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The Effect of Intravenous Sildenafil Citrate on Post Cardiac Surgery Acute Kidney Injury: A Double Blinded, Randomised, Placebo-controlled, Clinical Trial

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Summary

Background: We assessed whether intravenous sildenafil citrate would reduce acute kidney injury in at-risk patients undergoing cardiac surgery with cardiopulmonary bypass.

Methods: In a double blinded randomised controlled trial adult patients at increased risk of acute kidney injury undergoing cardiac surgery in a single UK tertiary centre were randomised with concealed allocation to receive sildenafil citrate; 12.5mg.kg^{-1} administered intravenously over 2 hours, or placebo; 5% dextrose solution, at the commencement of surgery. The primary outcome for the trial was serum creatinine measured at 6 post randomisation time points. Secondary outcomes considered clinical events and potential disease mechanisms. Effect estimates were expressed as mean differences (MD) or odds ratios (OR) with (95% confidence intervals).

Results: The analysis population comprised eligible randomised patients that underwent valve or combined valve surgery and coronary artery bypass grafts using cardiopulmonary bypass between May 2015 and June 2018 (n=60 Sildenafil; N=69 Placebo). There was no difference between the groups for primary outcome; MD 0.88µmol.L^{-1} (-5.82, 7.59). There was a small and possibly clinically insignificant increase in Multiple Organ Dysfunction Scores in the Sildenafil group, MD 0.54 (0.02, 1.07), p=0.044. The frequency of a composite clinical outcome for death, sepsis or organ failure was slightly higher in the sildenafil group; OR 3.19 (0.82, 12.36), p=0.094. Biomarkers of kidney injury, endothelial function, and inflammatory cell activation, were similar between the groups.

Conclusions: These results do not support the use of sildenafil citrate for kidney protection in adult cardiac surgery.

Trail registration number: ISRCTN18386427

Keywords: Acute kidney injury, cardiac surgery, cardiopulmonary bypass, phosphodiesterase type 5 inhibitors, sildenafil citrate.

Background

Acute kidney injury (AKI) occurs in up to one third of all patients following cardiac surgery. It is characterised by an acute decline in kidney function as determined by elevations in serum creatinine and results in significant increases in postoperative complications as well as an almost fourfold increase in the risk of postoperative death.[1, 2] Our understanding of the underlying processes is poor and there are no effective treatments.[3] Experimental studies have demonstrated that preservation of endogenous Nitric Oxide (NO) bioavailability is renoprotective in response to a variety of injurious stimuli.[4, 5] Endogenous NO activity is increased by administration of the phosphodiesterase (PDE) type 5 inhibitor sildenafil citrate. This is used clinically in the treatment of erectile dysfunction (Viagra®, Pfizer) and more recently as an intravenous formulation (Revatio®, Pfizer) for pulmonary hypertension and acute right ventricular failure.[6, 7] We have shown that intravenous sildenafil prevents post cardiopulmonary bypass (CPB) AKI in a preclinical swine model.[8] We have also shown that sildenafil administered at a dose of 12.5mg to adults during cardiac surgery is well tolerated, and achieves plasma levels known to be clinically effective in other clinical settings.[9] This Phase IIb efficacy trial tested the hypothesis that the administration of sildenafil would reduce postoperative AKI in cardiac surgery patients identified preoperatively as being at increased risk of developing kidney injury.

Methods

Trial design/ participants

The Effect of Sildenafil (REVATIO®) on Post Cardiac Surgery Acute Kidney Injury (AKI): A Randomised, Placebo-controlled Clinical Trial: The REVAKI-2 Trial (Registration ISRCTN18386427 on 01/10/2015) was a parallel group RCT conducted at a single tertiary cardiac surgery centre in the UK. Male and female adult patients undergoing CABG, open valve, or combined CABG and open valve surgery who were at increased risk of developing AKI as determined by a modified AKI risk score;[1] a predicted risk score of 20% equates to a positive predicted value for developing AKI of >55%, were eligible. Exclusions, listed in the online supplement, included patients with pre-existing AKI, sepsis, Stage 5 Chronic Kidney Disease, severe hepatic impairment, allergy to phosphodiesterase type 5 inhibitors, or recent treatment with CYP 3A4 inhibitors or guanylate cyclase stimulators. Participants provided written informed consent pre-operatively. The allocated intervention was administered at skin incision at the start of surgery. Participants were followed-up until discharge and at six weeks and three months after randomisation. The trial complied with the Declaration of Helsinki. The Yorkshire & The Humber Leeds East Research Ethics Committee (REC) approved the study (reference 15/YH/0489) on 07/12/2015. A detailed protocol has been reported elsewhere.[10] The University of Leicester was the trial sponsor. Changes to the trial after commencement are described in the online supplement.

Randomisation and Blinding

Participants were randomly assigned to either sildenafil or placebo in a 1:1 ratio, using an internet-based randomisation system (Sealed Envelope Ltd, MHRA recognised facility) with concealed allocation. Randomisation was stratified by (a) type of procedure: CABG, valve, CABG and valve, other; and (b) baseline eGFR: <60, ≥60. Randomisation occurred pre-operatively after written informed consent was given and eligibility confirmed and as close to the scheduled surgery time as possible. Patients, researchers and clinical staff were blinded to group allocation.

Interventions

Sildenafil citrate 12.5mg in 65mls of 5% dextrose solution was administered intravenously over 150 minutes starting at the time of skin incision. In the Placebo group, a 5% dextrose solution was administered to the same volume and timing. Trial interventions were administered via clear syringes marked only with the participant's trial number and the label *REVAKI-2 trial drug*. Details of perioperative care protocols, monitoring of protocol compliance, blinding of clinical staff, and other steps to mitigate bias are described in the online supplement.

Outcomes

Timings of outcome assessment are listed in Supplemental **Table S3**.

Primary outcome

The primary outcome for the trial was serum creatinine measured pre-operation (baseline), on return to cardiac intensive care unit (CICU), and at 6-12, 24, 48, 72 and 96 hours post-surgery.

Secondary outcomes

Secondary outcomes are listed in **Table S1** in the online supplement. Briefly these included serial measures of the estimated Glomerular Filtration Rate (eGFR) and Multiple Organ Dysfunction Scores (MODS, range 0-24, with higher scores indicating more severe organ dysfunction, as defined in a recent trial[11]) from baseline to 96 hours post-surgery, with a final serum creatinine sample for estimation of eGFR at 6 weeks, consensus clinical definitions of acute kidney, lung, liver, gut, brain and myocardial injury, and sepsis, death, and a composite of these outcomes. Biomarkers of the inflammatory response; serum interleukin (IL)-6, IL-8, IL-10, myocardial injury; serum troponin I, and urine biomarkers of inflammation; Neutrophil Gelatinase Associated Lipocalcin (NGAL), and injury; Tissue inhibitor metalloproteinase-2* IGF-binding protein-7 (Timp2*IGFBP7) were measured in serial serum and urine samples as described in **Table S2** in the online supplement. Adverse events were reported descriptively. The results of a pre-specified mechanistic analysis of platelet leucocyte and endothelial activation will be reported separately.

