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Preoperative volume replacement therapy in diabetic patients undergoing coronary artery bypass grafting surgery: results from an open parallel group randomised controlled trial (VeRDiCT)

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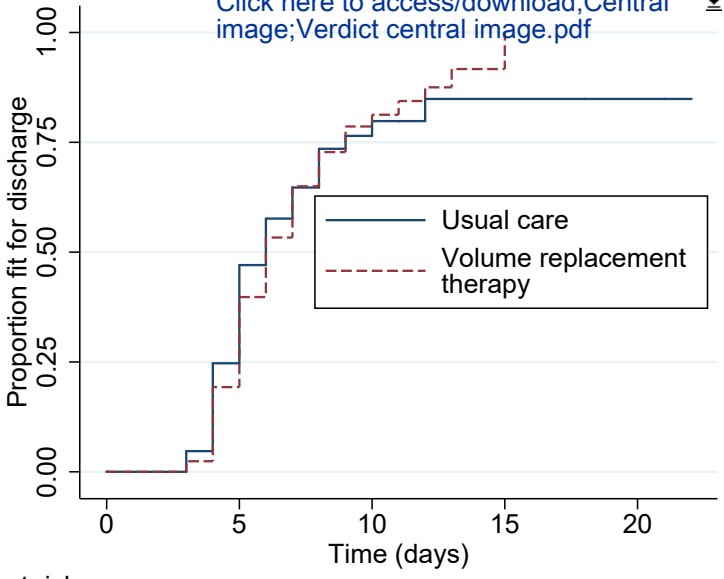
Author Comments:	Dear Editorial Office, RE: “Preoperative volume replacement therapy in diabetic patients undergoing coronary artery bypass grafting surgery: results from an open parallel group randomised controlled trial (VeRDiCT)”. Please find enclosed the 3rd version of our manuscript that we have revised to implement all the minor comments received from the Associate Editor and Reviewer. The minor changes made as shown in red and our answers to the comments are uploaded separately. We thanks the Editorial Office for the valuable contribution to our manuscript and are hopeful that it is now ready for publication. Yours sincerely

	Professor Raimondo Ascione
Abstract:	Objective: To investigate the effect of preoperative volume replacement therapy (VRT) on renal function, health outcome and time to fitness for discharge (TFFD) in diabetic patients undergoing coronary artery bypass grafting (CABG). Methods: In two parallel randomised controlled trials diabetic patients were allocated to preoperative VRT (1mL/kg/hour of Hartmann's solution for 12 hrs) or usual care. Primary outcome was TFFD. Secondary outcomes included acute kidney injury (AKI), postoperative complications, patient-reported quality of life (QoL), hospital resource use and markers of renal, cardiac, and inflammatory injury. Results: In total, 169 patients were randomized (84 VRT, 85 usual care; mean age 64 years; 88% male). TFFD was similar between groups (median 6 days; interquartile range (IQR) 5.0-9.0 in both groups; hazard ratio (HR) 0.95; 95% confidence interval (CI) 0.65-1.38; P=0.78). Post-operative AKI was not statistically different (VRT: 27.7% vs. usual care: 18.8%, odds ratio (OR) 1.72; 95% CI 0.82- 3.59; P=0.15). Estimated glomerular filtration rate [eGFR; mean difference (MD) -0.92; 95% CI -4.18 to 2.25; P=0.56], microalbumin/creatinine ratio [geometric mean ratio (GMR) 1.16; 95% CI 0.94-1.42; P=0.16], N-acetyl-beta-D-glucosaminidase [NAG; GMR 1.08; 95% CI 0.83-1.40;P=0.57], C-reactive protein [CRP; GMR 1.00; 95% CI 0.88-1.13; P=0.94], troponin T [Trop-T; GMR 1.18; 95% CI 0.78-1.79; P=0.39] and other secondary health outcomes were similar between groups. QoL improved in both groups at 3-months with no difference observed. Conclusions: The use of preoperative VRT is not superior to usual care in diabetic patients undergoing CABG.
Response to Reviewers:	Associate Editor The reviewers are pleased with the answers you have provided, and they are inclined to accept your manuscript now. A few remaining issues have to be settled first: The text of the visual abstract: in the 'key question': can you add the outcomes for which you want this VRT to be 'effective'? - and in the 'take-home message': the in-hospital mortality is not the main primary or secondary outcome you chose for this RCT - please leave this out or replace this sentence with a result for the primary outcome Many thanks. We have added in "key questions" the outcomes for which we had hypothesised that VRT would be effective in the visual abstract; see page 2, line 31. In addition, in "take-home message" we have removed the line on mortality and replaced it with our primary outcome; see page 2, line 39. Reviewer 1: The manuscript has improved and my previous remarks were all addressed by the authors. Just minor remaining comment; p11, l 256 the sentence "This indicates that preoperative VRT is safe." is unnecessary. Since there was no beneficial effect what so ever, the question of safety (i.e. no statistically significant harm) is really not important. Many thanks, we have removed the line suggested. Reviewer 2: I find that the authors have responded adequately to my queries, and I have nothing further to add at this point. Many thanks. This reviewer is fully satisfied with no more points raised.

Central image



Number at risk					
Usual care	85	64	7	3	2
Volume replacement therapy	83	63	8	1	0

Preoperative volume replacement therapy in diabetic patients undergoing coronary artery bypass grafting surgery: results from an open parallel group randomised controlled trial (VeRDiCT).

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Visual abstract

Key question

Will preoperative volume replacement therapy in diabetic CABG patients reduce time to fitness for discharge (TFFD)?

Key findings

Preoperative VRT is feasible and safe

Preoperative VRT was not superior to routine care

Take-home message

VRT did not reduce renal failure in diabetic CABG patients

VRT did not reduce postoperative TFFD

Abstract

Objective: To investigate the effect of preoperative volume replacement therapy (VRT) on renal function, health outcome and time to fitness for discharge (TFFD) in diabetic patients undergoing coronary artery bypass grafting (CABG).

Methods: In two parallel randomised controlled trials diabetic patients were allocated to preoperative VRT (1mL/kg/hour of Hartmann's solution for 12 hrs) or usual care. Primary outcome was TFFD. Secondary outcomes included acute kidney injury (AKI), postoperative complications, patient-reported quality of life (QoL), hospital resource use and markers of renal, cardiac, and inflammatory injury.

