha1-microglobulin for early detection of acute renal injury after cardiac surgery. Eur J Cardiothorac Surg. 2011;39(1):38-43.
39. Han WK, Wagener G, Zhu Y, Wang S, Lee HT. Urinary biomarkers in the early detection of acute kidney injury after cardiac surgery. Clin J Am Soc Nephrol. 2009;4(5):873-82.
40. Bagshaw SM, Bennett M, Haase M, Haase-Fielitz A, Egi M, Morimatsu H, et al. Plasma and urine neutrophil gelatinase-associated lipocalin in septic versus non-septic acute kidney injury in critical illness. Intensive Care Med. 2010;36(3):452-61.
41. Tecson KM, Erhardtsen E, Eriksen PM, Gaber AO, Germain M, Golestaneh L, et al. Optimal cut points of plasma and urine neutrophil gelatinase-associated lipocalin for the prediction of acute kidney injury among critically ill adults: retrospective determination and clinical validation of a prospective multicentre study. BMJ Open. 2017;7(7):e016028.
42. Gocze I, Jauch D, Gotz 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(6):1013-20.
43. 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(11):1551-61.

Table 1. Baseline Characteristics of Study Population.

Characteristic		GDT	Usual care
		144	143
	Age (median[IQR])	70.0 [65.5,75.0]	72 [67.0,77.0]
	Gender = F (%)	57 (39.9)	49 (34)
	Urgency = n(%)	7 (4.9)	6 (4.2)
	Weight (median[IQR])	72.00 (61.50,83.00)	75.00 (64.75,87.25)
Risk Factors			
	renal disease (%)	7 (4.9)	4 (2.8)
	Diabetes Mellitus (%)	20 (14.0)	26 (18.1)
	Cardiorespiratory Disease	45 (31.5)	51 (35.4
ASA grade			
	ASA 1 (%)	8 (5.6)	7 (4.9)
	ASA 2 (%)	85 (59.4)	68 (47.2)
	ASA 3 (%)	49 (34.3)	67 (46.5)
	ASA 4 (%)	1 (0.7)	2 (1.4)
Surgical Procedure			
	Laparoscopic (%)	19 (13.3)	23 (16.0)
	Open (%)	107 (74.8)	109 (75.7)
	Laparoscopic converted to open (%)	17 (11.9)	12 (8.3)
Procedure type			
	Upper Gastrointestinal (%)	51 (35.7)	55 (38.2)
	Lower Gastrointestinal (%)	37 (25.9)	40 (27.8)
	Small Bowel, Pancreas or both (%)	52 (37.1)	48 (33.3)
	Urological or Gynaecological surgery involving the gut (%)	2 (1.4)	1 (0.7)

GDT: goal directed therapy; ASA: American Society of Anesthesiologists

Table 2.
Postoperative outcomes for study population by treatment group

Outcome	All patients	GDT	Usual Care	p-value
Death at 180 days (number (%))	34/287 (11.8%)	15/144 (10.4%)	19/143 (13.3%)	0.569
Critical Care Free Days (median [IQR])	27.00 [24.00, 28.00]	27.00 [25.00, 28.00]	26.00 [23.00, 28.00]	0.274
24 and/or 72-hour NGAL ≥150 ng/ml (number (%))	59/292 (20.2%)	31/144 (21.5%)	28/143 (19.6%)	0.883
24-hour NGAL ≥150 ng/ml (number (%))	42/273 (15.4)	20/139 (14.3%)	22/134 (16.4%)	0.74
72-hour NGAL ≥150 ng/ml (number (%))	32/236 (13.6%)	18/124 (14.5%)	14/112 (12.5%)	0.71
Acute Kidney Injury stage 2-3 (number (%))	20/287 (7.0%)	9/144 (6.2%)	11/143 (7.7%)	0.804
Any primary complication (number (%))	143/287 (49.8%)	59/144 (41.0%)	84/143 (58.7%)	0.004
Infective complication (number (%))	92/287 (32.1%)	35/144 (24.3%)	57/143 (39.9%)	0.007

