



Clinical trial results:

Preoperative Volume Replacement vs. usual care in Diabetic patients having CABG surgery: a randomised controlled Trial

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2009-013159-31 |
| Trial protocol | GB |
| Global end of trial date | 23 August 2019 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 15 April 2020 |
| First version publication date | 15 April 2020 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CS/2009/3292 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN02159606 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | University Hospitals Bristol NHS Foundation Trust |
| Sponsor organisation address | Research & Innovation Dept, Level 3, UH Bristol Education Centre, Upper Maudlin Street, Bristol, United Kingdom, BS2 8AE |
| Public contact | University Hospitals Bristol NHS Foundation Trust, Research and Development Department, 0117 342 0233, R&DSponsorship@UHBristol.nhs.uk |
| Scientific contact | University of Bristol, Clinical Trials Evaluation Unit, 0117 342 3151, btc-mailbox@bristol.ac.uk |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 22 October 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 13 November 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 23 August 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The VeRDICT Trial is proposed to test the hypothesis that the postoperative incidence of renal insufficiency will be lower, and post-operative recovery faster, if diabetic patients are treated with volume replacement therapy prior to surgery. This treatment has already been shown to prevent acute kidney injury in certain clinical scenarios. Our principal objective is to compare the time from surgery until the patient is 'fit for discharge' in diabetics having coronary artery bypass surgery, randomly assigned to either receive preoperative volume replacement therapy, or to not (i.e. routine care).

Protection of trial subjects:

All potential participants were sent or given an invitation letter and patient information sheet (PIS) (approved by the local Research Ethics Committee,(REC)) describing the study. The patient had time to read the PIS and to discuss their participation with others outside the research team (e.g. relatives or friends) if they wished. Most patients had at least 24 hours to consider whether to participate. Full informed consent was obtained for every trial participant. The patient's GP was informed of their participation in the trial. All members of the direct healthcare team are contractually bound to abide by standard NHS conditions of confidentiality and the need to access medical records will be explained to each patient during the process of obtaining consent.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 15 July 2010 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 122 |
| Worldwide total number of subjects | 122 |
| EEA total number of subjects | 122 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |

| | |
|---------------------------|----|
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 56 |
| From 65 to 84 years | 66 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Of the 331 eligible patients screened, 128 provided written informed consent and agreed to take part in the study.

Pre-assignment

Screening details:

Between July 2010 and July 2014, a total of 444 patients were screened for inclusion in the trial, 113 of whom were ineligible.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Volume replacement therapy |

Arm description:

CABG with or without cardiopulmonary bypass (CPB), with preoperative volume replacement therapy (1 ml/kg/hr of Hartmann's solution for 12 consecutive hours prior to surgery).

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Hartmann's Solution (Compound Sodium Lactate Intravenous Infusion BP) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

The dosage is dependant on body mass as follows: 1ml/kg/hr for 12 hours, therefore, maximum dose (ml) = body mass x12

If for some reason there is less than 12 hours for administration of the IMP, such as a delay in admission to hospital until later than the normal start time for the infusion, or an event that occurs overnight (e.g. patient has a shower) resulting in the infusion being disconnected for a short period, the rate will be increased so that the full dose could be given. The dose will still be equivalent to 1ml/kg/hr for 12 hours, and therefore the maximum dose will stay the same. The minimum time that the IMP can be administered over is 8 hours.

| | |
|--|-----------------|
| Arm title | Usual care |
| Arm description: | |
| CABG with or without CPB with conventional preoperative management (no preoperative fluids). | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 ^[1] | Volume replacement therapy | Usual care |
|--|-------------------------------|------------|
| | | |
| Started | 60 | 61 |
| Completed | 60 | 61 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One patient allocated to the volume replacement therapy group was withdrawn post-randomisation, pre-operatively as they had AVR added to their CABG surgery and were therefore ineligible.

Baseline characteristics

Reporting groups

| | |
|--|----------------------------|
| Reporting group title | Volume replacement therapy |
| Reporting group description: CABG with or without cardiopulmonary bypass (CPB), with preoperative volume replacement therapy (1 ml/kg/hr of Hartmann's solution for 12 consecutive hours prior to surgery). | |
| Reporting group title | Usual care |
| Reporting group description: CABG with or without CPB with conventional preoperative management (no preoperative fluids). | |

| Reporting group values | Volume replacement therapy | Usual care | Total |
|---|----------------------------|--------------|-------|
| Number of subjects | 60 | 61 | 121 |
| Age categorical Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 0 |
| Newborns (0-27 days) | | | 0 |
| Infants and toddlers (28 days-23 months) | | | 0 |
| Children (2-11 years) | | | 0 |
| Adolescents (12-17 years) | | | 0 |
| Adults (18-64 years) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous Units: years | | | |
| median | 67 | 66 | |
| inter-quartile range (Q1-Q3) | 59.4 to 71.4 | 60.6 to 70.7 | - |
| Gender categorical Units: Subjects | | | |
| Female | 9 | 10 | 19 |
| Male | 51 | 51 | 102 |
| Pre-operative creatine > 160µmol/l Units: Subjects | | | |
| Yes | 4 | 3 | 7 |
| No | 56 | 58 | 114 |
| Ejection fraction < 50% Units: Subjects | | | |
| Yes | 11 | 12 | 23 |
| No | 49 | 49 | 98 |
| Age >= 70 years Units: Subjects | | | |
| Yes | 17 | 17 | 34 |
| No | 43 | 44 | 87 |
| Cardiac angiogram in last 5 days Units: Subjects | | | |
| Yes | 7 | 5 | 12 |

| | | | |
|---|----|----|-----|
| No | 53 | 56 | 109 |
| Chronic pulmonary disease Units: Subjects | | | |
| Yes | 6 | 8 | 14 |
| No | 54 | 53 | 107 |
| Extracardiac arteriopathy Units: Subjects | | | |
| Yes | 6 | 5 | 11 |
| No | 54 | 56 | 110 |
| Neurological dysfunction Units: Subjects | | | |
| Yes | 2 | 3 | 5 |
| No | 58 | 58 | 116 |
| Unstable angina Units: Subjects | | | |
| Yes | 2 | 3 | 5 |
| No | 58 | 58 | 116 |
| Myocardial infarction within 90 days Units: Subjects | | | |
| Yes | 19 | 13 | 32 |
| No | 41 | 48 | 89 |
| NYHA class Units: Subjects | | | |
| Class I | 17 | 9 | 26 |
| Class II | 28 | 36 | 64 |
| Class III | 15 | 14 | 29 |
| Class IV | 0 | 2 | 2 |
| CCS class Units: Subjects | | | |
| Asymptomatic | 10 | 7 | 17 |
| Class I | 9 | 3 | 12 |
| Class II | 15 | 28 | 43 |
| Class III | 21 | 18 | 39 |
| Class IV | 5 | 5 | 10 |
| >50% disease in left main stem Units: Subjects | | | |
| Yes | 14 | 9 | 23 |
| No | 46 | 52 | 98 |
| Number of diseased vessels Units: Subjects | | | |
| Single | 0 | 2 | 2 |
| Double | 17 | 15 | 32 |
| Triple | 42 | 44 | 86 |
| Unrecorded | 1 | 0 | 1 |
| Previous PCI Units: Subjects | | | |
| Yes | 13 | 7 | 20 |
| No | 47 | 54 | 101 |
| Previous MI Units: Subjects | | | |
| Yes | 33 | 28 | 61 |

