**Methods**

*Further details on* *statistical methods*

Continuous data are summarised using mean and standard deviation (or median and interquartile range (IQR)/geometric mean and 95% confidence interval (CI) if distributions are skewed) and categorical data as a number and percentage.

Model fit was assessed via standard methods (e.g. graphical plots) and if inadequate then transformations or alternative analysis methods were sought. Likelihood ratio tests were used to determine statistical significance. Analyses were adjusted for trial phase and age group (>12 months versus ≤12 months; note the ≤1 month age group contained only two participants, and therefore was combined with the 1-12 months group for the purposes of analysis). Analyses of cerebral function (GFAP) was stratified by age.

*Further details on mixed effects models used for modelling continuous longitudinal outcomes*

For renal function outcomes (measured at fixed points in time), mixed effects linear models were fitted with time as a categorical variable. Different variance/covariance structures were compared (using likelihood ratio tests) to best allow for the correlation between measurements taken at different times for the same patient. If a time x treatment interaction term was statistically significant at the 10% level then separate treatment effect estimates at each time point are presented. If the interaction was not statistically significant an overall treatment effect is reported.

GFAP data could not be analysed as a continuous outcome due to the large amount (40.8%) of readings below the lower limit of detection (LLD). Data were categorised into approximate quartiles (quartile one including all measurements below the LLD) and mixed effects ordinal logistic regression modelling used. The model needed to be stratified by age (<12 months/≥12 months) to ensure the proportional odds assumption was met.

For near infra-red spectroscopy (NIRS) (where measurements were not specified at fixed points in time), mixed effects linear models were fitted with time fitted as a continuous variable with random intercepts (patients) and slopes (times), allowing for different trajectories for different patients. This approach takes into account the actual times the measurements were taken. Quadratic time terms (or other powers) were included if they improved model fit.

For NEPSY data, the total number of individual domains where the child scored at or above the expected level was calculated. This was divided by the total number of individual domains (which varied according to the age of the child), to produce a proportion of domain scores at or above the expected level. If more than 50% of the individual domain scores were missing the overall proportion was set to missing. The proportion was analysed as a mixed effects linear model, with time as a categorical variable. If a time x treatment interaction term was statistically significant at the 10% level then separate treatment effect estimates at each time point are presented. If the interaction was not statistically significant an overall treatment effect is reported.

For renal function models separate parameter estimates were incorporated into models for: a) the mean baseline response across both treatment groups and b) at post-intervention time points for each treatment. This approach avoids the necessity to either exclude cases with missing baseline measures or to impute missing baseline values. This approach was not used for GFAP data as the distribution of baseline values differed between the treatment groups (and missing data amounts were minimal). For the remaining longitudinal outcomes baseline measurements were not collected.

*Further details on instrumental variables models*

Models were performed for each component of the primary outcome to estimate the unbiased effect of cardiopulmonary bypass (CPB) temperature, with randomised allocation as the instrument. These models were fitted with continuous outcomes rather than Cox proportional hazards models (i.e. ignoring censoring, although this was not an issue as there were no pre-hospital discharge deaths) due to computational issues. Generalised method of moments IV estimators were used.

Results

Table S1 Protocol deviations

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Thermic-1** | | | | **Thermic-2** | | | | **Overall** | | | |  | |
|  | **Randomised to normothermic (n=28)** | | **Randomised to hypothermic (n=31)** | | **Randomised to normothermic (n=70)** | | **Randomised to hypothermic (n=71)** | | **Randomised to normothermic (n=98)** | | **Randomised to hypothermic (n=102)** | | **Total (n=200)** | |
|  | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| **Treated as per allocation** | **18/18** | **100%** | **13/24** | **54%** | **59/70** | **84%** | **59/71** | **83%** | **77/88** | **88%** | **72/95** | **76%** | **149/183** | **81%** |
| **Temperature protocol deviation** | **0/18** | **0%** | **11/24** | **46%** | **11/70** | **16%** | **12/71** | **17%** | **11/88** | **13%** | **23/95** | **24%** | **34/183** | **19%** |
| **Treated with wrong intervention (cross over)1** | **0/18** | **0%** | **3/24** | **13%** | **2/70** | **3%** | **5/71** | **7%** | **2/88** | **2%** | **8/95** | **8%** | **10/183** | **5%** |
| Minimum temp ≥27, <31 °C | 0/18 | 0% |  |  | 2/70 | 3% |  |  | 2/88 | 2% |  |  | 2/183 | 1% |
| Minimum temp ≥34, <37 °C |  |  | 3/24 | 13% |  |  | 5/71 | 7% |  |  | 8/95 | 8% | 8/183 | 4% |
| **Treated with neither intervention** | **0/18** | **0%** | **8/24** | **33%** | **9/70** | **13%** | **7/71** | **10%** | **9/88** | **10%** | **15/95** | **16%** | **24/183** | **13%** |
| Minimum temp <27 °C | 0/18 | 0% | 1/24 | 4% | 0/70 | 0% | 1/71 | 1% | 0/88 | 0% | 2/95 | 2% | 2/183 | 1% |
| Minimum temp ≥31, <34 °C | 0/18 | 0% | 7/24 | 29% | 9/70 | 13% | 6/71 | 8% | 9/88 | 10% | 13/95 | 14% | 22/183 | 12% |
| **Reasons for deviations2** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Clinical reason |  |  |  |  | 3/11 | 27% | 0/12 | 0% | 3/11 | 27% | 0/12 | 0% | 3/23 | 13% |
| Oversight in theatre |  |  |  |  | 5/11 | 45% | 2/12 | 17% | 5/11 | 45% | 2/12 | 17% | 7/23 | 30% |
| Perfusionist mistake |  |  |  |  | 1/11 | 9% | 0/12 | 0% | 1/11 | 9% | 0/12 | 0% | 1/23 | 4% |
| Surgeon preference |  |  |  |  | 2/11 | 18% | 10/12 | 83% | 2/11 | 18% | 10/12 | 83% | 12/23 | 52% |

***Notes:***

*1 Such deviations were classified as major protocol deviations.*

*2 Reasons are available only for Thermic-2*

**Table S2 Patient demography (further details)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Thermic-1** | | | | **Thermic-2** | | | | **Overall** | | | |  | |
|  |  | **Randomised to normothermic (n=28)** | | **Randomised to hypothermic (n=31)** | | **Randomised to normothermic (n=70)** | | **Randomised to hypothermic (n=71)** | | **Randomised to normothermic (n=98)** | | **Randomised to hypothermic (n=102)** | | **Total (n=200)** | |
|  |  | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| **Drugs on admission** | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Beta blockers |  | 0/26 | 0% | 1/30 | 3% | 5/70 | 7% | 5/71 | 7% | 5/96 | 5% | 6/101 | 6% | 11/197 | 6% |
| Diuretics |  | 1/26 | 4% | 4/30 | 13% | 20/70 | 29% | 17/71 | 24% | 21/96 | 22% | 21/101 | 21% | 42/197 | 21% |
| ACE inhibitors |  | 6/26 | 23% | 4/30 | 13% | 10/70 | 14% | 9/71 | 13% | 16/96 | 17% | 13/101 | 13% | 29/197 | 15% |
| Sildinefil |  |  |  |  |  | 0/70 | 0% | 0/71 | 0% | 0/70 | 0% | 0/71 | 0% | 0/141 | 0% |
| Aspirin |  | 2/26 | 8% | 1/30 | 3% | 5/70 | 7% | 0/71 | 0% | 7/96 | 7% | 1/101 | 1% | 8/197 | 4% |
| Warfarin |  | 0/26 | 0% | 0/30 | 0% | 1/70 | 1% | 0/71 | 0% | 1/96 | 1% | 0/101 | 0% | 1/197 | 1% |
| Other1 |  | 1/28 | 4% | 0/31 | 0% | 18/70 | 26% | 22/71 | 31% | 19/98 | 19% | 22/102 | 22% | 41/200 | 21% |
| **Other** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Heart rhythm | Sinus | 26/26 | 100% | 27/27 | 100% | 69/70 | 99% | 68/71 | 96% | 95/96 | 99% | 95/98 | 97% | 190/194 | 98% |
|  | AF | 0/26 | 0% | 0/27 | 0% | 0/70 | 0% | 1/71 | 1% | 0/96 | 0% | 1/98 | 1% | 1/194 | 1% |
|  | Paced | 0/26 | 0% | 0/27 | 0% | 1/70 | 1% | 2/71 | 3% | 1/96 | 1% | 2/98 | 2% | 3/194 | 2% |
| Previous cardiac surgery1 | | 5/28 | 18% | 4/31 | 13% | 19/70 | 27% | 16/71 | 23% | 24/98 | 24% | 20/102 | 20% | 44/200 | 22% |
| Oxygen saturations (median)\* | | 98.0 | (98.0, 99.0) | 97.0 | (95.0, 98.0) | 98.0 | (97.0, 100.0) | 99.0 | (97.0, 100.0) | 98.0 | (97.0, 100.0) | 98.0 | (97.0, 100.0) | 98.0 | (97.0, 100.0) |
| History of spelling | | 0/27 | 0% | 0/26 | 0% | 4/70 | 6% | 5/71 | 7% | 4/97 | 4% | 5/97 | 5% | 9/194 | 5% |