GDT: goal directed therapy; NGAL: urinary neutrophil gelatinase-associated lipase

Table 3. Postoperative outcomes in patients who developed acute kidney injury

	Total	No Acute Kidney Injury	Acute Kidney Injury	p-value
N	287	267	20	
GENDER = M (%)	180 (62.7)	165 (61.8)	15 (75.0)	0.348
Age (median [IQR])	70.00 [66.00, 76.00]	70.00 [66.00, 76.00]	69.00 [65.75, 76.50]	0.680
NGAL (median [IQR]) Pre (ng/ml)	12.7 [5.4, 42.5]	13.3 [5.4, 41.0]	8.1 [5.1,70.9]	0.831
NGAL (median [IQR]) 24h (ng/ml)	48.5 [21.6, 104.6]	45.6 [20.6, 92.8]	78.0 [40.0, 512]	0.012
NGAL (median [IQR]) 72h (ng/ml)	42.4 [21.5, 88.3]	40.1 [20.2, 85.8]	130 [60.3, 777.4]	<0.001
NGAL:Cr (median [IQR]) Pre (ng/ml)	19 [9, 61]	18.6 [8.7, 56.3]	21.3 [9.8, 145.9]	0.512
NGAL:Cr (median [IQR]) 24h (ng/ml)	44 [23, 92]	43.3 [22.1, 87.7]	81.5 [37.5, 418]	0.014
NGAL:Cr (median [IQR]) 72h (ng/ml)	63 [32, 133]	60.3 [30.1, 123.1]	401 [63.1, 2403.4]	<0.001
Critical Care Free days (median [IQR])	27.00 [24.00, 28.00]	27.00 [25.00, 28.00]	11.50 [0.00, 20.50]	<0.001
Multi Organ Dysfunction Syndrome (%)	24 (8.4)	10 (3.8)	14 (70.0)	<0.001
Infective Complications (%)	92 (32.1)	79 (29.6)	13 (65.0)	0.002
Death (%)	34 (11.8)	25 (9.4)	9 (45.0)	<0.001

NGAL:urinary neutrophil gelatinase-associated lipase; NGAL:Cr: urinary neutrophil gelatinase-associated lipase creatinine ratio

Table 4. (supplementary relating to figures one & two)