Results: In total, 169 patients were randomized (84 VRT, 85 usual care; mean age 64 years; 88% male). TFFD was similar between groups (median 6 days; interquartile range (IQR) 5.0-9.0 in both groups; hazard ratio (HR) 0.95; 95% confidence interval (CI) 0.65-1.38; P=0.78). Post-operative AKI was not statistically different (VRT: 27.7% vs. usual care: 18.8%, odds ratio (OR) 1.72; 95% CI 0.82- 3.59; P=0.15). Estimated glomerular filtration rate [eGFR; mean difference (MD) -0.92; 95% CI -4.18 to 2.25; P=0.56], microalbumin/creatinine ratio [geometric mean ratio (GMR) 1.16; 95% CI 0.94-1.42; P=0.16], N-acetyl-beta-D-glucosaminidase [NAG; GMR 1.08; 95% CI 0.83- 1.40;P=0.57], C-reactive protein [CRP; GMR 1.00; 95% CI 0.88-1.13; P=0.94], troponin T [Trop-T; GMR 1.18; 95% CI 0.78-1.79; P=0.39] and other secondary health outcomes were similar between groups. QoL improved in both groups at 3-months with no difference observed.

Conclusions: The use of preoperative VRT is not superior to usual care in diabetic patients undergoing CABG.

Keywords: coronary artery bypass grafting, diabetes mellitus, renal failure, volume replacement therapy.

Introduction

Diabetes mellitus (DM) triggers postoperative complications following coronary artery bypass grafting (CABG) (1-2). DM affects 20% of all CABG patients (3-4), but its prevalence may be higher(5). The severity of acute kidney injury (AKI) varies from minor elevations of serum creatinine to anuric AKI requiring dialysis (6) and affects 10-50% of surgical patients (7, 8), triggered by DM (9-10). AKI is defined by the Risk, Injury, Failure, Loss, and End stage (RIFLE) criteria (11-12) and if severe enough to require dialysis it increases mortality 7-8 fold (13).

Diabetic patients may suffer preoperative renal impairment due to either diabetic nephropathy or diminished renal perfusion (14), exacerbated by diuretics, vasodilators, or angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (14, 15-16). These patients may benefit from preoperative volume replacement therapy (VRT), which increases eGFR (17). Isotonic crystalloid solutions are the first choice for VRT (18) as they have no nephrotoxic side-effects (18) and distribute rapidly into interstitial tissue. VRT prevents AKI following septic shock (18) and contrast-induced AKI (19). We hypothesised that pre-operative VRT might improve postoperative recovery by reducing postoperative AKI in DM patients.

We report the results of the VERDICT trial designed to compare the clinical effectiveness of VRT versus usual care in DM patients undergoing CABG surgery.

Materials and Methods:

Trial design:

A multi-centre, open parallel-group randomized controlled trial (RCT). Participants were randomly allocated to either preoperative VRT or usual care in a 1:1 ratio. The trial protocol is reported elsewhere (20).

Participants

Diabetic adults on oral or insulin medication, aged between 16 and 80 years and undergoing CABG were eligible. Previous cardiac surgery, renal failure requiring dialysis, congestive heart failure, left ventricular ejection fraction (LVEF) <30% and emergency/salvage surgery were exclusion criteria.

Trial Settings

The trial was conducted at the Bristol Heart Institute, Bristol, UK, sponsored by University Hospitals Bristol NHS Foundation Trust. The protocol was approved by the North Somerset & South Bristol Research Ethics Committee (reference 10/H0106/1) and the UK Medicines and Healthcare Products Regulatory Agency. The trial was registered (ISRCTN 02159606). All participants gave written informed consent. A parallel trial was conducted in Rabindranath Tagore International Institute, Kolkata (India) under separate governance arrangements, but using the same protocol and data collection. In India, the trial was sponsored by the host institution and approved by local hospital Ethics Committee, Reference: RTIICS-EC/006/2010.

Intervention

Eligible patients were randomised to either usual care or pre-operative VRT, which comprised 1mL/kg/hour of Hartmann's solution for 12 hours prior to surgery. All participants were fasted for 6 hours prior to surgery.

Surgical and clinical care methods

Surgery, anaesthesia, clinical care methods including fluid balance adhered to established protocols (20-25). Further details are provided in the Supplemental file.

Outcome Measures

Primary outcome: "time from surgery until first considered fit for discharge" (TFFD)

A participant had to have a normal temperature, pulse, respiratory rate, oxygen saturation on air, bowel function, and returned to preoperative level of mobility in order to be classified as TFFD.

Secondary outcomes:

Measures of AKI: need for dialysis, a 50% increase from pre-randomisation serum creatinine (RIFLE criteria), serial measurements of eGFR, microalbumin/creatinine ratio (mACr), and N-acetyl-beta-D-glucosaminidase (NAG);

Myocardial injury: serial measurements of plasma troponin T (cTnT);

Inflammatory activation: serial measurements of C-reactive protein (CRP);

Pre-operative blood glucose and haemoglobin A1c (HbA1c): measured post-VRT and prior to chest opening in fasting blood samples;

Clinical outcomes: death and post-operative complications from randomisation to 3 months post-surgery;

Patient-reported outcomes; participants' judgement about readiness for discharge and health-related quality of life measured using the coronary revascularisation outcome questionnaire (CROQ) pre-randomisation and at 3 months (UK cohort only) (23);

Use of hospital resources: intensive care unit (ICU) and hospital stay, use of health care resources (see supplementary file).

Serial blood samples were collected before randomisation, on completion of surgery, at 12 hours (creatinine, CTnT, CRP), 24 hours, 36 hours (creatinine), 48 hours, 72 hours (creatinine, cTnT CRP), 96 hours (creatinine), and 120 hours post-surgery. NAG, cTnT and CRP were measured in a sub-sample of the UK cohort.

Sample size

Full details of the sample size calculations are reported elsewhere (20). A sample size of 170 patients (85 per group) was chosen to detect a 25% difference in the proportion of patients FFD at 6 days between VRT and usual care groups (i.e. 75% versus 50%) with 90% power, assuming a 5% level of statistical significance (2−tailed).

Randomisation

Cohort minimisation was used to achieve balance between groups with respect to: preoperative creatinine, ejection fraction; age, cardiac angiogram in the 5 days prior to surgery, surgeon and gender. A password-protected secure database concealed allocations until data had been entered to confirm identity and eligibility.

Statistical methods

Analyses were based on a pre-specified statistical analysis plan (SAP) and performed on an intention-to-treat (ITT) basis (see also **Supplemental file**). Outcomes were compared using logistic regression (binary outcomes), linear regression (continuous outcomes), Cox proportional hazards regression with appropriate censoring (time-to-event outcomes) or mixed effects regression (continuous longitudinal outcomes). All analyses used the usual care group as the reference group and were adjusted for factors included in the cohort minimisation where possible. Results are reported as effect sizes with 95% confidence intervals. Serial measurements taken as part of routine care (e.g. blood gases) are described but not formally compared and frequencies of adverse events are tabulated. Pre-specified subgroup analyses were performed by adding an interaction term to the models. All analyses were performed in Stata version 14.0 (StataCorp LP, College Station, Tex).