| | | | |
|----------------------------------|----|----|-----|
| No | 27 | 33 | 60 |
| Diabetes | | | |
| Units: Subjects | | | |
| Type I | 1 | 7 | 8 |
| Type 2 insulin | 24 | 24 | 48 |
| Type 2 oral | 35 | 30 | 65 |
| Smoking | | | |
| Units: Subjects | | | |
| Current | 7 | 5 | 12 |
| Ex (>1 month) | 31 | 36 | 67 |
| Never | 22 | 20 | 42 |
| Hypertension requiring treatment | | | |
| Units: Subjects | | | |
| Yes | 55 | 55 | 110 |
| No | 5 | 6 | 11 |
| Hypercholesterolaemia | | | |
| Units: Subjects | | | |
| Yes | 57 | 52 | 109 |
| No | 3 | 9 | 12 |
| Neurological disease | | | |
| Units: Subjects | | | |
| Yes | 3 | 2 | 5 |
| No | 57 | 58 | 115 |
| Not recorded | 0 | 1 | 1 |
| Peptic ulceration | | | |
| Units: Subjects | | | |
| Yes | 0 | 2 | 2 |
| No | 60 | 59 | 119 |
| Heart rhythm | | | |
| Units: Subjects | | | |
| Sinus | 55 | 56 | 111 |
| AF | 3 | 3 | 6 |
| Block | 1 | 2 | 3 |
| Unrecorded | 1 | 0 | 1 |
| Pacemaker | | | |
| Units: Subjects | | | |
| Permanent | 2 | 1 | 3 |
| None | 58 | 60 | 118 |
| Operative priority | | | |
| Units: Subjects | | | |
| Elective | 41 | 46 | 87 |
| Urgent | 19 | 15 | 34 |
| Family history (cardiac) | | | |
| Units: Subjects | | | |
| Yes | 36 | 37 | 73 |
| No | 24 | 23 | 47 |
| Unrecorded | 0 | 1 | 1 |
| CPB used (intra-operative) | | | |
| Units: Subjects | | | |
| Yes | 20 | 19 | 39 |
| No | 40 | 42 | 82 |

| | | | |
|---|----|----|-----|
| Number of distal coronary anastomoses (intra-operative) Units: Subjects | | | |
| One | 7 | 7 | 14 |
| Two | 21 | 21 | 42 |
| Three | 25 | 29 | 54 |
| Four | 6 | 3 | 9 |
| Five | 1 | 1 | 2 |
| Number of arterial conduits (intra-operative) Units: Subjects | | | |
| None | 2 | 0 | 2 |
| One | 47 | 57 | 104 |
| Two | 9 | 4 | 13 |
| Three | 2 | 0 | 2 |
| Tranexamic used (intra-operative) Units: Subjects | | | |
| Yes | 50 | 55 | 105 |
| No | 10 | 6 | 16 |
| Cell saver set up (intra-operative) Units: Subjects | | | |
| Yes | 9 | 11 | 20 |
| No | 51 | 50 | 101 |
| Intra-operative insulin infusion Units: Subjects | | | |
| Yes | 36 | 36 | 72 |
| No | 24 | 25 | 49 |
| Intra-operative inotropes | | | |
| Excluding noradrenaline | | | |
| Units: Subjects | | | |
| Yes | 3 | 3 | 6 |
| No | 57 | 57 | 114 |
| Unrecorded | 0 | 1 | 1 |
| Intra-operative noradrenaline Units: Subjects | | | |
| Yes | 7 | 9 | 16 |
| No | 53 | 52 | 105 |
| Intra-operative pacing | | | |
| Excluding patients with pacing beforehand | | | |
| Units: Subjects | | | |
| Yes | 3 | 8 | 11 |
| No | 54 | 52 | 106 |
| Unrecorded | 3 | 1 | 4 |
| Intra-operative IABP Units: Subjects | | | |
| Yes | 1 | 0 | 1 |
| No | 59 | 61 | 120 |
| Need for defibrillation (intra-operative and post-operative) Units: Subjects | | | |
| Yes | 2 | 2 | 4 |
| No | 58 | 59 | 117 |

| | | | |
|--|---------------|---------------|-----|
| Arrhythmias on chest closure | | | |
| Excluding patients with permanent pacemaker beforehand | | | |
| Units: Subjects | | | |
| AF | 2 | 4 | 6 |
| Other | 0 | 2 | 2 |
| None, sinus rhythm | 56 | 54 | 110 |
| Unrecorded | 2 | 1 | 3 |
| BMI | | | |
| Units: kg/m2 | | | |
| median | 30 | 31 | |
| inter-quartile range (Q1-Q3) | 27.0 to 33.8 | 28.2 to 33.9 | - |
| EuroSCORE (additive) | | | |
| Units: N/A | | | |
| median | 3 | 2 | |
| inter-quartile range (Q1-Q3) | 2 to 4 | 2 to 4 | - |
| Logistic EuroSCORE | | | |
| Units: N/A | | | |
| median | 2.3 | 1.8 | |
| inter-quartile range (Q1-Q3) | 1.4 to 3.4 | 1.3 to 3.4 | - |
| Haemoglobin | | | |
| Units: g/dL | | | |
| median | 14 | 14 | |
| inter-quartile range (Q1-Q3) | 12.7 to 14.9 | 12.4 to 15.1 | - |
| Platelets | | | |
| Units: 10 ⁹ /L | | | |
| arithmetic mean | 251 | 241 | |
| standard deviation | ± 63.9 | ± 59.2 | - |
| Creatinine | | | |
| Units: µmol/l | | | |
| median | 86 | 87 | |
| inter-quartile range (Q1-Q3) | 76.5 to 108.5 | 75.0 to 100.0 | - |
| Total bypass time (intra-operative) | | | |
| Units: minute | | | |
| median | 80 | 79 | |
| inter-quartile range (Q1-Q3) | 64.5 to 95.0 | 64.0 to 103.0 | - |
| Cumulative cross-clamp time (intra-operative) | | | |
| Units: minute | | | |
| arithmetic mean | 48 | 49 | |
| standard deviation | ± 13.0 | ± 17.7 | - |
| Dose of tranexamic acid (intra-operative) | | | |
| Units: gram(s) | | | |
| median | 2 | 2 | |
| inter-quartile range (Q1-Q3) | 2 to 2 | 2 to 2 | - |
| Volume of cell saver infused (intra-operative) | | | |
| Units: millilitre(s) | | | |
| median | 240 | 238 | |
| inter-quartile range (Q1-Q3) | 100 to 400 | 0 to 1000 | - |
| Lowest haematocrit (intra-operative) | | | |
| Units: percent | | | |
| median | 31 | 31 | |

