Supplementary information

Supplement 2: supplementary online content

Provided by authors to supplement the manuscript entitled

"Care guided by tissue oxygenation and haemodynamic monitoring in off-pump coronary artery bypass grafting (Bottomline-CS): assessor blinded, single centre, randomised trial"

Short title:	BOTTOMLINE-CS trial
Sponsor:	Tianjin Chest Hospital
Sponsor contact:	Dr. Jiange Han Dr. Zhigang Guo Tianjin Chest Hospital Tianjin, China
Chief Investigators:	Drs. Jiange Han, Zhigang Guo, and Lingzhong Meng
Co-Investigator:	Dr. Daniel Sessler
Coordinating centre:	Department of Anesthesiology Tianjin Chest Hospital Tianjin, China

Steering Committee:

- Dr. Jiange Han, Tianjin Chest Hospital, Tianjin University, Tianjin, China
- Dr. Zhigang Guo, Tianjin Chest Hospital, Tianjin University, Tianjin, China
- Dr. Daniel Sessler, University of Texas Health Science Center (previously Cleveland Clinic), Houston, Texas, USA
- Dr. Lingzhong Meng, Indiana University School of Medicine (previously Yale University School of Medicine), Indianapolis, USA

Data and Safety Monitoring Board (DSMB):

- Dong-Xin Wang, M.D., Ph.D. (Potential chair), Professor and Chair, Department of Anesthesiology and Critical Care Medicine, Peking University First Hospital, 8 Xishiku Street, Beijing, 100034, China; Tel: 86 10 83572784; email: wangdongxin@hotmail.com
- Alparslan Turan, M.D., Professor and Vice-Chair, Department of Outcomes Research, Cleveland Clinic, 9500 Euclid Ave - P77, Cleveland, OH 44195, USA; Tel: 216-445-9857; Mobile: 216-217-2312; email: turana@ccf.org
- Karsten Bartels, MD, PhD, MBA, Professor and Vice Chair for Research, Robert Lieberman, MD, PhD Endowed Chair in Anesthesiology, Department of Anesthesiology, University of Nebraska Medical Center, 984455 Nebraska Medical Center, Omaha, NE 68198-4455, USA; karbartels@unmc.edu

BOTTOMLINE-CS Collaboration Group:

- Dr. Jiange Han, Tianjin Chest Hospital, Tianjin University (Co-chief investigator)
- Dr. Zhigang Guo, Tianjin Chest Hospital, Tianjin University (Co-chief investigator)

- Dr. Daniel Sessler, University of Texas Health Science Center, Houston (Co-investigator)
- Dr. Lingzhong Meng, Indiana University School of Medicine (previously Yale University School of Medicine) (Co-chief investigator)
- Dr. Wenqian Zhai, Tianjin Chest Hospital, Tianjin University (Research coordination)
- Dr. Zhenhua Wu, Tianjin Chest Hospital, Tianjin University (Postoperative management)
- Dr. Zhao Zhang, Tianjin Chest Hospital, Tianjin University (Data analysis)
- Dr. Min Ren, Tianjin Research Institute of Cardiovascular Disease (Data management)
- Dr. Tao Wang, Tianjin Chest Hospital, Tianjin University (Intraoperative management)
- Dr. Dongmei Meng, Tianjin Chest Hospital, Tianjin University (Postoperative follow-up)
- Dr. Ruifang Gao, Tianjin Chest Hospital, Tianjin University (Postoperative follow-up)
- Dr. Peng Sun, Tianjin Chest Hospital, Tianjin University (Preoperative assessment)
- Dr. Jianjian Yu, Tianjin Chest Hospital, Tianjin University (Postoperative follow-up)
- Dr. Yunfei Li, Tianjin Chest Hospital, Tianjin University (Preoperative assessment)
- Dr. Yi Ren, Tianjin Chest Hospital, Tianjin University (Preoperative assessment)
- Dr. Bingsha Zhao, Tianjin Chest Hospital, Tianjin University (Postoperative follow-up)
- Dr. Hong Xu, Tianjin Chest Hospital, Tianjin University (Postoperative follow-up)
- Dr. Ying Zhang, Tianjin Chest Hospital, Tianjin University (Preoperative assessment)
- Dr. Jiapeng Liu, Tianjin Chest Hospital, Tianjin University (Intraoperative management)
- Dr. Jianxu Er, Tianjin Chest Hospital, Tianjin University (Intraoperative management)
- Dr. Yuezi Song, Tianjin Chest Hospital, Tianjin University (Postoperative follow-up)
- Dr. Yidan Wang, Tianjin Chest Hospital, Tianjin University (Postoperative follow-up)
- Dr. Jing Sun, Tianjin Chest Hospital, Tianjin University (Postoperative management)
- Dr. Yifei Shi, Tianjin Chest Hospital, Tianjin University (Intraoperative management)
- Dr. Tong Zhao, Tianjin Chest Hospital, Tianjin University (Intraoperative management)
- Dr. Wei Dong, Tianjin Chest Hospital, Tianjin University (Intraoperative management)
- Dr. Liang Liu, Tianjin Chest Hospital, Tianjin University (Intraoperative management)
- Dr. Xiaowei Yang, Tianjin Chest Hospital, Tianjin University (Intraoperative management)
- Dr. Wenzhi Tian, Tianjin Chest Hospital, Tianjin University (Intraoperative management)
- Dr. Long Zhan, Tianjin Chest Hospital, Tianjin University (Intraoperative management)
- Dr. Hui Liu, Tianjin Chest Hospital, Tianjin University (Intraoperative management)
- Dr. Dangpei Kou, Tianjin Chest Hospital, Tianjin University (Intraoperative management)
- Dr. Wei Bian, Tianjin Chest Hospital, Tianjin University (Intraoperative management)
- Dr. Songhua Wu, Tianjin Chest Hospital, Tianjin University (Postoperative management)
- Dr. Jie Li, Tianjin Chest Hospital, Tianjin University (Postoperative management)
- Dr. Chang Xie, Tianjin Chest Hospital, Tianjin University (Postoperative management)
- Dr. Yaobang Bai, Tianjin Chest Hospital, Tianjin University (Postoperative management)
- Dr. Daoyu Wang, Tianjin Chest Hospital, Tianjin University (Postoperative management)
- St. He Jiao, Tianjin University (Postoperative follow-up)
- Dr. Nan Jiang, Tianjin Chest Hospital, Tianjin University (Cardiac surgeon)
- Dr. Lianqun Wang, Tianjin Chest Hospital, Tianjin University (Cardiac surgeon)
- Dr. Bo Fu, Tianjin Chest Hospital, Tianjin University (Cardiac surgeon)
- Dr. Junzhe Zhang, Tianjin Chest Hospital, Tianjin University (Cardiac surgeon)

Content

Supplementary table 1: Definitions of the primary and secondary outcomes

Outcomes	Definition
Primary outcome	The primary outcome was a collapsed (one or more) composite of serious complications. Component complications were cerebral (postoperative delirium, cognitive decline, or stroke), cardiac (non-fatal cardiac arrest, myocardial injury, heart failure, or newly diagnosed symptomatic ventricular arrhythmia), respiratory failure, renal injury (acute kidney injury stages II or III), infections (deep surgical site or organ/space infection, pneumonia, confirmed bloodstream infection, uncertain source infection, or sepsis), and mortality. For each component outcome, we required a Clavien-Dindo grade II classification or higher.
Secondary outcomes	Secondary outcomes included the components of the primary composite outcome, including cerebral complications (as a composite outcome), cardiac complications (as a composite outcome), respiratory failure, renal complications (as a composite outcome), infectious complications (as a composite outcome), and mortality. In addition, the secondary outcomes also included new-onset atrial fibrillation, postoperative delirium, postoperative cognitive decline, and length of hospital stay.
Cerebral complications	Cerebral complications included postoperative delirium, cognitive decline, or stroke. Delirium was evaluated using the Confusion Assessment Method (3D-CAM) or the CAM for the Intensive Care Unit (CAM-ICU), dependent on the patient's intubation status on postoperative days 1-5.[1] Cognitive function was measured preoperatively and on postoperative days 5 and 30 with the Montreal Cognitive Assessment (MoCA version 7.1).[2] A decrease in MoCA score by 2 points or more indicated postoperative cognitive decline. A perioperative stroke was identified as a cerebral infarction of ischemic or haemorrhagic aetiology occurring during surgery or within 30 days post-surgery.[3]
Cardiac complications	Cardiac complications, assessed within 30 days postoperatively and could include non-fatal cardiac arrest—defined as a successful resuscitation from cardiac asystole, chaotic rhythm, or pulseless electrical activity necessitating basic or advanced life support.[4 5] Myocardial injury was recognised as any myocardial infarction as per the 4th universal definition,[6] or troponin elevation due to myocardial ischemia, excluding non-ischemic causes, within the first 30 days post-surgery. Heart failure was defined as a complex clinical syndrome characterised by symptoms such as dyspnoea and fatigue and evidence of cardiac dysfunction as a cause of these symptoms.[7] New-onset symptomatic ventricular arrhythmia included premature ventricular complexes, ventricular tachycardia, and ventricular fibrillation that occurred during or after surgery and required treatment.
Respiratory failure	Respiratory failure was defined as the requirement of respiratory support (intubation, continuous positive airway pressure, bilevel positive airway pressure, or high-flow nasal cannula oxygen therapy) for acute respiratory insufficiency for more than 6 hours after surgery.[8] Respiratory failure was assessed within the postoperative 30 days.
Renal complications	Renal complications were determined within seven days post-surgery, defined as acute kidney injury stages II (2.0-2.9-fold increase in creatinine) or III (3-fold increase in creatinine, an increase of creatinine from baseline by ⩾4 mg/dl (⩾353.6 µmol/L), or initiation of renal replacement therapy) based on Kidney Disease Improving Global Guidelines (KDIGO).[9 10] By convention in perioperative studies, urine output was not considered since it can be unreliable or unavailable.[11]
Infectious complications	Infectious complications, evaluated within 30 days postoperatively, included deep surgical site or organ/space infection, pneumonia, confirmed bloodstream infection, uncertain source infection, or sepsis.
Atrial fibrillation	Atrial fibrillation, assessed within postoperative 30 days, was defined as irregular heartbeats originating from atrium.
Length of hospital stay	The length of hospital stay was defined in days from POD 1 to until hospital discharge excluding death.