Results:

Patient recruitment and follow-up

Between July 2010 and July 2014, 175 patients consented to join the trial and 169 were randomised; 85 to usual care and 84 to VRT. One participant was found to be ineligible prior to surgery and was withdrawn. There were 26 protocol deviations; 22 were related to the volume and/or duration of VRT, two participants randomised to VRT received usual care (**Figure 1** and Supplementary Table S1). Follow-up data to 3 months was available for 146/166 survivors (88%).

Baseline characteristics, Fluid management and Operative details

Baseline characteristics were similar between groups (**Table 1**, Supplementary Tables S2 and S3). The median age was 64 years (IQR 58-70) and 88% of patients were male. The mean volume of Hartmann's solution administered in the VRT group was 984 ml (SD 243.4). Cardiopulmonary bypass was used in 27.1% of participants in the usual care group versus 26.5% in the VRT group. The number of grafts was similar between groups. The median volume of perioperative fluid administered was 4000ml (IQR 3000-4500) in the usual care group and 3750 ml (IQR 3000-4500) in the VRT group (**Table 2,** Supplemental Table S4).

Primary Outcome:

Time until fitness for discharge (TFFD)

The median TFFD was 6.0 days (IQR 5.0-9.0) in both groups (hazard ratio (HR) 0.95; 95% CI 0.65-1.38; P=0.78; **Figure 2, Central image,** and Supplementary Table S5). Participants in India were classified fit earlier than in the UK (**Figure 2B**, Supplementary Table S5). A sensitivity analysis restricted to the UK sub-group did not alter the conclusion (Supplementary Table S5). No subgroup differences were found; the results were similar by risk (high versus low) and type of anti-diabetic treatment (oral medication only versus insulin +/- oral treatment) (Supplementary Figure S1).

Secondary Outcomes

Measures of renal injury

The need for dialysis was 3.5% (3/85) in the usual care group and 0% (0/83) in the VRT group. AKI by RIFLE criteria was 19% (16/85) in the usual care group and 28% (23/83) in the VRT group (odds ratio (OR) 1.72; 95% CI 0.82-3.59; P=0.15, **Table 3,** Supplementary Figure S3). The effect size did not differ by type of anti-diabetic medication (Supplementary Figure S2). Serial eGFR (mean difference (MD) -0.92; 95% CI -4.18 to 2.35; P=0.56), mACr (geometric mean ratio (GMR) 1.16; 95% CI 0.94-1.42; P=0.16), and NAG (GMR 1.08; 95% CI 0.83-1.40; P=0.57) were similar between groups (**Figure 3 A-C,** Supplementary Table S6).

Pre-operative blood glucose and HbA1c levels

Pre-operative post-VRT blood glucose and HbA1c levels were similar between groups (GMR 0.97; 95% CI 0.81-1.17; P=0.76 and GMR 0.92; 95% CI 0.81-1.04; P=0.16 respectively, Supplementary Table S6).

Myocardial injury and inflammatory activation

Levels of cTnT and CRP rose following surgery in both groups, but no difference was observed between groups (CRP; GMR 1.00; 95% CI 0.88-1.13; P=0.94; cTnT; GMR 1.18; 95% CI 0.78-1.79; P=0.39; **Figure 4A-B,** Supplementary Table S6).

Clinical outcomes

Post-operative complications up to 3-months post-surgery are summarised in **Table 3** and Supplemental Figure S3. In-hospital morbidity/mortality was similar between groups (91.8%, (78/85) in the usual care group, 89.2% (74/83) in the (74/83) in the VRT group, OR=0.76 (0.27, 2.16), p=0.60). The cumulative rate of all-cause mortality, AKI requiring dialysis, and myocardial infarction (MI), was 9.4% (8/85) in the usual care group versus 6.0% (5/83) in the VRT group (Supplementary Tables S7 and S8).

Patient-assessed outcomes

Most participants felt they were discharged at the right time (93.5% (72/77) in the usual care group, 81.3% (61/75) in the VRT group, supplementary Table S9). Scores derived from the CROQ are shown in **Table 4.** There was a marked improvement in QoL after surgery across all dimensions, which was similar between groups (core total score MD 0.46 (-1.39, 2.31), p=0.63).

Use of hospital resources

ICU and hospital stay were similar between groups. The median cost was £11,501 (IQR 10487-13815) in the usual care group versus £11,821 (IQR 10878- 13798) in the VRT group (GMR 1.04; 95% CI 0.96-1.12; P=0.37, Supplementary Table S9).

Discussion:

The results of the VERDICT trial suggest that administering VRT before surgery to patients with DM does not provide clinical benefit in the early postoperative period; TFFD and other health outcomes were similar between the usual care and VRT groups.

Our results contrast with the Prevention of Contrast Renal Injury with Different Hydration Strategies (POSEIDON) trial, which demonstrated that VRT was associated with a reduction in contrast-induced AKI following coronary angiography, with the odds of AKI decreasing for each 100mL increase in VRT administered (19). The higher incidence of AKI observed in VERDICT compared to POSEIDON likely reflects the greater invasiveness of CABG versus coronary angiography and differences in the patient population. VERDICT only included diabetic participants, whereas in POSEIDON only half the cohort (51%) had diabetes (19).

The solution used for VRT and the volume administered also differed between the two trials. POSEIDON used saline rather than Hartmann's solution. However, both are isotonic crystalloid solutions regarded as first choice for VRT (26). The VRT administered preoperatively in VERDICT was 3-5 fold less than in POSEIDON, but the total volume of perioperative fluid administered was higher, reflecting differences in fluid management between open cardiac surgery and percutaneous cardiac catheterisation.

POSEIDON also showed a reduced rate of all-cause mortality, AKI requiring dialysis and MI in the VRT group, a trend observed in our study. In-hospital mortality in VERDICT was lower than that reported by others in diabetic patients (2-3,5,9) for reasons which are not entirely clear. Few patients were excluded on the basis of past history or co-morbidities. Noticeably, participants in India were classified fit for discharge earlier than those in the UK, possibly reflecting differences in service provision and patient-pathway.

AKI by RIFLE criteria was 18.8% in the control group vs 27.7% in the VRT group. However, mortality and AKI requiring dialysis were both 0% in the VRT group, with similar markers of renal injury between groups.

Patient-reported outcomes are set to transform the way clinical performance and outcomes are measured in healthcare systems (27). In VERDICT, QoL improved after surgery in both groups with a trend for higher patient satisfaction in the VRT group, which did not reach significance.

Strengths and Limitations

The trial has strengths and limitations. Strengths include minimisation of bias through concealed allocation. The trial was acceptable, over 50% of UK patients approached, agreed to take part. Blood samples were analysed in a single hospital laboratory in each country and laboratory personnel were blinded to the group allocation.

Regarding limitations, there was heterogeneity in the participants in terms of age range, diabetic status and geographical derivation. Some outcomes were collected in the UK only, reducing the power for these outcomes, and the study was not powered to detect differences rates of adverse events (e.g. AKI). The number of protocol deviations might have diluted the effect of VRT, although most were relatively minor (i.e. either the volume or duration of VRT used). Additionally, the VRT given preoperatively was relatively small compared to the volume of fluid given peri-operatively to all participants as part of routine care. This may have limited or masked the efficacy of VRT. The lack of blinding represents a further weakness.