| | | | |
|------------------------------|--------------|--------------|---|
| inter-quartile range (Q1-Q3) | 28.0 to 35.9 | 27.5 to 36.0 | - |
| Dose/weight of VRT | | | |
| Units: N/A | | | |
| median | 12 | 0 | |
| inter-quartile range (Q1-Q3) | 11.7 to 12.0 | 0 to 0 | - |
| Duration of VRT | | | |
| Units: hours | | | |
| median | 12 | 0 | |
| inter-quartile range (Q1-Q3) | 11.4 to 12.5 | 0 to 0 | - |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Volume replacement therapy |
| Reporting group description: CABG with or without cardiopulmonary bypass (CPB), with preoperative volume replacement therapy (1 ml/kg/hr of Hartmann's solution for 12 consecutive hours prior to surgery). | |
| Reporting group title | Usual care |
| Reporting group description: CABG with or without CPB with conventional preoperative management (no preoperative fluids). | |
| Subject analysis set title | High risk - VRT group |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Subgroup of patients with high risk - VRT group | |
| Subject analysis set title | Low risk - VRT group |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Subgroup of patients with low risk - VRT group | |
| Subject analysis set title | High risk - usual care group |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Subgroup of patients with high risk - usual care group | |
| Subject analysis set title | Low risk - usual care group |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Subgroup of patients with low risk - usual care group | |
| Subject analysis set title | Oral treatment only - VRT group |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Subgroup of patients receiving oral treatment only - VRT group | |
| Subject analysis set title | Oral treatment only - usual care group |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Subgroup of patients receiving oral treatment only - usual care group | |
| Subject analysis set title | Insulin +/- oral treatment - VRT group |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Subgroup of patients receiving insulin +/- oral treatment - VRT group | |
| Subject analysis set title | Insulin +/- oral treatment - usual care group |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: Subgroup of patients receiving insulin +/- oral treatment - usual care group | |

Primary: Time to fitness for discharge

| | |
|---|-------------------------------|
| End point title | Time to fitness for discharge |
| End point description: Time until patients first classified as fit for 'discharge' | |
| End point type | Primary |
| End point timeframe: Post-op in-hospital | |

| End point values | Volume replacement therapy | Usual care | High risk - VRT group | Low risk - VRT group |
|---------------------------------------|----------------------------|-----------------|-----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 60 | 61 | 22 | 38 |
| Units: Days | | | | |
| median (inter-quartile range (Q1-Q3)) | 7 (5 to 12) | 7 (5 to 12) | 9 (5 to 13) | 7 (5 to 9) |

| End point values | High risk - usual care group | Low risk - usual care group | Oral treatment only - VRT group | Oral treatment only - usual care group |
|---------------------------------------|------------------------------|-----------------------------|---------------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 23 | 37 | 35 | 30 |
| Units: Days | | | | |
| median (inter-quartile range (Q1-Q3)) | 7 (5 to 12) | 7 (5 to 9) | 7 (5 to 12) | 7 (5 to 12) |

| End point values | Insulin +/- oral treatment - VRT group | Insulin +/- oral treatment - usual care group | | |
|---------------------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 25 ^[1] | 31 | | |
| Units: Days | | | | |
| median (inter-quartile range (Q1-Q3)) | 7 (5 to 999) | 7 (5 to 12) | | |

Notes:

[1] - 75th percentile (Q3) is undefined. 999 entered

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Time to fitness for discharge |
| Comparison groups | Volume replacement therapy v Usual care |
| Number of subjects included in analysis | 121 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7867 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1.7 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.25 |

| | |
|--|--|
| Statistical analysis title | Time to fitness for discharge - high risk |
| Statistical analysis description: | |
| Comparing time to fitness for discharge between VRT and usual care groups in high risk patients only | |
| Comparison groups | High risk - VRT group v High risk - usual care group |
| Number of subjects included in analysis | 45 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.83 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.32 |
| upper limit | 2.13 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.4 |

| | |
|---|--|
| Statistical analysis title | Time to fitness for discharge - low risk |
| Statistical analysis description: | |
| Comparing time to fitness for discharge between VRT and usual care groups in low risk patients only | |
| Comparison groups | Low risk - VRT group v Low risk - usual care group |
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 2.08 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.35 |

| | |
|---|---|
| Statistical analysis title | Time to fitness for discharge - oral treatment |
| Statistical analysis description: | |
| Comparing time to fitness for discharge between VRT and usual care groups for patients receiving oral treatment only for their diabetes | |
| Comparison groups | Oral treatment only - VRT group v Oral treatment only - usual |

| | |
|---|----------------------------|
| | care group |
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 2.07 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.35 |

| | |
|---|--|
| Statistical analysis title | Time to fitness for discharge - insulin +/- oral |
| Statistical analysis description: | |
| Comparing time to fitness for discharge between VRT and usual care groups for patients receiving insulin +/- oral treatment only for their diabetes | |
| Comparison groups | Insulin +/- oral treatment - VRT group v Insulin +/- oral treatment - usual care group |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.32 |
| upper limit | 2.28 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.43 |

Secondary: Acute kidney injury

| | |
|--|---------------------|
| End point title | Acute kidney injury |
| End point description: | |
| AKI = YES if any post-operative measurement $\geq 1.5 \times$ baseline | |
| End point type | Secondary |
| End point timeframe: | |
| Serum creatinine measured from blood samples collected preoperatively (baseline, pre-trial intervention) and at 0, 24, 48, 72, 96, and 120 hours | |

| End point values | Volume replacement therapy | Usual care | Oral treatment only - VRT group | Oral treatment only - usual care group |
|-----------------------------|----------------------------|-----------------|---------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 60 | 61 | 35 | 30 |
| Units: Subjects | | | | |
| Yes | 18 | 13 | 9 | 7 |
| No | 42 | 48 | 26 | 23 |

| End point values | Insulin +/- oral treatment - VRT group | Insulin +/- oral treatment - usual care group | | |
|-----------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 25 | 31 | | |
| Units: Subjects | | | | |
| Yes | 9 | 6 | | |
| No | 16 | 25 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Acute kidney injury |
| Comparison groups | Volume replacement therapy v Usual care |
| Number of subjects included in analysis | 121 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2377 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 3.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.7 |

| | |
|--|--|
| Statistical analysis title | Acute kidney injury - oral treatment only |
| Statistical analysis description: | |
| Comparing acute kidney injury between VRT and usual care groups in patients receiving oral treatment only for their diabetes | |
| Comparison groups | Oral treatment only - usual care group v Oral treatment only - VRT group |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.34 |
| upper limit | 3.41 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.63 |

| | |
|---|--|
| Statistical analysis title | Acute kidney injury - insulin +/- oral treatment |
| Statistical analysis description: | |
| Comparing acute kidney injury between VRT and usual care groups in patients receiving insulin +/- oral treatment for their diabetes | |
| Comparison groups | Insulin +/- oral treatment - VRT group v Insulin +/- oral treatment - usual care group |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.48 |
| upper limit | 15.04 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.36 |

| | |
|---|--------------------|
| Secondary: Hospital morbidity | |
| End point title | Hospital morbidity |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Post-intervention to hospital discharge | |

| | | | | |
|-----------------------------|----------------------------|-----------------|--|--|
| End point values | Volume replacement therapy | Usual care | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 61 | | |
| Units: Subjects | | | | |
| Yes | 51 | 54 | | |
| No | 9 | 7 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | In-hospital morbidity |
| Comparison groups | Volume replacement therapy v Usual care |
| Number of subjects included in analysis | 121 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5547 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.25 |
| upper limit | 2.12 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.4 |