Supplementary table 2: Patients excluded from the modified intention-to-treat population

Research #	Group	Reason
1362	Control	Surgery cancellation
1715	Control	Surgery cancellation
0748	Control	Surgery cancellation
1186	Intervention	Surgery cancellation
1868	Intervention	Surgery cancellation
0564	Control	Lost in follow-up
0584	Control	Lost in follow-up
0759	Control	Lost in follow-up
0048	Intervention	Lost in follow-up
0361	Intervention	Lost in follow-up
0506	Intervention	Lost in follow-up
0613	Intervention	Lost in follow-up
0709	Intervention	Lost in follow-up
0745	Intervention	Lost in follow-up
1196	Intervention	Lost in follow-up
1211	Intervention	Lost in follow-up
1492	Intervention	Lost in follow-up
1657	Intervention	Lost in follow-up
1854	Intervention	Lost in follow-up

Supplementary table 3: Preoperative baseline characteristics in the modified intention-to-treat population (Refer to table 1 for more information)

Characteristics	Guided care (n = 967)	Usual care (n = 974)
Beta blocker, no. (%)	838 (86.7)	818 (84.0)
ACEI, no. (%)	36 (3.7)	27 (2.8)
CCB, no. (%)	405 (41.9)	394 (40.5)
Isosorbide mononitrate, no. (%)	885 (91.5)	889 (91.3)
Diuretic, no. (%)	96 (9.9)	102 (10.5)
Antidiabetic agent, no. (%)	448 (46.3)	443 (45.5)
ARB, no. (%)	337 (34.9)	355 (36.4)
Statin, no. (%)	943 (97.5)	951 (97.6)
Median stroke volume (IQR), mL*	64 (52 – 78)	64 (52 – 79)
Median SVR (IQR), dyn·s·cm^{-5}*	1560 (1268 – 1931)	1539 (1261 – 1865)
Mean SBP (SD), mmHg*	126 (17)	126 (18)
Mean DBP (SD), mmHg*	68 (11)	67 (10)

ACEI, angiotensin converting enzyme inhibitors; CCB, calcium channel blockers; ARB, angiotensin receptor blockers; IQR, interquartile range; SVR, systemic vascular resistance; SBP, systolic blood pressure; SD, standard deviation; DBP, diastolic blood pressure

* The measurements of these physiological variables were performed on the ward 24-48 hours before the scheduled surgery.

Supplementary table 4: Intraoperative and postoperative intervention and laboratory data based on the modified intention-to-treat population*

Characteristics	Guided care (n = 967)	Usual care (n = 974)	Group difference (95% CI)	P value
Intraoperative data				
Epinephrine, no. (%)	40 (4.1)	29 (3.0)	0.8 (-2.1 to 3.7)	0.21
Milrinone, no. (%)	30 (3.1)	34 (3.5)	-0.3 (-1.0 to 1.6)	0.73
Esmolol, no. (%)	300 (31.0)	281 (28.9)	2.6 (-7.6 to 12.8)	0.32
Median colloid (IQR), mL	200 (0 – 500)	100 (0 – 500)	0.0 (-0.0 to 0.0)	0.41
Median urine output (IQR), mL	800 (500 – 1000)	800 (500 – 1000)	-0.0 (-50.0 to 0.0)	0.24
Mean lowest haemoglobin (SD), g/dL	11.1 (1.6)	11.3 (1.7)	-0.1 (-0.3 to 0.0)	0.09
Median highest lactate (IQR), mmol/L	1.1 (0.9 – 1.4)	1.1 (0.9 – 1.5)	-0.0 (-0.1 to 0.0)	0.08
Median surgery time (IQR), mins	190 (167 – 223)	192 (164 – 223)	0.0 (-3.0 to 5.0)	0.67
Median numbers of bypass (IQR)	3 (2 – 3)	3 (2 – 3)	-0.0 (-0.0 to 0.0)	0.85
Postoperative/ICU data				
Median propofol (IQR), mg	500 (20 – 1000)	500 (20 – 850)	0.0 (-0.0 to 10.0)	0.24
Dexmedetomidine, no. (%)	233 (24.1)	257 (26.4)	-3.0 (-5.2 to -0.8)	0.27
Sufentanil, no. (%)	310 (32.1)	287 (29.5)	3.0 (-8.0 to 13.9)	0.24
Median butorphanol (IQR), mg	5 (0 – 8)	5 (0 – 8)	0.0 (-0.0 to 0.0)	0.41
Noradrenaline, no. (%)	357 (36.9)	393 (40.3)	-3.6 (-6.1 to -0.1)	0.13
Epinephrine, no. (%)	19 (2.0)	18 (1.8)	0.1 (-1.9 to 1.6)	0.98
Metaraminol, no. (%)	85 (8.8)	74 (7.6)	1.1 (-0.2 to 2.4)	0.38
Nicardipine, no. (%)	30 (3.1)	37 (3.8)	-0.5 (-2.8 to 1.8)	0.47
Urapidil, no. (%)	195 (20.2)	179 (18.4)	1.9 (-8.7 to 12.9)	0.35
Median crystalloid (IQR), mL	1415 (539)	1397 (526)	17.7 (-29.8 to 65.1)	0.47
Median colloid (IQR), mL	1160 (900 – 1400)	1150 (850 – 1358)	0.0 (-0.0 to 20.0)	0.65
Packed red blood cell, no. (%)	284 (29.4)	304 (31.2)	-2.2 (-4.8 to 0.4)	0.40
Median fresh frozen plasma (IQR), mL	600 (400 – 800)	600 (400 – 800)	0.0 (-0.0 to 0.0)	0.70
Median wound drainage (IQR), mL	480 (340 – 655)	480 (340 – 660)	-0.0 (-20.0 to 20.0)	0.87
Median lowest haemoglobin (IQR), g/dL†	10.6 (1.5)	10.5 (1.5)	0.1 (-0.0 to 0.2)	0.37
Median highest lactate (IQR), mmol/L‡	2.0 (1.4 – 2.5)	1.9 (1.5 – 2.5)	0.0 (-0.0 to 0.1)	0.72
Median highest glucose (IQR), mg/dL§	10.6 (8.9 – 12.5)	10.7 (9.0 – 12.6)	-0.1 (-0.4 to 0.1)	0.42
Median mechanical ventilation (IQR), hours¶	12 (10 – 17)	12 (10 – 16)	0.0 (-0.0 to 1.0)	0.06
Median duration ICU stay (IQR), days¶	2 (2 – 2)	2 (2 – 2)	0.0 (-0.0 to 0.0)	0.39

CI, confidence interval; IQR, interquartile range; SD, standard deviation; ICU, intensive care unit.

* Summary statistics are presented as no (%) for interventions administered in less than 50% of patients and as mean (SD) or median (IQR) for interventions administered in more than 50% of patients.

† The postoperative lowest haemoglobin data were missing in six patients in the guided care group and three in the usual care group.

‡ The postoperative highest Lactate data were missing in four patients in the guided care group and six in the usual care group.

§ The postoperative highest glucose data were missing in four patients in the guided care group and five in the usual care group.

¶ The mechanical ventilation time and duration during ICU stay data were missing in one patient in the guided care group and two in the usual care group.