**Notes:**

*ACE=angiotensin-converting enzyme, AF=atrial fibrillation*

*1 Details are given below:*

***Missing data:***

***\**** *14 patients (Thermic-1 only: 5 normothermic, 9 hypothermic)*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Thermic-1** | | **Thermic-2** | | **Overall** | |  |
|  |  | **Randomised to normothermic (n=28)** | **Randomised to hypothermic (n=31)** | **Randomised to normothermic (n=70)** | **Randomised to hypothermic (n=71)** | **Randomised to normothermic (n=98)** | **Randomised to hypothermic (n=102)** | **Total (n=200)** |
|  |  | **n** | **n** | **n** | **n** | **n** | **n** | **n** |
| **Other cardiac conditions** | | **16** | **16** | **37** | **33** | **52** | **49** | **102** |
| Aortic stenosis/repair/replacement/ LVOTO | | 4 | 5 | 4 | 6 | 8 | 11 | 19 |
| Pulmonary stenosis/repair/ replacement/RVOTO | | 0 | 4 | 7 | 7 | 7 | 11 | 18 |
| Ross Procedure | | 0 | 0 | 3 | 4 | 3 | 4 | 7 |
| Complex (TGA, truncus, hypoplastic left heart, senning) | | 0 | 0 | 3 | 1 | 3 | 1 | 4 |
| Conduits |  | 0 | 0 | 1 | 2 | 1 | 2 | 3 |
| AV valve repair |  | 7 | 6 | 4 | 1 | 11 | 7 | 18 |
| Closed heart procedure | | 0 | 0 | 1 | 1 | 1 | 1 | 2 |
| PAPVD |  | 1 | 0 | 2 | 1 | 3 | 1 | 4 |
| Other |  | 4 | 1 | 13 | 11 | 17 | 12 | 29 |
| Multiple conditions | 2 conditions | 7 | 8 | 17 | 12 | 24 | 20 | 44 |
|  | 3 conditions | 0 | 0 | 3 | 3 | 3 | 3 | 6 |
| **Other drugs at admission** | |  |  | **18** | **22** | **18** | **22** | **40** |
| Antibiotics |  |  |  | 0 | 3 | 0 | 3 | 3 |
| Pre op prep antibiotics (MSSA) | |  |  | 1 | 1 | 1 | 1 | 2 |
| Antifungal |  |  |  | 1 | 0 | 1 | 0 | 1 |
| Beta blockers/Angiotensin 11 receptor blocker | |  |  | 1 | 0 | 1 | 0 | 1 |
| Digoxin |  |  |  | 1 | 0 | 1 | 0 | 1 |
| Anti-platelet |  |  |  | 0 | 0 | 0 | 0 | 0 |
| Gastro related |  |  |  | 7 | 10 | 7 | 10 | 17 |
| Vitamin and iron supplements | |  |  | 1 | 2 | 1 | 2 | 3 |
| Inhalers |  |  |  | 1 | 3 | 1 | 3 | 4 |
| Other |  |  |  | 1 | 2 | 1 | 2 | 3 |
| Multiple drugs |  |  |  | 4 | 1 | 4 | 1 | 5 |
| **Previous cardiac surgery** | |  |  | **19** | **16** | **19** | **16** | **35** |
| Closed |  |  |  | 1 |  | 1 |  | 1 |
| Open |  |  |  | 14 | 13 | 14 | 13 | 27 |
| Multiple procedures |  |  |  | 4 | 3 | 4 | 3 | 7 |

**Notes:**

*LVOTO=left ventricular outflow tract obstruction, RVOTO=right ventricular outflow tract obstruction, TGA=transposition of the great arteries, AV=atrioventricular, PAPVD=partial anomalous pulmonary venous drainafe, MSSA=methicillin-sensitive ataphylococcal aureus*

**Table S3 Intraoperative characteristics (further details)**

|  |  | **Thermic-1** | | | | **Thermic-2** | | | | **Overall** | | | |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Randomised to normothermic (n=28)** | | **Randomised to hypothermic (n=31)** | | **Randomised to normothermic (n=70)** | | **Randomised to hypothermic (n=71)** | | **Randomised to normothermic (n=98)** | | **Randomised to hypothermic (n=102)** | | **Total (n=200)** | |
|  |  | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| **Blood saving techniques** | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Tranexamic acid | | 1/26 | 4% | 0/29 | 0% | 39/70 | 56% | 39/70 | 56% | 40/96 | 42% | 39/99 | 39% | 79/195 | 41% |
| If YES, dose - median (IQR) g | |  |  |  |  | 0.3 | (0.1, 0.5) | 0.3 | (0.2, 0.6) | 0.3 | (0.1, 0.5) | 0.3 | (0.2, 0.6) | 0.3 | (0.1, 0.5) |
| Cell saver set-up | | 0/13 | 0% | 0/11 | 0% | 19/67 | 28% | 18/69 | 26% | 19/80 | 24% | 18/80 | 23% | 37/160 | 23% |
| If YES, volume infused - median (IQR) ml\* | |  |  |  |  | 41.5 | (0.0, 249.0) | 0.0 | (0.0, 167.5) | 41.5 | (0.0, 249.0) | 0.0 | (0.0, 167.5) | 0.0 | (0.0, 208.0) |
| **Arrhythmias** | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Arrhythmias on cross-clamp removal | None | 23/24 | 96% | 27/28 | 96% | 49/66 | 74% | 45/66 | 68% | 72/90 | 80% | 72/94 | 77% | 144/184 | 78% |
| AV block | 1/24 | 4% | 0/28 | 0% | 11/66 | 17% | 15/66 | 23% | 12/90 | 13% | 15/94 | 16% | 27/184 | 15% |
| Nodal | 0/24 | 0% | 0/28 | 0% | 5/66 | 8% | 3/66 | 5% | 5/90 | 6% | 3/94 | 3% | 8/184 | 4% |
| VT | 0/24 | 0% | 0/28 | 0% | 1/66 | 2% | 1/66 | 2% | 1/90 | 1% | 1/94 | 1% | 2/184 | 1% |
| VF | 0/24 | 0% | 0/28 | 0% | 0/66 | 0% | 1/66 | 2% | 0/90 | 0% | 1/94 | 1% | 1/184 | 1% |
| JET | 0/24 | 0% | 1/28 | 4% | 0/66 | 0% | 1/66 | 2% | 0/90 | 0% | 2/94 | 2% | 2/184 | 1% |
| Arrhythmias on chest closure | None | 23/25 | 92% | 27/29 | 93% | 61/67 | 91% | 60/67 | 90% | 84/92 | 91% | 87/96 | 91% | 171/188 | 91% |
| AV block | 1/25 | 4% | 1/29 | 3% | 1/67 | 1% | 3/67 | 4% | 2/92 | 2% | 4/96 | 4% | 6/188 | 3% |
| Nodal | 1/25 | 4% | 0/29 | 0% | 5/67 | 7% | 3/67 | 4% | 6/92 | 7% | 3/96 | 3% | 9/188 | 5% |
| JET | 0/25 | 0% | 1/29 | 3% | 0/67 | 0% | 1/67 | 1% | 0/92 | 0% | 2/96 | 2% | 2/188 | 1% |
| Cardioversion | | 0/24 | 0% | 0/27 | 0% | 2/69 | 3% | 2/71 | 3% | 2/93 | 2% | 2/98 | 2% | 4/191 | 2% |
| Defibrillation |  | 1/24 | 4% | 1/27 | 4% | 1/69 | 1% | 1/71 | 1% | 2/93 | 2% | 2/98 | 2% | 4/191 | 2% |
| Pacing | None | 24/25 | 96% | 27/29 | 93% | 59/70 | 84% | 60/71 | 85% | 83/95 | 87% | 87/100 | 87% | 170/195 | 87% |
|  | Single chamber | 1/25 | 4% | 2/29 | 7% | 6/70 | 9% | 6/71 | 8% | 7/95 | 7% | 8/100 | 8% | 15/195 | 8% |
|  | Dual chamber | 0/25 | 0% | 0/29 | 0% | 5/70 | 7% | 5/71 | 7% | 5/95 | 5% | 5/100 | 5% | 10/195 | 5% |
| **Inotropes on coming off CPB** | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Any inotropes on coming off CPB | | 17/17 | 100.0% | 24/24 | 100.0% | 64/64 | 100.0% | 69/69 | 100.0% | 81/81 | 100.0% | 93/93 | 100.0% | 174/174 | 100.0% |
| Adrenaline |  | 1/25 | 4% | 0/29 | 0% | 4/70 | 6% | 3/71 | 4% | 5/95 | 5% | 3/100 | 3% | 8/195 | 4% |
| If yes, concentration – median (IQR) µg/kg/min | | 5.0 | (5.0, 5.0) |  |  | 1.0 | (0.1, 6.0) | 0.2 | (0.0, 0.5) | 2.0 | (0.1, 5.0) | 0.2 | (0.0, 0.5) | 0.3 | (0.1, 3.5) |
| Noradrenaline | | 0/25 | 0% | 0/29 | 0% | 2/70 | 3% | 0/71 | 0% | 2/95 | 2% | 0/100 | 0% | 2/195 | 1% |
| If YES, concentration – median (IQR) µg/kg/min | |  |  |  |  | 0.1 | (0.0, 0.1) |  |  | 0.1 | (0.0, 0.1) |  |  | 0.1 | (0.0, 0.1) |
| Dopamine |  | 17/28 | 61% | 24/31 | 77% | 59/70 | 84% | 62/71 | 87% | 76/98 | 78% | 86/102 | 84% | 162/200 | 81% |
| If YES, concentration – median (IQR) µg/kg/min | | 7.8 | (0.0, 19.8) | 13.5 | (3.5, 31.0) | 5.0 | (5.0, 5.0) | 5.0 | (5.0, 5.0) | 5.0 | (5.0, 10.0) | 5.0 | (5.0, 10.0) | 5.0 | (5.0, 10.0) |
| Milrinone |  | 1/25 | 4% | 1/29 | 3% | 45/70 | 64% | 52/71 | 73% | 46/95 | 48% | 53/100 | 53% | 99/195 | 51% |
| If YES, concentration – median (IQR) µg/kg/min | | 0.5 | (0.5, 0.5) | 0.5 | (0.5, 0.5) | 0.5 | (0.5, 0.5) | 0.5 | (0.5, 0.5) | 0.5 | (0.5, 0.5) | 0.5 | (0.5, 0.5) | 0.5 | (0.5, 0.5) |
| Dobutamine |  | 0/25 | 0% | 0/29 | 0% | 0/70 | 0% | 1/71 | 1% | 0/95 | 0% | 1/100 | 1% | 1/195 | 1% |
| If YES, concentration – median (IQR) µg/kg/min | |  |  |  |  |  |  | 5.0 | (5.0, 5.0) |  |  | 5.0 | (5.0, 5.0) | 5.0 | (5.0, 5.0) |
| Enoximone |  | 0/25 | 0% | 0/29 | 0% | 0/70 | 0% | 0/71 | 0% | 0/95 | 0% | 0/100 | 0% | 0/195 | 0% |
| If YES, concentration – median (IQR) µg/kg/min | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Other details** | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Insulin infusion | |  |  |  |  | 0/70 | 0% | 0/71 | 0% | 0/70 | 0% | 0/71 | 0% | 0/141 | 0% |
| Vasodilator |  |  |  |  |  | 5/70 | 7% | 5/71 | 7% | 5/70 | 7% | 5/71 | 7% | 10/141 | 7% |