Sample size

On the basis that the observed standard deviation for serum creatinine values from the MARACAS Study (NCT02315183) was 37µmol/L, and the mean observed correlation between baseline and 5 post surgery measures of 0.84 we estimated that a sample size of 56 patients per group would have a 90% power to detect an mean difference of 10µmol/L for serum creatinine values between treatment and placebo groups with an alpha value of 0.05, after adjustment for baseline values. We aimed to recruit 126 patients (63 per group) anticipating that 10% of patients would be treated outside of the protocol, withdrawn or lost to follow up. This sample size would also allow us to detect an absolute reduction in the frequency of AKI from 65% to 40% with an 80% power and 5% significance (2-tailed).

Statistical analysis

The primary analysis population included all randomised participants, excluding patients who did not undergo surgery or provide baseline eGFR. Outcomes are reported by intention to treat and were directed by a pre-specified Statistical Analysis Plan (appended to the online supplement). Continuous variables are summarised using the mean and standard deviation (SD) (or median and interquartile range (IQR) if the distribution is skewed), and categorical data are summarised as a number and percentage. The primary analysis of the primary outcome compared all available data with no imputation using a Linear Mixed Effects model adjusted for the stratification variables, baseline

eGFR and surgical procedure. Treatment effect was estimated with placebo as the reference group and reported with a 95% confidence interval (CI). A Likelihood ratio test was used to determine statistical significance, and two tailed p-values<0.05 were considered statistically significant. The overall treatment effect for the primary outcome was estimated across the post-surgery time points with adjustment for baseline value. A model with time*treatment interaction effect estimate was also fitted. Significant differences either in the overall effect or for individual time points were considered evidence of a treatment effect. Sub-group analyses considered the interaction between the treatment effect and stratification variables.

Analyses of secondary outcomes were carried out using Linear Mixed Effects models (for continuous variables that were measured at multiple time points), Linear regression models (for continuous variables with a single measure), Logistic models (binary variables), or Cox proportional-hazards models (time to event variables) as described above (adjusted for the stratification variables, baseline eGFR and surgical procedure). All analyses were performed in Stata version 15.0 (StataCorp LP, College Station, Texas, USA).

RESULTS

Trial cohort and patient flows

The flow of patients through the trial is shown in **Figure 1**. There were 129 patients recruited and randomised between September 2015 and September 2018 which made up the analysis population, 60 of whom were allocated to Sildenafil and 69 to Placebo. Of the 129 randomised patients, 4 did not undergo surgery, 4 patients died prior to hospital discharge. Follow up was complete for 117 patients (93.6%) at 3 months. Details of patient withdrawals are listed in **Table S3** in the online supplement.

Participant Characteristics

Baseline demographic, clinical, and operative characteristics were similar in the two groups (**Table 1** and **Table S4**). The median AKI risk score was 29.6 (IQR 24.5 to 38) in the Sildenafil group and 30.1 (IQR 25.8 to 40) in the Placebo Group. The median age of participants was 72 years (IQR 52 to88) and 81% were male. Overall, 42 (33.60%) participants were listed for CABG surgery, 39(31.20%) for valve surgery and 44 (35.20%) were listed for combined CABG and valve surgery or other. At baseline, mean eGFR was 70.7 $ml.min^{-1}.m^2$ (20.1) in the Sildenafil Group and 75.6$ml.min^{-1}.m^2$ (23.6) in the Placebo group. By chance a higher proportion of participants in the Sildenafil group 8 (13.79%) underwent redo surgery versus the Placebo group 2 (2.99%). This was reflected in longer bypass; Sildenafil median 1.76 hours (1.36 to 2.17) versus Placebo median 1.58 hours (1.17 to 2.03) and cross-clamp times; Sildenafil median 1.19 hours (0.82 to 1.57) versus Placebo median 1.03 hours (0.75-1.27)**.**

Measures of Process

Two patients in the placebo group had the infusion stopped prematurely due to hypotension. One participant in the intervention group was found ineligible intraoperatively; ejection fraction <30%, and did not receive the allocated treatment. (**Table S5**). Diastolic, systolic, and mean arterial blood pressure, haematocrit, blood loss, transfusion, and change in body weight between baseline and 3 days post-surgery were similar in Sildenafil and Placebo Group (**Figure S1** and **Table S4**). Rates of hypotension requiring treatment with vasopressors were similar 30 (52%) Sildenafil versus 32 (47%) Placebo. There were no anaphylactic reactions to the study medication. All participants were alive at the end of the surgery.

Primary outcome

Table 2 and **Figure 2A** show the results of the analyses of the primary outcome. For the primary intention to treat analysis Sildenafil did not reduce serum creatinine up to 96 hours following surgery; mean difference 0.88 $\mu mol.L^{-1}$ (-5.82 to 7.59), p=0.797. No pre-specified secondary,

sensitivity, or sub-group analyses indicated a treatment effect of Sildenafil. A *post hoc* sensitivity analysis that excluded patients undergoing redo procedures did not demonstrate a treatment effect.

Secondary outcomes

Figure 2, Table S7 and **Figures S2** and **S3** show the results of the analyses of secondary outcomes. There was no treatment effect for Sildenafil on eGFR up to 6 weeks post-surgery. MODS (scale 0-24) were higher in the Sildenafil group, mean difference 0.54 (0.02 to 1.07), p=0.044. The composite outcome of sepsis, low cardiac output, lung, liver, brain or gut injury was higher in the Sildenafil group, but this was not statistically significant Odds Ratio, OR, 3.19 (0.82 to 12.36), p=0.094. Time to extubation, hazard ratio, HR 0.80, (0.55 to 1.17), cardiac intensive care unit (CICU) discharge, HR 1.15, (0.79 to 1.68), and discharge from the cardiac unit, HR=0.98, (0.68 to 1.42), were similar. The groups were similar with respect to biomarker concentrations for inflammation (IL6, IL8, IL10), and kidney injury (Urine NGAL and Timp2*IGFBP7 (**Table S12**). Serum Troponin was higher in the Sildenafil group but this was not statistically different; mean difference 21503µmol.L^{-1} (-3557 to 46564), p=0.091 (**Figure 2C**). The time to resolution of arterial hyperlactatemia (>2.0 mmol.L^{-1}) was longer in the Sildenafil arm; median 3 hours (1.4 to 13.27) versus Placebo median 1.67 hours (1.23 to 9.8). Serious expected adverse events to three months were similar between the groups (**Table S13**).

DISCUSSION

Main findings

The results of the REVAKI-2 trial do not support the hypothesis that sildenafil citrate reduces the severity of post cardiac surgery AKI. Unexpectedly, Sildenafil increased MODS relative to placebo. This was not reflected by significant differences in clinical outcomes or in serum or urine biomarkers of kidney and myocardial injury.