Supplementary table 5: Intraoperative pre- and post-induction point-of-care tissue oxygenation measurements in the modified intention-to-treat population

Characteristic	Guided care (n = 967)	Usual care (n = 974)	Group difference (95% CI)	P value
Left $SctO_2$				
Mean pre-induction measurement (SD), %	74 (5)	74 (5)	0.5 (0.0 to 0.9)	0.16
Mean post-induction measurement (SD), %	74 (5)	74 (6)	0.4 (-0.1 to 0.9)	0.29
Right $SctO_2$				
Mean pre-induction measurement (SD), %	74 (5)	74 (5)	-0.1 (-0.6 to 0.3)	0.66
Mean post-induction measurement (SD), %	74 (5)	73 (6)	-0.0 (-1.0 to 0.0)	0.55
$SstO_2$				
Mean pre-induction measurement (SD), %	76 (5)	77 (6)	0.0 (-0.0 to 1.0)	0.56
Mean post-induction measurement (SD), %	77 (5)	77 (6)	0.3 (-0.2 to 0.8)	0.39

CI, confidence interval; $SctO_2$, cerebral tissue oxygen saturation; SD, standard deviation; $SstO_2$, somatic tissue oxygen saturation

Supplementary table 6: Postoperative tissue oxygenation and haemodynamic data in the modified intention-to-treat population*

Characteristic	Guided care (n = 967)	Usual care (n = 974)	Group difference (95% CI)	P value
Left $SctO_2$†				
Within ±10% baseline for 80% of time, no. (%)	489 (63.7)	478 (61.4)	3.0 (-8.3 to 14.3)	0.38
Median AUC beyond ±10% baseline (IQR), %·min	135.7 (5.2 – 917.3)	199.8 (13.5 – 980.6)	-64.1 (-95.0 to -33.2)	0.07
Right $SctO_2$‡				
Within ±10% baseline for 80% of time, no. (%)	496 (64.6)	469 (60.2)	4.6 (-10.0 to 19.2)	0.09
Median AUC beyond ±10% baseline (IQR), %·min	219.9 (14.0 – 1028.1)	220.5 (23.0 – 905.8)	-0.4 (-14.3 to -13.5)	0.62
$SstO_2$§				
Within ±10% baseline for 80% of time, no. (%)	480 (62.5)	459 (58.9)	4.6 (-9.9 to 19.1)	0.17
Median AUC beyond ±10% baseline (IQR), %·min	286.6 (34.8 – 1380.2)	356.9 (47.5 – 1566.5)	-64.2 (-103.5 to 0.3)	0.10
Haemodynamics¶				
Median MAP AUC beyond ±10% baseline (IQR), mmHg·min	4770.8 (2706.6 – 8727.7)	5032.5 (2560.0 – 9699.9)	-261.1 (-417.5 to -104.7)	0.22
Median MAP AUC <65 mmHg (IQR), mmHg·min	74.2 (6.7 – 333.7)	90.5 (12.4 – 446.1)	-12.3 (-28.4 to 3.5)	0.03
Median CO AUC beyond ±10% baseline (IQR), L	1139.2 (571.3 – 2222.5)	1271.2 (609.6 – 2363.3)	-131.9 (-181.1 to -82.7)	0.14

CI, confidence interval; $SctO_2$, cerebral tissue oxygen saturation; AUC, area under the curve; IQR, interquartile range; $SstO_2$, somatic tissue oxygen saturation; MAP, mean arterial pressure; CO, cardiac output

* Patients experiencing equipment malfunctions or with less than 30 minutes of postoperative tissue oxygenation data were excluded. For postoperative monitoring exceeding 24 hours, only data from the initial 24 hours were analysed.
† Left $SctO_2$ data were missing in 150 patients in the guided care group and 144 in the usual care group.
‡ Right $SctO_2$ data were missing in 142 patients in the guided care group and 143 in the usual care group.
§ $SstO_2$ data were missing in 146 patients in the guided care group and 145 in the usual care group.
¶ MAP and CO data were missing in 152 patients in the guided care group and 142 in the usual care group.

Supplementary table 7: The primary, secondary, and sub-composite outcomes based on the modified intention-to-treat population

Outcomes	Guided care (n = 967)	Usual care (n = 974)	Risk ratio or median difference (95% CI)	P value*†‡
Primary outcome§				
Composite of complications¶	457 (47.3)	466 (47.8)	0.99 (0.90 to 1.08)	0.83
Count (proportional odds)	NA	NA	0.79 (0.51 to 1.21)	0.28
Common effect GEE	NA	NA	0.95 (0.87 to 1.04)	0.24
Average relative effect GEE	NA	NA	0.95 (0.51 to 2.02)	0.82
Composite of serious complications#	90 (9.3)	89 (9.1)	1.02 (0.77 to 1.35)	0.96
Secondary outcomes				
Cerebral complications	311 (32.2)	309 (31.7)	1.01 (0.89 to 1.15)	0.88
Postoperative delirium**	193 (20.0)	201 (20.7)	0.97 (0.81 to 1.15)	0.74
Postoperative cognition decline**	148 (15.3)	144 (14.8)	1.04 (0.84 to 1.28)	0.80
Stroke	6 (0.6)	15 (1.5)	0.40 (0.14 to 0.99)	0.08
Cardiac complications	91 (9.4)	82 (8.4)	1.12 (0.84 to 1.49)	0.49
Non-fatal cardiac arrest	6 (0.6)	6 (0.6)	1.01 (0.32 to 3.21)	>0.99
Heart failure	39 (4.0)	30 (3.1)	1.31 (0.82 to 2.11)	0.31
Myocardial injury	20 (2.1)	19 (2.0)	1.06 (0.57 to 1.99)	0.98
Angina	6 (0.6)	4 (0.4)	1.51 (0.43 to 5.89)	0.74
Ventricular arrhythmia	41 (4.2)	38 (3.9)	1.08 (0.70 to 1.68)	0.80
Atrial fibrillation	293 (30.3)	295 (30.3)	1.00 (0.87 to 1.15)	>0.99
Respiratory failure††	89 (9.2)	99 (10.2)	0.91 (0.69 to 1.19)	0.52
Renal complications‡‡	14 (1.4)	14 (1.4)	1.01 (0.48 to 2.12)	>0.99
Acute kidney injury stages II	10 (1.0)	9 (0.9)	1.12 (0.45 to 2.80)	0.99
Acute kidney injury stages III	4 (0.4)	5 (0.5)	0.80 (0.20 to 3.03)	>0.99
Infectious complications	137 (14.2)	170 (17.5)	0.81 (0.66 to 1.00)	0.06
Deep surgical site infection	8 (0.8)	9 (0.9)	0.90 (0.34 to 2.33)	>0.99
Organ/space infection	8 (0.8)	13 (1.3)	0.62 (0.25 to 1.46)	0.39
Pneumonia	88 (9.1)	121 (12.4)	0.73 (0.56 to 0.95)	0.02
Confirmed bloodstream infection	10 (1.0)	10 (1.0)	1.01 (0.42 to 2.44)	>0.99
Uncertain source infection	32 (3.3)	40 (4.1)	0.81 (0.51 to 1.27)	0.42
Sepsis	3 (0.3)	4 (0.4)	0.76 (0.15 to 3.42)	>0.99
Mortality	15 (1.6)	17 (1.7)	0.89 (0.44 to 1.77)	0.88
Median length of hospital stay (IQR), days§§	9 (7 – 12)	9 (7 – 12)	0.0 (0.0 to 0.0)	0.37

CI, confidence interval; NA, not applicable; GEE, generalised estimating equations; IQR, interquartile range.

* The p-value for pneumonia was 0.60 after adjusting for multiple comparisons using the Holm-Bonferroni method. The p-values exceeded 0.99 for other comparisons.
† All outcomes underwent adjustments for pre-existing imbalances in baseline characteristics, using multivariable log-binomial regression models per the pre-established Statistical Analysis Plan. The calculated threshold for the absolute standardised difference was 0.089. The absolute standardised differences were 0.091 for the baseline systemic vascular resistance and 0.108 for the baseline haemoglobin concentration, so we adjusted for both in primary and secondary outcome analyses. The adjusted p-values for infectious complications and pneumonia were 0.05 and 0.02, respectively. For all other comparisons, the adjusted p-values exceeded 0.05.
‡ We performed additional adjustments based on known prognostic factors, including age, sex, body mass index, and history of hypertension and diabetes, using multivariable log-binomial regression models. The adjusted p-values for infectious complications and pneumonia were 0.05 and 0.04, respectively. For all other comparisons, the adjusted p-values exceeded 0.05.

§ In the analysis of binary composite outcome, we used various testing methods: standard methods (including the combination of any and no events, event counting, and individual component analysis) and multivariate GEE methods, the common effect test and the average relative effect test.[12]
¶ Statistical significance for the primary outcome was defined as a one-sided Z-value < -1.932 (P<0.03). In this study, the z-value for the primary outcome was -0.258 (P=0.83), indicating a lack of statistical significance.
# The composite of serious complications included stroke, non-fatal cardiac arrest, heart failure, new-onset symptomatic ventricular arrhythmia, acute kidney injury stage III, sepsis, and mortality.
** Due to mortality, postoperative delirium and cognitive decline data were unavailable in two patients in the guided care group and three in the usual care group.
†† Due to mortality, respiratory failure data was unavailable in one patient in the usual care group.
‡‡ Due to mortality, renal complication data were unavailable in one patient in the usual care group.
§§ Due to mortality, length of hospital stay data were unavailable in 15 patients in the guided care group and 17 in the usual care group.