**Notes:**

*IQR=interquartile range, AV=atrioventricular, VT=ventricular tachycardia, VF=ventricular fibrillation, JET=junctional ectopic tachycardia, CPB=cardiopulmonary bypass*

***Missing data:******\**** *3 patients (Thermic-2 only: 1 normothermic, 2 hypothermic)*

**Table S4 Primary outcome: inotrope type**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Thermic-1** | | | | **Thermic-2** | | | | **Overall** | | | |  | |
|  |  | **Randomised to normothermic (n=28)** | | **Randomised to hypothermic (n=31)** | | **Randomised to normothermic (n=70)** | | **Randomised to hypothermic (n=71)** | | **Randomised to normothermic (n=98)** | | **Randomised to hypothermic (n=102)** | | **Total (n=200)** | |
|  |  | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| Noradrenaline |  | 0/4 | 0% | 0/4 | 0% | 1/70 | 1% | 2/71 | 3% | 1/74 | 1% | 2/75 | 3% | 3/149 | 2% |
| If YES, total dose - median (IQR) ml | |  |  |  |  | 115.0 | (115.0, 115.0) | 54.5 | (30.0, 79.1) | 115.0 | (115.0, 115.0) | 54.5 | (30.0, 79.1) | 79.1 | (30.0, 115.0) |
| Adrenaline |  | 0/4 | 0% | 0/4 | 0% | 2/70 | 3% | 2/71 | 3% | 2/74 | 3% | 2/75 | 3% | 4/149 | 3% |
| If YES, total dose - median (IQR) ml | |  |  |  |  | 72.0 | (64.0, 80.0) | 2.0 | (2.0, 2.0) | 72.0 | (64.0, 80.0) | 2.0 | (2.0, 2.0) | 33.0 | (2.0, 72.0) |
| Dopamine |  | 17/28 | 61% | 24/31 | 77% | 51/70 | 73% | 58/71 | 82% | 54/75 | 72% | 61/76 | 80% | 115/151 | 76% |
| If YES, total dose - median (IQR) ml | | 15 | (10.0, 20.5) | 18 | (11.8, 38.3) | 17.5 | (10.0, 28.0) | 13.5 | (7.5, 28.5) | 17.5 | (10.0, 28.0) | 13.5 | (7.5, 28.5) | 15.1 | (9.0, 28.3) |
| Milirinone |  | 1/4 | 25% | 1/4 | 25% | 48/70 | 69% | 51/71 | 72% | 49/74 | 66% | 52/75 | 69% | 101/149 | 68% |
| If YES, total dose - median (IQR) ml | |  |  |  |  | 23.5 | (16.5, 43.0) | 24.0 | (15.0, 63.3) | 23.5 | (16.5, 43.0) | 24.0 | (15.0, 63.3) | 24.0 | (15.5, 44.5) |
| Dobutamine |  | 0/4 | 0% | 0/4 | 0% | 0/70 | 0% | 1/71 | 1% | 0/74 | 0% | 1/75 | 1% | 1/149 | 1% |
| If YES, total dose - median (IQR) ml | |  |  |  |  |  |  | 7.0 | (7.0, 7.0) |  |  | 7.0 | (7.0, 7.0) | 7.0 | (7.0, 7.0) |
| Enoximone |  | 0/4 | 0% | 0/2 | 0% | 0/70 | 0% | 0/71 | 0% | 0/74 | 0% | 0/73 | 0% | 0/147 | 0% |
| If YES, total dose - median (IQR) ml | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Number of different inotropes | 0 | 2/5 | 40% | 2/5 | 40% | 7/70 | 10% | 8/71 | 11% | 9/75 | 12% | 10/76 | 13% | 19/151 | 12% |
| 1 | 2/5 | 40% | 2/5 | 40% | 26/70 | 37% | 17/71 | 24% | 28/75 | 37% | 19/76 | 25% | 47/151 | 31% |
| 2 | 1/5 | 20% | 1/5 | 20% | 35/70 | 50% | 41/71 | 58% | 36/75 | 48% | 42/76 | 55% | 78/151 | 52% |
| 3 | 0/5 | 0% | 0/5 | 0% | 2/70 | 3% | 5/71 | 7% | 2/75 | 3% | 5/76 | 7% | 7/151 | 5% |

***Notes:***

*IQR= interquartile range*

*Thermic-1 data on inotropes was not included in the primary analysis due to the large amount of missing data*

Table S5 Inotrope score and vasoactive-inotrope score (VIS) summarised by group

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Randomised to normothermic (n=70)** | | **Randomised to hypothermic (n=71)** | | **Overall (141)** | |
|  |  | **Median** | **IQR** | **Median** | **IQR** | **Median** | **IQR** |
| Maximum inotrope score (IS) | 0-24 hours | 5.0 | (0.0, 5.0) | 5.0 | (5.0, 5.0) | 5.0 | (1.0, 5.0) |
| 24-48 hours | 0.0 | (0.0, 5.0) | 0.0 | (0.0, 5.0) | 0.0 | (0.0, 5.0) |
| 0-48 hours | 5.0 | (0.0, 5.0) | 5.0 | (5.0, 5.0) | 5.0 | (1.0, 5.0) |
| Maximum vasoactive-inotrope score (VIS) | 0-24 hours | 7.5 | (5.0, 10.0) | 10.0 | (5.0, 10.0) | 10.0 | (5.0, 10.0) |
| 24-48 hours | 5.0 | (0.0, 5.0) | 0.0 | (0.0, 5.0) | 3.5 | (0.0, 5.0) |
| 0-48 hours | 7.5 | (5.0, 10.0) | 10.0 | (5.0, 10.0) | 10.0 | (5.0, 10.0) |
| Mean IS | 0-24 hours | 3.0 | (0.0, 5.0) | 3.0 | (1.0, 5.0) | 3.0 | (0.0, 5.0) |
|  | 24-48 hours | 0.0 | (0.0, 0.0) | 0.0 | (0.0, 1.0) | 0.0 | (0.0, 0.0) |
|  | 0-48 hours | 1.0 | (0.0, 2.0) | 1.0 | (0.0, 3.0) | 1.0 | (0.0, 2.0) |
| Mean VIS | 0-24 hours | 5.0 | (2.0, 9.0) | 6.0 | (3.0, 9.0) | 5.0 | (3.0, 9.0) |
|  | 24-48 hours | 0.0 | (0.0, 5.0) | 0.0 | (0.0, 5.0) | 0.0 | (0.0, 5.0) |
|  | 0-48 hours | 3.0 | (1.0, 7.0) | 3.0 | (1.0, 6.0) | 3.0 | (1.0, 6.0) |

