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## Supplementary data

### Statistical Methods—Further Details

When analyzing myocardial troponin T (cTnT) release, the baseline and posttreatment values were modelled jointly to avoid having to exclude or impute cases with missing baseline measures. Similarly, when analysing measures of ischaemic stress assessed in the myocardial biopsies, the measurement taken 5 minutes following CPB institution (control biopsy) was modelled jointly with the reperfusion biopsy taken 10 minutes after releasing the cross clamp. When analysing intubation time, and length of stay outcomes, any patient who died prior to the event was treated as a censored observation.

**Table E1 Protocol deviations**

	Randomised to Conventional group (n=84)		Randomised to Hybrid group (n=81)		Overall (n=165)	
	n	%	n	%	n	%
	Any protocol deviations	8	9.5%	2	2.5%	10
Randomised but not treated	4	4.8%	1	1.2%	5	3.0%
	Treated in Conventional group (n=80)		Treated in Hybrid group (n=80)		Overall (n=160)	
	n	%	n	%	n	%
	Did not meet eligibility criteria	1	1.3%	0	0.0%	1
Did not receive allocated treatment	0	0.0%	1	1.3%	1	0.6%
Only received CABG	3	3.8%	0	0.0%	3	1.9%
Only received valve	0	0.0%	0	0.0%	0	0.0%

**Table E2 Details of protocol deviations where available**

<b>Allocation</b>	<b>Centre</b>	<b>Further details</b>
<i>Randomised but not treated</i>		
Conventional	A	Patient had porcelain aorta, operation did not proceed
Conventional	B	Patient consented and withdrew prior to surgery
Conventional	B	Only received AVR only
Conventional	B	Patient withdrew consent so data not collected
Hybrid	C	During Pre-operative period Pulmonary Artery pressure was found to be higher than systemic pressure, with Right Ventricular pressure being 110mmHg. In view of these findings surgery was not carried out given the extremely high risk associated with this condition.
<i>Did not meet eligibility criteria</i>		
Conventional	B	Creatinine level was 176 µm/l
<i>Did not receive allocated treatment</i>		
Hybrid	A	The patient had conventional surgery as the surgeon was not comfortable with the available cardiac stabiliser
<i>Only received CABG</i>		
Conventional	A	Reason was not given on study case report form
Conventional	A	Porcelain aorta.
Conventional	A	Intra-operative echocardiogram showing only mild valvular disease.

**Table E3 Withdrawals**

		Randomised to Conventional surgery (n=84)		Randomised to Hybrid surgery (n=81)		Overall (n=165)	
		n	%	n	%	n	%
Any withdrawal		4	5%	1	1%	5	3%
<i>Time of</i>	Pre-op	2		1		3	
<i>withdrawal</i>	Intra-op	2		0		2	
<i>Decision taken by</i>	Patient	2		0		2	
	Clinician	2		1		3	
<i>Reason for</i>	Surgery not needed	0		1		1	
<i>withdrawal</i>	Operation aborted	1		0		1	
	Only CABG needed	1		0		1	
	Reason unknown	2		0		2	

**Table E4 Intra-operative characteristics, additional information**

	Conventional		Hybrid		Overall	
	(n=80)		(n=80)		(n=160)	
	n	%	n	%	n	%
<b>Operation time (mins) (Median, IQR)</b>	<b>288</b>	<b>(220, 403)</b>	<b>300</b>	<b>(245, 405)</b>	<b>297</b>	<b>(230, 403)</b>
Lowest HCT (Mean, SD)	23.5	4.12	22.4	3.77	23.0	3.97
Lowest temperature (°C) (Median, IQR)	30.0 (28.0, 32.0)		30.2 (28.0, 32.0)		30.0 (28.0, 32.0)	
No sinus rhythm on cross clamp removal	36	46.3%	21	26.5%	57	35.6%
<i>AV Block</i>	19	24.4%	14	17.6%	33	20.8%
<i>Atrial fibrillation</i>	8	10.3%	3	3.8%	11	7.0%
<i>Ventricular fibrillation</i>	7	9.0%	3	3.8%	10	6.3%
<i>Junctional rhythm</i>	2	2.6%	1	1.3%	3	1.9%
DC Cardioversion	16	20.0%	10	12.5%	26	16.3%
Intra-operative IABP	5	7.1%	4	5.4%	9	6.3%
Duration (hrs) (Median, IQR)	3.0 (3.0, 5.0)		19.8 (2.8, 65.5)		3.5 (3.0, 36.0)	
Intra-operative transfusion requirements <sup>1</sup>						
RBC (Products, Patients)	109	42	119	46	228	88
FFP (Products, Patients)	16	7	25	12	41	19
Platelets (Products, Patients)	59	22	81	30	140	52