Strengths and Limitations

The REVAKI-2 trial selected an enriched cohort of patients at increased risk of AKI; 48% of participants developed AKI in the placebo group, although this was less than expected. The trial was double-blinded with concealed allocation, detailed documentation of process, objective ascertainment of outcomes, and very low levels of attrition. It evaluated, for the first time to our knowledge, an intravenous sildenafil dose with documented short-acting pharmacokinetics that aimed to prevent the early phase drop in endogenous NO bioactivity, and reduce augmentation of late NO mediated oxidative stress that has been documented in animal models of AKI.[4, 12] The trial used detailed analyses of the primary outcome as well as complementary clinical measures and biomarkers of injury and dysfunction in multiple organ systems. The principal limitation of the trial was use of serum creatinine as the primary outcome. The limited sensitivity and specificity of this biomarker for AKI is well recognised. This is offset by the clinical applicability of changes in serum creatinine in current consensus definitions of AKI,[13] and the ease, accuracy, and reproducibility of its measurement. Combined with similar values for two putative urine biomarkers of AKI; NGAL and Timp2*IGFBP7, we conclude that Sildenafil is very unlikely to have renoprotective effects in cardiac surgery patients. Another limitation is that baseline eGFR was slightly lower and the proportion of patients undergoing redo-surgery was higher in the Sildenafil group. However pre-specified sensitivity analysis, stratified by eGFR at baseline, as well as a *post hoc* sub-group analysis restricted to those patients who underwent first time cardiac surgery did not demonstrate any treatment effect, supporting our overall conclusion.

Clinical relevance

The trial has two novel findings: 1. the intervention was designed based on findings in a porcine model of post CPB where AKI is characterised by alterations in NO activity, and where multiple interventions, including sildenafil, that target these processes have been shown to be renoprotective.[8, 14] Plasma sildenafil levels that were therapeutic in the porcine model, and are effective in other clinical settings,[9] had no treatment effect in adult cardiac surgery patients. In a younger cohort (median age 48 years) undergoing surgery for rheumatic valve disease, Lei and colleagues demonstrated that NO added to the CPB circuit or inhalational gases for up to 24 hours post-surgery significantly reduced AKI.[15] This effect was attributed to the quenching of plasma cell

free Hb released during CPB by NO, an effect that may not be reproduced by phosphodiesterase inhibition. Conversely, atrial natriuretic peptide (ANP) which acts in part via phosphodiesterase inhibition is renoprotective in adults undergoing cardiac surgery when administered for up to several days post-surgery.[16, 17] A longer duration of sildenafil treatment may have elicited a different result, or other pleiotropic effects of ANP may underlie these observations. 2. MODS scores were higher in the Sildenafil group. The effect size was small, and less than the minimum clinically important difference for MODS specified in a previous trial.[11] The risk of over interpretation of this small and probably clinically non-significant difference notwithstanding it is noteworthy that the direction of the treatment effect was driven predominantly by differences in serum bilirubin values. The treatment effects for serum troponin values were also in the direction of injury, similar to the results of a RCT of pre-surgery oral sildenafil in children undergoing cardiac surgery.[18] These findings are at odds with pre-clinical studies indicating a cardioprotective effect of sildenafil in ischaemia reperfusion injury.[19] This potential safety signal of sildenafil requires further study.

Conclusions

We did not demonstrate a renoprotective effect for intravenous sildenafil in adult cardiac surgery patients at increased risk of AKI.

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Disclosures

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). The remaining authors declare that there are no conflicts of interest.

Details of Contributors

All of the study authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the analyses. GJM (Chief Investigator) and MW conceived the trial. GJM, NJB, and MW wrote the application for funding (with others) and designed the trial. HA, LJD, NK, DS, PP, and TK managed the conduct of the trial and performed the research procedures. SB and ASDP managed the data during the trial and carried out the statistical analyses. HA, MW, SB, TK, and GJM drafted the report. All authors reviewed the report for important intellectual content and approved the final version.

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Table 1: Participant demographics and past history

Characteristic		Placebo (N=67)		Sildenafil (N=58)		Overall (N=125)	
		n	%	n	%	n	%
DEMOGRAPHY							
Sex (Female)		10	14.93	14	24.14	24	19.2
Age (Years) (Mean, Range)		72	(52,88)	72	(54,88)	72	(52,88)
BMI (Median, IQR)		30.9	(26.6,36.3)	31.1	(27.7,35.4)	31	(27.1,35.7)
AKI Risk Score (Median, IQR)		30.1	(25.8,40)	29.6	(24.5,38)	29.95	(25.6,39.8)
Cardiac Disease							
NYHA class	I	7	10.45	7	12.07	14	11.20
	II	50	74.63	37	63.79	87	69.60
	III	8	11.94	11	18.97	19	15.20
	IV	1	1.49	0	0.00	1	0.80
	Missing	1	1.49	3	5.17	4	3.20
CCS class	Asymptomatic	21	31.34	19	32.76	40	32.00
	I	27	40.30	19	32.76	46	36.80
	II	15	22.39	15	25.86	30	24.00
	III	1	1.49	3	5.17	4	3.20
	IV	1	1.49	0	0.00	1	0.80
	Missing	2	2.99	2	3.45	4	3.20
LV function	Good (>49%)	47	70.15	37	63.79	84	67.20
	Moderate (30-49%)	16	23.88	19	32.76	35	28.00
	Poor (<30%)	3	4.48	2	3.45	5	4.00
	Missing	1	1.49	0	0.00	1	0.80
>50% disease in left main stem		4	5.97	5	8.62	9	7.20
≤ 50% disease in left main stem		63	94.03	51	87.93	114	91.20
Missing		0	0.00	2	3.45	2	1.60
Coronary disease, number of vessels*	None	24	35.82	12	20.69	36	28.80
	Single	14	20.90	12	20.69	26	20.80
	Double	5	7.46	12	20.69	17	13.60
	Triple	23	34.33	20	34.48	43	34.40
	Missing	1	1.49	2	3.45	2	2.40

Characteristic		Placebo (N=67)		Sildenafil (N=58)		Overall (N=125)	
		n	%	n	%	n	%
BLOOD AND URINE RESULTS							
Haemoglobin (Mean, SD)		128.8	20.1	129.6	17.5	129.2	18.8
Haematocrit (Mean, SD)		37.8	5.5	38.3	4.8	38.0	5.2
Platelets (Median, IQR)		203	(168,245)	194	(164.5,237.5)	196	(166,238)
Serum Creatinine (Median, IQR)		89	(73,103)	92	(79,110)	90	(75,106)
Estimated Glomerular Filtration rate (eGFR) (Mean, SD)		75.6	23.6	70.7	20.1	73.3	22.1
MEDICAL HISTORY							
Diabetic	Yes	24	35.82	26	44.83	50	40.00
	No	42	62.69	32	55.17	74	59.20
	Missing	1	1.49	0	0.00	1	0.80
Diet	Yes	4	5.97	3	5.17	7	5.60
	Not Applicable	43	64.18	32	55.17	75	60.00
	Missing	20	29.85	23	39.66	43	34.40
Oral	Yes	14	20.90	17	29.31	31	24.80
	Not Applicable	43	64.18	32	55.17	75	60.00
	Missing	10	14.93	9	15.52	19	15.20
Insulin	Yes	7	10.45	7	12.07	14	11.20
	Not Applicable	43	64.18	32	55.17	75	60.00
	Missing	17	25.37	19	32.76	36	28.80
Pacemaker	Yes	4	5.97	5	8.62	9	7.20
	No	62	92.54	53	91.38	115	92.00
	Missing	1	1.49	0	0.00	1	0.80
Temporary	Yes	0	0.00	0	0.00	0	0.00
Permanent	Yes	1	1.49	5	8.62	6	4.80
	Not Applicable	63	94.03	53	91.38	116	92.80
	Missing	3	4.48	0	0.00	3	2.40
CVA or TIA	Yes	2	2.99	1	1.72	3	2.40
	No	64	95.52	56	96.55	120	96.00
	Missing	1	1.49	1	1.72	2	1.60
Smoking status	Current	5	7.46	2	3.45	7	5.60