**Notes:**

*IS=inotrope score, VIS=vasoactive-inotrope score*

**Figure S1 Kaplan-Meier curve for duration of inotropic support**



**Figure S2 Kaplan-Meier curve for intubation time**



**Figure S3 Kaplan-Meier curve for length of postoperative stay**



Table S6 Secondary outcomes

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | Thermic-1 | | | | Thermic-2 | | | | Overall | | | |
|  | | Randomised to normothermic (n=28) | | Randomised to hypothermic (n=31) | | Randomised to normothermic (n=70) | | Randomised to hypothermic (n=71) | | Randomised to normothermic (n=98) | | Randomised to hypothermic (n=102) | |
|  | | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| **In hospital mortality and morbidity** | |  |  |  |  |  |  |  |  |  |  |  |  |
| Mortality |  | 0/28 | 0% | 0/31 | 0% | 0/70 | 0% | 0/71 | 0% | 0/98 | 0% | 0/102 | 0% |
| Morbidity | Any complication1 | 6/27 | 22% | 12/29 | 41% | 25/69 | 36% | 30/71 | 42% | 31/96 | 32% | 42/100 | 42% |
|  | Suspected peri-operative MI | 0/27 | 0% | 0/30 | 0% | 1/70 | 1% | 0/71 | 0% | 1/97 | 1% | 0/101 | 0% |
|  | Cardiac arrest | 0/27 | 0% | 1/30 | 3% | 1/70 | 1% | 0/71 | 0% | 1/97 | 1% | 1/101 | 1% |
|  | Arrhythmia | 2/27 | 7% | 4/30 | 13% | 8/70 | 11% | 10/71 | 14% | 10/97 | 10% | 14/101 | 14% |
|  | Haemodynamic support | 2/27 | 7% | 1/30 | 3% | 2/70 | 3% | 0/71 | 0% | 4/97 | 4% | 1/101 | 1% |
|  | Pericardial effusion | 0/27 | 0% | 1/30 | 3% | 3/70 | 4% | 10/71 | 14% | 3/97 | 3% | 11/101 | 11% |
|  | Pulmonary complications | 2/26 | 8% | 4/30 | 13% | 4/70 | 6% | 8/71 | 11% | 6/96 | 6% | 12/101 | 12% |
|  | Renal complications | 0/26 | 0% | 0/30 | 0% | 1/70 | 1% | 1/71 | 1% | 1/96 | 1% | 1/101 | 1% |
|  | GI complications | 0/26 | 0% | 0/30 | 0% | 1/70 | 1% | 1/71 | 1% | 1/96 | 1% | 1/101 | 1% |
|  | Neurological complications | 0/26 | 0% | 0/30 | 0% | 0/70 | 0% | 0/71 | 0% | 0/96 | 0% | 0/101 | 0% |
|  | Thromboembolic complications | 0/26 | 0% | 0/30 | 0% | 0/70 | 0% | 0/71 | 0% | 0/96 | 0% | 0/101 | 0% |
|  | Infective complications | 1/26 | 4% | 3/28 | 11% | 15/69 | 22% | 14/71 | 20% | 16/95 | 17% | 17/99 | 17% |
|  | Re-operation |  |  |  |  | 1/71 | 1% | 3/70 | 4% | 1/71 | 1% | 3/70 | 4% |
|  | Other complications | 0/26 | 0% | 2/30 | 7% | 5/70 | 7% | 4/71 | 6% | 5/96 | 5% | 6/101 | 6% |
| PICU length of stay - median (IQR) hours | |  |  |  |  | 41.9 | (25.0, 51.0) | 42.5 | (24.4, 52.3) | 41.9 | (25.0, 51.0) | 42.5 | (24.4, 52.3) |
| **Blood loss and transfusion requirements** | |  |  |  |  |  |  |  |  |  |  |  |  |
| Total chest drain loss – median (IQR) ml | | 130.0 | (95.0, 240.0) | 160.0 | (127.5, 267.5) | 110.0 | (80.0, 160.0) | 137.5 | (90.0, 185.0) | 117.5 | (90.0, 175.0) | 145.0 | (100.0, 200.0) |
| Total chest drain loss in first 24 hours – median (IQR) ml | |  |  |  |  | 132.5 | (80.0, 160.0) | 110.0 | (80.0, 150.0) | 132.5 | (80.0, 160.0) | 110.0 | (80.0, 150.0) |
| Any blood product transfusion2 | | 13/26 | 50% | 17/29 | 59% | 57/68 | 84% | 52/71 | 73% | 70/94 | 74% | 69/100 | 69% |
| Any RBC transfusions | | 10/26 | 38% | 13/29 | 45% | 57/68 | 84% | 50/71 | 70% | 67/94 | 71% | 63/100 | 63% |
| Any FFP transfusions | | 8/26 | 31% | 12/29 | 41% | 5/68 | 7% | 2/71 | 3% | 13/94 | 14% | 14/100 | 14% |
| Any platelet transfusions | | 0/26 | 0% | 1/29 | 3% | 9/68 | 13% | 5/71 | 7% | 9/94 | 10% | 6/100 | 6% |
| Any cryoprecipitate transfusions | | 0/26 | 0% | 0/29 | 0% | 8/68 | 12% | 10/71 | 14% | 8/94 | 9% | 10/100 | 10% |

**Notes:**

1 It was assumed all patients in Thermic-1 did not have a re-operation (data is missing) for the purposes of calculating the composite “any complication”.

2 Intra-operative or post-operative.

*MI=myocardial infarction, GI=gastrointestinal, PICU=paediatric intensive care unit, IQR=interquartile range, RBC=red blood cells, FFP=fresh frozen plasma*

Table S7 Echocardiographic findings

|  |  | **Thermic-1** | | | | **Thermic-2** | | | | **Overall** | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Randomised to normothermic (n=28)** | | **Randomised to hypothermic (n=31)** | | **Randomised to normothermic (n=70)** | | **Randomised to hypothermic (n=71)** | | **Randomised to normothermic (n=98)** | | **Randomised to hypothermic (n=102)** | |
|  |  | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |
| **Pre-operative** | |  |  |  |  |  |  |  |  |  |  |  |  |
| LV function | Good | 13/14 | 93% | 16/16 | 100% | 50/55 | 91% | 46/50 | 92% | 63/69 | 91% | 62/66 | 94% |
|  | Mildly impaired | 0/14 | 0% | 0/16 | 0% | 5/55 | 9% | 4/50 | 8% | 5/69 | 7% | 4/66 | 6% |
|  | Moderately impaired | 1/14 | 7% | 0/16 | 0% | 0/55 | 0% | 0/50 | 0% | 1/69 | 1% | 0/66 | 0% |
| Fraction shortening – median (IQR) % \* | | 37.5 | (24.0, 41.0) | 42.5 | (37.0, 43.0) | 37.0 | (35.0, 44.0) | 41.0 | (36.0, 43.0) | 37.0 | (34.0, 42.0) | 41.0 | (36.0, 43.0) |
| Ejection fraction – median (IQR) % ^ | | 75.5 | (71.0, 80.0) | 80.5 | (80.0, 81.0) | 71.5 | (54.2, 79.8) | 79.7 | (75.6, 83.0) | 72.8 | (68.3, 80.0) | 79.9 | (76.0, 81.9) |
| RV function | Good | 2/2 | 100% | 4/5 | 80% | 37/43 | 86% | 35/38 | 92% | 39/45 | 87% | 39/43 | 91% |
|  | Mildly impaired | 0/2 | 0% | 0/5 | 0% | 4/43 | 9% | 3/38 | 8% | 4/45 | 9% | 3/43 | 7% |
|  | Moderately impaired | 0/2 | 0% | 1/5 | 20% | 0/43 | 0% | 0/38 | 0% | 0/45 | 0% | 1/43 | 2% |
|  | Severely impaired | 0/2 | 0% | 0/5 | 0% | 2/43 | 5% | 0/38 | 0% | 2/45 | 4% | 0/43 | 0% |
| RVOT velocity given | | 2 |  | 4 |  | 24 |  | 28 |  | 26 |  | 32 |  |
| If YES, velocity – median (IQR) m/s | | 2.4 | (2.2, 2.6) | 3.1 | (2.5, 3.5) | 4.3 | (3.0, 4.8) | 4.1 | (2.3, 4.8) | 4.1 | (2.6, 4.8) | 3.8 | (2.3, 4.8) |
| TR velocity given | | 4 |  | 4 |  | 16 |  | 16 |  | 20 |  | 20 |  |
| If YES, velocity – median (IQR) m/s | | 2.6 | (2.4, 2.8) | 4.0 | (3.2, 4.6) | 3.0 | (2.7, 3.9) | 2.7 | (2.5, 3.5) | 2.9 | (2.6, 3.8) | 2.8 | (2.5, 4.0) |
| **Post-operative** | |  |  |  |  |  |  |  |  |  |  |  |  |
| LV function | Good | 17/19 | 89% | 19/21 | 90% | 52/62 | 84% | 58/66 | 88% | 69/81 | 85% | 77/87 | 89% |
|  | Mildly impaired | 0/19 | 0% | 2/21 | 10% | 8/62 | 13% | 5/66 | 8% | 8/81 | 10% | 7/87 | 8% |
|  | Moderately impaired | 2/19 | 11% |  | 0% | 1/62 | 2% | 2/66 | 3% | 3/81 | 4% | 2/87 | 2% |
|  | Severely impaired | 0/19 | 0% |  | 0% | 1/62 | 2% | 1/66 | 2% | 1/81 | 1% | 1/87 | 1% |
| Fraction shortening – median (IQR) % † | | 35.0 | (27.0, 48.0) | 37.0 | (36.0, 38.0) | 31.0 | (30.0, 37.0) | 37.5 | (29.0, 40.0) | 31.0 | (28.0, 39.0) | 37.0 | (30.0, 40.0) |
| Ejection fraction – median (IQR) % ‡ | | 59.0 | (59.0, 59.0) | 75.5 | (74.0, 77.0) | 49.0 | (49.0, 49.0) | 61.0 | (61.0, 61.0) | 54.0 | (49.0, 59.0) | 74.0 | (61.0, 77.0) |
| RV function | Good | 5/5 | 100% | 9/9 | 100% | 44/59 | 75% | 47/60 | 78% | 49/64 | 77% | 56/69 | 81% |
|  | Mildly impaired | 0/5 | 0% | 0/9 | 0% | 13/59 | 22% | 10/60 | 17% | 13/64 | 20% | 10/69 | 14% |
|  | Moderately impaired | 0/5 | 0% | 0/9 | 0% | 2/59 | 3% | 2/60 | 3% | 2/64 | 3% | 2/69 | 3% |
|  | Severely impaired | 0/5 | 0% | 0/9 | 0% | 0/59 | 0% | 1/60 | 2% | 0/64 | 0% | 1/69 | 1% |
| RVOT velocity given | | 1 |  | 6 |  | 18 |  | 23 |  | 19 |  | 29 |  |
| If YES, velocity – median (IQR) m/s | | 2.4 | (2.4, 2.4) | 2.0 | (1.4, 3.5) | 1.9 | (1.3, 2.4) | 2.0 | (1.2, 2.5) | 2.0 | (1.3, 2.4) | 2.0 | (1.3, 2.5) |
| TR velocity given | | 4 |  | 2 |  | 13 |  | 18 |  | 17 |  | 20 |  |
| If YES, velocity – median (IQR) m/s | | 2.0 | (1.9, 2.2) | 2.5 | (2.2, 2.8) | 2.4 | (2.3, 3.0) | 2.4 | (2.0, 2.8) | 2.4 | (2.0, 2.5) | 2.4 | (2.0, 2.8) |

**Notes:**

*LV=left ventricular, IQR=interquartile range, RV=right ventricular, RVOT=right ventricular outflow tract, TR=tricuspid regurgitation*

***Missing data:***

*\* Thermic-1 (18 normothermic, 23 hypothermic), Thermic-2 (50 normothermic, 50 hypothermic)*