<sup>1</sup> Data on all transfusions given, either intraoperatively or postoperatively, are reported in Table E5. *HCT* haematocrit; *IQR* inter-quartile range; *AV* Atrio-ventricular; *DC* Direct Current; *RBC* Red Blood Cells; *FFP* Fresh Frozen Plasma; *IABP* intra-aortic balloon pump; *IQR* interquartile range; *GTN* glyceryl trinitrate; *SNP* sodium nitroprusside. Missing data (conventional, hybrid): Lowest HCT, Lowest core temperature, Rhythm on clamp removal: 2 (2, 0).

**Table E5 secondary outcomes**

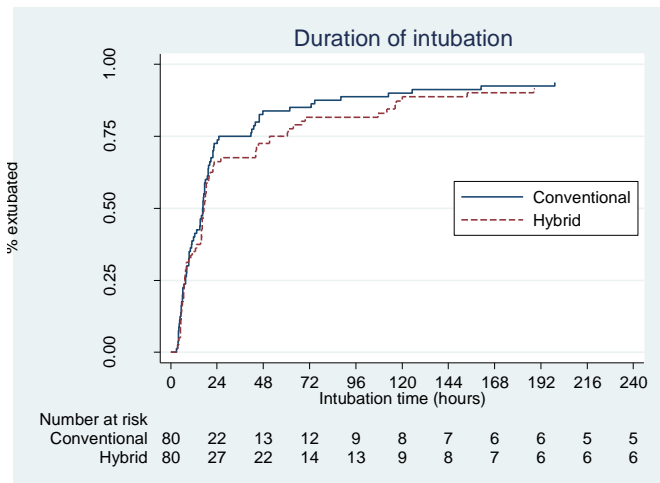
	Conventional		Hybrid		OR/HR	P-value
	1 (n=80)		(n=80)		GMR	
	n	%	n	%	(95% CI)	
<b>INTRA-OP OUTCOMES</b>						
<i>Duration of CPB (mins) (Median, IQR)</i>	142	(105, 195)	153	(115, 233)	GMR=1.07 (0.98, 1.16)	0.120
<i>Duration of CA (mins) (Median, IQR)</i>	98	(79, 135)	89	(63, 118)	GMR=0.84 (0.77, 0.93)	0.0004
<b>INTRA-OP/POST-OP TRANSFUSION</b>						
Any transfusion requirement	66	82.5%	65	82.3%	OR= 0.87 (0.35, 2.18)	0.773
<i>Red blood cells (units, patients)</i>	222	65	249	62		
<i>Fresh frozen plasma (units, patients)</i>	72	17	80	23		
<i>Platelets (units, patients)</i>	120	28	143	33		
<i>Cryoprecipitate (units, patients)</i>	4	2	10	3		
<b>POST-OP COMPLICATIONS</b>						
Any subsystem organ complication	44	55.0%	51	63.8%	OR= 1.49 (0.72, 3.08)	0.279
<i>Cardiovascular</i>	39	48.8%	39	48.8%		
<i>Pulmonary</i>	9	11.3%	10	12.5%		
<i>Infective</i>	13	16.3%	14	17.5%		
<i>Renal</i>	5	6.3%	6	7.5%		
<i>Gastrointestinal</i>	2	2.5%	5	6.3%		
<i>Neurological</i>	2	2.5%	8	10.0%		