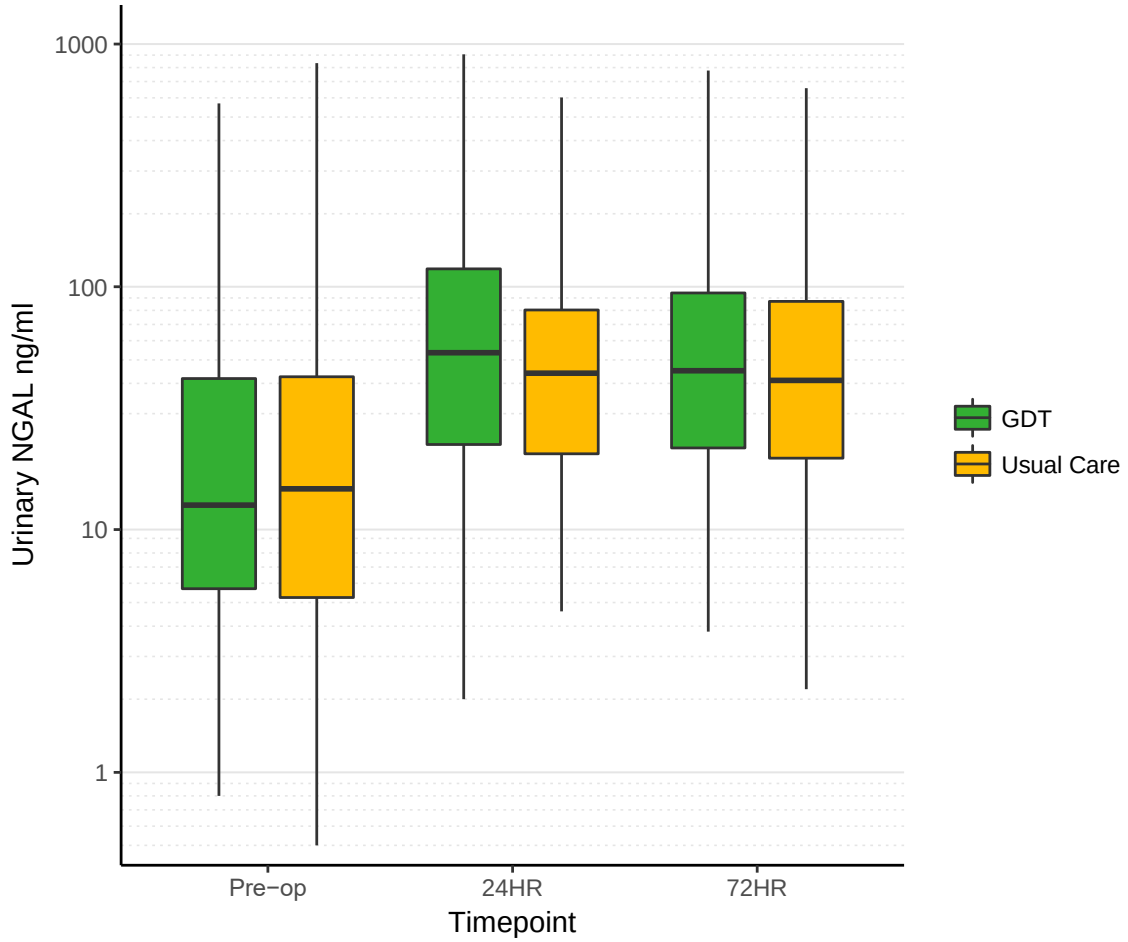
NGAL and NGAL:Cr results by treatment group allocation

		All	GDT	Usual care	p-value
Pre-operative					
	n	269	137	132	
	NGAL (median [IQR])	12.7 [5.4, 42.5]	12.6 [5.7, 41.9]	14.6 [5.1, 42.6]	0.877
	NGAL:Cr (median [IQR])	19 [9, 61]	18 [9, 57]	20 [9, 67]	0.865
24h					
	n	236	139	134	
	NGAL (median [IQR])	48.5 [21.6, 104.6]	53.5 [22.4, 118.6]	44.1 [20.5, 80.2]	0.379
	NGAL:Cr (median [IQR])	44 [23, 92]	45 [0.23, 0.95]	43 [21, 89]	0.629
72h					
	n	273	124	112	
	NGAL (median [IQR])	42.4 [21.5, 88.3]	45.10 [21.7, 94.4]	41.15 [19.7, 87.0]	0.503
	NGAL:Cr (median [IQR])	63 [32, 133]	66 [32, 150]	63 [32, 110]	0.620

NGAL:urinary neutrophil gelatinase-associated lipase; NGAL:Cr: urinary neutrophil gelatinase-associated lipase creatinine ratio