*^ Thermic-1 (26 normothermic, 29 hypothermic), Thermic-2 (66 normothermic, 60 hypothermic)*

*† Thermic-1 (24 normothermic, 26 hypothermic), Thermic-2 (57 normothermic, 53 hypothermic)*

*‡ Thermic-1 (27 normothermic, 29 hypothermic), Thermic-2 (69 normothermic, 70 hypothermic)*

Figure S4 Routine blood gases: pH



**Notes:**

*XC=cross-clamp, SD=standard deviation*

Figure S5 Routine blood gases: pO2



**Notes:**

*XC=cross-clamp, IQR=interquartile range*

Figure S6 Routine blood gases: pCO2



**Notes:**

*XC=cross-clamp, SD=standard deviation*

Figure S7 Routine blood gases: SaO2



**Notes:**

*XC=cross-clamp, IQR=interquartile range*

Figure S9 Routine blood gases: glucose



**Notes:**

*XC=cross-clamp, SD=standard deviation*

Figure S10 Routine blood gases: lactate



**Notes:**

*XC=cross-clamp, IQR=interquartile range*

Figure S11 Routine blood gases: base



**Notes:**

*XC=cross-clamp, SD=standard deviation*

Figure S12 Routine blood gases: haematocrit



**Notes:**

*XC=cross-clamp, SD=standard deviation*

Figure S13 Routine blood gases: potassium



**Notes:**

*XC=cross-clamp, SD=standard deviation*

Figure S14 Routine blood gases: calcium



**Notes:**

*XC=cross-clamp, SD=standard deviation*

**Figure S15 Routine blood tests: haemoglobin**

****

**Notes:**

*SD=standard deviation*

**Figure S16 Routine blood tests: white blood cells**

****

**Notes:**

*IQR=interquartile range, WBC=white blood cells*

**Figure S17 Routine blood tests: platelets**

****

**Notes:**

*IQR=interquartile range*

**Figure S18 Routine blood tests: neutrophils**

****

**Notes:**

*IQR=interquartile range*

**Figure S19 Routine blood tests: sodium**

****

**Notes:**

*SD=standard deviation*

**Figure S20 Routine blood tests: potassium**

****

**Notes:**

*SD=standard deviation*

**Figure S21 Routine blood tests: calcium**

****

**Notes:**

*SD=standard deviation*

**Figure S22 Routine blood tests: bilirubin**

****

**Notes:**

*IQR=interquartile range*

**Figure S23 Routine blood tests: alkaline phosphate**

****

**Notes:**

*IQR=interquartile range*

**Figure S24 Routine blood tests: total protein**

****

**Notes:**

*SD=standard deviation*

**Figure S25 Routine blood tests: albumin**

****

**Notes:**

*IQR=interquartile range*

**Figure S26 Routine blood tests: prothrombin time**

****

**Notes:**

*IQR=interquartile range*

**Figure S27 Routine blood tests: APTT**

****

**Notes:**

*APTT=activated partial thromboplastin time, IQR=interquartile range*

**Figure S28 NIRS**

****

***Notes:***

*Mixed effects linear models were fitted with time fitted as a continuous variable with random intercepts (patients) and slopes (times), allowing for different trajectories for different patients.*

*NIRS measurements taken at times more than two hours after the start of CPB have been excluded from both the model and graph.*

*The model includes time3 and time-2terms. Both treatment\*time3 and treatment\*time-2 were not statistically significant.*

*MD=mean difference, SD=standard deviation, NIRS=near infra-red spectroscopy*

Table S8 Renal function

|  | **Thermic-1** | | | | **Thermic-2** | | | | **Overall** | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Randomised to normothermic (n=28)** | | **Randomised to hypothermic (n=31)** | | **Randomised to normothermic (n=70)** | | **Randomised to hypothermic (n=71)** | | **Randomised to normothermic (n=98)** | | **Randomised to hypothermic (n=102)** | |
|  | **Med** | **IQR** | **Med** | **IQR** | **Med** | **IQR** | **Med** | **IQR** | **Med** | **IQR** | **Med** | **IQR** |
| **Urea nitrogen (mmol/L)** | |  |  |  |  |  |  |  |  |  |  |  |
| Pre-operative | 4.2 | (3.4, 5.1) | 4.5 | (3.9, 5.3) | 4.5 | (3.5, 5.5) | 4.4 | (3.7, 5.1) | 4.4 | (3.5, 5.4) | 4.4 | (3.7, 5.2) |
| Operation end | 4.5 | (3.7, 5.1) | 4.6 | (3.8, 5.7) | 4.8 | (4.2, 5.5) | 4.7 | (4.1, 5.5) | 4.7 | (3.8, 5.5) | 4.7 | (4.0, 5.6) |
| Day 1 | 5.6 | (5.0, 6.5) | 5.8 | (5.2, 6.8) | 5.4 | (4.7, 6.6) | 5.4 | (4.9, 6.5) | 5.5 | (4.7, 6.6) | 5.6 | (4.9, 6.5) |
| Day 2 | 4.9 | (4.6, 6.5) | 6.4 | (5.2, 7.9) | 4.6 | (3.8, 5.6) | 5.8 | (4.4, 7.3) | 4.8 | (3.9, 5.6) | 5.8 | (4.6, 7.5) |
| Day 3 | 5.3 | (4.9, 6.5) | 5.2 | (4.3, 6.6) | 4.7 | (3.7, 5.8) | 5.4 | (4.3, 7.3) | 4.8 | (3.9, 5.8) | 5.4 | (4.3, 6.9) |
| **Serum creatinine (µmol/L)** | |  |  |  |  |  |  |  |  |  |  |  |
| Pre-operative | 60.0 | (55.5, 69.5) | 58.5 | (49.0, 66.5) | 29.0 | (23.0, 37.0) | 29.0 | (24.0, 40.0) | 34.0 | (25.0, 54.0) | 37.0 | (26.0, 52.0) |
| Operation end | 58.0 | (55.0, 65.0) | 54.5 | (47.5, 64.0) | 32.0 | (24.0, 39.0) | 30.0 | (25.0, 42.0) | 37.0 | (27.0, 55.0) | 38.0 | (26.0, 52.0) |
| Day 1 | 61.0 | (56.0, 68.0) | 59.0 | (53.0, 75.0) | 30.0 | (25.0, 39.0) | 32.5 | (27.0, 41.0) | 35.0 | (27.0, 56.5) | 38.0 | (29.0, 55.0) |
| Day 2 | 60.0 | (54.0, 69.0) | 60.0 | (57.0, 71.0) | 30.0 | (24.0, 37.0) | 32.0 | (28.0, 39.5) | 32.5 | (25.0, 46.0) | 35.0 | (29.0, 50.0) |
| Day 3 | 55.0 | (52.0, 76.0) | 55.5 | (49.0, 65.5) | 29.0 | (24.0, 40.0) | 32.0 | (25.0, 44.0) | 30.0 | (24.0, 42.0) | 38.0 | (27.0, 49.0) |
| **Urinary albumin (mg/L)** | |  |  |  |  |  |  |  |  |  |  |  |
| Pre-operative |  |  |  |  | 17.0 | (6.0, 36.0) | 27.0 | (8.0, 51.0) | 17.0 | (6.0, 36.0) | 27.0 | (8.0, 51.0) |
| XC removal |  |  |  |  | 35.0 | (17.0, 49.0) | 27.0 | (12.0, 56.0) | 35.0 | (17.0, 49.0) | 27.0 | (12.0, 56.0) |
| XC + 4 hours |  |  |  |  | 22.0 | (6.0, 46.0) | 23.5 | (15.0, 41.5) | 22.0 | (6.0, 46.0) | 23.5 | (15.0, 41.5) |
| XC + 24 hours |  |  |  |  | 24.0 | (11.0, 42.0) | 31.0 | (10.5, 82.0) | 24.0 | (11.0, 42.0) | 31.0 | (10.5, 82.0) |
| XC + 48 hours |  |  |  |  | 11.5 | (3.0, 40.0) | 33.0 | (9.0, 87.0) | 11.5 | (3.0, 40.0) | 33.0 | (9.0, 87.0) |
| **Urinary creatinine (mmol/L)** | |  |  |  |  |  |  |  |  |  |  |  |
| Pre-operative |  |  |  |  | 4.5 | (2.7, 6.2) | 6.5 | (3.8, 8.0) | 4.5 | (2.7, 6.2) | 6.5 | (3.8, 8.0) |
| XC removal |  |  |  |  | 2.5 | (1.0, 3.2) | 2.4 | (1.3, 4.8) | 2.5 | (1.0, 3.2) | 2.4 | (1.3, 4.8) |
| XC + 4 hours |  |  |  |  | 2.6 | (1.8, 3.3) | 3.2 | (2.3, 4.8) | 2.6 | (1.8, 3.3) | 3.2 | (2.3, 4.8) |
| XC + 24 hours |  |  |  |  | 1.9 | (1.3, 4.6) | 4.2 | (2.0, 7.3) | 1.9 | (1.3, 4.6) | 4.2 | (2.0, 7.3) |
| XC + 48 hours |  |  |  |  | 2.7 | (0.6, 4.9) | 5.6 | (1.8, 10.8) | 2.7 | (0.6, 4.9) | 5.6 | (1.8, 10.8) |
| **RBP (ng/ml)** |  |  |  |  |  |  |  |  |  |  |  |  |
| Pre-operative |  |  |  |  | 60.2 | (26.9, 99.3) | 72.1 | (41.1, 88.4) | 60.2 | (26.9, 99.3) | 72.1 | (41.1, 88.4) |
| XC removal |  |  |  |  | 120.5 | (97.9, 137.5) | 99.1 | (79.3, 131.9) | 120.5 | (97.9, 137.5) | 99.1 | (79.3, 131.9) |
| XC + 4 hours |  |  |  |  | 90.5 | (35.1, 131.1) | 91.4 | (56.3, 134.4) | 90.5 | (35.1, 131.1) | 91.4 | (56.3, 134.4) |
| XC + 24 hours |  |  |  |  | 18.2 | (3.8, 59.9) | 28.9 | (5.6, 88.2) | 18.2 | (3.8, 59.9) | 28.9 | (5.6, 88.2) |
| XC + 48 hours |  |  |  |  | 33.6 | (12.3, 67.7) | 70.5 | (14.6, 117.8) | 33.6 | (12.3, 67.7) | 70.5 | (14.6, 117.8) |
| **NAG (U/L)** |  |  |  |  |  |  |  |  |  |  |  |  |
| Pre-operative |  |  |  |  | 2.0 | (0.9, 2.8) | 2.0 | (1.1, 4.9) | 2.0 | (0.9, 2.8) | 2.0 | (1.1, 4.9) |
| XC removal |  |  |  |  | 3.2 | (2.7, 7.7) | 2.8 | (1.2, 4.5) | 3.2 | (2.7, 7.7) | 2.8 | (1.2, 4.5) |
| XC + 4 hours |  |  |  |  | 2.8 | (1.4, 10.4) | 3.5 | (2.0, 6.6) | 2.8 | (1.4, 10.4) | 3.5 | (2.0, 6.6) |
| XC + 24 hours |  |  |  |  | 1.4 | (0.6, 4.3) | 3.4 | (0.7, 6.3) | 1.4 | (0.6, 4.3) | 3.4 | (0.7, 6.3) |
| XC + 48 hours |  |  |  |  | 3.9 | (1.5, 6.8) | 3.9 | (1.6, 11.7) | 3.9 | (1.5, 6.8) | 3.9 | (1.6, 11.7) |
| **NGAL (ng/ml)** |  |  |  |  |  |  |  |  |  |  |  |  |
| Pre-operative |  |  |  |  | 3.6 | (1.8, 9.6) | 3.8 | (2.4, 14.4) | 3.6 | (1.8, 9.6) | 3.8 | (2.4, 14.4) |
| XC removal |  |  |  |  | 20.1 | (10.1, 52.8) | 13.5 | (6.1, 34.0) | 20.1 | (10.1, 52.8) | 13.5 | (6.1, 34.0) |
| XC + 4 hours |  |  |  |  | 12.6 | (3.8, 37.3) | 42.3 | (10.7, 99.2) | 12.6 | (3.8, 37.3) | 42.3 | (10.7, 99.2) |
| XC + 24 hours |  |  |  |  | 1.5 | (0.4, 6.9) | 7.8 | (0.8, 22.6) | 1.5 | (0.4, 6.9) | 7.8 | (0.8, 22.6) |
| XC + 48 hours |  |  |  |  | 3.3 | (2.5, 6.9) | 8.1 | (2.7, 13.9) | 3.3 | (2.5, 6.9) | 8.1 | (2.7, 13.9) |