Supplementary table 8: The safety outcomes based on the modified intention-to-treat population

Safety outcomes	Overall (n = 1941)	Guided care (n = 967)	Usual care (n = 974)	Risk ratio (95% CI)	P value
Intraoperative conversion to CPB, no. (%)	17 (0.9)	8 (0.8)	9 (0.9)	0.89 (0.35 to 2.31)	> 0.99
Anaphylactic shock, no. (%)	2 (0.2)	1 (0.103)	1 (0.102)	1.16 (0.07 to 18.76)	> 0.99
Postoperative haemorrhage, no. (%)*	5 (0.3)	2 (0.2)	3 (0.3)	0.67 (0.11 to 4.01)	> 0.99

CI, confidence interval; CPB, cardiopulmonary bypass.

* Postoperative haemorrhage was defined as the requirement of urgent bring-back surgery for haemostasis.

Supplementary table 9: Patients with protocol violations

Research sequence number	Group	Reason*	Exclusion†
The following based on intraoperative and postoperative information			
0047	Control	Intraoperative conversion to CPB	Yes
0577	Control	Intraoperative conversion to CPB	Yes
0629	Control	Intraoperative conversion to CPB	Yes
1236	Control	Intraoperative conversion to CPB	Yes
1532	Control	Intraoperative conversion to CPB	Yes
1800	Control	Intraoperative conversion to CPB	Yes
1878	Control	Intraoperative conversion to CPB	Yes
1940	Control	Intraoperative conversion to CPB	Yes
1945	Control	Intraoperative conversion to CPB	Yes
0013	Intervention	Intraoperative conversion to CPB	Yes
0097	Intervention	Intraoperative conversion to CPB	Yes
0758	Intervention	Intraoperative conversion to CPB	Yes
0997	Intervention	Intraoperative conversion to CPB	Yes
1298	Intervention	Intraoperative conversion to CPB	Yes
1321	Intervention	Intraoperative conversion to CPB	Yes
1554	Intervention	Intraoperative conversion to CPB	Yes
1916	Intervention	Intraoperative conversion to CPB	Yes
0039	Control	Ineligible patients	Yes
0245	Intervention	Ineligible patients	Yes
0090	Intervention	Ineligible patients	Yes
The following based on research monitoring			
0040	Intervention	Unsatisfactory intervention	Yes
0104	Intervention	Unsatisfactory intervention	Yes
0110	Intervention	Unsatisfactory intervention	Yes
0130	Intervention	Unsatisfactory intervention	Yes
0155	Intervention	Unsatisfactory intervention	Yes
0171	Intervention	Unsatisfactory intervention	Yes
0174	Intervention	Unsatisfactory intervention	Yes
0210	Intervention	Unsatisfactory intervention	Yes
0217	Intervention	Unsatisfactory intervention	Yes
0269	Intervention	Unsatisfactory intervention	Yes
0295	Intervention	Monitor malfunctioning or data missing	Yes
0341	Intervention	Unsatisfactory intervention	Yes
0373	Intervention	Insufficient data	Yes
0415	Intervention	Unsatisfactory intervention	Yes
0430	Intervention	Unsatisfactory intervention	Yes
0450	Intervention	Unsatisfactory intervention	Yes
0455	Intervention	Unsatisfactory intervention	Yes
0459	Intervention	Unsatisfactory intervention	Yes
0462	Intervention	Unsatisfactory intervention	Yes
0497	Intervention	Unsatisfactory intervention	Yes
0502	Intervention	Monitor malfunctioning or data missing	Yes
0580	Intervention	Unsatisfactory intervention	Yes
0656	Intervention	Unsatisfactory intervention	Yes
0668	Intervention	Insufficient data	Yes
0718	Intervention	Unsatisfactory intervention	Yes
0766	Intervention	Unsatisfactory intervention	Yes
0783	Intervention	Unsatisfactory intervention	Yes
0837	Intervention	Unsatisfactory intervention	Yes
0850	Intervention	Unsatisfactory intervention	Yes
0885	Intervention	Unsatisfactory intervention	Yes
0930	Intervention	Insufficient data	Yes
0938	Intervention	Unsatisfactory intervention	Yes
0965	Intervention	Monitor malfunctioning or data missing	Yes
0991	Intervention	Unsatisfactory intervention	Yes
1077	Intervention	Insufficient data	Yes

1092	Intervention	Unsatisfactory intervention	Yes
1095	Intervention	Insufficient data	Yes
1119	Intervention	Monitor malfunctioning or data missing	Yes
1161	Intervention	Unsatisfactory intervention	Yes
1202	Intervention	Monitor malfunctioning or data missing	Yes
1469	Intervention	Unsatisfactory intervention	Yes
1470	Intervention	Insufficient data	Yes
1527	Intervention	Unsatisfactory intervention	Yes
1673	Intervention	Unsatisfactory intervention	Yes
1712	Intervention	Unsatisfactory intervention	Yes
1743	Intervention	Unsatisfactory intervention	Yes
1759	Intervention	Unsatisfactory intervention	Yes
1764	Intervention	Unsatisfactory intervention	Yes
1772	Intervention	Unsatisfactory intervention	Yes
1836	Intervention	Unsatisfactory intervention	Yes
1839	Intervention	Unsatisfactory intervention	Yes
1844	Intervention	Unsatisfactory intervention	Yes
1863	Intervention	Insufficient data	Yes
1882	Intervention	Unsatisfactory intervention	Yes
1959	Intervention	Unsatisfactory intervention	Yes
0416	Control	Monitor malfunctioning or data missing	No
0447	Control	Insufficient data	No
0693	Control	Monitor malfunctioning or data missing	No
0736	Control	Insufficient data	No
0843	Control	Monitor malfunctioning or data missing	No
0874	Control	Insufficient data	No
0990	Control	Monitor malfunctioning or data missing	No
1002	Control	Monitor malfunctioning or data missing	No
1170	Control	Insufficient data	No
1193	Control	Monitor malfunctioning or data missing	No
1201	Control	Monitor malfunctioning or data missing	No
1214	Control	Insufficient data	No
1261	Control	Monitor malfunctioning or data missing	No
1280	Control	Monitor malfunctioning or data missing	No
1371	Control	Monitor malfunctioning or data missing	No
1380	Control	Insufficient data	No
1388	Control	Insufficient data	No
1548	Control	Insufficient data	No
1551	Control	Insufficient data	No
1632	Control	Insufficient data	No
1711	Control	Insufficient data	No
1728	Control	Insufficient data	No

CPB, cardiopulmonary bypass.

* The reasons for protocol violations are explained as follows.

- Intraoperative conversion to CPB = The planned surgical procedure was changed from off-pump to on-pump coronary artery bypass grafting during surgery.
- Ineligible patients = the patient under 60 years of age.
- Unsatisfactory intervention = The intervention was considered unsatisfactory if the time percentage of the cerebral tissue oxygen saturation/somatic tissue oxygen saturation measurements falling within the 90-110% ward baseline range during surgery in the guided-care group was less than 80%.
- Insufficient data = at least 50% of the tissue oxygenation or haemodynamics monitoring data were missing, or artefacts or the monitoring duration of either tissue oxygenation or haemodynamics was less than 30 minutes.

- Monitor malfunctioning or data missing = tissue oxygenation or haemodynamics monitoring malfunctioning or the monitoring data for either tissue oxygenation or haemodynamics were not collected.

† "Yes" indicates that patients were excluded from the per-protocol population, while "No" indicates that patients were included in the per-protocol population.

Supplementary table 10: Demographic and preoperative baseline characteristics in the per-protocol population