Conclusion

The administration of preoperative VRT in diabetic patients undergoing CABG did not improve early postoperative outcomes for patients; it did not reduce the time until patients were fit for discharge from hospital.

Acknowledgements

We thank all trial team members involved in VERDICT, the surgeons and all the patients consenting to take part at both centres. This trial was delivered in collaboration with the Clinical Trials and Evaluation Unit (CTEU), a UKCRC registered clinical trials unit which, as part of the Bristol Trials Centre is in receipt of National Institute for Health Research (NIHR) CTU support funding. The views and opinions expressed in this report are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health and Social Care.

Funding statement

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Conflict of interest statement

The authors declare no financial or other conflicting interests.

Figure Legends

Figure 1: Consort diagram - Flow of participants

CABG: Coronary Artery Bypass Grafting; DOSA: Day of surgery admission; PIL: Patient Information Leaflet; VRT: Volume Replacement Therapy; ASEPSIS: Serous, Erythema, Purulent, Separation, Isolation, Stay infection criteria; CROQ: coronary revascularisation outcome questionnaire

Notes:

[1] There is no screening data available for India patients who did not consent

[2] Two India patients were randomised but have no screening or follow-up data available. These patients are not included

Figure 2: Time until fitness for discharge (TFFD)

A: TFFD in the VRT and usual care groups; **B**: TFFD in the VRT and usual care groups in the two centres in UK and India

Figure 3 Markers of renal injury

A: Estimate Glomerular Filtration Rate (eGFR); **B**: microalbumin/creatinine ratio (mACr); **C**: N-acetyl-beta-D-glucosaminidase (NAG). Treatment effect and 95% CI for the effect of VRT versus routine care on eGFR, mACr, and NAG. MD: mean difference; SD: standard deviation; GMR: geometric mean ratio; CI: confidence interval

Figure 4 Troponin T and C-Reactive Protein (CRP)

A: CRP release; **B**: Troponin T. Treatment effect and 95% CI for the effect of VRT versus routine care on CRP and Troponin T release. GMR: geometric mean ratio; CI: confidence interval

Table 1 Participant characteristics

Characteristic		Usual care (n=85)		VRT (n=83)		Overall (n=168)	
		n	%	n	%	n	%
DEMOGRAPHICS							
Age – median (IQR) years		63	(58.3, 68.7)	65	(59.0, 69.8)	64	(58.4, 69.5)
Female gender		10/85	11.8%	10/83	12.0%	20/168	11.9%
BMI – median (IQR) ▪		30	(25.4, 32.8)	28	(23.0, 32.6)	29	(24.2, 32.6)
CARDIAC HISTORY							
NYHA class	I-II	66/85	76.7%	67/83	80.7%	133/168	79.2%
	III-IV	19/85	22.4%	16/83	19.3%	35/168	20.8%
CCS class	No angina	8/85	9.4%	10/83	12.0%	18/168	10.7%
	I-II	53/85	62.3%	46/83	55.4%	99/168	59.0%
	III-IV	24/85	28.3%	27/83	32.5%	51/168	30.4%
>50% disease in left main stem		12/85	14.1%	16/82	19.5%	28/167	16.8%
Number of diseased vessels	Single	3/85	3.5%	1/81	1.2%	4/166	2.4%
	Double	17/85	20.0%	18/81	22.2%	35/166	21.1%
	Triple	65/85	76.5%	62/81	76.5%	127/166	76.5%
Previous PCI		7/85	8.2%	14/83	16.9%	21/168	12.5%
Previous MI		37/85	43.5%	40/83	48.2%	77/168	45.8%
Heart rhythm	Sinus	80/85	94.1%	77/81	95.1%	157/166	94.6%
	AF	3/85	3.5%	3/81	3.7%	6/166	3.6%
	Block	2/85	2.4%	1/81	1.2%	3/166	1.8%
Pacemaker	Permanent	1/85	1.2%	2/82	2.4%	3/167	1.8%
OTHER MEDICAL HISTORY							
Creatinine – median (IQR) µmol/l×		89	(78, 106)	92	(77, 112)	90	(78, 110)
Neurological disease		3/84	3.6%	6/83	7.2%	9/167	5.4%
Diabetes	Type I	7/85	8.2%	1/81	1.2%	8/166	4.8%
	Type 2 insulin	27/85	31.8%	28/81	34.6%	55/166	33.1%
	Type 2 oral	51/85	60.0%	52/81	64.2%	103/166	62.0%
Smoking	Current	9/85	10.6%	13/83	15.7%	22/168	13.1%
	Ex (>1 month)	47/85	55.3%	39/83	47.0%	86/168	51.2%
Family history (cardiac)		44/82	53.7%	40/82	48.8%	84/164	51.2%
Hypercholesterolaemia		65/85	76.5%	72/80	90.0%	137/165	83.0%
Operative priority	Elective	70/85	82.4%	63/82	76.8%	133/167	79.6%
	Urgent	15/85	17.6%	19/82	23.2%	34/167	20.4%
Logistic EuroSCORE–median (IQR) *		1.8	(1.3, 2.9)	2.3	(1.5, 3.4)	2.1	(1.4, 3.3)
STUDY INTERVENTION							
VRT administered – mean (SD) ml°[1]				984	243.4	984	243.4

Notes: IQR: interquartile range; BMI: body mass index; NYHA: New York Heart Association; CCS: Canadian Cardiovascular Society; PCI: percutaneous coronary intervention; MI: myocardial infarction; AF: atrial fibrillation; SD: standard deviation, VRT: volume replacement therapy.

[1] *It was not possible to determine the actual dose received for patients recruited in India*

Missing data (Usual care, VRT): ▪ 1 patient with missing data (1, 0), × 1 patient with missing data (0, 1), * 3 patients with missing data (1, 2), ^ 2 patients with missing data (1, 1), ° 5 patients with missing data (0, 5).