	Conventional		Hybrid		OR/HR	
	l (n=80)		(n=80)		GMR	P-value
	n	%	n	%	(95% CI)	
Low cardiac output <sup>1</sup>	29	36.3%	26	32.5%	OR= 0.84 (0.39, 1.79)	0.649
Blood loss (12 hours post-op; ml) (Median, IQR)	363	(228, 615)	400	(245, 600)	GMR= 0.96 (0.78, 1.18)	0.696
Extubation time (hours) (Median, IQR) <sup>2</sup>	16.5	(7.6, 24.9)	17.1	(7.1, 51.3)	HR=0.93 (0.68, 1.29)	0.668
ICU stay (hours) (Median, IQR) <sup>3</sup>	51.3	(22.7, 121.0)	67.5	(23.5, 122.2)	HR=0.93 (0.66,1.30)	0.667
Hospital stay (days) (Median, IQR)	10.0	(7.0, 14.0)	9.0	(8.0, 13.0)	HR=0.97 (0.69, 1.35)	0.852

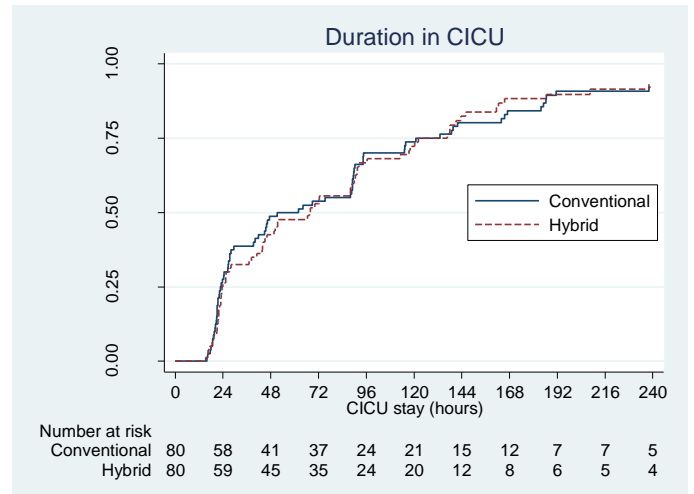
<sup>1</sup> Defined as adrenaline, dopamine, dobutamine or enoximone (at a dose of  $\geq 5\mu\text{g}/\text{kg}/\text{min}$ ) or IABP given consecutively to patient for 3 hours or more; <sup>2</sup>Includes any re-intubation (number of re-intubations in conventional group=7, in hybrid group=8); <sup>3</sup> Includes any readmission (number of readmissions in conventional group=1, in hybrid group=0); ICU= intensive care unit; IABP= intra-aortic balloon pump. Missing data (conventional, hybrid): Duration of cardiopulmonary bypass, Duration of aortic cross clamp: 2 (2, 0). Transfusion requirements: 1 (0, 1).