Secondary: Participants with eGFR <60ml/min on at least 2 of the 8 post-operative times

| | |
|---|--|
| End point title | Participants with eGFR <60ml/min on at least 2 of the 8 post-operative times |
| End point description: | |
| Conditional mean imputation used to impute missing values of eGFR. | |
| End point type | Secondary |
| End point timeframe: | |
| Estimated glomerular filtration rate (eGFR) from serum creatinine measured from blood samples collected preoperatively (baseline, pre-trial intervention), and at 0, 12, 24, 36, 48, 72, 96 and 120 hours after the operation | |

| End point values | Volume replacement therapy | Usual care | | |
|-----------------------------|----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 61 | | |
| Units: Subjects | | | | |
| Yes | 31 | 28 | | |
| No | 29 | 33 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | eGFR<60 mL/min |
| Comparison groups | Volume replacement therapy v Usual care |
| Number of subjects included in analysis | 121 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4219 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.38 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 3.01 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.55 |

Secondary: Pre-operative post-intervention blood glucose

| | |
|--------------------------|---|
| End point title | Pre-operative post-intervention blood glucose |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Pre-op post-intervention | |

| End point values | Volume replacement therapy | Usual care | | |
|---------------------------------------|----------------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 28 | | |
| Units: mmol/L | | | | |
| median (inter-quartile range (Q1-Q3)) | 6.5 (5.5 to 8.1) | 6.9 (5.5 to 8.6) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Pre-operative post-intervention blood glucose |
| Comparison groups | Volume replacement therapy v Usual care |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.759 |
| Method | Regression, Linear |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 0.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 1.17 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.09 |

Secondary: Pre-operative post-intervention HbA1c

| | |
|--------------------------|---------------------------------------|
| End point title | Pre-operative post-intervention HbA1c |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Pre-op post-intervention | |

| End point values | Volume replacement therapy | Usual care | | |
|---------------------------------------|----------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 28 | | |
| Units: mmol/L | | | | |
| median (inter-quartile range (Q1-Q3)) | 53.5 (47.5 to 60.5) | 54.5 (47.0 to 70.5) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Pre-operative post-intervention HbA1c |
| Comparison groups | Usual care v Volume replacement therapy |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.162 |
| Method | Regression, Linear |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 0.92 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.81 |
| upper limit | 1.04 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.06 |

Secondary: eGFR

| | |
|---|-----------|
| End point title | eGFR |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Estimated glomerular filtration rate (eGFR) from serum creatinine measured from blood samples collected preoperatively (baseline, pre-trial intervention), and at 0, 12, 24, 36, 48, 72, 96 and 120 hours after the operation | |

| End point values | Volume replacement therapy | Usual care | Oral treatment only - VRT group | Oral treatment only - usual care group |
|--------------------------------------|----------------------------|-----------------|---------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 60 | 61 | 35 | 30 |
| Units: mmol/min | | | | |
| arithmetic mean (standard deviation) | | | | |
| Pre-operative | 70.5 (± 18.9) | 69 (± 16) | 74.2 (± 14.9) | 73.9 (± 16.6) |
| Operation end | 76.0 (± 17.0) | 75.7 (± 15.8) | 78.9 (± 14.2) | 78.9 (± 14.0) |
| Operation end + 12 hours | 69.7 (± 19.2) | 69.7 (± 19.6) | 73.7 (± 17.9) | 75.7 (± 17.1) |
| Operation end + 24 hours | 60.7 (± 20.3) | 62.5 (± 21.7) | 64.7 (± 19.1) | 66.6 (± 20.0) |
| Operation end + 36 hours | 59.5 (± 22.9) | 60.5 (± 23.5) | 63.2 (± 20.2) | 63.1 (± 20.8) |
| Operation end + 48 hours | 59.4 (± 23.8) | 58.7 (± 23) | 60.8 (± 22.4) | 62.8 (± 20.9) |
| Operation end + 72 hours | 62.2 (± 24.8) | 63.3 (± 24.4) | 66.2 (± 23.5) | 66.9 (± 22.8) |
| Operation end + 96 hours | 64.9 (± 25.0) | 66.7 (± 24.2) | 66.6 (± 24.4) | 72.3 (± 21.8) |
| Operation end + 120 hours | 65.0 (± 24.5) | 71.0 (± 21.3) | 67.7 (± 24.6) | 74.3 (± 20.1) |

| End point values | Insulin +/- oral treatment - VRT group | Insulin +/- oral treatment - usual care group | | |
|--------------------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 25 | 31 | | |
| Units: mmol/min | | | | |
| arithmetic mean (standard deviation) | | | | |
| Pre-operative | 63.5 (± 24.1) | 63.7 (± 14.1) | | |
| Operation end | 71.5 (± 20.1) | 72.7 (± 17.0) | | |
| Operation end + 12 hours | 63.6 (± 20.0) | 62.9 (± 20.4) | | |
| Operation end + 24 hours | 55.1 (± 21.1) | 58.2 (± 22.8) | | |
| Operation end + 36 hours | 54.9 (± 25.8) | 57.9 (± 26.1) | | |
| Operation end + 48 hours | 57.7 (± 25.8) | 55.6 (± 24.4) | | |
| Operation end + 72 hours | 56.1 (± 26.1) | 59.9 (± 25.8) | | |
| Operation end + 96 hours | 62.5 (± 26.2) | 61.1 (± 25.7) | | |
| Operation end + 120 hours | 62.0 (± 24.5) | 67.3 (± 22.5) | | |