Characteristics	Guided care (n = 901)	Usual care (n = 964)
Mean age (SD), year	69 (5)	69 (5)
Male, no. (%)	647 (71.8)	667 (69.2)
Mean height (SD), cm	168 (8)	168 (8)
Mean weight (SD), kg	71 (11)	71 (11)
Mean BMI (SD), kg/m^2	25.3 (3.4)	25.2 (3.1)
Beta blocker, no. (%)	783 (86.9)	810 (84.0)
ACEI, no. (%)	35 (3.9)	26 (2.7)
CCB, no. (%)	375 (41.6)	390 (40.5)
Isosorbide mononitrate, no. (%)	824 (91.5)	880 (91.3)
Diuretic, no. (%)	88 (9.8)	102 (10.6)
Antidiabetic agent, no. (%)	426 (47.3)	440 (45.6)
ARB, no. (%)	313 (34.7)	350 (36.3)
Statin, no. (%)	878 (97.4)	941 (97.6)
Smoking, no. (%)	532 (59.0)	550 (57.1)
Diabetes, no. (%)	392 (43.5)	416 (43.2)
Hypertension, no. (%)	669 (74.3)	700 (72.6)
Arrhythmia, no. (%)	96 (10.7)	82 (8.5)
Severe carotid artery stenosis, no. (%)	82 (9.1)	85 (8.8)
ASA physical status III, no. (%)	895 (99.3)	959 (99.5)
NYHA functional class II, no. (%)	867 (96.2)	928 (96.3)
Median MET score (IQR)*	4 (3 – 5)	4 (3 – 5)
Median EuroSCORE (IQR)†	4 (3 – 5)	4 (3 – 5)
Mean MoCA score (SD)‡	22 (5)	21 (5)
Mean left $SctO_2$ (SD), %§	72 (4)	72 (4)
Mean right $SctO_2$ (SD), %§	71 (4)	71 (5)
Mean $SstO_2$ (SD), %§	74 (5)	74 (5)
Median cardiac output (IQR), L/min§	4.3 (3.5 – 5.3)	4.4 (3.5 – 5.3)
Median stroke volume (IQR), mL§	64 (53 – 79)	65 (53 – 79)
Median SVR (IQR), dyn·s·cm^{-5}§	1548 (1262 – 1915)	1539 (1261 – 1865)
Median heart rate (IQR), bpm§	67 (61 – 74)	67 (61 – 74)
Mean SBP (SD), mmHg§	126 (17)	126 (18)
Mean DBP (SD), mmHg§	68 (11)	67 (11)
Mean MAP (SD), mmHg§	90 (12)	90 (12)
Median haemoglobin (IQR), g/L	133 (124 – 143)	132 (121 – 142)
Median creatinine (IQR), umol/L	77 (66 – 89)	77 (66 – 88)
Median troponin T (IQR), ug/L	0.02 (0.01 – 0.04)	0.02 (0.01 – 0.04)
Median CK-MB (IQR), U/L	14 (12 – 17)	13 (11 – 16)
Median BNP (IQR), pg/mL	50 (20 – 138)	50 (20 – 140)
Median left ventricular EF (IQR), %	59 (55 – 62)	59 (55 – 62)

SD, standard deviation; BMI, body mass index; ACEI, angiotensin converting enzyme inhibitors; CCB, calcium channel blockers; ARB, angiotensin receptor blockers; ASA, American Society of Anesthesiologists; NYHA, New York Heart Association; MET, metabolic equivalent of task; IQR, interquartile range; EuroSCORE, European system for cardiac operative risk evaluation; MoCA, Montreal cognitive assessment; $SctO_2$, cerebral tissue oxygen saturation; $SstO_2$, somatic tissue oxygen saturation; SVR, systemic vascular resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; CK-MB, creatine kinase MB; BNP, B-type natriuretic peptide; EF, ejection fraction

* MET score represents the energy expenditure of physical activities relative to resting metabolic rate. One MET equals resting energy expenditure, with activities classified as low (<3

METs), moderate (3–6 METs), or high intensity (>6 METs).
† EuroSCORE is a system that estimates the predicted operative mortality risk in cardiac surgery based on patient-related, cardiac, and surgical factors.
‡ MoCA scores range from 0 to 30, with higher scores indicating better cognitive function. A score of 26 or above is considered normal, while scores below 26 suggest cognitive impairment.
§ These physiological variables were measured on the ward 24-48 hours before the scheduled surgery.

Supplementary table 11: Intraoperative and postoperative intervention and laboratory data based on the per-protocol population*

Characteristics	Guided care (n = 901)	Usual care (n = 964)	Group difference (95% CI)	P value
Intraoperative data				
Mean midazolam (SD), mg	1.7 (0.9)	1.6 (1.0)	0.1 (0.1 to 0.2)	0.001
Median propofol (IQR), mg	398 (296 – 480)	320 (200 – 472)	60.0 (45.0 to 78.0)	<0.001
Median sevoflurane (IQR), mL	20 (15 – 38)	30 (20 – 50)	-10.0 (-15.1 to -5.0)	<0.001
Median cisatracurium (IQR), mg	55 (45 – 70)	49 (35 – 60)	6.0 (5.0 to 10.0)	<0.001
Median sufentanil (IQR), ug	350 (275 – 450)	300 (220 – 380)	50.0 (50.0 to 50.0)	<0.001
Norepinephrine, no. (%)	329 (36.5)	482 (50.0)	-13.7 (-18.3 to -9.1)	<0.001
Epinephrine, no. (%)	33 (3.7)	24 (2.5)	0.9 (-2.4 to 4.2)	0.18
Metaraminol, no. (%)	470 (52.2)	348 (36.1)	16.3 (-20.9 to 53.5)	<0.001
Milrinone, no. (%)	29 (3.2)	31 (3.2)	0.0 (-1.2 to 1.2)	0.99
Nicardipine, no. (%)	312 (34.6)	394 (40.9)	-6.6 (-11.4 to -1.9)	0.006
Urapidil, no. (%)	19 (2.1)	43 (4.5)	-1.8 (-3.1 to -0.5)	0.007
Esmolol, no. (%)	278 (30.9)	276 (28.6)	2.7 (-7.8 to 13.4)	0.32
Tranexamic acid, no. (%)	537 (59.6)	369 (38.3)	21.3 (16.8 to 25.9)	<0.001
Dexmedetomidine, no. (%)	373 (41.4)	568 (58.9)	-17.5 (-22.1 to -12.9)	<0.001
Mean crystalloid (SD), mL	2262 (573)	2087 (573)	175.8 (124.0 to 227.6)	<0.001
Median colloid (IQR), mL	100 (0 – 500)	100 (0 – 500)	0.0 (-0.0 to 0.0)	0.69
Mean autologous blood (SD), mL	351 (249)	381 (293)	-34.5 (-58.5 to -10.5)	0.02
Mean blood loss (SD), mL	531 (273)	579 (331)	-49.6 (-76.4 to -22.9)	<0.001
Median urine output (IQR), mL	800 (500 – 1000)	800 (500 – 1000)	-0.0 (-50.0 to 0.0)	0.31
Mean lowest haemoglobin (SD), g/dL	11.1 (1.6)	11.3 (1.7)	-0.1 (-0.3 to 0.0)	0.09
Median highest lactate (IQR), mmol/L	1.1 (0.9 – 1.4)	1.1 (0.9 – 1.5)	-0.0 (-0.1 to 0.0)	0.11
Median highest glucose (IQR), mg/dL	7.1 (6.2 – 8.4)	7.5 (6.3 – 9.0)	-0.3 (-0.5 to -0.2)	<0.001
Median surgery time (IQR), mins	190 (166.5 – 222)	191 (163 – 221)	-1.0 (-3.0 to 5.0)	0.57
Median numbers of bypass (IQR)	3 (2 – 3)	3 (2 – 3)	-0.0 (-0.0 to 0.0)	0.91
Postoperative/ICU data				
Median propofol (IQR), mg	500 (20 – 950)	500 (20 – 850)	0.0 (-0.0 to 0.4)	0.38
Dexmedetomidine, no. (%)	220 (24.4)	254 (26.3)	-2.5 (-12.1 to 7.9)	0.37
Sufentanil, no. (%)	289 (32.1)	285 (29.6)	2.9 (-8.0 to 13.8)	0.26
Median butorphanol (IQR), mg	4 (0 – 8)	4 (0 – 8)	0.0 (-0.0 to 0.0)	0.51
Norepinephrine, no. (%)	324 (36.0)	388 (40.2)	-4.5 (-9.3 to -0.2)	0.06
Epinephrine, no. (%)	17 (1.9)	17 (1.8)	0.1 (-1.5 to 1.6)	0.98
Metaraminol, no. (%)	77 (8.5)	73 (7.6)	0.9 (-12.0 to 5.4)	0.49
Nicardipine, no. (%)	29 (3.2)	36 (3.7)	-0.5 (-3.3 to 2.3)	0.63
Urapidil, no. (%)	184 (20.4)	176 (18.3)	2.1 (-9.4 to 11.4)	0.26
Esmolol, no. (%)	12 (1.3)	30 (3.1)	-1.8 (-5.1 to 1.5)	0.02
Median crystalloid (IQR), mL	1380 (1010 – 1625)	1338 (1017 – 1600)	25.0 (0.0 to 50.0)	0.35
Median colloid (IQR), mL	1150 (900 – 1400)	1150 (850 – 1352.5)	0.0 (-0.0 to 20.0)	0.66
Packed red blood cell, no. (%)	264 (29.3)	300 (31.1)	-2.2 (-12.3 to 7.2)	0.42
Median fresh frozen plasma (IQR) ,mL	600 (400 – 800)	600 (400 – 800)	0.0 (-0.0 to 0.0)	0.88
Median wound drainage (IQR) ,mL	480 (340 – 640)	480 (340 – 660)	-0.0 (-20.0 to 20.0)	0.63
Median urine output (IQR), mL	1800 (1400 – 2300)	1750 (1300 – 2200)	100.0 (0.0 to 150.0)	0.02
Median lowest haemoglobin (IQR), g/dL†	10.5 (9.6 – 11.6)	10.4 (9.5 – 11.6)	0.1 (-0.0 to 0.2)	0.20
Median highest lactate (IQR), mmol/L‡	2.0 (1.4 – 2.5)	1.9 (1.4 – 2.4)	0.0 (-0.0 to 0.1)	0.58
Median highest glucose (IQR), mg/dL§	10.6 (8.8 – 12.5)	10.6 (8.9 – 12.5)	-0.1 (-0.3 to 0.2)	0.59
Median mechanical ventilation (IQR), hours¶	12 (10 – 17)	12 (10 – 16)	0.0 (0.0 to 1.0)	0.03
Median duration ICU stay (IQR), days¶	2 (2 – 2)	2 (2 – 2)	0.0 (-0.0 to 0.0)	0.29

CI, confidence interval; SD, standard deviation; IQR, interquartile range; ICU, intensive care unit.