Characteristic		Placebo (N=67)		Sildenafil (N=58)		Overall (N=125)	
		n	%	n	%	n	%
	Never	15	22.39	17	29.31	32	25.60
	Ex (>1 month)	46	68.66	38	65.52	84	67.20
	Missing	1	1.49	1	1.72	2	1.60
Redo cardiac surgery	Yes	2	2.99	4	6.90	6	4.80
	No	65	97.01	54	93.10	119	95.20
Myocardial infarction	Yes	8	11.94	12	20.69	20	16.00
	No	58	86.57	46	79.31	104	83.20
	Missing	1	1.49	0	0.00	1	0.80
MEDICATIONS							
Nitrates until theatre	Yes	2	2.99	3	5.17	5	4.00
	No	4	5.97	3	5.17	7	5.60
	Not Applicable	61	91.04	52	89.66	113	90.40
Clexane within 12 hours preoperatively	Yes	0	0.00	0	0.00	0	0.00
	No	6	8.96	6	10.34	12	9.60
	Not Applicable	61	91.04	52	89.66	113	90.40
Anti-platelet agents and dual anti-platelet for 5 days preoperatively	Yes	5	7.46	2	3.45	7	5.60
	No	1	1.49	4	6.90	5	4.00
	Not Applicable	61	91.04	52	89.66	113	90.40
CYP3A4 inhibitors within last month	Yes	0	0.00	0	0.00	0	0.00
	No	6	8.96	6	10.34	12	9.60

Characteristic		Placebo (N=67)		Sildenafil (N=58)		Overall (N=125)	
		n	%	n	%	n	%
	Not Applicable	61	91.04	52	89.66	113	90.40

Table 2: Primary analysis of Primary Outcome

Analysis	Randomised to Placebo (N=67)		Randomised to Sildenafil (N=58)		Treatment Effect	
	Median	(IQR)	Median	(IQR)	Adjusted Mean Difference (95% Confidence Intervals)	P Value
Primary Intention to treat						
Baseline	89	(73,103)	92	(79,110)		
CICU	91.5	(80,112)	95.5	(79,118)	Reference Group	
6-12 hours	101	(84,127)	104.5	(84,129)	8.16 (3.32,13.00)	0.001
24 hours	99	(79,127)	106	(87,138)	13.19 (8.36,18.01)	0.000
48 hours	100	(82,139)	107.5	(86,153)	18.88 (14.05,23.7)	0.000
72 hours	96.5	(76,117)	108	(88,137)	12.04 (6.96,17.13)	0.000
96 hours	97	(78,112)	110	(89,131)	6.95 (1.84,12.06)	0.008
Intervention (SILDENAFIL)					**0.88 (-5.82,7.59)**	**0.797**

Notes:

All treatment estimates are reported with adjustment for baseline values. Raw data expressed as Median (Interquartile Range).

Number of individuals contributing to each analysis by treatment group and overall: Overall: 123, Placebo: 66, Sildenafil: 57

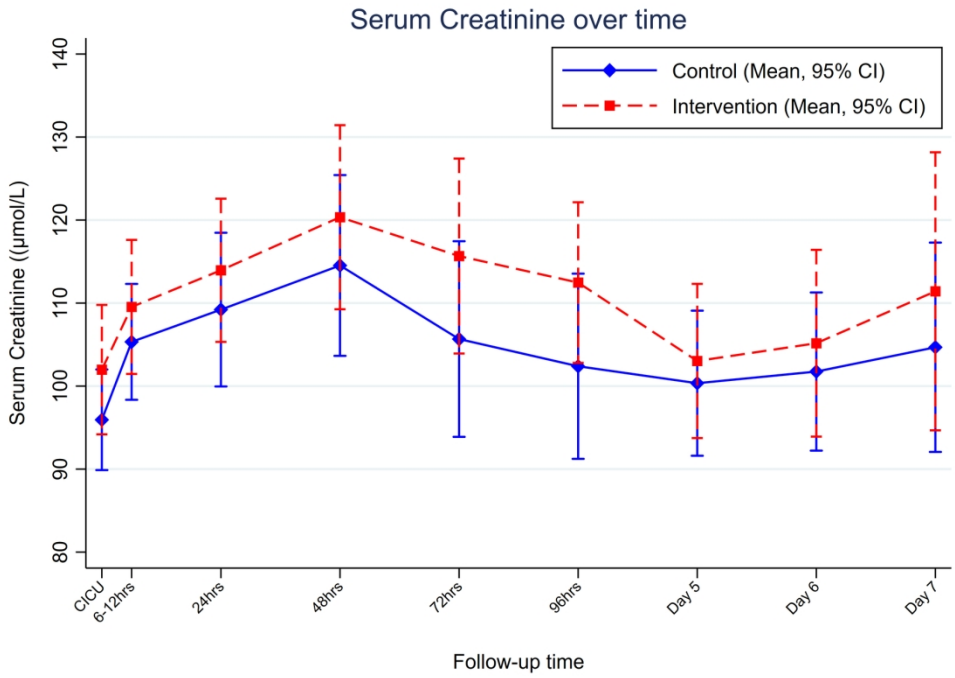

Figure 2A. Serum Creatinine Values. Data expressed as Mean (SD)

82x60mm (600 x 600 DPI)

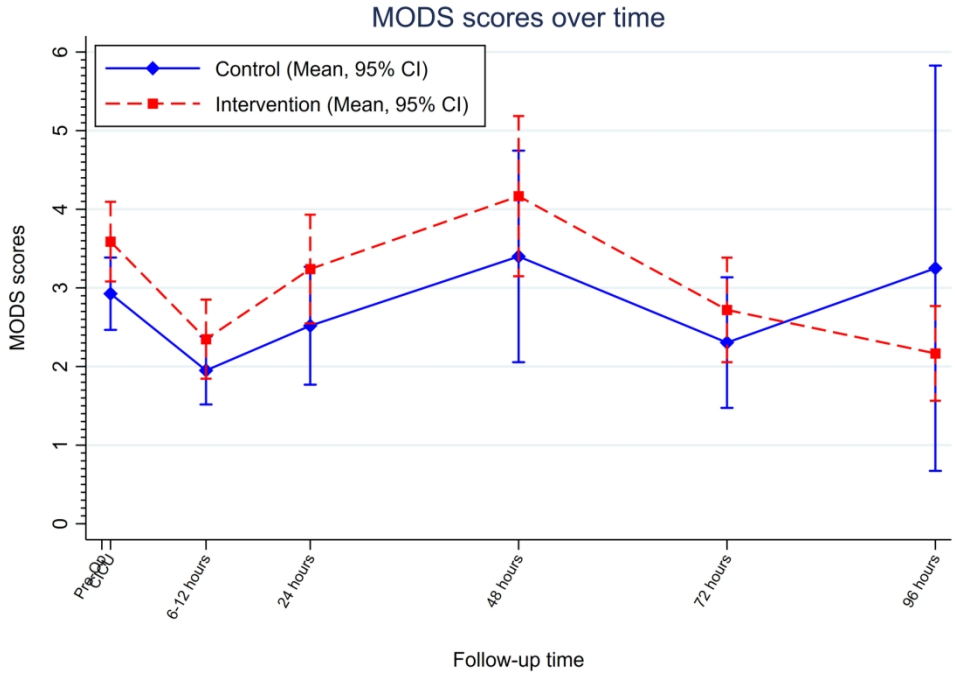

Figure 2B. Multiple Organ Dysfunction Scores. Data expressed as Mean (SD)