Figure one

Urinary NGAL at 3 discrete timepoints comparing GDT group against usual care

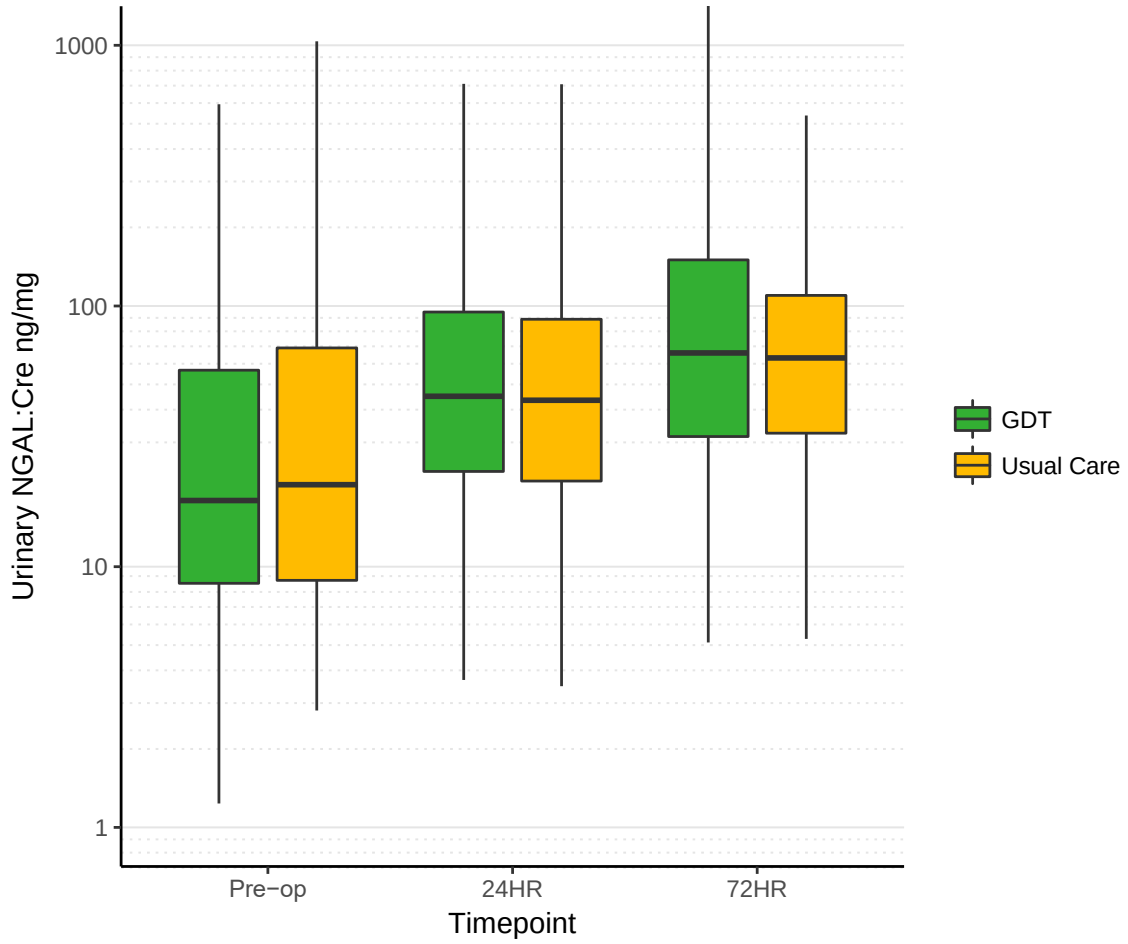


GDT: goal directed therapy

Relationship between the presence of a biomarker of acute kidney injury (urinary neutrophil gelatinase-associated lipase) and allocation to a goal directed therapy algorithm or usual care for perioperative fluid therapy in a high risk surgical population at three time points (before surgery, 24 hours after surgery and 72 hours after surgery).

Figure Two

Urinary NGAL: creatinine ratio at 3 discrete timepoints comparing GDT group against usual care