* Summary statistics are presented as no (%) for interventions administered in less than 50% of patients and as mean (SD) or median (IQR) for interventions administered in more than 50% of patients.

† The postoperative lowest haemoglobin data were missing in five patients in the guided care group and three in the usual care group.
‡ The postoperative highest lactate data were missing in four patients in the guided care group and six in the usual care group.
§ The postoperative highest glucose data were missing in four patients in the guided care group and five in the usual care group.
¶ The mechanical ventilation time and duration during ICU stay data were missing in one patient in the guided care group and two in the usual care group.

Supplementary table 12: Baseline and intraoperative tissue oxygenation and haemodynamic data in the per-protocol population*

Characteristic	Guided care (n = 901)	Usual care (n = 964)	Group difference (95% CI)	P value
Left $SctO_2$†				
Mean ward baseline (SD), %	72 (4)	72 (4)	-0.1 (-0.5 to 0.2)	0.51
Mean pre-induction measurement (SD), %	74 (5)	74 (5)	0.5 (0.0 to 0.9)	0.16
Mean post-induction measurement (SD), %	74 (5)	74 (6)	0.4 (-0.1 to 0.9)	0.29
Within ±10% baseline for 80% of time, no. (%)	901 (100.0)	564 (59.9)	40.1 (36.4 to 46.4)	<0.001
Median AUC beyond ±10% baseline (IQR), %·min	7.1 (1.3 – 33.0)	56.8 (6.9 – 206.9)	-48.6 (-61.8 to -36.8)	<0.001
Right $SctO_2$‡				
Mean ward baseline (SD), %	72 (5)	73 (5)	-0.0 (-0.5 to 0.4)	0.48
Mean pre-induction measurement (SD), %	74 (5)	74 (5)	-0.1 (-0.6 to 0.3)	0.66
Mean post-induction measurement (SD), %	73 (5)	73 (6)	-0.0 (-1.0 to 0.0)	0.55
Within ±10% baseline for 80% of time, no. (%)	901 (100.0)	553 (58.7)	41.2 (37.2 to 45.3)	<0.001
Median AUC beyond ±10% baseline (IQR), %·min	11.6 (2.2 – 41.3)	61.1 (9.7 – 210.2)	-46.5 (-60.2 to -35.5)	<0.001
$SstO_2$§				
Mean ward baseline (SD), %	74 (5)	74 (5)	0.0 (-0.5 to 0.5)	0.75
Mean pre-induction measurement (SD), %	76 (5)	77 (6)	0.0 (-0.0 to 1.0)	0.56
Mean post-induction measurement (SD), %	77 (5)	77 (6)	0.3 (-0.2 to 0.8)	0.39
Within ±10% baseline for 80% of time, no. (%)	901 (100.0)	553 (58.7)	42.2 (38.4 to 46.1)	<0.001
Median AUC beyond ±10% baseline (IQR), %·min	3.2 (0.0 – 21.1)	43.3 (2.3 – 290.5)	-38.1 (-53.7 to -27.6)	<0.001
Haemodynamics¶				
Mean MAP ward baseline (SD), mmHg	90 (13)	90 (12)	0.7 (-0.3 to 1.7)	0.27
Median MAP AUC beyond ±10% baseline (IQR), mmHg·min	1686.0 (972.3 – 2785.5)	1854.8 (1149.4 – 3059.5)	-161.2 (-270.7 to -51.8)	0.004
Median MAP AUC <65 mmHg (IQR), mmHg·min	167.0 (48.6 – 381.3)	206.1 (79.4 – 408.2)	-25.1 (-41.7 to -9.3)	0.001
Median CO ward baseline (IQR), L/min	4.3 (3.5 – 5.3)	4.4 (3.5 – 5.3)	-0.1 (-0.2 to 0.0)	0.19
Median CO AUC beyond ±10% baseline (IQR), L	140.7 (75.8 – 272.6)	163.0 (99.4 – 284.2)	-18.6 (-28.9 to -8.2)	0.001

CI, confidence interval; $SctO_2$, cerebral tissue oxygen saturation; SD, standard deviation; AUC, area under the curve; IQR, interquartile range; $SstO_2$, somatic tissue oxygen saturation; MAP, mean arterial pressure; CO, cardiac output

* Patients experiencing equipment malfunctions or with less than 30 minutes of intraoperative tissue oxygenation data were excluded.
†All patients had left $SctO_2$ baseline measurements. Left $SctO_2$ data were missing in 19 patients in the usual care group.
‡ All patients had right $SctO_2$ baseline measurements. Right $SctO_2$ data were missing in 18 patients in the usual care group.
§ All patients had $SstO_2$ baseline measurements. $SstO_2$ data were missing in 19 patients in the usual care group.
¶ All patients had MAP and CO baseline measurements. MAP and CO data were missing in 18 patients in the usual care group.

Supplementary table 13: Postoperative tissue oxygenation and haemodynamic data in the per-protocol population*

Characteristic	Guided care (n = 901)	Usual care (n = 964)	Group difference (95% CI)	P value
Left $SctO_2$†				
Within ±10% baseline for 80% of time, no. (%)	461 (64.1)	473 (61.3)	2.8 (-7.7 to 13.3)	0.29
Median AUC beyond ±10% baseline (IQR), %·min	137.2 (5.2 – 916.4)	199.6 (13.5 – 904.8)	-62.4 (-104.3 to -20.5)	0.10
Right $SctO_2$‡				
Within ±10% baseline for 80% of time, no. (%)	463 (64.4)	463 (60.1)	4.3 (-9.9 to 18.5)	0.09
Median AUC beyond ±10% baseline (IQR), %·min	209.3 (21.7 – 894.4)	220.5 (14.9 – 1027.7)	0.0 (-8.5 to 10.7)	0.92
$SstO_2$§				
Within ±10% baseline for 80% of time, no. (%)	454 (63.1)	453 (58.8)	4.3 (-9.0 to 17.6)	0.09
Median AUC beyond ±10% baseline (IQR), %·min	287.7 (34.7 – 1368.0)	341.0 (37.5 – 1567.4)	-53.3 (-92.3 to -14.3)	0.20
Haemodynamics¶				
Median MAP AUC beyond ±10% baseline (IQR), mmHg·min	4653.1 (2691.0 – 8666.7)	5015.3 (2536.5 – 9749.5)	-311.2 (-420.7 to -202.2)	0.21
Median MAP AUC <65 mmHg (IQR), mmHg·min	74.1 (6.3 – 333.5)	87.5 (12.3 – 445.0)	-13.2 (-29.7 to 32.7)	0.04
Median CO AUC beyond ±10% baseline (IQR), L	1130.7 (563.5 – 2199.6)	1276.9 (607.0 – 2358.0)	-140.1 (-189.2 to -91.1)	0.11

CI, confidence interval; $SctO_2$, cerebral tissue oxygen saturation; AUC, area under the curve; IQR, interquartile range; $SstO_2$, somatic tissue oxygen saturation; MAP, mean arterial pressure; CO, cardiac output

* Patients experiencing equipment malfunctions or with less than 30 minutes of postoperative tissue oxygenation data were excluded. For postoperative monitoring exceeding 24 hours, only data from the initial 24 hours were analysed.
† Left $SctO_2$ data were missing in 142 patients in the guided care group and 144 in the usual care group.
‡ Right $SctO_2$ data were missing in 134 patients in the guided care group and 143 in the usual care group.
§ $SstO_2$ data were missing in 138 patients in the guided care group and 145 in the usual care group.
¶ MAP and CO data were missing in 151 patients in the guided care group and 139 in the usual care group.