Statistical analyses

| Statistical analysis title | eGFR |
|---|---|
| Comparison groups | Usual care v Volume replacement therapy |
| Number of subjects included in analysis | 121 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5799 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.59 |
| upper limit | 2.48 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.8 |

| Statistical analysis title | eGFR - oral treatment only |
|---|--|
| Statistical analysis description: | |
| Comparing eGFR between VRT and usual care groups in patients receiving oral treatment only for their diabetes | |
| Comparison groups | Oral treatment only - VRT group v Oral treatment only - usual care group |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.23 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.92 |
| upper limit | 4.46 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.39 |

| | |
|--|--|
| Statistical analysis title | eGFR - insulin +/- oral treatment |
| Statistical analysis description: | |
| Comparing eGFR between VRT and usual care groups in patients receiving insulin +/- oral treatment for their diabetes | |
| Comparison groups | Insulin +/- oral treatment - VRT group v Insulin +/- oral treatment - usual care group |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -2.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.46 |
| upper limit | 4.87 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.65 |

| | |
|--|-------------------------------|
| Secondary: Microalbumin/creatinine ratio | |
| End point title | Microalbumin/creatinine ratio |
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| Measured in urine samples collected preoperatively (baseline, pre-trial intervention) and at 0, 24, 48 and 120 hours | |

| End point values | Volume replacement therapy | Usual care | Oral treatment only - VRT group | Oral treatment only - usual care group |
|---------------------------------------|----------------------------|------------------|---------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 60 | 61 | 35 | 30 |
| Units: mg/mmol | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Pre-operative | 1.2 (0.5 to 3.9) | 1.4 (0.8 to 2.9) | 1 (0.5 to 3.5) | 1.1 (0.6 to 2.3) |
| Operation end | 3.4 (2.0 to 9.7) | 5.1 (2.1 to 8.7) | 2.9 (1.8 to 9.7) | 4.2 (1.2 to 8.5) |
| Operation end + 24 hours | 2.9 (1.8 to 7.1) | 3.2 (2.0 to 6.1) | 2.9 (1.7 to 5.1) | 3.4 (1.9 to 6.6) |
| Operation end + 48 hours | 5.1 (2.1 to 8.0) | 3.6 (2.1 to 6.7) | 4.4 (2.1 to 7.4) | 3.6 (2.2 to 5.3) |
| Operation end + 120 hours | 1.6 (1.1 to 7.1) | 2.0 (1.4 to 4.1) | 1.6 (1.1 to 5) | 1.6 (0.6 to 2.9) |

| End point values | Insulin +/- oral treatment - VRT group | Insulin +/- oral treatment - usual care group | | |
|---------------------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 25 | 31 | | |
| Units: mg/mmol | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Pre-operative | 2 (0.7 to 5.5) | 1.7 (1.1 to 4.1) | | |
| Operation end | 3.9 (2.5 to 8.6) | 5.6 (2.8 to 9) | | |
| Operation end + 24 hours | 3.4 (1.9 to 8.1) | 3.1 (2 to 5.8) | | |
| Operation end + 48 hours | 5.2 (2.2 to 9.2) | 3.7 (2.1 to 6.9) | | |
| Operation end + 120 hours | 2.2 (1.1 to 16.1) | 2.7 (2 to 6.1) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Microalbumin/creatinine ratio |
| Comparison groups | Volume replacement therapy v Usual care |
| Number of subjects included in analysis | 121 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5604 |
| Method | Mixed models analysis |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 1.37 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.13 |

| | |
|---|--|
| Statistical analysis title | Microalbumin/creatinine ratio - oral treatment |
| Statistical analysis description: Comparing microalbumin/creatinine ratio between VRT and usual care groups in patients receiving oral treatment only for their diabetes | |
| Comparison groups | Oral treatment only - usual care group v Oral treatment only - VRT group |
| Number of subjects included in analysis | 65 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.73 |
| upper limit | 1.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.17 |

| | |
|--|--|
| Statistical analysis title | Microalbumin/creatinine ratio - insulin +/- oral |
| Statistical analysis description: Comparing microalbumin/creatinine ratio between VRT and usual care groups in patients receiving insulin +/- oral treatment for their diabetes | |
| Comparison groups | Insulin +/- oral treatment - VRT group v Insulin +/- oral treatment - usual care group |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 1.17 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.29 |

Secondary: C-reactive protein

| | |
|------------------------|--------------------|
| End point title | C-reactive protein |
| End point description: | |

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Measured preoperatively (baseline, pre-trial intervention) and at 0, 12, 24, 48, 72 and 120 hours after the operation. | |

| End point values | Volume replacement therapy | Usual care | | |
|---------------------------------------|----------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 28 | | |
| Units: mg/L | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Pre-operative | 2 (1 to 4) | 2 (1 to 3) | | |
| Operation end | 1 (1 to 3) | 1 (1 to 2) | | |
| Operation end + 12 hours | 45 (36 to 58.5) | 44 (36.5 to 59.5) | | |
| Operation end + 24 hours | 132 (123 to 183) | 167.5 (133.5 to 180) | | |
| Operation end + 48 hours | 241.5 (199 to 287) | 249 (184 to 290) | | |
| Operation end + 72 hours | 232 (174 to 295) | 249 (198 to 284) | | |
| Operation end + 120 hours | 91.5 (61 to 124) | 97 (63 to 132) | | |

Statistical analyses

| Statistical analysis title | C-reactive protein |
|---|---|
| Comparison groups | Volume replacement therapy v Usual care |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9353 |
| Method | Regression, Linear |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.89 |
| upper limit | 1.11 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.05 |

Secondary: Troponin T

| | |
|-----------------|------------|
| End point title | Troponin T |
|-----------------|------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Measured preoperatively (baseline, pre-trial intervention) and at 0, 12, 24, 48, 72 and 120 hours after the operation.

| End point values | Volume replacement therapy | Usual care | | |
|---------------------------------------|----------------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 28 | | |
| Units: µg/L | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Pre-operative | 12 (9.5 to 13.5) | 9 (6 to 21) | | |
| Operation end | 166 (86 to 267) | 129.5 (76.5 to 226.5) | | |
| Operation end + 12 hours | 234.5 (130 to 364) | 197 (80 to 320) | | |
| Operation end + 24 hours | 200 (103 to 258) | 177 (70 to 249) | | |
| Operation end + 48 hours | 145 (87 to 193) | 142 (68 to 225) | | |
| Operation end + 72 hours | 123 (75.5 to 189.5) | 132 (70 to 179) | | |
| Operation end + 120 hours | 89.5 (54 to 158) | 66 (34 to 111) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Troponin T |
| Comparison groups | Volume replacement therapy v Usual care |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4923 |
| Method | Regression, Linear |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 1.14 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.64 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.21 |

Secondary: N-acetyl glucosaminidase (NAG)

| | |
|-----------------|--------------------------------|
| End point title | N-acetyl glucosaminidase (NAG) |
|-----------------|--------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Measured in urine samples collected preoperatively (baseline, pre-trial intervention) and at 0, 24, 48 and 120 hours

| End point values | Volume replacement therapy | Usual care | Oral treatment only - VRT group | Oral treatment only - usual care group |
|---------------------------------------|----------------------------|-------------------|---------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 36 | 37 | 22 | 18 |
| Units: U/g | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Pre-operative | 1.9 (1.3 to 3.6) | 2.4 (1.7 to 3.9) | 1.8 (1.1 to 2.9) | 2.1 (1.5 to 3.9) |
| Operation end | 4.3 (2.2 to 7.7) | 4.6 (1.9 to 7.3) | 3.5 (2 to 6.7) | 4.1 (1.7 to 5.7) |
| Operation end + 24 hours | 8.6 (5.9 to 15.1) | 6.8 (4.7 to 14.9) | 8.6 (6 to 13.5) | 6.2 (4.2 to 12.3) |
| Operation end + 48 hours | 7.8 (3.3 to 19.4) | 8.4 (2.3 to 15.4) | 5.3 (2.9 to 12.1) | 6.0 (2.2 to 12.8) |
| Operation end + 120 hours | 7 (4.1 to 9.4) | 6 (3.9 to 9.8) | 5.9 (3.8 to 8.6) | 4.8 (3.6 to 6.2) |