82x60mm (600 x 600 DPI)

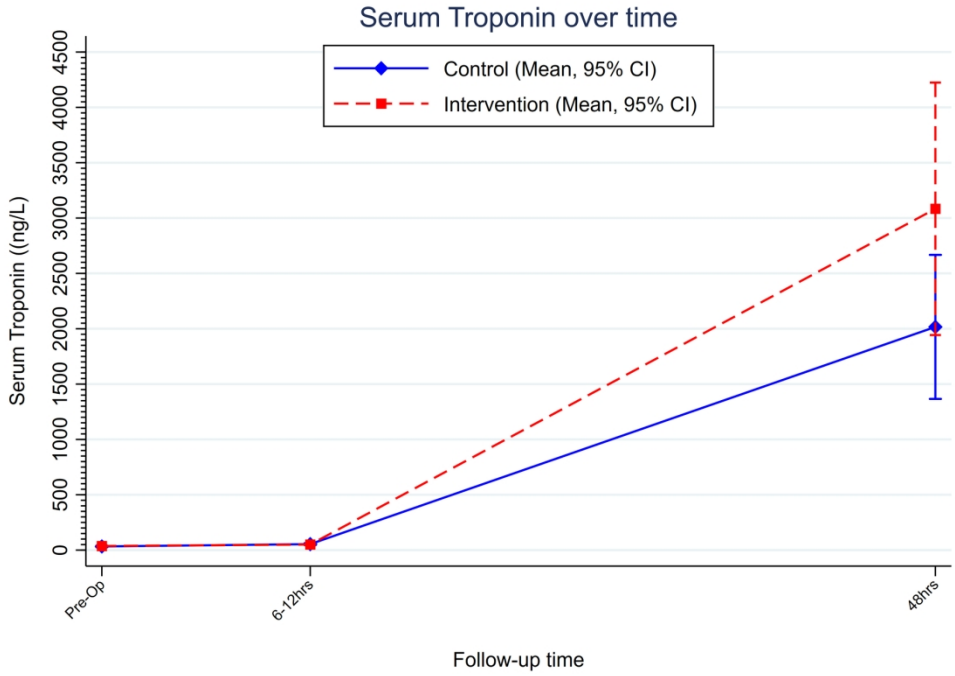

Figure 2C. Serum Troponin. Data expressed as Mean (SD)

82x60mm (600 x 600 DPI)

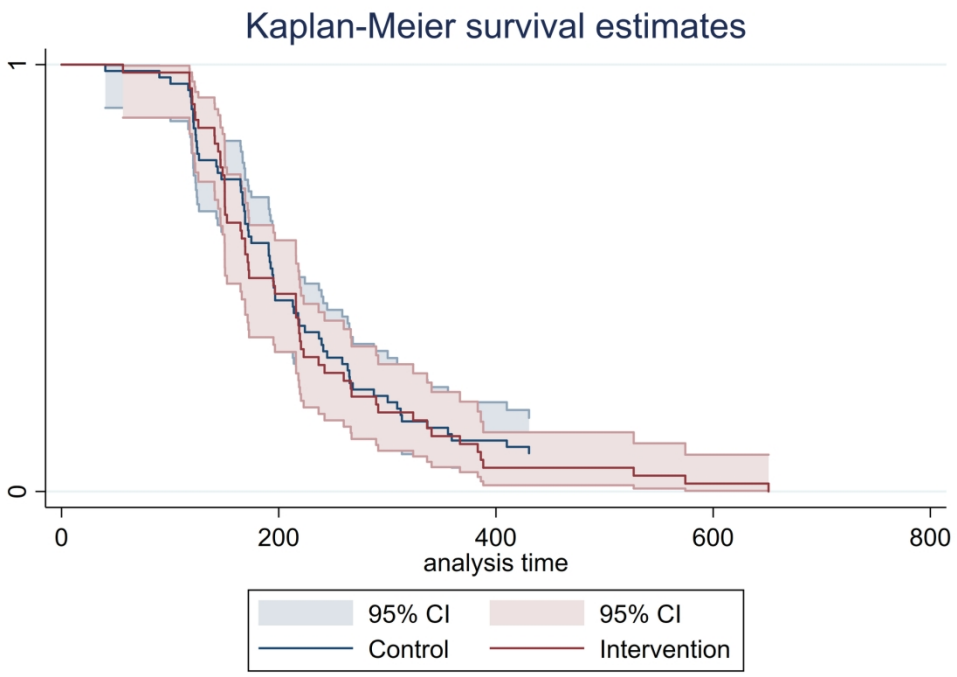

Figure 2D. Time to Discharge from Cardiac Unit in participants allocated to Sildenafil or Placebo. Data expressed as Mean (SD)

82x60mm (600 x 600 DPI)

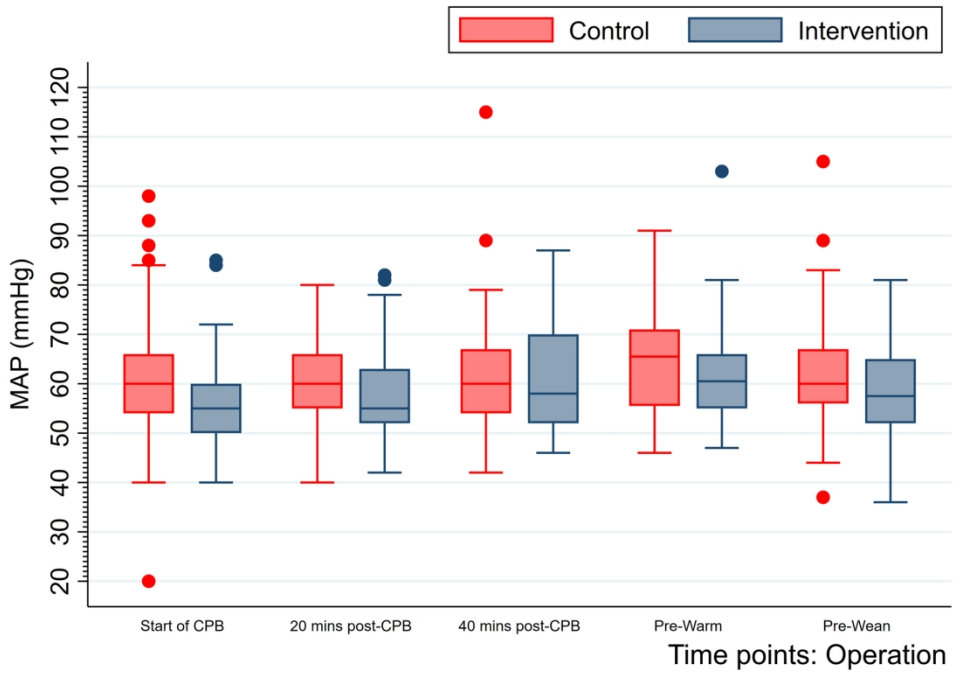

Figure S1A. Panels show serial measurements of Blood Pressure

82x60mm (600 x 600 DPI)