**Figure E1 Intubation time (A), intensive care (B) and hospital stay (C) by group**

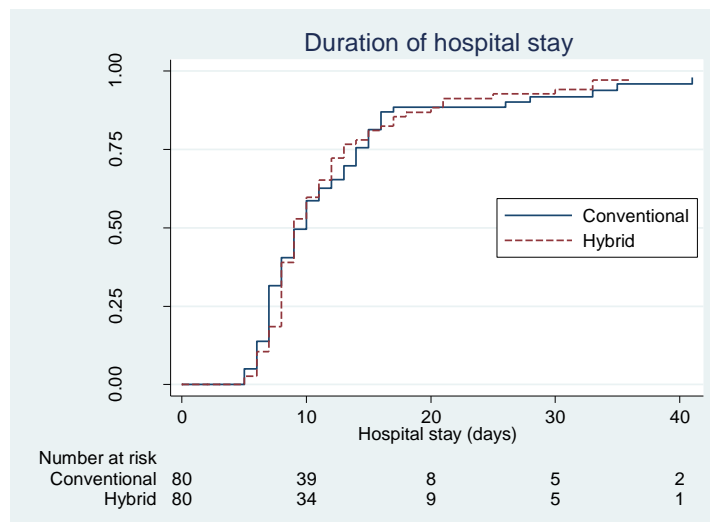
**(A) Intubation time**



**(B) Stay in cardiac intensive care**



**(B) Stay in hospital**





**Table E6 In-hospital adverse events**

	Randomised to			Randomised to			Overall		
	Conventional surgery			Hybrid surgery					
	(n=80)			(n=80)			(n=160)		
	Events	Patients	% <sup>1</sup>	Events	Patients	% <sup>1</sup>	Events	Patients	% <sup>1</sup>
<b>CARDIAC COMPLICATIONS</b>	49	39	49%	43	39	49%	92	78	49%
Post-operative MI	1	1	1%	0	0	0%	1	1	1%
Any arrhythmias	42	37	46%	36	36	45%	78	73	46%
<i>SVT/AF</i>	39	37	46%	35	35	44%	74	72	45%
<i>VF/VT</i>	3	3	4%	0	0	0%	3	3	2%
<i>Other</i>	0	0	0%	1	1	1%	1	1	1%
<b>PULMONARY COMPLICATIONS</b>	15	9	11%	14	10	13%	29	19	12%
Re-intubation	4	4	5%	6	6	8%	10	10	6%
Tracheostomy	4	4	5%	3	3	4%	7	7	4%
Mask CPAP	6	6	8%	5	5	6%	11	11	7%
ARDS	1	1	1%	0	0	0%	1	1	1%
<b>INFECTIVE COMPLICATIONS</b>	16	13	16%	19	14	18%	35	27	17%
Septicaemia	2	2	3%	2	2	3%	4	4	3%
Chest infection	11	10	13%	14	14	18%	25	24	15%
Sternotomy infection	3	3	4%	3	1	1%	6	4	3%
<b>RENAL COMPLICATIONS</b>	5	5	6%	7	6	8%	12	11	7%
Need for haemofiltration/dialysis	5	5	6%	7	6	8%	12	11	7%
<b>GI COMPLICATIONS</b>	2	2	3%	6	5	6%	8	7	4%
Peptic ulcer/ GI bleed/ Perforation	1	1	1%	3	3	4%	4	4	3%
Other GI (e.g. bowel obstruction)	1	1	1%	3	3	4%	4	4	3%
<b>CEREBRAL COMPLICATIONS</b>	2	2	3%	9	8	10%	11	10	6%
Stroke	1	1	1%	2	2	3%	3	3	2%
Transient Ischaemic Attack	0	0	0%	2	2	3%	2	2	1%
Coma or confusion state	2	2	3%	5	4	5%	7	6	4%
<b>OTHER ADVERSE EVENT<sup>2</sup></b>	5	3	4%	3	3	4%	8	6	4%

<sup>1</sup> Percentage of patients; <sup>2</sup> One patient in the conventional group had a pleural effusion drained associated with surgical rewiring, 1 patient developed a left lung consolidation and an episode of ileus, and 1 had sternal oozing, and cellulitis in both legs. In the hybrid group 1

patient suffered a grand mal seizure, 1 had a convulsion, and 1 patient had haemodynamic instability.

Note. There was one patient who crossed over from hybrid to conventional surgery. This patient experienced a stroke as adverse event.

*MI* myocardial infarction; *SVT* supraventricular tachycardia; *AF* atrial fibrillation; *VT* ventricular tachycardia; *VF* ventricular fibrillation; *CPAP* continuous positive airway pressure; *ARDS* Acute respiratory distress syndrome; *GI* gastrointestinal. Missing data (conventional, hybrid): Post-operative MI: 2 (1, 1).