| End point values | Insulin +/- oral treatment - VRT group | Insulin +/- oral treatment - usual care group | | |
|---------------------------------------|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 14 | 19 | | |
| Units: U/g | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Pre-operative | 2.1 (1.7 to 6.7) | 3 (1.9 to 4.5) | | |
| Operation end | 4.6 (2.8 to 9.8) | 5.9 (3.0 to 10.4) | | |
| Operation end + 24 hours | 8.9 (5.9 to 19.2) | 10.5 (5.0 to 20.7) | | |
| Operation end + 48 hours | 17.4 (6.5 to 26.4) | 9.7 (5.2 to 19.1) | | |
| Operation end + 120 hours | 9.3 (7.3 to 13.4) | 9.3 (6.5 to 14.3) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | N-acetyl glucosaminidase (NAG) |
| Comparison groups | Volume replacement therapy v Usual care |
| Number of subjects included in analysis | 73 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4912 |
| Method | Regression, Linear |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 1.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.14 |

| | |
|--|--|
| Statistical analysis title | NAG - oral treatment only |
| Statistical analysis description: | |
| Comparing NAG between VRT and usual care groups in patients receiving oral treatment only for their diabetes | |
| Comparison groups | Oral treatment only - VRT group v Oral treatment only - usual care group |
| Number of subjects included in analysis | 40 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 1.25 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.91 |
| upper limit | 1.72 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.2 |

| | |
|---|--|
| Statistical analysis title | NAG - insulin +/- oral treatment |
| Statistical analysis description: | |
| Comparing NAG between VRT and usual care groups in patients receiving insulin +/- oral treatment for their diabetes | |
| Comparison groups | Insulin +/- oral treatment - VRT group v Insulin +/- oral treatment - usual care group |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 33 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Mixed models analysis |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 0.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.48 |
| upper limit | 1.27 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.19 |

Secondary: CROQ core total score

| | |
|---|-----------------------|
| End point title | CROQ core total score |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Pre-operatively and 3 months post-randomisation | |

| End point values | Volume replacement therapy | Usual care | | |
|---------------------------------------|----------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 61 | | |
| Units: N/A | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Pre-operative | 47.2 (40.1 to 52) | 47.6 (42.1 to 52) | | |
| 3 months post-operative | 54 (48.3 to 56.6) | 53.6 (47.9 to 56.4) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | CROQ score total score |
| Comparison groups | Volume replacement therapy v Usual care |
| Number of subjects included in analysis | 121 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5967 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.66 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.78 |
| upper limit | 3.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.24 |

Secondary: CROQ symptoms score

| | |
|---|---------------------|
| End point title | CROQ symptoms score |
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| Pre-operative and 3 months post-operative | |

| End point values | Volume replacement therapy | Usual care | | |
|---------------------------------------|----------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 61 | | |
| Units: N/A | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Pre-operative | 69 (50 to 85.7) | 68.8 (48.2 to 85.7) | | |
| 3 months post-operative | 92.9 (85.7 to 100) | 92.9 (79.1 to 96.4) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | CROQ symptoms score |
| Comparison groups | Volume replacement therapy v Usual care |
| Number of subjects included in analysis | 121 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5901 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.57 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.12 |
| upper limit | 7.26 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.9 |

Secondary: CROQ physical functioning score

| | |
|---|---------------------------------|
| End point title | CROQ physical functioning score |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Pre-operative and 3 months post-operative | |

| End point values | Volume replacement therapy | Usual care | | |
|---------------------------------------|----------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 59 | 61 | | |
| Units: N/A | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Pre-operative | 56.3 (31.3 to 91.7) | 56.3 (25 to 85.7) | | |
| 3 months post-operative | 90.7 (65.7 to 100) | 83.5 (62.5 to 93.8) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | CROQ physical functioning score |
| Comparison groups | Volume replacement therapy v Usual care |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.993 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.61 |
| upper limit | 9.52 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.88 |

Secondary: CROQ cognitive functioning score

| | |
|-----------------|----------------------------------|
| End point title | CROQ cognitive functioning score |
|-----------------|----------------------------------|

| |
|------------------------|
| End point description: |
|------------------------|

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

| |
|----------------------|
| End point timeframe: |
|----------------------|

| |
|---|
| Pre-operative and 3 months post-operative |
|---|

| End point values | Volume replacement therapy | Usual care | | |
|---------------------------------------|----------------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 61 | | |
| Units: N/A | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Pre-operative | 80 (53.3 to 100) | 86.7 (60 to 100) | | |
| 3 months post-operative | 83.4 (63.4 to 100) | 90 (60 to 100) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | CROQ cognitive functioning score |
| Comparison groups | Volume replacement therapy v Usual care |
| Number of subjects included in analysis | 121 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.6638 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.62 |
| upper limit | 10.45 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.35 |

Secondary: CROQ psychosocial functioning score

| | |
|-----------------|-------------------------------------|
| End point title | CROQ psychosocial functioning score |
|-----------------|-------------------------------------|

| |
|------------------------|
| End point description: |
|------------------------|

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-operative and 3 months post-operative

| End point values | Volume replacement therapy | Usual care | | |
|---------------------------------------|----------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 61 | | |
| Units: N/A | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| Pre-operative | 62.5 (39.3 to 80.4) | 68.8 (47.3 to 82.1) | | |
| 3 months post-operative | 85.7 (62.5 to 92.9) | 85.7 (67.9 to 92.9) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | CROQ psychosocial functioning score |
| Comparison groups | Volume replacement therapy v Usual care |
| Number of subjects included in analysis | 121 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2563 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 4.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.31 |
| upper limit | 12.71 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.09 |

Secondary: CROQ satisfaction score

| | |
|-------------------------|-------------------------|
| End point title | CROQ satisfaction score |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 3 months post-operative | |

| End point values | Volume replacement therapy | Usual care | | |
|---------------------------------------|----------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 51 | 53 | | |
| Units: N/A | | | | |
| median (inter-quartile range (Q1-Q3)) | 86.7 (75 to 100) | 79.2 (62.5 to 91.7) | | |

Statistical analyses

| Statistical analysis title | CROQ satisfaction score |
|---|---|
| Statistical analysis description: | |
| Comparing CROQ satisfaction score between VRT and usual care groups at 3 months post-operation. Multiple imputation used to account for missing data. | |
| Comparison groups | Usual care v Volume replacement therapy |
| Number of subjects included in analysis | 104 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.123 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 5.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.56 |
| upper limit | 12.86 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.63 |

Secondary: CROQ adverse effects score

| | |
|---|----------------------------|
| End point title | CROQ adverse effects score |
| End point description: | |
| Adverse effects score categorised into quartiles and summarised | |
| End point type | Secondary |
| End point timeframe: | |
| 3 months post-operative | |

| End point values | Volume replacement therapy | Usual care | | |
|-----------------------------|----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 51 | 54 | | |
| Units: Subjects | | | | |
| Quartile 1: <72.7 | 8 | 12 | | |
| Quartile 2: ≥ 72.7 & < 84.1 | 13 | 14 | | |
| Quartile 3: ≥ 84.1 & < 93.2 | 14 | 12 | | |
| Quartile 4: ≥ 93.2 | 16 | 16 | | |