Table 2 Intraoperative and postoperative details

Intraoperative/postoperative characteristic		Randomised to usual care (n=85)		Randomised to VRT (n=83)		Overall (n=168)	
		n	%	n	%	n	%
BYPASS DATA							
CPB used		23/85	27.1%	22/83	26.5%	45/168	26.8%
If YES, total CPB time – median (IQR) mins		84	(64.0, 115.0)	80	(66.0, 98.0)	80	(66.0, 103.0)
If YES, cumulative cross-clamp time – mean (SD) mins×		46	20.0	44	16.8	45	18.2
GRAFT DETAILS							
No of distal coronary anastomoses	1	8/85	9.4%	8/83	9.6%	16/168	9.5%
	2	23/85	27.1%	26/83	31.3%	49/168	29.2%
	3+	54/85	63.5%	49/83	59.0%	103/168	61.3%
ROUTINE INTERVENTIONS							
Intraoperative							
Insulin infusion		55/85	64.7%	51/83	61.4%	106/168	63.1%
Inotropes[1]		24/83	28.9%	24/83	28.9%	48/166	28.9%
Pacing[2]		8/84	9.5%	6/80	7.5%	14/164	8.5%
IABP		0/85	0.0%	1/83	1.2%	1/168	0.6%
Intraoperative and postoperative							
Need for defibrillation		5/85	5.9%	3/83	3.6%	8/168	4.8%
Arrhythmias[3]							
	AF	5/84	6.0%	2/81	2.5%	7/165	4.2%
	Other[4]	2/84	2.4%	0/81	0.0%	2/165	1.2%

Notes:

[1] Excluding noradrenaline

[2] Excludes patients with pacing beforehand

[3] Excludes patients with a permanent pacemaker beforehand

[4] Other arrhythmias on chest closure: sub brady-nodal (usual care) and first-degree heart block (usual care).

CPB: cardiopulmonary bypass; IQR: interquartile range; IABP: intra-aortic balloon pump; AF: atrial fibrillation.

Missing data (usual care, VRT):

× 2 patients with missing data (2, 0)

Table 3 Post-intervention complications

	Randomised to usual care (n=85)		Randomised to VRT (n=83)	
	Events/patients	**%**	**Events/patients**	**%**
Any complication	241/78	92.9%	253/76	92.7%
Pre-discharge complications	223/78	91.8%	228/74	89.2%
Death	1/1	1.2%	0/0	0.0%
Myocardial infarction[1]	6/6	7.1%	5/5	6.0%
SVT/AF requiring treatment	21/21	24.7%	24/24	29.6%
VF/VT requiring treatment	0/0	0.0%	2/2	2.5%
Pacing[2]	6/6	7.1%	8/8	9.8%
Need for IABP	1/1	1.2%	2/2	2.4%
Low cardiac output	2/2	2.4%	2/2	2.6%
Re-intubation[3]	4/4	4.8%	6/4	4.9%
Mask CPAP	13/13	15.3%	7/7	8.6%
ARDS	1/1	1.2%	0/0	0.0%
Renal failure				
Need for dialysis	3/3	3.5%	0/0	0.0%
AKI	16/16	18.8%	23/23	27.7%
Permanent stroke	1/1	1.2%	0/0	0.0%
Transient stroke	0/0	0.0%	3/3	3.6%
Sepsis	24/17	20.7%	18/16	20.3%
Respiratory infection	19/15	18.5%	19/15	18.5%
Re-operation[4]	3/3	3.5%	3/3	3.6%
Sternal debridement/rewiring	2/2	2.4%	2/2	2.4%
Other[5]	95/64	75.3%	93/59	71.1%
Post-discharge complications	18/12	16.0%	25/12	15.8%
Death	1/1	1.3%	0/0	0.0%
Myocardial infarction[6]	0/0	0.0%	2/2	2.6%
SVT/AF requiring treatment	1/1	1.3%	2/2	2.6%
Pleural effusion	2/2	2.6%	1/1	1.3%
Respiratory infection	1/1	1.3%	4/4	5.3%
Wound infection	3/3	4.0%	3/3	3.9%
Sternal debridement/rewiring	2/2	2.7%	1/1	1.3%
Other[7]	8/6	8.0%	11/10	13.2%

Notes:

MI: myocardial infarction; SVT/AF: supraventricular tachycardia/atrial fibrillation; VF/VT: ventricular fibrillation/ventricular tachycardia; IABP: intra-aortic balloon pump; CPAP: continuous positive airway pressure; ARDS: acute respiratory distress syndrome; GI: gastrointestinal; TIA: transient ischemic attack.

Events experienced by two crossovers (VRT to usual care): Sepsis (n=1), re-operation (n=1), other (n=4).

[1] For troponin levels of patients with a suspected MI pre-discharge see supplementary material Table S2

[2] Type of pacing (usual care, VRT): Single (5, 6), double (1, 1), temporary (6, 7), permanent (0, 1)

[3] Duration of re-intubation, usual care group: 14.2 hours, 19 hours, 28 hours, not extubated. VRT group: 49.7 hours, 31.1 hours, 15.8 hours, 105.1 hours

[4] Type of re-operation (usual care, VRT): Chest reopened for bleeding (2, 2), Sternal flap reconstruction (0, 1)

[5] For details of other pre-discharge events see supplementary material Table S10

[6] For troponin levels of patients with a suspected MI post-discharge see supplementary material Table S2

[7] For details of other post-discharge events see supplementary material Table S11

Table 4 Patient-reported outcome - Quality of life – CROQ

		Randomised to usual care (n=85)		Randomised to VRT (n=83)		Effect (95% CI)	p-value
		Median	IQR	Median	IQR		
Core total	Pre-operative*	49	(44.9, 52.6)	48	(42.1, 52.3)		
	3 months post-operatively▪	55	(51.9, 56.8)	55	(51.3, 56.8)	MD=0.46 (-1.39, 2.31)	0.63
Symptoms	Pre-operative◦	73	(53.6, 86.3)	75	(51.8, 89.3)		
	3 months post-operatively×	96	(89.3, 100.0)	96	(89.3, 100.0)	MD=0.82 (-3.40, 5.03)	0.70
Physical functioning	Pre-operative▪▪	69	(43.8, 81.3)	69	(37.5, 87.5)		
	3 months post-operatively**	94	(71.9, 100.0)	100	(81.3, 100.0)	MD=0.41 (-6.63, 7.45)	0.91
Cognitive functioning	Pre-operative××	87	(66.7, 100.0)	87	(60.0, 100.0)		
	3 months post-operatively◦◦	93	(73.3, 100.0)	93	(66.7, 100.0)	MD=0.01 (-6.57, 6.60)	1.0
Psychosocial functioning	Pre-operative××	72	(55.4, 82.1)	68	(48.2, 82.1)		
	3 months post-operatively¥	88	(73.2, 92.9)	86	(73.2, 92.9)	MD=3.55 (-2.44, 9.55)	0.25
Satisfaction	Pre-operative						
	3 months post-operatively¥¥	78	(66.7, 91.7)	86	(73.3, 94.4)	MD[1]=4.88 (-0.55, 10.31)	0.08
Adverse effects	Pre-operative						
	3 months post-operatively◦◦	91	(77.3, 95.5)	92	(77.3, 95.5)		
Adverse events categorised into quartiles	<77.3	18	24.3%	14	20.0%		
	≥77.3 and <90.9	16	21.6%	17	24.3%		
	≥90.9 and <95.5	9	12.2%	11	15.7%		
	≥95.5	31	41.9%	28	40.0%	OR[2]=1.88 (0.61, 2.33)	0.62

Missing data (usual care, VRT):
* 5 patients with missing data (1, 4), ▪ 22 patients with missing data (11, 11), ◦ 5 patients with missing data (2, 3), × 24 patients with missing data (14, 10), ▪▪ 8 patients with missing data (2, 6), ** 25 patients with missing data (13, 12), ×× 9 patients with missing data (3, 6), ◦◦ 24 patients with missing data (11, 13), ¥ 23 patients with missing data (11, 12), ¥¥ 25 patients with missing data (12, 13). IQR: interquartile range; OR: odd ratio; CI: confidence interval.