**Notes:**

*XC=cross-clamp, RBP=retinal binding protein, NAG= N-acetyl-β-glucosaminidase, NGAL=neutrophil gelatinase-associated lipocalin*

*For numbers of patients with each urine measurement see* ***Figure 4*** *in the manuscript and* ***Figure S29****.*

Table S9 Renal function: treatment estimates for models with statistically significant treatment by time interactions

|  | **GMR** | **95% CI** |
| --- | --- | --- |
| **Urea nitrogen (mmol/L)** | |  |
| Operation end | 0.99 | 0.93 to 1.05 |
| Day 1 | 0.97 | 0.90 to 1.05 |
| Day 2 | 0.86 | 0.77 to 0.97 |
| Day 3 | 0.92 | 0.80 to 1.04 |
| **Serum creatinine (µmol/L)** | |  |
| Operation end | 1.02 | 0.97 to 1.06 |
| Day 1 | 0.98 | 0.93 to 1.04 |
| Day 2 | 0.93 | 0.86 to 1.01 |
| Day 3 | 0.89 | 0.81 to 0.98 |
| **Urinary albumin (mg/L)** | |  |
| XC removal | 1.47 | 0.84 to 2.57 |
| XC + 4 hours | 0.90 | 0.52 to 1.54 |
| XC + 24 hours | 0.64 | 0.34 to 1.20 |
| XC + 48 hours | 0.32 | 0.14 to 0.74 |
| **NGAL (ng/ml)** |  |  |
| XC removal | 1.49 | 0.70 to 3.20 |
| XC + 4 hours | 0.47 | 0.22 to 1.02 |
| XC + 24 hours | 0.55 | 0.16 to 1.91 |
| XC + 48 hours | 0.57 | 0.19 to 1.71 |

**Notes:**

*XC=cross-clamp, NGAL=neutrophil gelatinase-associated lipocalin, GMR=geometric mean ratio, CI=confidence interval*

Figure S29 Renal Function



***Notes:***

*CI=confidence interval, GMR=geometric mean ratio, XC=cross-clamp RBP=retinal binding protein, MD=mean difference, NAG=N-acetyl-β-glucosaminidase.*

*All estimates are geometric means ± 95% CI*

*Further details are given in* ***supplementary table S8****.*

**Figure S30 Renal function boxplots**

****

***Notes:***

*XC=cross-clamp, NGAL=neutrophil gelatinase-associated lipocalin.*

*Further details are given in* ***supplementary table S8****.*

**Figure S31 Renal function boxplots**

**

***Notes:***

*XC=cross-clamp RBP=retinal binding protein, MD=mean difference, NAG=N-acetyl-β-glucosaminidase.*

*Further details are given in* ***supplementary table S8****.*

Table S10 Cerebral function – GFAP (Thermic 2 only)

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Randomised to**  **normothermic (n=70)** | | **Randomised to**  **hypothermic (n=71)** | | **Overall (n=141)** | |
|  |  | **n** | **%** | **n** | **%** | **n** | **%** |
| Pre-operative | Below the lower limit of detection (≤1.5µg/L) | 33/69 | 47.8% | 23/70 | 32.9% | 56/139 | 40.3% |
|  | If >1.5µg/L, median (IQR) µg/L | 3.2 | (2.2, 10.2) | 3.7 | (1.9, 12.5) | 3.5 | (1.9, 11.3) |
| XC removal | Below the lower limit of detection (≤1.5µg/L) | 29/67 | 43.3% | 26/69 | 37.7% | 55/136 | 40.4% |
|  | If >1.5µg/L, median (IQR) µg/L | 4.1 | (2.8, 9.0) | 4.0 | (2.2, 11.2) | 4.1 | (2.5, 9.3) |
| XC removal + 30 mins | Below the lower limit of detection (≤1.5µg/L) | 29/68 | 42.6% | 29/68 | 42.6% | 58/136 | 42.6% |
| If >1.5µg/L, median (IQR) µg/L | 4.8 | (2.5, 8.6) | 4.2 | (2.7, 16.0) | 4.8 | (2.5, 10.6) |
| XC removal + 2 hours | Below the lower limit of detection (≤1.5µg/L) | 28/65 | 43.1% | 22/66 | 33.3% | 50/131 | 38.2% |
| If >1.5µg/L, median (IQR) µg/L | 3.7 | (2.5, 10.4) | 3.0 | (2.1, 7.5) | 3.1 | (2.1, 9.2) |
| XC removal + 6 hours | Below the lower limit of detection (≤1.5µg/L) | 27/67 | 40.3% | 23/67 | 34.3% | 50/134 | 37.3% |
| If >1.5µg/L, median (IQR) µg/L | 3.5 | (2.1, 9.7) | 4.3 | (2.3, 9.4) | 3.8 | (2.2, 9.7) |
| XC removal + 24 hours | Below the lower limit of detection (≤1.5µg/L) | 20/53 | 37.7% | 28/58 | 48.3% | 48/111 | 43.2% |
| If >1.5µg/L, median (IQR) µg/L | 4.3 | (3.0, 11.5) | 4.0 | (2.3, 14.4) | 4.3 | (2.6, 13.5) |
| XC removal + 48 hours | Below the lower limit of detection (≤1.5µg/L) | 8/16 | 50.0% | 9/16 | 56.3% | 17/32 | 53.1% |
| If >1.5µg/L, median (IQR) µg/L | 2.8 | (2.4, 6.4) | 4.5 | (1.9, 5.3) | 2.9 | (2.1, 5.3) |