Statistical analyses

| Statistical analysis title | CROQ adverse effects score |
|--|---|
| Statistical analysis description: | |
| CROQ adverse effects score categorised into quartiles and compared between VRT and usual care groups | |
| Comparison groups | Volume replacement therapy v Usual care |
| Number of subjects included in analysis | 105 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.52 |
| Method | Ordered logistic regression |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.38 |
| upper limit | 2.15 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.45 |

Secondary: Cost of healthcare resources

| | |
|---|------------------------------|
| End point title | Cost of healthcare resources |
| End point description: | |
| Costs assessed included duration of operation, intensive care unit (ICU)/high dependency unit (HDU) and ward stay, additional interventions to treat complications, readmissions and re-operations. | |
| End point type | Secondary |
| End point timeframe: | |
| During hospital stay | |

| End point values | Volume replacement therapy | Usual care | | |
|---------------------------------------|---------------------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 60 | | |
| Units: Pounds | | | | |
| median (inter-quartile range (Q1-Q3)) | 11820.8 (10878.4 to 13798.1) | 11501.1 (10487 to 13815.2) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Cost of healthcare resources |
| Comparison groups | Usual care v Volume replacement therapy |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3703 |
| Method | Regression, Linear |
| Parameter estimate | Geometric mean ratio |
| Point estimate | 1.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.96 |
| upper limit | 1.12 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.04 |

Other pre-specified: Duration of operation

| | |
|------------------------|-----------------------|
| End point title | Duration of operation |
| End point description: | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Duration of operation | |

| End point values | Volume replacement therapy | Usual care | | |
|--------------------------------------|----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 61 | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 3 (± 0.9) | 4 (± 1.0) | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Duration of ICU/HDU stay

| | |
|-----------------|--------------------------|
| End point title | Duration of ICU/HDU stay |
|-----------------|--------------------------|

End point description:

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Length of ICU/HDU stay

| End point values | Volume replacement therapy | Usual care | | |
|---------------------------------------|----------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 60 | | |
| Units: hours | | | | |
| median (inter-quartile range (Q1-Q3)) | 93 (58 to 121.5) | 94 (66.8 to 123.4) | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Duration of ward stay

| | |
|-----------------|-----------------------|
| End point title | Duration of ward stay |
|-----------------|-----------------------|

End point description:

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Length of ward stay

| End point values | Volume replacement therapy | Usual care | | |
|---------------------------------------|----------------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 61 | | |
| Units: hours | | | | |
| median (inter-quartile range (Q1-Q3)) | 74 (49.9 to 112.4) | 72 (28 to 122.1) | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Duration of ventilation

| | |
|-----------------|-------------------------|
| End point title | Duration of ventilation |
|-----------------|-------------------------|

End point description:

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Duration of in-hospital ventilation

| End point values | Volume replacement therapy | Usual care | | |
|---------------------------------------|----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 61 | | |
| Units: hours | | | | |
| median (inter-quartile range (Q1-Q3)) | 6 (4.6 to 10) | 7 (4.8 to 9.6) | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Any transfusion

| | |
|-----------------|-----------------|
| End point title | Any transfusion |
|-----------------|-----------------|

End point description:

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

In-hospital

| End point values | Volume replacement therapy | Usual care | | |
|-----------------------------|----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 61 | | |
| Units: Subjects | | | | |
| Yes | 20 | 16 | | |
| No | 40 | 45 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: If transfusion, units received

| | |
|--|--------------------------------|
| End point title | If transfusion, units received |
| End point description: | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Units of blood received during transfusion | |

| End point values | Volume replacement therapy | Usual care | | |
|---------------------------------------|----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 16 | | |
| Units: units | | | | |
| median (inter-quartile range (Q1-Q3)) | 1 (1 to 2) | 3 (1 to 6) | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Activated factor VII used

| | |
|------------------------|---------------------------|
| End point title | Activated factor VII used |
| End point description: | |
| End point type | Other pre-specified |
| End point timeframe: | |
| In-hospital | |

| End point values | Volume replacement therapy | Usual care | | |
|-----------------------------|----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 61 | | |
| Units: Subjects | | | | |
| Yes | 1 | 0 | | |
| No | 59 | 61 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Colloid/crystalloid received

| | |
|------------------------|------------------------------|
| End point title | Colloid/crystalloid received |
| End point description: | |
| End point type | Other pre-specified |
| End point timeframe: | |
| In-hospital | |

| End point values | Volume replacement therapy | Usual care | | |
|-----------------------------|----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 61 | | |
| Units: Subjects | | | | |
| Yes | 60 | 61 | | |
| No | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Discharge destination

| | |
|------------------------|-----------------------|
| End point title | Discharge destination |
| End point description: | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Hospital discharge | |

| End point values | Volume replacement therapy | Usual care | | |
|-----------------------------|----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 61 | | |
| Units: Subjects | | | | |
| Home | 57 | 54 | | |
| Other ward within hospital | 0 | 2 | | |
| Other hospital | 3 | 2 | | |
| Other (e.g. nursing home) | 0 | 2 | | |
| Patient died | 0 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Readmitted to hospital

| | |
|-----------------|------------------------|
| End point title | Readmitted to hospital |
|-----------------|------------------------|

End point description:

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Any hospital readmission within 3 months post-operation

| End point values | Volume replacement therapy | Usual care | | |
|-----------------------------|----------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 60 | 60 | | |
| Units: Subjects | | | | |
| Yes | 11 | 8 | | |
| No | 49 | 48 | | |
| Unknown | 0 | 4 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

In-hospital and up to 3 months post-operatively

Adverse event reporting additional description:

All expected adverse events reported as event names (not put through medical dictionary).

Unexpected adverse events reported using MedDRA dictionary.