**Table E7 Other Post-operative characteristics**

	Conventional group		Hybrid group		Overall (n=160)	
	(n=80)		(n=80)			
	n	%	n	%	n	%
Post-operative IABP	5	6.3%	6	7.5%	11	6.9%
Duration (hours) (Median, IQR)	60.0	(43.0, 157.0)	40.5	(23.0, 61.0)	57.0	(23.0, 67.0)
Post-operative transfusion (first 24 hours)						
Red blood cells (products, patients)	99	50	123	53	222	103
Fresh frozen plasma (products, patients)	31	11	33	15	64	26
Platelets (products, patients)	18	9	42	19	60	28
Cryoprecipitate (products, patients)	2	1	2	1	4	2
Chest reopened	14	17.5%	9	11.3%	23	14.4%
<i>Bleeding</i>	<i>10</i>		<i>6</i>		<i>16</i>	
<i>Low cardiac output</i>	<i>4</i>		<i>2</i>		<i>6</i>	
<i>Mediastinitis/rewiring</i>	<i>0</i>		<i>1</i>		<i>1</i>	

*HDU* high dependency unit, *IQR* interquartile range, *IABP* intra-aortic balloon pump, *GTN* glyceryl trinitrate, *SNP* sodium nitroprusside

**Table E8 Troponin**

	Randomised to		Randomised to		GMR (95% CI)	P-value
	Conventional surgery (n=67)		Hybrid surgery (n=71)			
	Median	IQR	Median	IQR		
Pre-op	13.9	(10.4, 26.9)	14.4	(10.3, 27.0)		
1 hour post-op	614.6	(421, 1130)	756.7	(433, 1360)		
4 hour post-op	861.1	(518, 1425)	847.7	(498, 1422)		
12 hour post-op	652.8	(403, 1029)	778.3	(408, 1209)		
24 hour post-op	554.9	(370, 995)	666.0	(382, 1116)		
48 hour post-op	471.3	(303, 714)	430.1	(298, 746)		
72 hour post-op	411.4	(286, 613)	356.7	(253, 555)		
Test for treatment*time interaction						0.183
Overall estimate of treatment effect					1.04 (0.87, 1.24)	0.675

Data available for 138 patients, though not all patients have data at all time points.

*Pre-op* pre-operative; *post-op* post-operative; *IQR* interquartile range; *GMR* geometric mean ratio; *CI* confidence interval; *UK* United Kingdom; *CABG* coronary artery bypass graft

Missing data at each time point (conventional, hybrid); pre-op (0, 1) 1 hour (0, 1), 4 hours (0, 2), 12 hours (2, 1), 24 hours (0, 0), 48 hours (0, 3), 72 hours (4,6)

**Table E9 Reperfusion Biopsies**

	Randomised to		Randomised to		MD/GMR (95% CI)	P-value
	Conventional surgery (n=19)		Hybrid surgery (n=17)			
	Median	IQR	Median	IQR		
ATP	2.35	(1.65, 3.77)	2.73	(1.60, 3.35)	MD= -0.21 (-0.94, 0.52)	0.570
ADP	2.06	(1.47, 2.44)	1.73	(1.00, 2.35)	GMR= 0.81 (0.63, 1.05)	0.099
AMP	0.94	(0.40, 1.04)	0.70	(0.41, 0.97)	GMR= 0.72 (0.51, 1.02)	0.056
ATP/ADP	1.35	(1.06, 1.58)	1.51	(1.22, 1.81)	MD= 0.03 (-0.28, 0.34)	0.827
ATP/AMP	3.13	(2.26, 4.20)	4.17	(2.98, 5.45)	MD= 0.73 (-0.45, 1.91)	0.206
Lactate	5.53	(4.08, 8.70)	4.63	(2.88, 8.72)	GMR= 0.82 (0.58, 1.16)	0.237

Three patients (2 conventional, 1 hybrid) are omitted from the table due to missing/inaccurate reperfusion biopsies. However, they still contributed to the analyses as they had a successful control (baseline) biopsy taken.

*ATP* adenosine triphosphate; *ADP* adenosine diphosphate; *AMP* adenosine monophosphate; *IQR* interquartile range; *GMR* geometric mean ratio; *MD* mean difference; *CI* confidence interval;