**Notes:**

*XC=cross-clamp, GFAP=glial fibrillary acidic protein*

Table S11 NEPSY (Thermic-2 only)

|  |  | **Randomised to normothermic (N=70)** | | | **Randomised to hypothermic (N=71)** | | | **Overall (n=141)** | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **N** | **Median** | **IQR** | **N** | **Median** | **IQR** | **N** | **Median** | **IQR** |
| **Attention and executive functioning** | |  |  |  |  |  |  |  |  |  |
| Auditory attention  (ages 5-16) | 3 months post-op | 7 | 9.0 | (7.0, 12.0) | 13 | 9.0 | (9.0, 10.0) | 20 | 9.0 | (8.0, 10.0) |
| 12 months post-op | 7 | 8.0 | (4.0, 10.0) | 9 | 11.0 | (8.0, 13.0) | 16 | 9.0 | (6.0, 12.5) |
| Responses set  (ages 7-16) | 3 months post-op | 6 | 10.0 | (10.0, 12.0) | 6 | 7.0 | (5.0, 11.0) | 12 | 10.0 | (6.5, 11.5) |
| 12 months post-op | 5 | 8.0 | (7.0, 10.0) | 5 | 8.0 | (7.0, 9.0) | 10 | 8.0 | (7.0, 10.0) |
| Inhibition  (ages 5-16) | 3 months post-op | 7 | 12.0 | (9.0, 14.0) | 15 | 10.0 | (6.0, 14.0) | 22 | 11.0 | (8.0, 14.0) |
| 12 months post-op | 7 | 13.0 | (11.0, 16.0) | 14 | 12.5 | (11.0, 18.0) | 21 | 13.0 | (11.0, 16.0) |
| Statue  (ages 3-6) | 3 months post-op | 8 | 11.5 | (10.5, 12.0) | 12 | 10.5 | (10.0, 11.0) | 20 | 11.0 | (10.0, 12.0) |
| 12 months post-op | 5 | 10.0 | (9.0, 12.0) | 8 | 11.5 | (8.0, 12.0) | 13 | 11.0 | (9.0, 12.0) |
| **Language** |  |  |  |  |  |  |  |  |  |  |
| Body part naming  (ages 3-4) | 3 months post-op | 7 | 11.0 | (9.0, 12.0) | 7 | 9.0 | (8.0, 12.0) | 14 | 10.5 | (9.0, 12.0) |
| 12 months post-op | 4 | 6.5 | (6.0, 7.5) | 5 | 9.0 | (8.0, 10.0) | 9 | 8.0 | (7.0, 9.0) |
| Comprehension of instructions (ages 3-16) | 3 months post-op | 15 | 9.0 | (9.0, 13.0) | 22 | 10.0 | (7.0, 12.0) | 37 | 10.0 | (8.0, 12.0) |
| 12 months post-op | 11 | 10.0 | (7.0, 13.0) | 20 | 9.5 | (7.5, 12.0) | 31 | 10.0 | (7.0, 13.0) |
| Phonological processing  (ages 3-16) | 3 months post-op | 13 | 13.0 | (12.0, 14.0) | 21 | 10.0 | (7.0, 12.0) | 34 | 12.0 | (8.0, 13.0) |
| 12 months post-op | 11 | 13.0 | (11.0, 15.0) | 19 | 10.0 | (9.0, 13.0) | 30 | 11.5 | (10.0, 14.0) |
| **Memory and learning** |  |  |  |  |  |  |  |  |  |  |
| Memory for faces  (ages 5-16) | 3 months post-op | 8 | 10.0 | (9.5, 11.0) | 15 | 10.0 | (9.0, 12.0) | 23 | 10.0 | (9.0, 11.0) |
| 12 months post-op | 7 | 12.0 | (8.0, 14.0) | 15 | 11.0 | (9.0, 15.0) | 22 | 11.5 | (8.0, 14.0) |
| Narrative memory  (ages 3-16) | 3 months post-op | 13 | 10.0 | (7.0, 11.0) | 21 | 8.0 | (6.0, 13.0) | 34 | 9.0 | (6.0, 12.0) |
| 12 months post-op | 11 | 12.0 | (8.0, 13.0) | 19 | 9.0 | (7.0, 12.0) | 30 | 10.5 | (8.0, 13.0) |
| Sentence repetition  (ages 3-6) | 3 months post-op | 8 | 7.5 | (6.5, 9.5) | 14 | 11.0 | (7.0, 11.0) | 22 | 9.0 | (7.0, 11.0) |
| 12 months post-op | 6 | 7.5 | (7.0, 8.0) | 9 | 9.0 | (8.0, 11.0) | 15 | 8.0 | (7.0, 11.0) |
| **Sensorimotor** |  |  |  |  |  |  |  |  |  |  |
| Finger tapping - dominant hand repetition (ages 5-16) | 3 months post-op | 8 | 9.5 | (8.5, 11.0) | 15 | 8.0 | (7.0, 10.0) | 23 | 9.0 | (7.0, 10.0) |
| 12 months post-op | 7 | 10.0 | (7.0, 10.0) | 15 | 8.0 | (6.0, 10.0) | 22 | 8.5 | (7.0, 10.0) |
| Finger tapping - dominant hand sequences (ages 5-16) | 3 months post-op | 8 | 11.0 | (10.0, 12.0) | 15 | 10.0 | (9.0, 10.0) | 23 | 10.0 | (9.0, 12.0) |
| 12 months post-op | 7 | 12.0 | (11.0, 14.0) | 14 | 9.5 | (9.0, 12.0) | 21 | 10.0 | (9.0, 12.0) |
| Imitating hand positions  (ages 3-12) | 3 months post-op | 14 | 10.5 | (8.0, 13.0) | 20 | 11.0 | (9.0, 12.5) | 34 | 11.0 | (9.0, 13.0) |
| 12 months post-op | 10 | 10.5 | (9.0, 14.0) | 18 | 11.0 | (8.0, 12.0) | 28 | 11.0 | (8.5, 12.0) |
| **Social perception** |  |  |  |  |  |  |  |  |  |  |
| Affect recognition  (ages 3-16) | 3 months post-op | 15 | 10.0 | (8.0, 13.0) | 22 | 10.0 | (8.0, 10.0) | 37 | 10.0 | (8.0, 11.0) |
| 12 months post-op | 11 | 10.0 | (8.0, 12.0) | 20 | 10.5 | (8.0, 11.0) | 31 | 10.0 | (8.0, 11.0) |
| **Visuospatial processing** |  |  |  |  |  |  |  |  |  |  |
| Block construction  (ages 3-16) | 3 months post-op | 15 | 11.0 | (7.0, 14.0) | 22 | 11.0 | (7.0, 12.0) | 37 | 11.0 | (7.0, 12.0) |
| 12 months post-op | 11 | 11.0 | (8.0, 14.0) | 20 | 9.0 | (7.0, 12.5) | 31 | 10.0 | (7.0, 14.0) |

**Notes:**

*NEPSY=NEPSY second edition psychometric tool*

**Table S12 Sensitivity analysis: re-analysing inotropic support using only dopamine**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Thermic-1** | | | | **Thermic-2** | | | | **Overall** | | | |  |  |
|  | **Randomised to normothermic (n=28)** | | **Randomised to hypothermic (n=31)** | | **Randomised to normothermic (n=70)** | | **Randomised to hypothermic (n=71)** | | **Randomised to normothermic (n=98)** | | **Randomised to hypothermic (n=102)** | | **HR (95% CI)** | **p-value** |
|  | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** |  |  | **n** | **%** |  |  |
| Dopamine | 17/28 | 61% | 24/31 | 77% | 65/70 | 93% | 66/71 | 93% | 82/98 | 84% | 90/102 | 88% |  |  |
| If YES, duration – median (IQR) hours | 19.0 | (12.0, 22.0) | 20.0 | (11.0, 24.0) | 16.0 | (5.0, 23.0) | 13.0 | (5.0, 26.0) | 17.0 | (6.0, 23.0) | 15.0 | (6.0, 24.0) | 1.01 (0.75, 1.37) | 0.93 |
| If YES, total dose – median (IQR) ml | 15 | (10.0, 20.5) | 18 | (11.8, 38.3) | 5 | (5.0, 5.0) | 5 | (5.0, 5.0) | 5 | (5.0, 10.0) | 5 | (5.0, 10.0) |  |  |

***Notes:***

*Dopamine was the only inotrope collected in Thermic-1*

*HR=hazard ratio, CI=confidence interval*

**Figure S32 Kaplan-Meier curve for duration of dopamine support**



Table S13 Sensitivity analyses: excluding patients with protocol deviations from the primary outcome analyses

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Randomised to normothermic (N=98)** | | **Randomised to hypothermic (N=102)** | | **HR (95% CI)** | **p-value** |
|  | **Med** | **IQR** | **Med** | **IQR** |  |  |
| **All protocol deviations** | **n=87** | | **n=79** | |  |  |
| Duration of inotropic support (hours) | 20.0 | (15.0, 39.0) | 21.0 | (15.0, 44.0) | 1.00 (0.69, 1.44) | 0.98 |
| Intubation time (hours) | 10.0 | (5.6, 25.3) | 17.1 | (7.0, 26.8) | 1.12 (0.83, 1.53) | 0.45 |
| Length of stay (days) | 5.0 | (5.0, 7.0) | 6.0 | (5.0, 7.0) | 1.04 (0.76, 1.42) | 0.80 |
| **Major protocol deviations1** | **n=96** | | **n=94** | |  |  |
| Duration of inotropic support (hours) | 21.0 | (15.0, 39.0) | 21.0 | (16.0, 44.0) | 1.03 (0.73, 1.46) | 0.87 |
| Intubation time (hours) | 10.6 | (5.9, 25.3) | 17.2 | (6.8, 26.8) | 1.16 (0.87, 1.55) | 0.30 |
| Length of stay (days) | 6.0 | (5.0, 7.0) | 6.0 | (5.0, 8.0) | 1.11 (0.83, 1.48) | 0.50 |

*Notes:*

*1 A major protocol deviation is defined as either: patient in the normothermic group with surgery performed at <31°C, or patient in the hypothermic group with surgery performed at ≥34°C.*

*HR=hazard ratio, CI=confidence interval*

**Figure S33 Subgroup analyses: primary and secondary outcomes by trial phase**

|  |  |
| --- | --- |
| 1. **Primary outcomes and clinical secondary outcomes** | 1. **Renal function** |

*Notes:*

*HR=hazard ratio, CI=confidence interval, OR=odds ratio, GMR=geometric mean ratio*

**Table S14 Instrumental variable estimates**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | **Instrumental variable models** | | **Corresponding ITT models1** | |
|  | **N** | **GMR (95% CI)** | **p-value** | **GMR (95% CI)** | **p-value** |
| Inotrope duration2 | 140 | 1.01 (0.95, 1.07) | 0.82 | 1.01 (0.76, 1.34) | 0.93 |
| Intubation time3 | 182 | 0.95 (0.89, 1.02) | 0.17 | 0.80 (0.60, 1.07) | 0.14 |
| Length of stay4 | 181 | 1.00 (0.97, 1.03) | 0.89 | 0.99 (0.87, 1.12) | 0.85 |