For all events, 'non-serious adverse events' includes ALL events (serious and non-serious). This is consistent with the trial publication.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|----------|
| Dictionary name | Not used |
|-----------------|----------|

| | |
|--------------------|---|
| Dictionary version | 1 |
|--------------------|---|

Reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Volume replacement therapy |
|-----------------------|----------------------------|

Reporting group description:

CABG with or without cardiopulmonary bypass (CPB), with preoperative volume replacement therapy (1 ml/kg/hr of Hartmann's solution for 12 consecutive hours prior to surgery).

| | |
|-----------------------|------------|
| Reporting group title | Usual care |
|-----------------------|------------|

Reporting group description:

CABG with or without CPB with conventional preoperative management (no preoperative fluids).

| Serious adverse events | Volume replacement therapy | Usual care | |
|---|----------------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 23 / 60 (38.33%) | 22 / 61 (36.07%) | |
| number of deaths (all causes) | 0 | 2 | |
| number of deaths resulting from adverse events | 0 | 2 | |
| Vascular disorders | | | |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Haemofiltration/dialysis | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 0 / 60 (0.00%) | 3 / 61 (4.92%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reoperation | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 3 / 61 (4.92%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Re-intubation and ventilation | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 3 / 61 (4.92%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inotropes | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mask CPAP | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary artery catheter | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Death - unknown cause | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Reproductive system and breast disorders | | | |
| Tachypnoea | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion/pneumothorax | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 4 / 61 (6.56%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolus | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood potassium increased | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 60 (1.67%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia/Atrial fibrillation | | | |
| subjects affected / exposed | 5 / 60 (8.33%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular fibrillation/Ventricular tachycardia | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pacing | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion/haemorrhage | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Hiatus hernia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peptic ulcer/GI bleed/perforation | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Urinary retention | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute kidney injury | | | |
| subjects affected / exposed | 18 / 60 (30.00%) | 13 / 61 (21.31%) | |
| occurrences causally related to treatment / all | 0 / 18 | 0 / 13 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 6 / 61 (9.84%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 5 / 60 (8.33%) | 4 / 61 (6.56%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest infection | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 1 / 61 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Wound infection | | | |
| subjects affected / exposed | 3 / 60 (5.00%) | 3 / 61 (4.92%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound dehiscence | | | |
| subjects affected / exposed | 2 / 60 (3.33%) | 3 / 61 (4.92%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Volume replacement therapy | Usual care | |
|---|----------------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 53 / 60 (88.33%) | 54 / 61 (88.52%) | |
| Vascular disorders | | | |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Surgical and medical procedures | | | |
| Haemofiltration/dialysis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 3 / 61 (4.92%) | |
| occurrences (all) | 0 | 3 | |
| Re-operation | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 3 / 61 (4.92%) | |
| occurrences (all) | 1 | 3 | |
| Re-intubation and ventilation | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 3 / 61 (4.92%) | |
| occurrences (all) | 1 | 3 | |

| | | | |
|--|------------------|------------------|--|
| Inotropes | | | |
| subjects affected / exposed | 19 / 60 (31.67%) | 32 / 61 (52.46%) | |
| occurrences (all) | 20 | 32 | |
| Vasodilation procedure | | | |
| subjects affected / exposed | 21 / 60 (35.00%) | 15 / 61 (24.59%) | |
| occurrences (all) | 21 | 15 | |
| IABP | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 1 / 61 (1.64%) | |
| occurrences (all) | 1 | 1 | |
| Mask CPAP | | | |
| subjects affected / exposed | 7 / 60 (11.67%) | 12 / 61 (19.67%) | |
| occurrences (all) | 7 | 12 | |
| Pulmonary artery catheter | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 1 / 61 (1.64%) | |
| occurrences (all) | 1 | 1 | |
| General disorders and administration site conditions | | | |
| Oedema | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Pleural effusion/pneumothorax | | | |
| subjects affected / exposed | 4 / 60 (6.67%) | 4 / 61 (6.56%) | |
| occurrences (all) | 4 | 4 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 61 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tachypnoea | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 61 (1.64%) | |
| occurrences (all) | 0 | 1 | |
| Epistaxis | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 0 / 61 (0.00%) 0 | |
| Investigations Blood potassium increased subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 0 / 61 (0.00%) 0 | |
| Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 61 (1.64%) 1 | |
| Cardiac disorders Cardiac arrest subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 1 / 61 (1.64%) 1 | |
| Myocardial infarction subjects affected / exposed occurrences (all) | 7 / 60 (11.67%) 7 | 6 / 61 (9.84%) 6 | |
| Supraventricular tachycardia/Atrial fibrillation subjects affected / exposed occurrences (all) | 23 / 60 (38.33%) 23 | 20 / 61 (32.79%) 20 | |
| Ventricular fibrillation/Ventricular tachycardia subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 0 / 61 (0.00%) 0 | |
| Pacing subjects affected / exposed occurrences (all) | 4 / 60 (6.67%) 4 | 6 / 61 (9.84%) 6 | |
| Pericardial effusion/haemorrhage subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 2 | 1 / 61 (1.64%) 1 | |
| Cardiac failure congestive subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 0 / 61 (0.00%) 0 | |
| Chest pain subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 61 (1.64%) 1 | |

| | | | |
|--|------------------------|------------------------|--|
| Low cardiac output syndrome subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 2 / 61 (3.28%) 2 | |
| Nervous system disorders Transient ischaemic attack subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 0 / 61 (0.00%) 0 | |
| Cerebrovascular accident subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 61 (1.64%) 1 | |
| Seizure subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 61 (1.64%) 1 | |
| Gastrointestinal disorders Hiatus hernia subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 61 (1.64%) 1 | |
| Peptic ulcer/GI bleed/perforation subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 2 / 61 (3.28%) 2 | |
| Skin and subcutaneous tissue disorders Skin ulcer subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 61 (1.64%) 1 | |
| Renal and urinary disorders Urinary retention subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 0 / 61 (0.00%) 0 | |
| Acute kidney injury subjects affected / exposed occurrences (all) | 18 / 60 (30.00%) 18 | 13 / 61 (21.31%) 13 | |
| Endocrine disorders Hypoglycaemia subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 1 / 61 (1.64%) 1 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|--|------------------------|------------------------|--|
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 2 | 0 / 61 (0.00%) 0 | |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 2 | 0 / 61 (0.00%) 0 | |
| Infections and infestations | | | |
| Sepsis subjects affected / exposed occurrences (all) | 13 / 60 (21.67%) 12 | 24 / 61 (39.34%) 17 | |
| Respiratory infection subjects affected / exposed occurrences (all) | 17 / 60 (28.33%) 14 | 19 / 61 (31.15%) 15 | |
| Chest infection subjects affected / exposed occurrences (all) | 4 / 60 (6.67%) 4 | 1 / 61 (1.64%) 1 | |
| Wound infection subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | 3 / 61 (4.92%) 3 | |
| Wound dehiscence subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 2 | 4 / 61 (6.56%) 3 | |
| Osteomyelitis subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 0 / 61 (0.00%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 24 October 2011 | Update to primary endpoint and to safety section |
| 16 January 2013 | Addition of new outcomes and timepoints for outcomes; sample size amended for tubular injury outcome; clarification added to the dosage and regimen section for the study medication; clarification of the end of trial definition; amendment of wording regarding collection, storage, labelling etc. of samples; amendment regarding documentation of drug administration; amendment regarding process for reporting SAEs; amendment of list of expected adverse events. |
| 04 September 2013 | Clarification that due to time restraints the pre-op CROQ can be completed alongside randomisation as long as the CROQ is completed prior to informing the patient of the treatment allocation. Clarification of the rule on randomisation if the pre-op creatinine result is not available in time. Sample size amended for tubular injury outcome and for secondary outcomes (i) to (I). MicroRNA and other biochemical predictors will also be measured in urine. Key data collection points table changed to include other biochemical predictors of health outcome for blood samples and to include microRNA and other biochemical predictors of health outcome in urine samples. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31539025>