Notes:
[1] multiple imputation used to impute missing data for 25 cases; [2] multiple imputation used to impute missing data for 24 cases and adverse effects score then categorised into quartiles and modelled using ordinal logistic regression

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Figure 1

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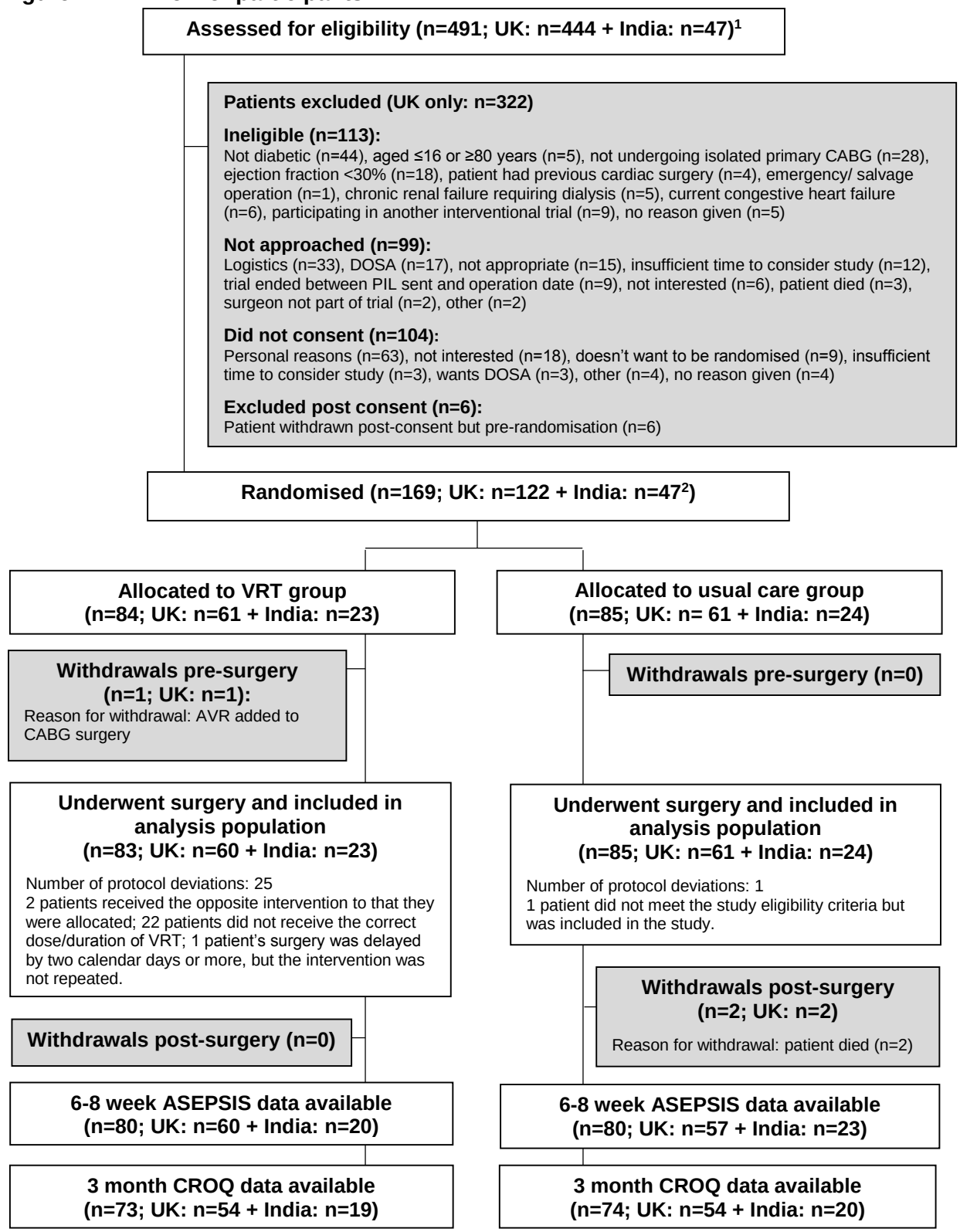
Figure F1 Flow of participants



[1]There is no screening data available for India patients who did not consent
[2]Two India patients were randomised but have no screening or follow-up data available. These patients are not included in the flow chart

Figure 2

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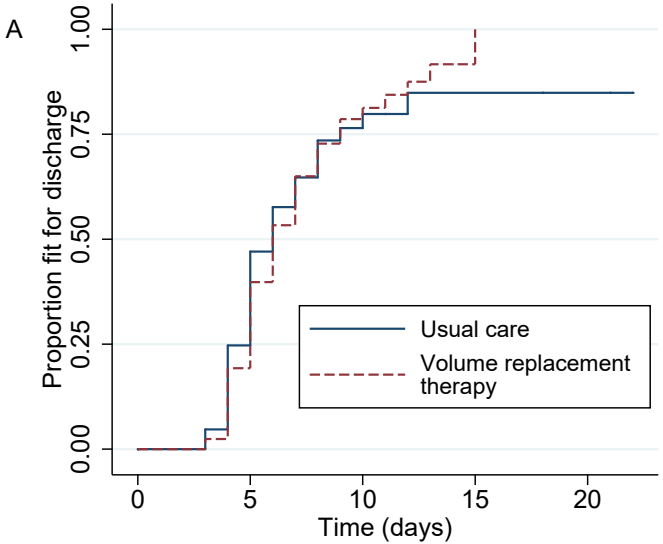
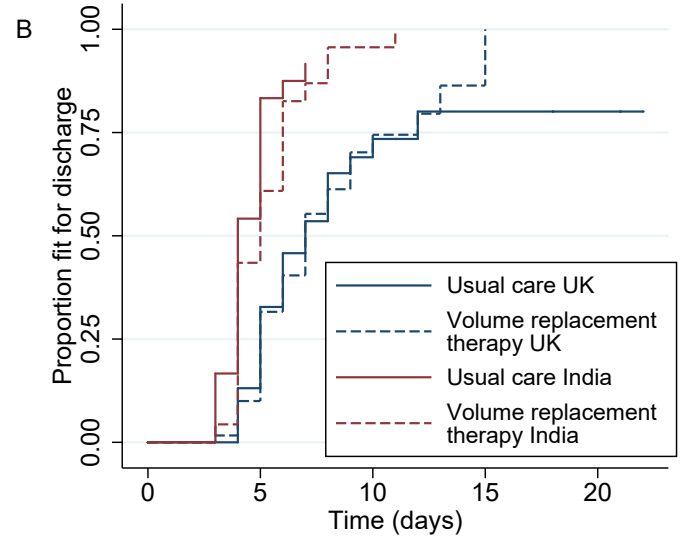