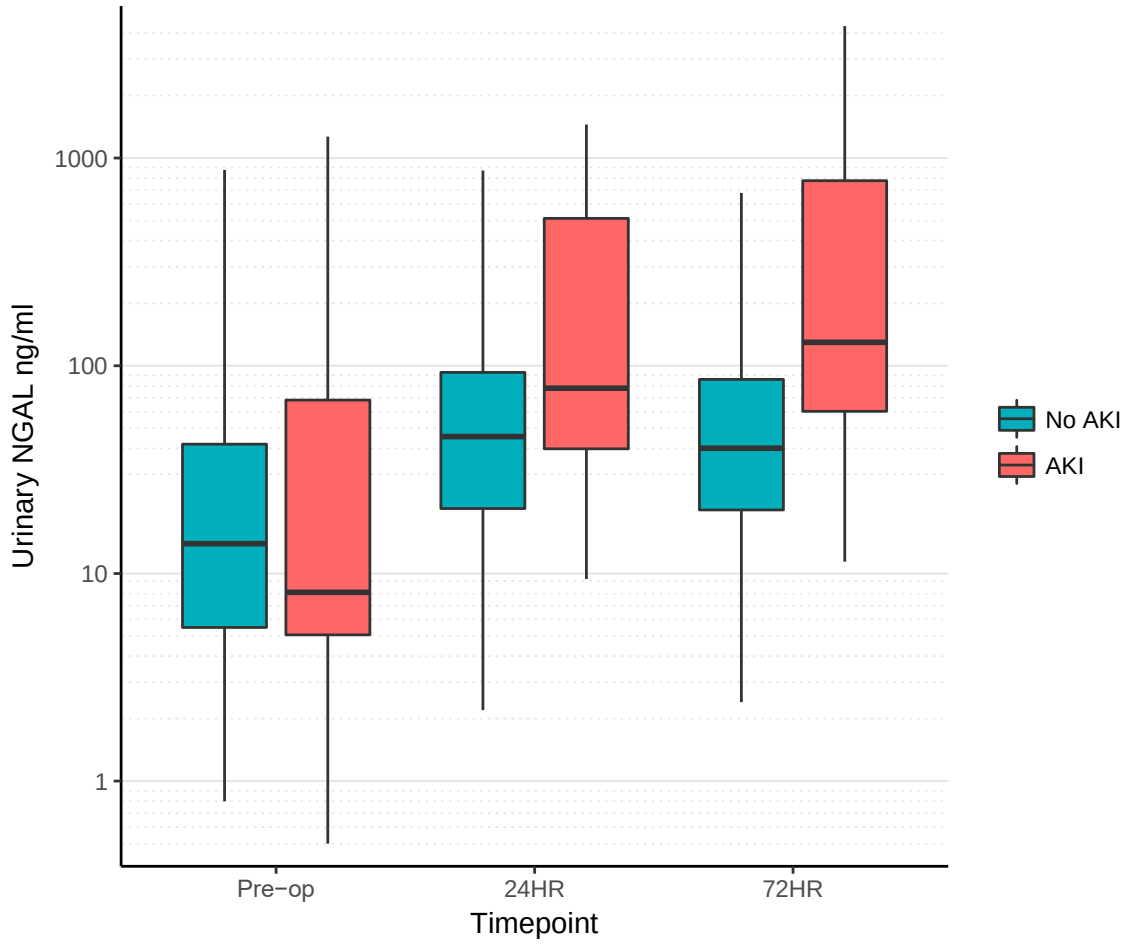


GDT: goal directed therapy

Relationship between the presence of a biomarker of acute kidney injury (urinary neutrophil gelatinase-associated lipase) and its ratio to urinary creatinine (urinary neutrophil gelatinase-associated lipase: creatinine ratio) and allocation to a goal directed therapy algorithm or usual care for perioperative fluid therapy in a high risk surgical population at three time points (before surgery, 24 hours after surgery and 72 hours after surgery).

Figure Three

Urinary NGAL at 3 discrete timepoints comparing study population with acute kidney injury with no acute kidney injury