Supplementary table 14: The primary, secondary, and sub-composite outcomes based on the per-protocol population

Outcomes	Guided care (n = 901)	Usual care (n = 964)	Risk ratio or median difference (95% CI)	P value*†‡
Primary outcome				
Composite of complications§	418 (46.4)	460 (47.7)	0.97 (0.88 to 1.07)	0.60
Composite of serious complications¶	83 (9.2)	85 (8.8)	1.04 (0.78 to 1.39)	0.83
Secondary outcomes				
Cerebral complications	284 (31.5)	305 (31.6)	1.00 (0.87 to 1.14)	≥0.99
Postoperative delirium#	176 (19.6)	200 (20.8)	0.94 (0.78 to 1.13)	0.55
Postoperative cognition decline#	138 (15.3)	142 (14.7)	1.04 (0.84 to 1.29)	0.77
Stroke	3 (0.3)	13 (1.3)	0.25 (0.06 to 0.76)	0.03
Cardiac complications	85 (9.4)	77 (8.0)	1.18 (0.88 to 1.59)	0.31
Non-fatal cardiac arrest	4 (0.4)	6 (0.6)	0.71 (0.18 to 2.49)	0.83
Heart failure	37 (4.1)	26 (2.7)	1.52 (0.93 to 2.52)	0.12
Myocardial injury	19 (2.1)	18 (1.9)	1.13 (0.59 to 2.15)	0.84
Angina	6 (0.7)	4 (0.4)	1.60 (0.46 to 6.26)	0.67
Ventricular arrhythmia	38 (4.2)	37 (3.9)	1.10 (0.70 to 1.71)	0.77
Atrial fibrillation	265 (29.4)	291 (30.2)	0.97 (0.85 to 1.12)	0.75
Respiratory failure**	84 (9.3)	97 (10.1)	0.93 (0.70 to 1.22)	0.65
Renal complications††	13 (1.4)	12 (1.2)	1.16 (0.53 to 2.56)	0.87
Acute kidney injury stages II	10 (1.1)	8 (0.8)	1.34 (0.53 to 3.49)	0.71
Acute kidney injury stages III	3 (0.3)	4 (0.4)	0.80 (0.16 to 3.63)	>0.99
Infectious complications	124 (13.8)	168 (17.4)	0.79 (0.64 to 0.98)	0.04
Deep surgical site infection	7 (0.8)	8 (0.8)	0.94 (0.33 to 2.60)	>0.99
Organ/space infection	7 (0.8)	13 (1.3)	0.58 (0.22 to 1.40)	0.33
Pneumonia	80 (8.9)	119 (12.3)	0.72 (0.55 to 0.94)	0.02
Confirmed bloodstream infection	7 (0.8)	9 (0.9)	0.83 (0.30 to 2.22)	0.91
Uncertain source infection	30 (3.3)	38 (3.9)	0.84 (0.52 to 1.35)	0.56
Sepsis	2 (0.2)	4 (0.4)	0.53 (0.07 to 2.73)	0.74
Mortality	13 (1.4)	17 (1.8)	0.82 (0.39 to 1.67)	0.71
Median length of hospital stay (IQR), days‡‡	9.0 (7.0 – 12.2)	9.0 (7.0 – 12.0)	0.0 (0.0 to 0.0)	0.51

CI, confidence interval; NA, not available; IQR, interquartile range.

* Based on the Holm-Bonferroni method, the adjusted p-values for stroke, infectious complications, and pneumonia were 0.884, 0.910, and 0.494, respectively. The p-values exceeded 0.99 for other comparisons.
† All outcomes underwent adjustments for pre-existing imbalances in baseline characteristics, using multivariable log-binomial regression models per the pre-established Statistical Analysis Plan. The calculated threshold for the absolute standardised difference was 0.089. The absolute standardised differences were 0.091 for the baseline systemic vascular resistance and 0.108 for the baseline haemoglobin concentration, so we adjusted for both in primary and secondary outcome analyses. The adjusted p-values for stroke, infectious complications, and pneumonia were 0.03, 0.03 and 0.02, respectively. The adjusted p-values exceeded 0.05 for all other comparisons.
‡ We performed additional adjustments based on known prognostic factors, including age, sex, body mass index, and history of hypertension and diabetes, using multivariable log-binomial regression models. The adjusted p-values for stroke, infectious complications, and pneumonia were 0.03, 0.03 and 0.02, respectively. The adjusted p-values exceeded 0.05 for all other comparisons.

§ Statistical significance for the primary outcome was defined as a one-sided Z-value < -1.932 (P<0.03). In this study, the z-value for the primary outcome was -0.573 (P=0.60), indicating a lack of statistical significance.
¶The composite of serious complications included stroke, non-fatal cardiac arrest, heart failure, new-onset symptomatic ventricular arrhythmia, acute kidney injury stage III, sepsis, and mortality.
Due to mortality, postoperative delirium and cognitive decline data were unavailable in three patients in the usual care group.
** Due to mortality, respiratory failure data was unavailable in one patient in the usual care group.
†† Due to mortality, renal complication data were unavailable in one patient in the usual care group.
‡‡ Due to mortality, length of hospital stay data were unavailable in 13 patients in the guided care group and 17 in the usual care group.

Supplementary table 15: The safety outcomes based on the per-protocol population

Safety outcomes	Overall (n = 1865)	Guided care (n = 901)	Usual care (n = 964)	Risk ratio (95% CI)	P value
Anaphylactic shock, no. (%)	1 (0.05)	1 (0.11)	0 (0.00)	NA	> 0.99
Postoperative haemorrhage, no. (%)*	5 (0.26)	2 (0.22)	3 (0.31)	0.71 (0.12 to 4.26)	> 0.99

CI, confidence interval; NA, not available.

* Postoperative haemorrhage was defined as the requirement of urgent bring-back surgery for haemostasis.

Supplementary table 16: Sensitivity analysis of the primary outcome based on different missing mechanisms

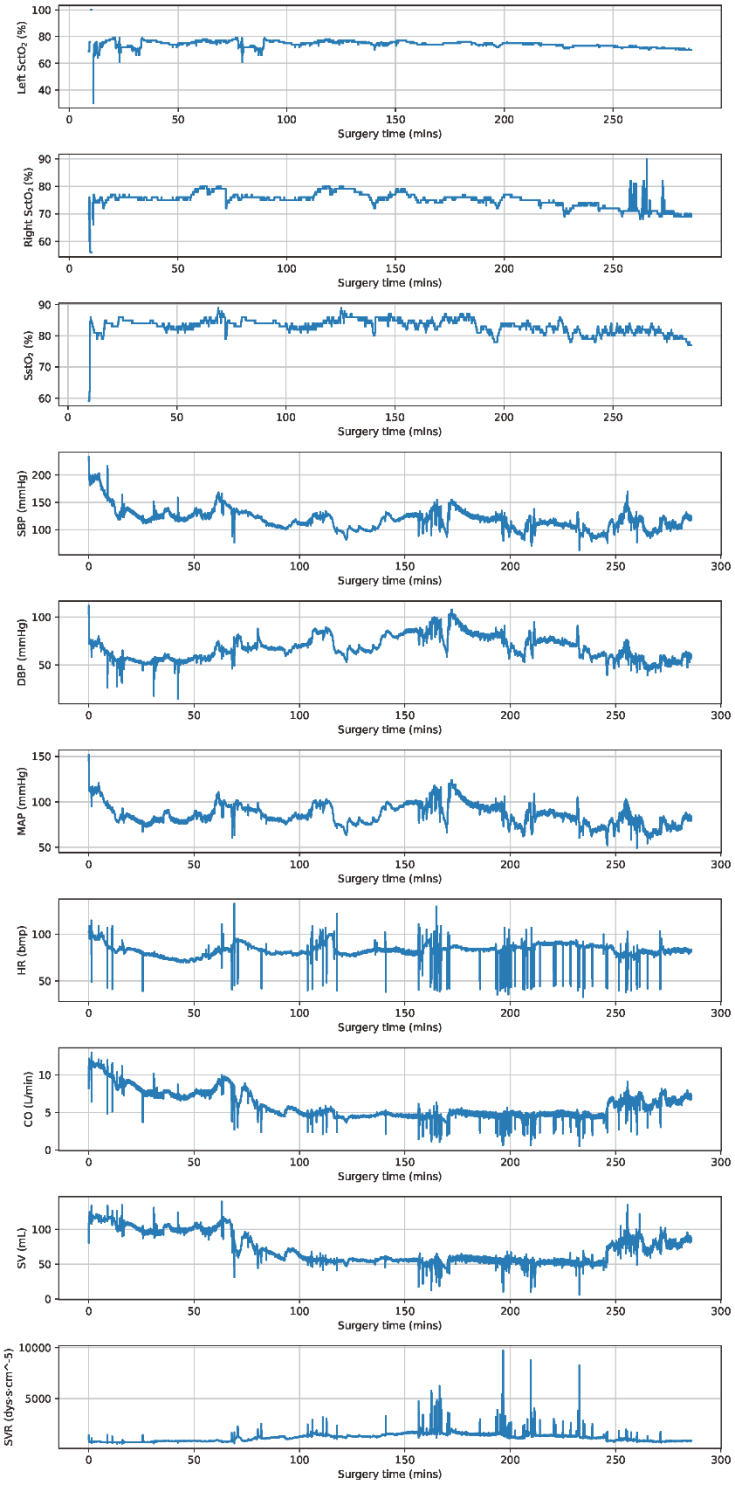
Outcomes after imputation	Guided care (n = 980)	Usual care (n = 980)	Risk ratio (95% CI)	P value
Missing completely at random*	457 (47.3)	466 (47.8)	0.99 (0.90 to 1.08)	0.83
Multiple imputations by Markov Chain Monte Carlo†	463 (47.2)	470 (48.0)	0.98 (0.89 to 1.08)	0.79
Best-case scenario analysis‡	457 (46.6)	472 (48.2)	0.97 (0.88 to 1.06)	0.53
Worst-case scenario analysis‡	470 (48.0)	466 (47.6)	1.01 (0.92 to 1.11)	0.89
Selection models§	462 (47.1)	470 (48.0)	0.98 (0.90 to 1.08)	0.75

CI, confidence interval.