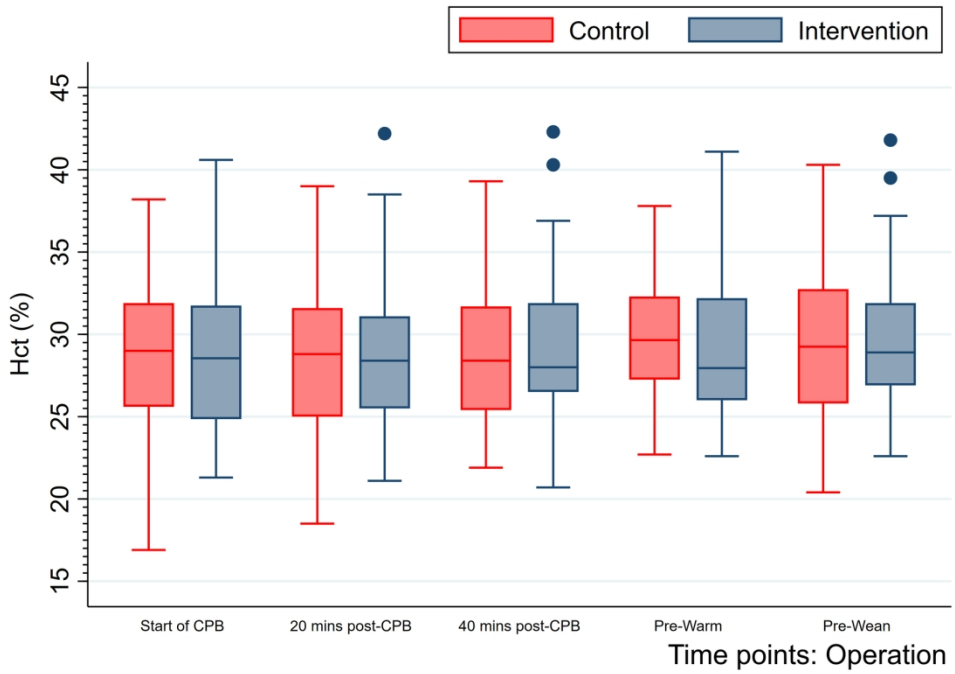

Figure S1B. Panels show serial measurements of Haematocrit

82x60mm (600 x 600 DPI)

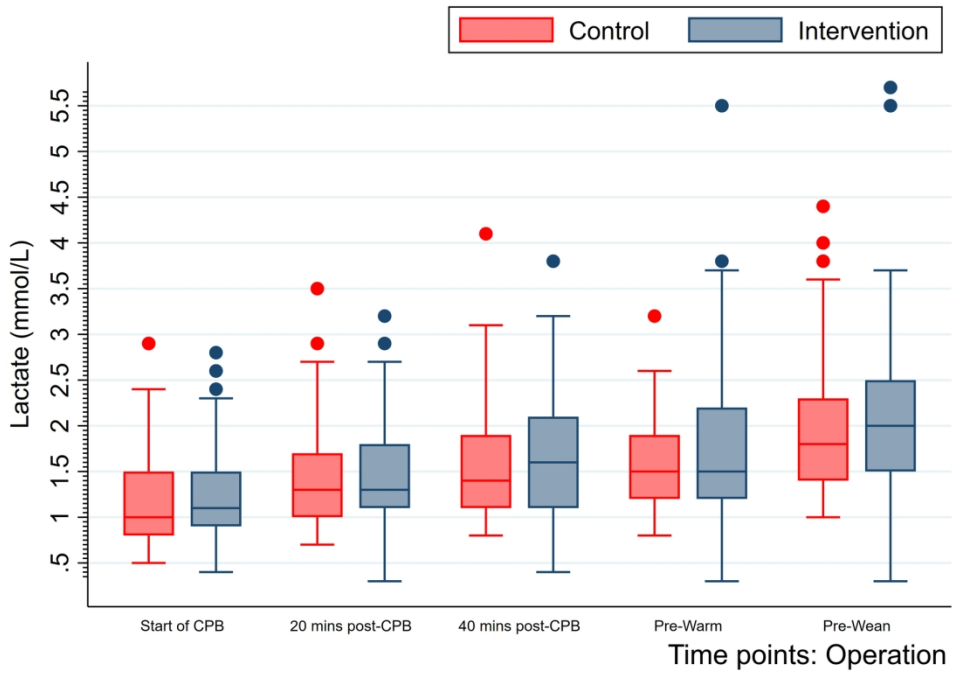

Figure S1C. Panels show serial measurements of Lactate.

82x60mm (600 x 600 DPI)

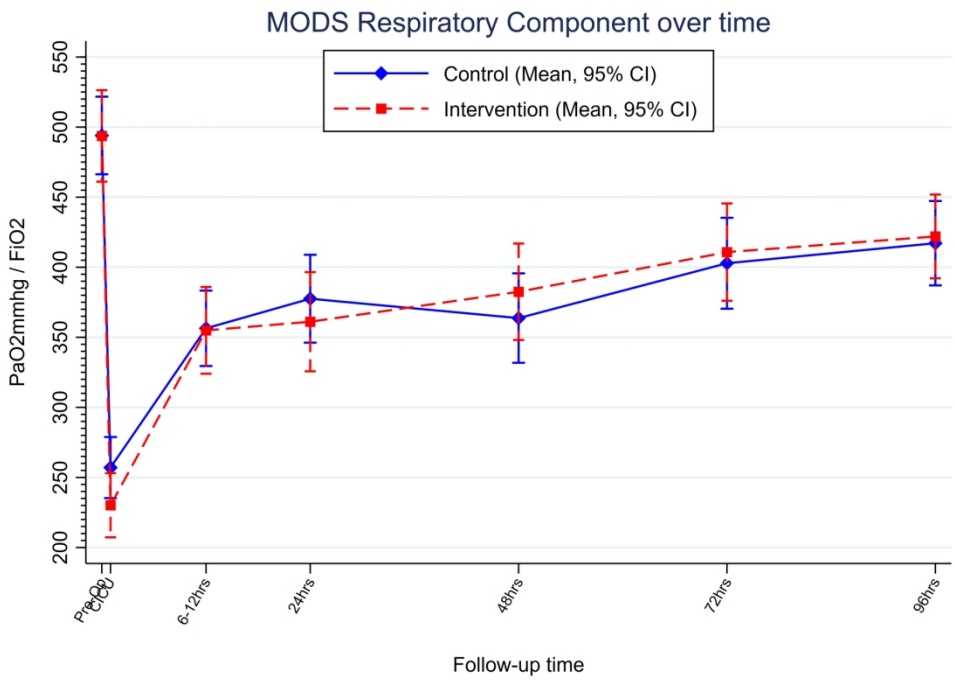

Figure S2. MODS Scores Component 1: Respiratory

82x60mm (600 x 600 DPI)