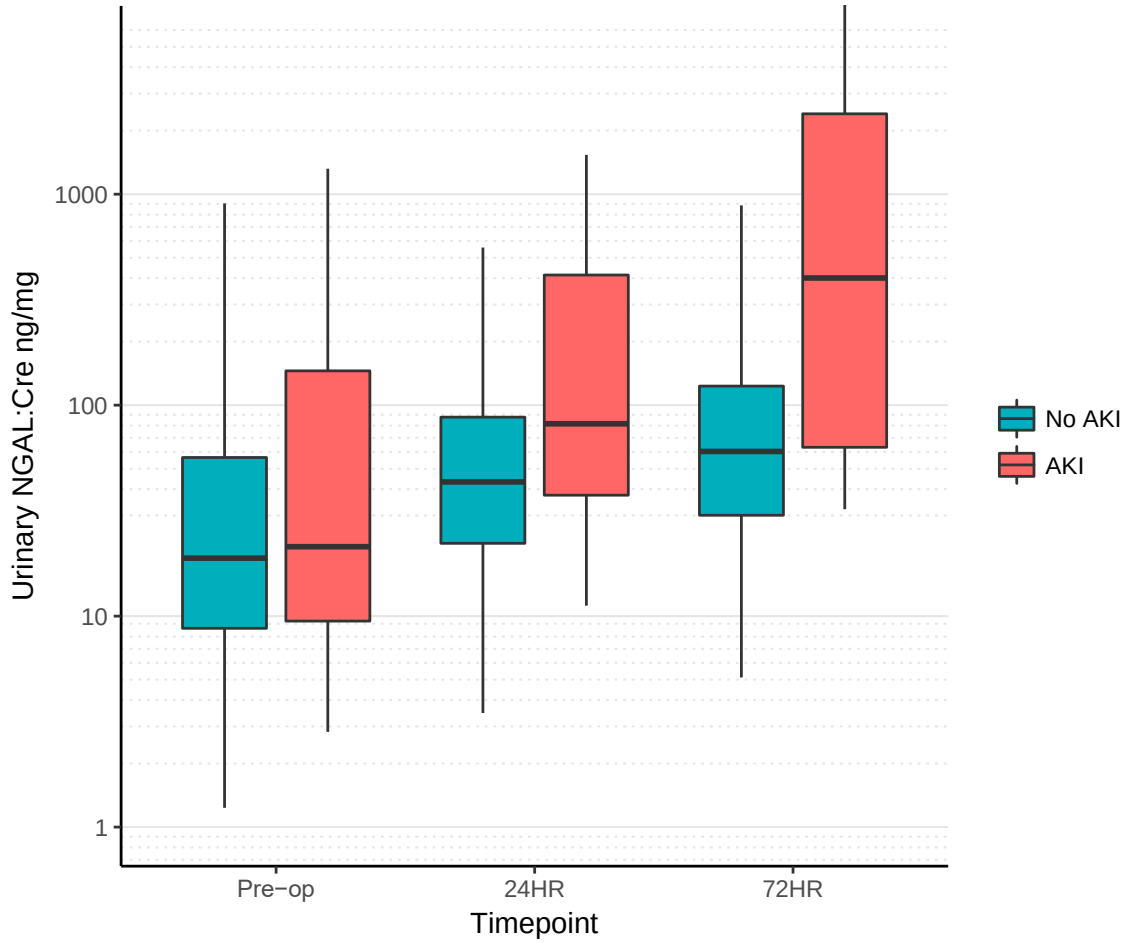


No AKI: no acute kidney injury; AKI: acute kidney injury

Relationship between the presence of a biomarker of acute kidney injury (urinary neutrophil gelatinase-associated lipase) and the diagnosis of acute kidney injury by Kidney Disease: Improving Global Outcomes (KDIGO) stage two and three in a high risk surgical population at three time points (before surgery, 24 hours after surgery and 72 hours after surgery).

Figure Four

Urinary NGAL: creatinine ratio at 3 discrete timepoints comparing study population with acute kidney injury with no acute kidney injury



No AKI: no acute kidney injury; AKI: acute kidney injury

Relationship between the presence of a biomarker of acute kidney injury (urinary neutrophil gelatinase-associated lipase) and its ratio to urinary creatinine (urinary neutrophil gelatinase-associated lipase: creatinine ratio) and the diagnosis of acute kidney injury by Kidney Disease: Improving Global Outcomes (KDIGO) stage two and three in a high risk surgical population at three time points (before surgery, 24 hours after surgery and 72 hours after surgery).