Number at risk					
Usual care	85	64	7	3	2
Volume replacement therapy	83	63	8	1	0



Number at risk					
UK: Usual care	61	53	7	3	2
Volume replacement therapy	60	50	7	1	0
India: Usual care	24	11	0	0	0
Volume replacement therapy	23	13	1	0	0

Figure3a

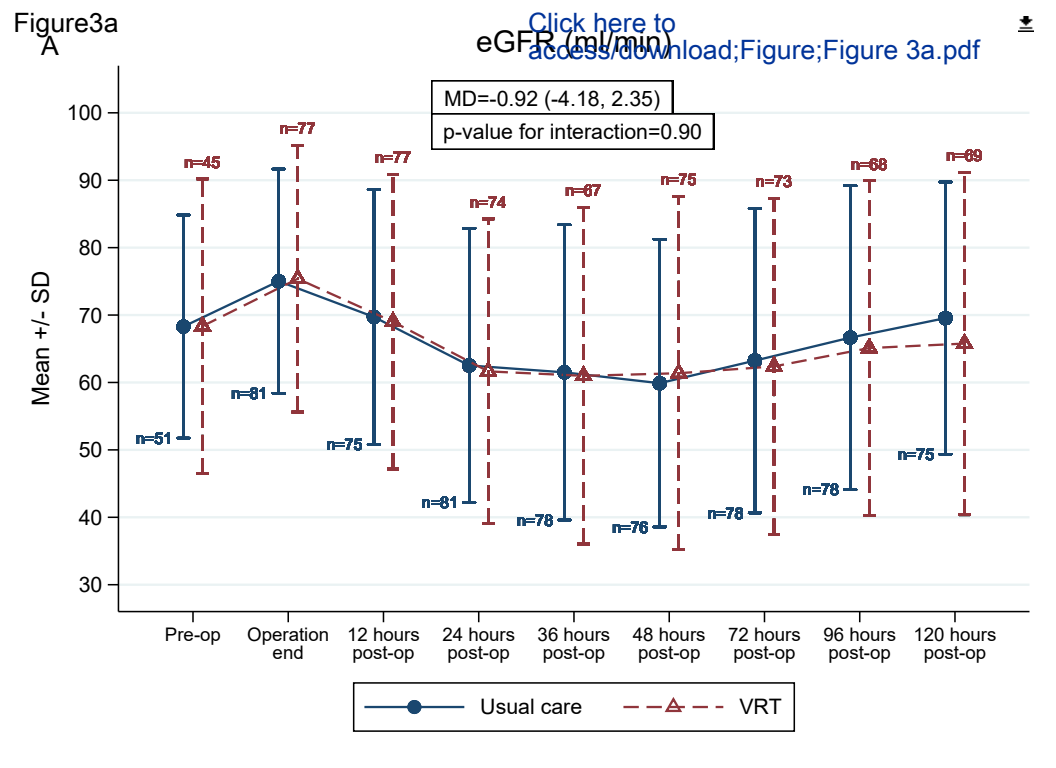


Figure3b

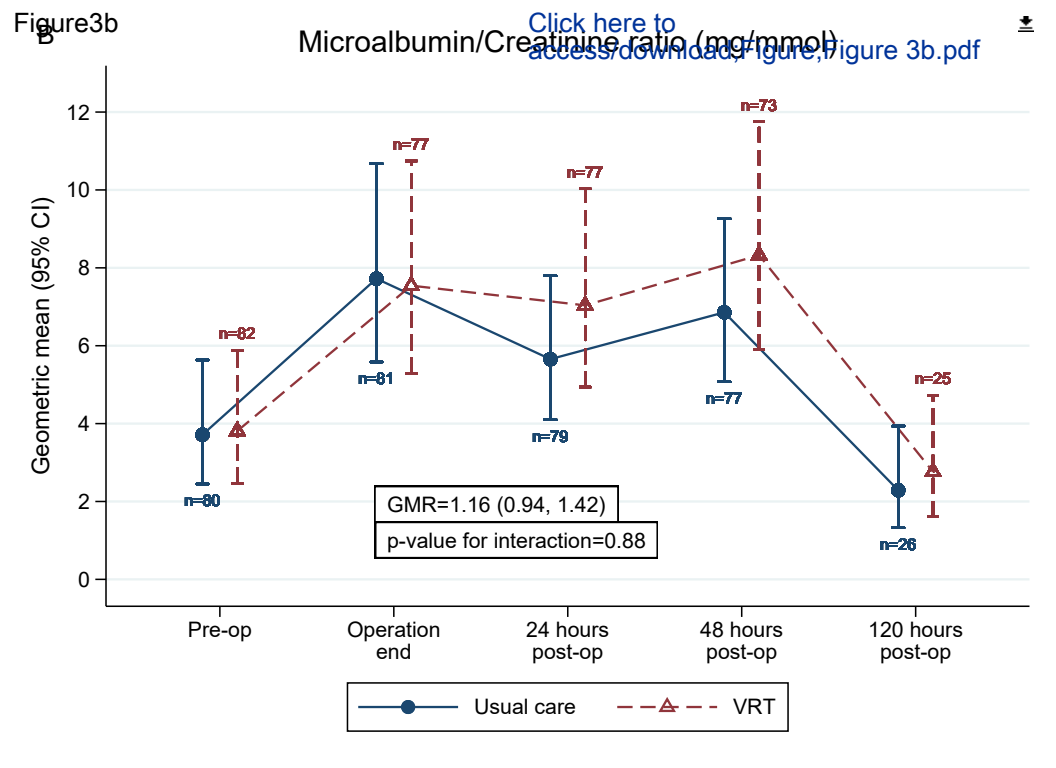


Figure3c

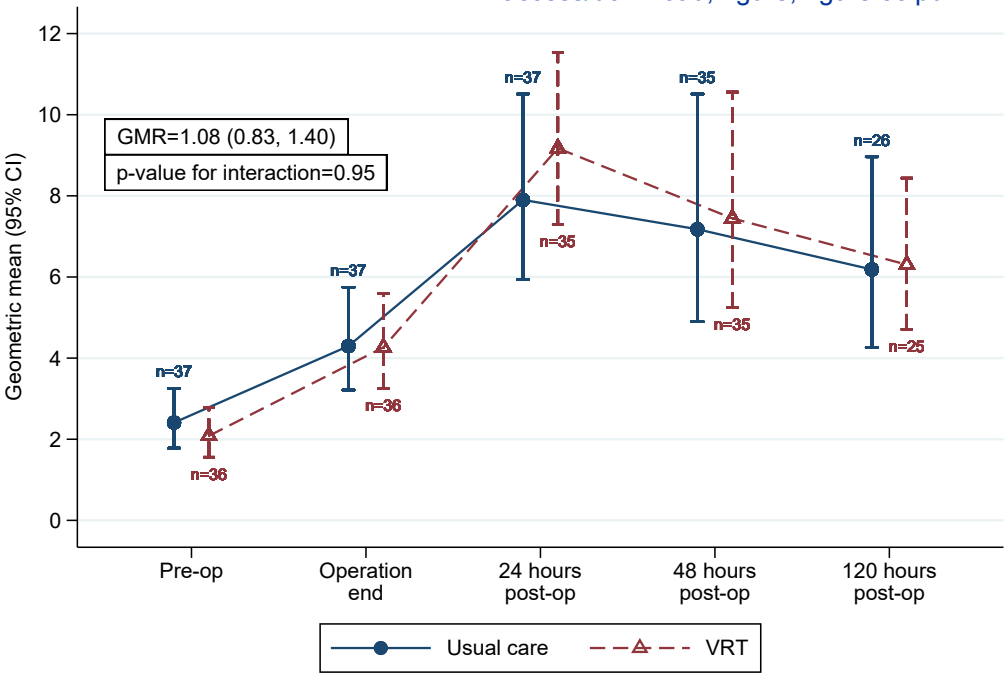


Figure4a

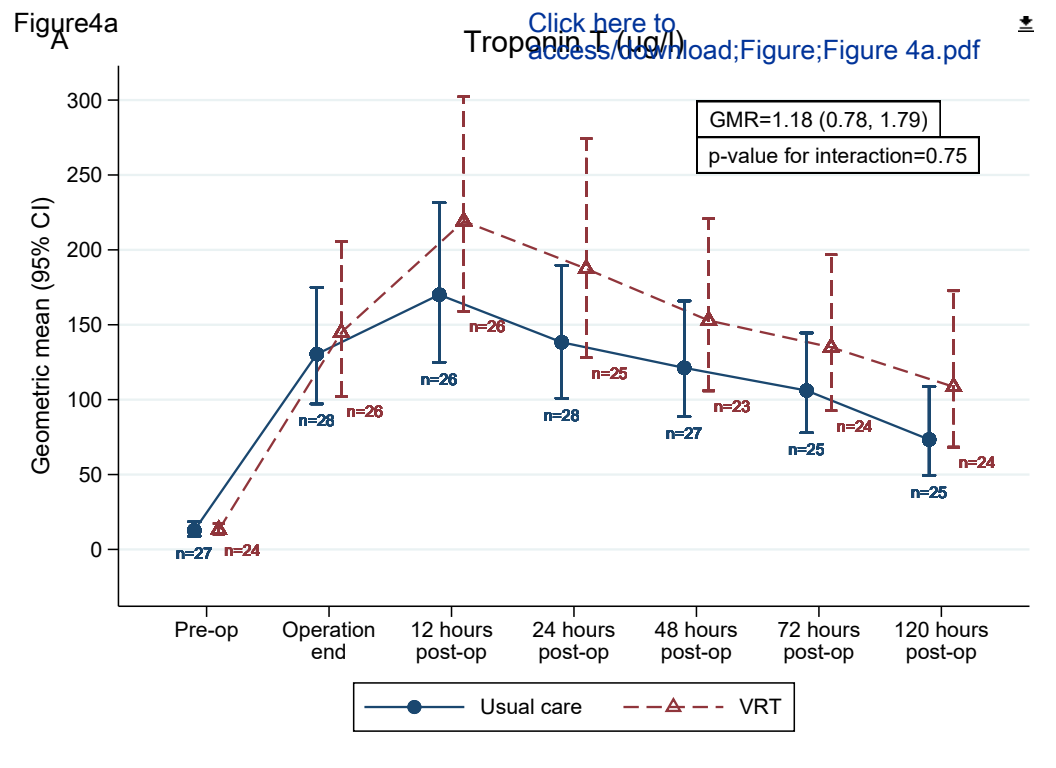
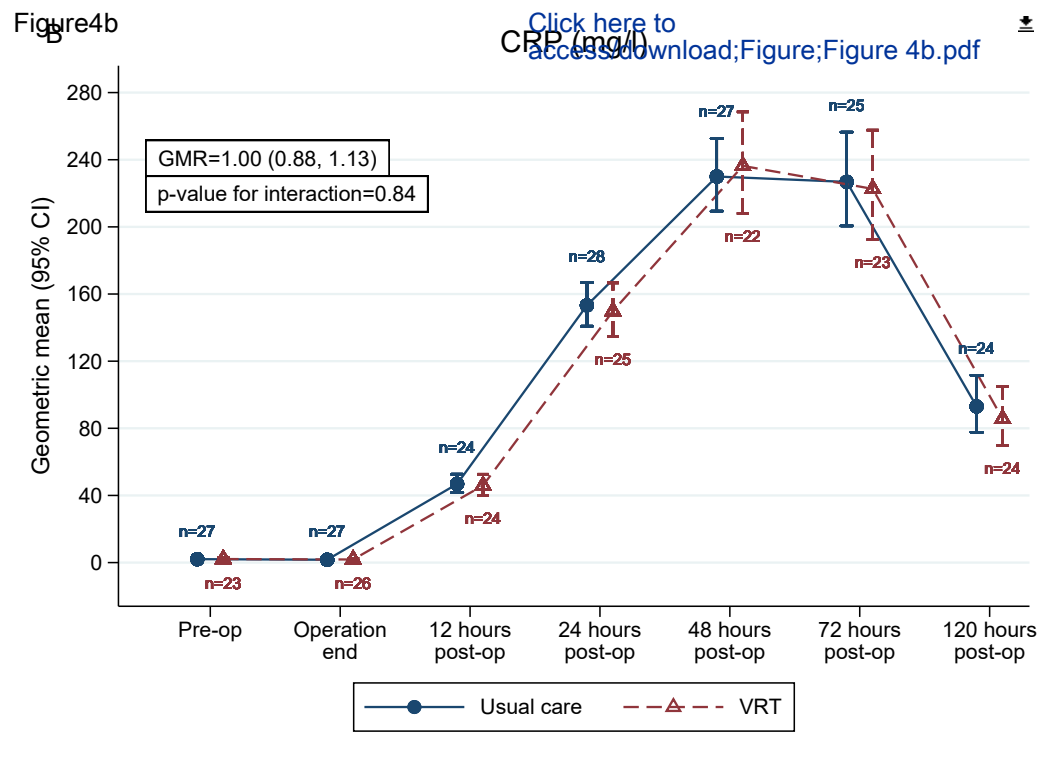


Figure4b



Supplementary file