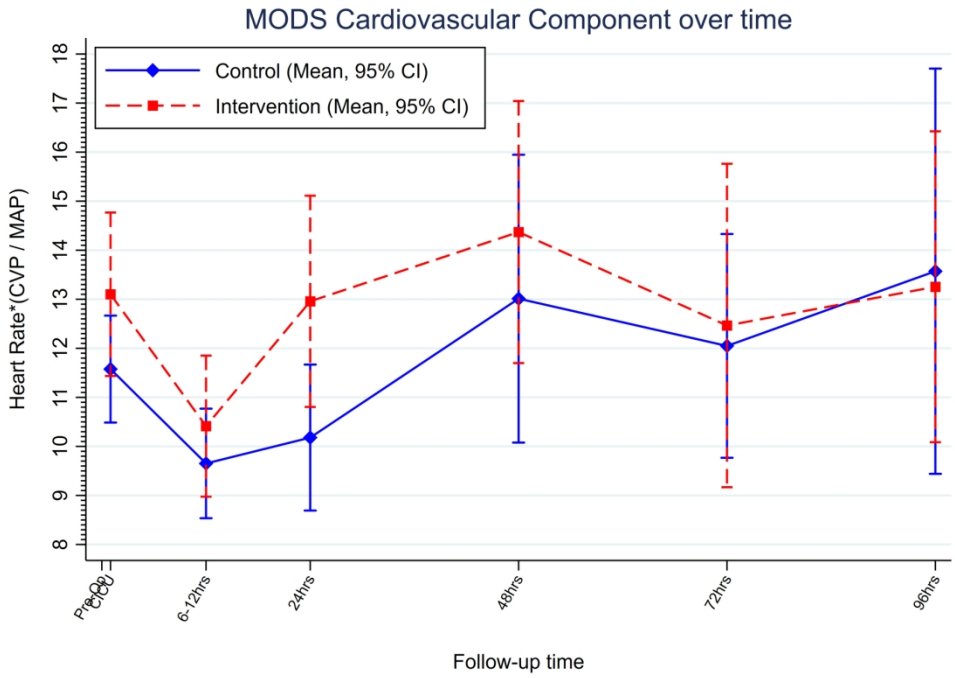

Figure S2. MODS Scores Component 2: Cardiovascular

82x60mm (600 x 600 DPI)

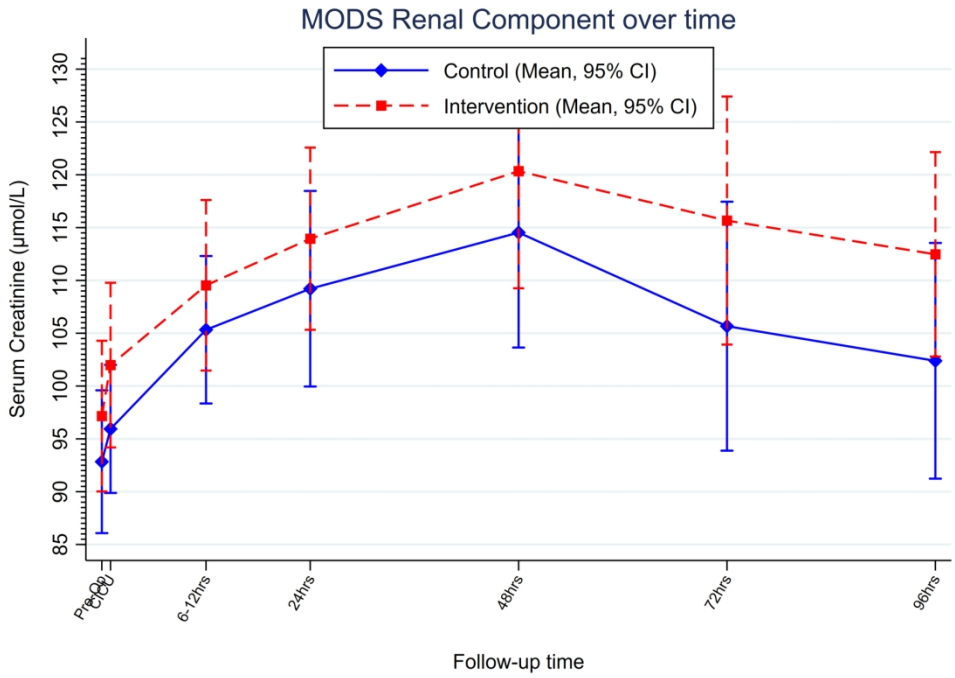

Figure S2. MODS Scores Component 3: Renal

82x60mm (600 x 600 DPI)

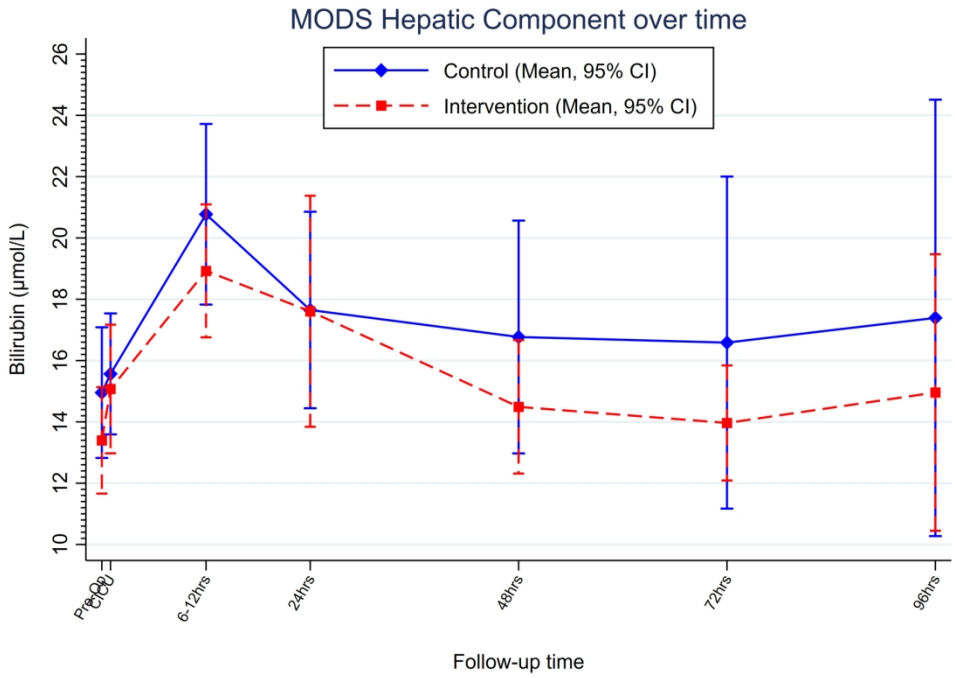

Figure S2. MODS Scores Component 4: Hepatic

82x60mm (600 x 600 DPI)