* In the primary analysis, patients without outcome data were excluded, corresponding to missing completely at random. The final analysis included 967 patients in the guided care group and 974 in the usual care group.
† We generated 20 datasets for multiple imputations using the Markov Chain Monte Carlo (MCMC) method to create stationary distribution chains and simulate samples. Each dataset was analysed using a log-binomial model. The estimated coefficients and standard errors based on these models were combined using robust methods for the final estimates. The multiple imputation was implemented using the R packages (mice, brms)
‡ We imputed all missing outcomes as successes in the intervention group and failures in the control group for the best-case scenario and the opposite for the worst-case scenario.
§ We predicted the missing outcomes using logistic regression models that included age, sex, body mass index, smoking, history of myocardial infarction, diabetes, hypertension, stroke, surgery time, and number of bypasses. The imputation was implemented using the R packages (mice, lme4)

Supplementary figure 1: Illustration of fluctuating tissue oxygenation and haemodynamic measurements during off-pump coronary artery bypass grafting in an individual patient

$SctO_2$, cerebral tissue oxygen saturation; $SstO_2$, somatic tissue oxygen saturation; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; CO, cardiac output; SV, stroke volume; SVR, systemic vascular resistance

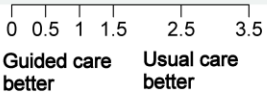

Left $SctO_2$ (%)
Right $SctO_2$ (%)
$SstO_2$ (%)
SBP (mmHg)
DBP (mmHg)
MAP (mmHg)
HR (bmp)
CO (L/min)
SV (mL)
SVR (dys·s·cm^-5)
Surgery time (mins)

Supplementary figure 2: Forest plot of the primary, secondary, and sub-composite outcomes based on the per-protocol population

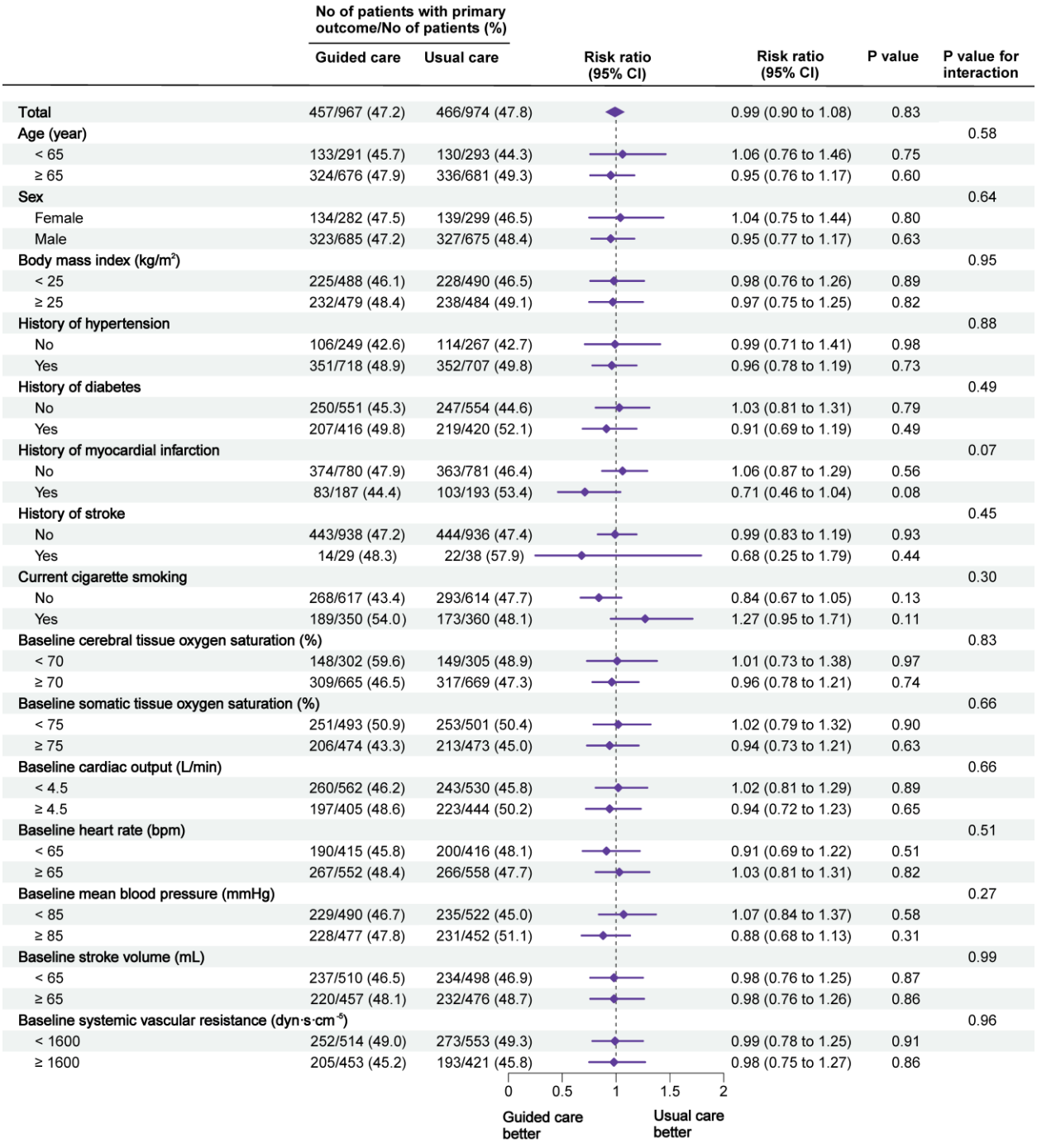
CI, confidence interval

* None of the p values for secondary outcomes were significant after adjustments for multiple comparisons using the Bonferroni-Holm method.
† The post hoc composite of serious complications included stroke, non-fatal cardiac arrest, heart failure, new-onset symptomatic ventricular arrhythmia, acute kidney injury stage III, sepsis, and mortality.

Outcomes	Guided care (n = 901)	Usual care (n = 964)	Risk ratio (95% CI)	P value*
	n (%)			
Primary outcome				
Composite of complications	418 (46.4)	460 (47.7)	0.97 (0.88 to 1.07)	0.60
Composite of serious complications†	83 (9.2)	85 (8.8)	1.04 (0.78 to 1.39)	0.83
Secondary outcomes				
Cerebral complications	284 (31.5)	305 (31.6)	1.00 (0.87 to 1.14)	>0.99
Postoperative delirium	176 (19.6)	200 (20.8)	0.94 (0.78 to 1.13)	0.55
Postoperative cognition decline	138 (15.3)	142 (14.7)	1.04 (0.84 to 1.29)	0.77
Stroke	3 (0.3)	13 (1.3)	0.25 (0.06 to 0.76)	0.03
Cardiac complications	85 (9.4)	77 (8.0)	1.18 (0.88 to 1.59)	0.31
Non−fatal cardiac arrest	4 (0.4)	6 (0.6)	0.71 (0.18 to 2.49)	0.83
Heart failure	37 (4.1)	26 (2.7)	1.52 (0.93 to 2.52)	0.12
Myocardial injury	19 (2.1)	18 (1.9)	1.13 (0.59 to 2.15)	0.84
Angina	6 (0.7)	4 (0.4)	1.60 (0.46 to 6.26)	0.67
Ventricular arrhythmia	38 (4.2)	37 (3.9)	1.10 (0.70 to 1.71)	0.77
Atrial fibrillation	265 (29.4)	291 (30.2)	0.97 (0.85 to 1.12)	0.75
Respiratory failure	84 (9.3)	97 (10.1)	0.93 (0.70 to 1.22)	0.65
Renal complications	13 (1.4)	12 (1.2)	1.16 (0.53 to 2.56)	0.87
Acute kidney injury stages II	10 (1.1)	8 (0.8)	1.34 (0.53 to 3.49)	0.71
Acute kidney injury stages III	3 (0.3)	4 (0.4)	0.80 (0.16 to 3.63)	>0.99
Infectious complications	124 (13.8)	168 (17.4)	0.79 (0.64 to 0.98)	0.04
Deep surgical site infection	7 (0.8)	8 (0.8)	0.94 (0.33 to 2.60)	>0.99
Organ/space infection	7 (0.8)	13 (1.3)	0.58 (0.22 to 1.40)	0.33
Pneumonia	80 (8.9)	119 (12.3)	0.72 (0.55 to 0.94)	0.02
Confirmed bloodstream infection	7 (0.8)	9 (0.9)	0.83 (0.30 to 2.22)	0.91
Uncertain source infection	30 (3.3)	38 (3.9)	0.84 (0.52 to 1.35)	0.56
Sepsis	2 (0.2)	4 (0.4)	0.53 (0.07 to 2.73)	0.74
Mortality	13 (1.4)	17 (1.8)	0.82 (0.39 to 1.67)	0.71



Supplementary figure 3: Subgroup analysis of the primary outcome



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