***Notes:***

*1 These models are linear regressions (on the log scale) of group on outcome (i.e. ignoring censoring), with the hypothermic group as the reference group. These are comparable models to the IV models*

*2 Outcome only collected for Thermic-2, and one outlier excluded*

*3 Temperature missing for 17 Thermic-1 patients, and one outlier excluded*

*4 Temperature missing for 17 Thermic-1 patients, and two outliers excluded*

*ITT=intention-to-treat, GMR=geometric mean ratio, IV= Instrumental variable*

**Table S15 Expected and unexpected adverse events and serious adverse events both in-hospital and during trial follow-up (Thermic 2 only)**

|  |  | **Randomised to normothermic (N=70)** | | | | **Randomised to hypothermic (N=71)** | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **AEs** | | **SAEs** | | **AEs** | | **SAEs** | |
|  |  | **Events/ Patients** | **%** | **Events/ Patients** | **%** | **Events/ Patients** | **%** | **Events/ Patients** | **%** |
| **ANY EVENT** | |  |  | **66/27** | **39%** |  |  | **61/29** | **41%** |
| **Any expected event** | | **56/25** | **36%** | **34/19** | **28%** | **53/29** | **41%** | **30/21** | **30%** |
| Suspected MI | | 1/1 | 1% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
| Cardiac arrest | | 1/1 | 1% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
| Arrhythmias |  | 11/8 | 11% | 1/1 | 1% | 16/10 | 14% | 4/3 | 4% |
|  | SVT/AF requiring treatment | 1/1 | 1% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
|  | VF/VT requiring treatment | 1/1 | 1% | 1/1 | 1% | 0/0 | 0% | 0/0 | 0% |
|  | Heart block | 4/4 | 6% | 0/0 | 0% | 3/3 | 4% | 1/1 | 1% |
|  | JET | 0/0 | 0% | 0/0 | 0% | 4/4 | 6% | 0/0 | 0% |
|  | New pacing | 5/5 | 7% | 0/0 | 0% | 9/9 | 13% | 3/3 | 4% |
| Haemodynamic support | | 4/2 | 3% | 3/1 | 1% | 0/0 | 0% | 0/0 | 0% |
|  | LVAD | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
|  | ECMO | 1/1 | 1% | 1/1 | 1% | 0/0 | 0% | 0/0 | 0% |
|  | Vasodilator used | 2/2 | 3% | 1/1 | 1% | 0/0 | 0% | 0/0 | 0% |
|  | Low cardiac output | 1/1 | 1% | 1/1 | 1% | 0/0 | 0% | 0/0 | 0% |
| Pericardial effusion | | 3/3 | 4% | 1/1 | 1% | 10/10 | 14% | 3/3 | 4% |
| Pulmonary complications | | 6/4 | 6% | 1/1 | 1% | 8/8 | 11% | 6/6 | 8% |
|  | Bronchomalacia | 0/0 | 0% | 0/0 | 0% | 1/1 | 1% | 1/1 | 1% |
|  | Tracheostomy | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
|  | Mask CPAP | 1/1 | 1% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
|  | ARDS | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
|  | Pneumothorax/effusion requiring drainage | 4/4 | 6% | 0/0 | 0% | 2/2 | 3% | 1/1 | 1% |
|  | Chylothorax | 0/0 | 0% | 0/0 | 0% | 1/1 | 1% | 0/0 | 0% |
|  | Re-intubation | 1/1 | 1% | 1/1 | 1% | 4/4 | 6% | 4/4 | 6% |
| Haemofiltration/dialysis | | 1/1 | 1% | 0/0 | 0% | 1/1 | 1% | 0/0 | 0% |
| GI complications | | 1/1 | 1% | 1/1 | 1% | 1/1 | 1% | 1/1 | 1% |
|  | Peptic ulcer/GI bleed/perforation | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
|  | Pancreatitis | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
|  | Necrotising enterocolitis | 0/0 | 0% | 0/0 | 0% | 1/1 | 1% | 1/1 | 1% |
|  | Other GI | 1/1 | 1% | 1/1 | 1% | 0/0 | 0% | 0/0 | 0% |
| Neurological complications | | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
|  | Permanent stroke | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
|  | TIA | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
|  | Paraplegia | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
|  | Phrenic nerve palsy | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
|  | Recurrent laryngeal nerve palsy | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
| Pulmonary embolus | | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
| Infective complications | | 24/17 | 25% | 24/17 | 25% | 15/14 | 20% | 15/14 | 20% |
|  | Mediastinitis | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
|  | Sepsis | 24/17 | 25% | 24/17 | 25% | 15/14 | 20% | 15/14 | 20% |
| Re-operation |  | 3/3 | 4% | 3/3 | 4% | 1/1 | 1% | 1/1 | 1% |
| Wound dehiscence requiring treatment | | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
| Excess bleeding | | 0/0 | 0% | 0/0 | 0% | 1/1 | 1% | 0/0 | 0% |
| Residual anatomical abnormalities | | 1/1 | 1% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
| Death |  | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% | 0/0 | 0% |
| **Any unexpected event** | |  |  | **32/17** | **24%** |  |  | **31/17** | **24%** |
| Abdominal pain | |  |  | 1/1 | 1% |  |  | 0/0 | 0% |
| Accidental overdose | |  |  | 1/1 | 1% |  |  | 0/0 | 0% |
| Barium swallow | |  |  | 1/1 | 1% |  |  | 0/0 | 0% |
| Bladder catheterisation | |  |  | 0/0 | 0% |  |  | 1/1 | 1% |
| Bronchiolitis | |  |  | 1/1 | 1% |  |  | 2/2 | 3% |
| Cardiac arrest | |  |  | 1/1 | 1% |  |  | 0/0 | 0% |
| Cardiac pacemaker adjustment | |  |  | 0/0 | 0% |  |  | 1/1 | 1% |
| Catheterisation cardiac | |  |  | 0/0 | 0% |  |  | 1/1 | 1% |
| Continuous positive airway pressure | |  |  | 0/0 | 0% |  |  | 1/1 | 1% |
| Coronary artery bypass | |  |  | 1/1 | 1% |  |  | 0/0 | 0% |
| Cough |  |  |  | 0/0 | 0% |  |  | 3/1 | 1% |
| Craniocerebral injury | |  |  | 0/0 | 0% |  |  | 1/1 | 1% |
| Diabetes mellitus | |  |  | 1/1 | 1% |  |  | 0/0 | 0% |
| Dyspnoea |  |  |  | 0/0 | 0% |  |  | 2/2 | 3% |
| Embolism |  |  |  | 1/1 | 1% |  |  | 0/0 | 0% |
| Endocarditis |  |  |  | 1/1 | 1% |  |  | 0/0 | 0% |
| Failure to thrive | |  |  | 1/1 | 1% |  |  | 0/0 | 0% |
| Gastroenteritis Escherichia coli | |  |  | 1/1 | 1% |  |  | 0/0 | 0% |
| Gastroenteritis rotavirus | |  |  | 1/1 | 1% |  |  | 1/1 | 1% |
| Gastroenteritis viral | |  |  | 0/0 | 0% |  |  | 1/1 | 1% |
| Gastrointestinal surgery | |  |  | 0/0 | 0% |  |  | 1/1 | 1% |
| Gastrostomy tube site complication | |  |  | 1/1 | 1% |  |  | 0/0 | 0% |
| Hyperbaric oxygen therapy | |  |  | 0/0 | 0% |  |  | 1/1 | 1% |
| Hyperglycaemia | |  |  | 1/1 | 1% |  |  | 0/0 | 0% |
| Incisional hernia | |  |  | 0/0 | 0% |  |  | 1/1 | 1% |
| Influenza |  |  |  | 0/0 | 0% |  |  | 1/1 | 1% |
| International normalised ratio decrease | |  |  | 1/1 | 1% |  |  | 0/0 | 0% |
| International normalised ratio increase | |  |  | 1/1 | 1% |  |  | 0/0 | 0% |
| Lower respiratory tract infection | |  |  | 2/2 | 3% |  |  | 0/0 | 0% |
| Myalgia |  |  |  | 1/1 | 1% |  |  | 0/0 | 0% |
| Pneumothorax | |  |  | 0/0 | 0% |  |  | 1/1 | 1% |
| Pyrexia |  |  |  | 1/1 | 1% |  |  | 2/2 | 3% |
| Respiratory syncytial virus bronchiolitis | |  |  | 0/0 | 0% |  |  | 1/1 | 1% |
| Staphylococcal infection | |  |  | 1/1 | 1% |  |  | 0/0 | 0% |
| Stridor |  |  |  | 1/1 | 1% |  |  | 0/0 | 0% |
| Thermal burn |  |  |  | 0/0 | 0% |  |  | 1/1 | 1% |
| Tracheomalacia | |  |  | 0/0 | 0% |  |  | 1/1 | 1% |
| Upper respiratory tract infection | |  |  | 0/0 | 0% |  |  | 2/2 | 3% |
| Ventricular septal defect repair | |  |  | 1/1 | 1% |  |  | 0/0 | 0% |
| Ventricular tachycardia | |  |  | 2/2 | 3% |  |  | 0/0 | 0% |
| Viral infection | |  |  | 3/3 | 4% |  |  | 4/4 | 6% |
| Vomiting |  |  |  | 3/3 | 4% |  |  | 1/1 | 1% |
| pH body fluid |  |  |  | 1/1 | 1% |  |  | 0/0 | 0% |

***Notes:***

*AE=adverse event, SAE=serious adverse event, MI=myocardial infarction, SVT= supraventricular tachycardia, AF=atrial fibrillation, VF=ventricular fibrillation, VT=ventricular tachycardia, JET=junctional ectopic tachycardia, LVAD= left ventricular assist device, ECMO= extracorporeal membrane oxygenation, CPAP=continuous positive airway pressure, ARDS= acute respiratory distress syndrome, GI=gastrointestinal, TIA= transient ischemic attack*