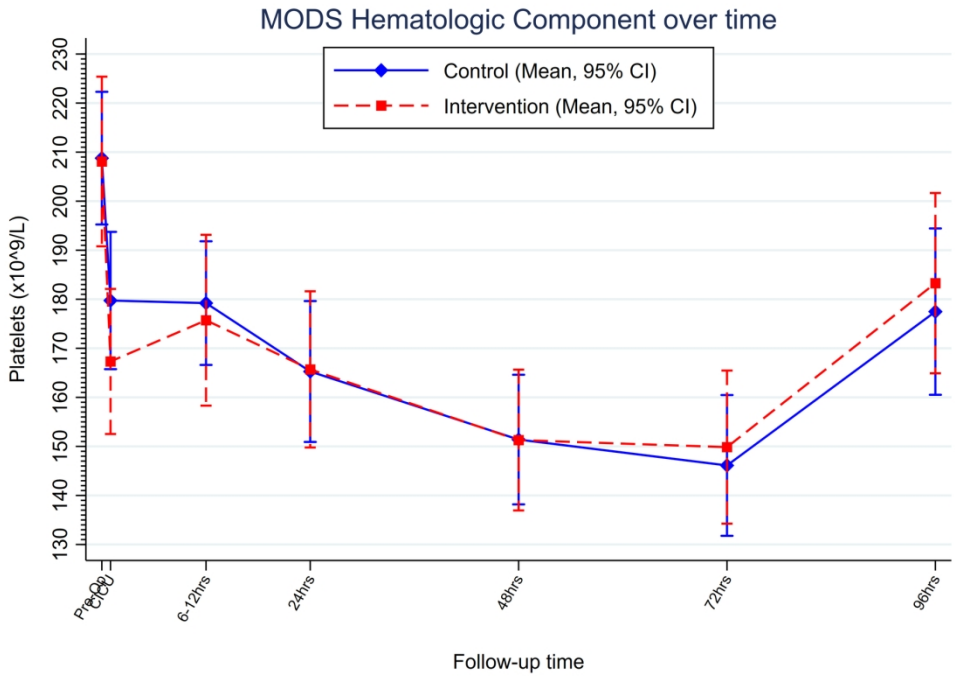

Figure S2. MODS Scores Component 5: Hematologic

82x60mm (600 x 600 DPI)

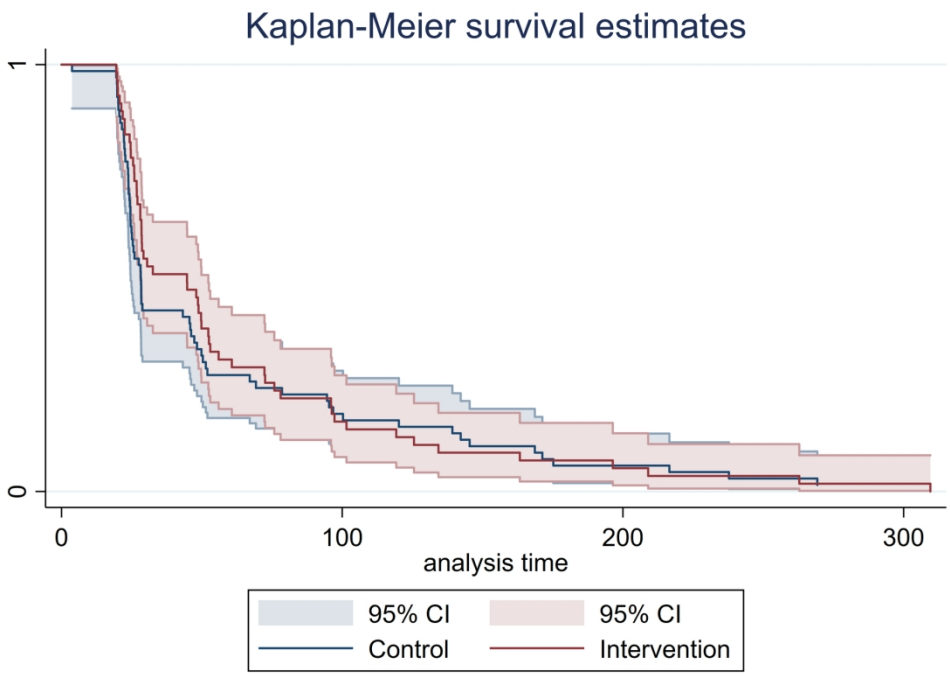

Figure S3A. Secondary Outcomes: Time to discharge from ICU.

82x60mm (600 x 600 DPI)

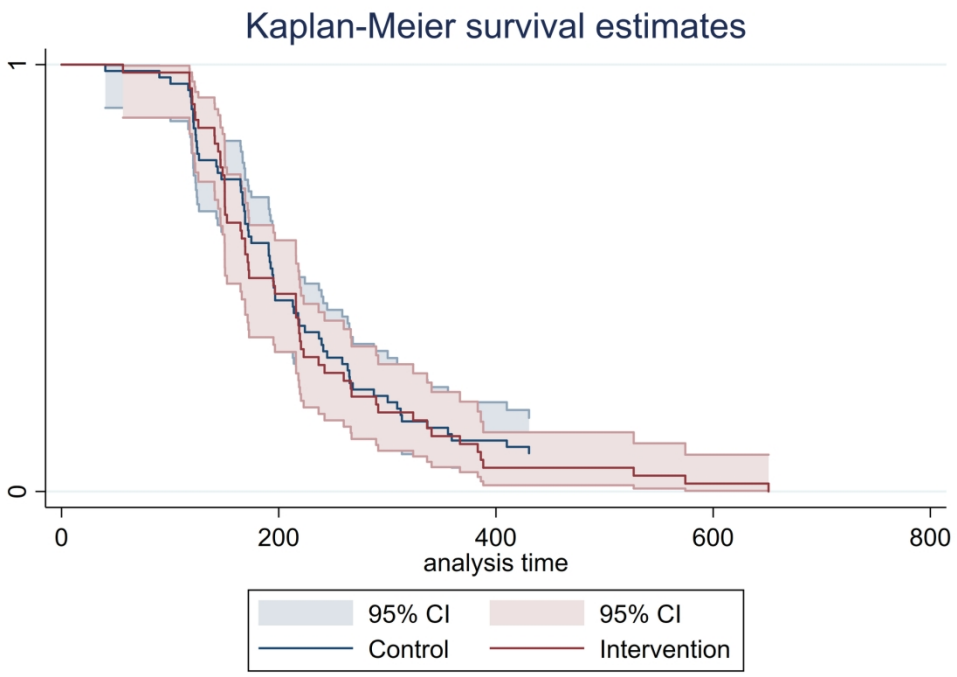

Figure S3B. Secondary Outcomes: Time to discharge from Hospital Unit.

82x60mm (600 x 600 DPI)

Figure 1. Flow of Participants showing eligibility, recruitment, protocol deviations, withdrawals and loss to follow-up in the REVAKI-2 trial.