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Personalised haemodynamic management targeting baseline cardiac index in high-risk patients undergoing major abdominal surgery: a randomised single-centre clinical trial

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Abstract

Background: Despite several clinical trials on haemodynamic therapy, the optimal intraoperative haemodynamic management for high-risk patients undergoing major abdominal surgery remains unclear. We tested the hypothesis that personalised haemodynamic management targeting each individual's baseline cardiac index at rest reduces postoperative morbidity.

Methods: In this single-centre trial, 188 high-risk patients undergoing major abdominal surgery were randomised to either routine management or personalised haemodynamic management requiring clinicians to maintain personal baseline cardiac index (determined at rest preoperatively) using an algorithm that guided intraoperative i.v. fluid and/or dobutamine administration. The primary outcome was a composite of major complications (European Perioperative Clinical Outcome definitions) or death within 30 days of surgery. Secondary outcomes included postoperative morbidity (assessed by a postoperative morbidity survey), hospital length of stay, mortality within 90 days of surgery, and neurocognitive function assessed after postoperative Day 3.

Results: The primary outcome occurred in 29.8% (28/94) of patients in the personalised management group, compared with 55.3% (52/94) of patients in the routine management group (relative risk: 0.54, 95% confidence interval [CI]: 0.38 to 0.77; absolute risk reduction: −25.5%, 95% CI: −39.2% to −11.9%; $P<0.001$). One patient assigned to the personalised management group, compared with five assigned to the routine management group, died within 30 days after surgery ($P=0.097$). There were no clinically relevant differences between the two groups for secondary outcomes.

Conclusions: In high-risk patients undergoing major abdominal surgery, personalised haemodynamic management reduces a composite outcome of major postoperative complications or death within 30 days after surgery compared with routine care.

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Editor's key points

- The optimal target for haemodynamic management of high-risk noncardiac surgical patients remains unclear.
- Individualised haemodynamic management may be a rational approach to reduce postoperative morbidity.
- In this single-centre study, high-risk patients were randomised to either routine care or a therapeutic algorithm aimed at maintaining preoperative cardiac index.
- This personalised approach reduced major postoperative complications substantially within 30 days after surgery.

Major complications and mortality are common after major surgery,[1–4] particularly in patients with co-morbidities undergoing major surgical procedures.[3,5] Perioperative goal-directed haemodynamic therapy may decrease postoperative complications in high-risk patients.[6,7] However, because haemodynamic targets have varied between trials, the optimal haemodynamic treatment strategy for high-risk surgical patients remains unclear.[8,9]

The choice of the haemodynamic target value is likely to be critical,[10] as indicated by goal-directed therapy algorithms using cardiac output monitors that are associated with reductions in postoperative mortality.[6] Previous perioperative goal-directed therapy trials directly aimed at a maximisation of stroke volume,[7] used dynamic cardiac preload variables to maximise cardiac output[11,12] or used fixed population-based values as a haemodynamic target.[13,14] However, haemodynamic variables used as targets—including cardiac output—vary considerably amongst individuals.[15] In contrast to a 'one-size-fits-all approach', a precision or personalised strategy may be more beneficial.[16]

We hypothesised that the individual patient's preoperative cardiac index at rest may be the optimal haemodynamic target to refine intraoperative management.[16] We conducted a randomised clinical trial to test whether personalised haemodynamic management, by maintaining preoperative personal cardiac index at rest with fluids and the inotrope dobutamine, reduces complications or death within 30 days after surgery, compared with routine management in high-risk patients undergoing major abdominal surgery. We also tested the secondary hypotheses that personalised haemodynamic management may reduce the systemic inflammatory response[17] and promote neurocognitive recovery after surgery, as suggested by protocolised haemodynamic management trials.[18,19]

Methods

Trial design

We conducted a single-centre prospective randomised controlled clinical trial, Targeting preoperatively Assessed Personal cardiac Index in major abdominal suRgery patients (TAPIR), at the University Medical Center Hamburg-Eppendorf (Hamburg, Germany). Patients provided written informed consent before study enrolment. The trial was registered at ClinicalTrials.gov (NCT02834377) in May 2016.

Inclusion criteria

Adults ≥18 yr scheduled for major abdominal surgery expected to last ≥90 min or cause blood loss exceeding 1000 ml were eligible for study enrolment. At least one predefined patient-related high-risk criterion was also required (details regarding the high-risk criteria are provided in the Supplementary Appendix).

Exclusion criteria

We excluded patients who were pregnant, had palliative or emergency surgery, or who participated in another interventional trial.

Randomisation and procedures to minimise bias

Randomisation took place after the baseline cardiac index measurements to minimise study bias and to be able to compare baseline cardiac index between patients in the personalised and routine management groups. The staff responsible for baseline cardiac index measurements was not blinded to group allocation, because they were also in charge of data collection throughout the study (OD and ML). After baseline cardiac index assessment, the patients were randomised 1:1 without stratification based on computer-generated codes to routine management or to a personalised haemodynamic management algorithm. Allocation was concealed in sequentially numbered opaque envelopes. The patients were blinded to group allocation, but clinicians responsible for intraoperative care in the personalised management group could not be. However, all outcomes were assessed by investigators blinded to patient allocation.

Study interventions

All subjects

We assessed the baseline cardiac index at rest using noninvasive pulse wave analysis (finger-cuff technology).[20,21] We used the CNAP® system (CNSystems Medizintechnik GmbH, Graz, Austria) that has been validated against pulmonary artery thermodilution.[22] A research staff member visited the subject and measured the baseline cardiac index at rest the evening before surgery on the ward with the subject being awake and lying in supine position. The CNAP finger-cuff technology derives a continuous arterial pressure waveform from the finger-cuff pressure that is needed to keep the blood volume in the finger constant during the cardiac cycle.[23] The arterial pressure signal derived by the finger-cuff is calibrated to brachial blood pressure values obtained with an oscillometric upper-arm cuff. Based on pulse wave analysis, cardiac index is estimated from the noninvasively obtained arterial pressure waveform using a proprietary algorithm.[21,24,25] We

defined the average cardiac index value observed over a five min period as the personal baseline cardiac index at rest and used this value as target value in the personalised management group. Except for the study interventions, all other diagnostic and therapeutic decisions were at the discretion of the treating clinicians.

Intervention group (personalised management)

The study intervention started at the beginning of surgery and continued throughout anaesthesia. Study investigators were present throughout surgery to supervise the intervention. Patients allocated to the personalised management group received balanced crystalloids at a baseline infusion rate of 6 ml kg^{-1} h^{-1} and additional 500 ml fluid boluses (either colloid or crystalloid as per clinician preference) and dobutamine according to the treatment algorithm (Fig. 1) to maintain intraoperative cardiac index at individualised preoperative values measured at rest. We measured intraoperative cardiac index using invasive pulse wave analysis (radial arterial catheter). We used the ProAQT® system (PULSION Medical Systems, Feldkirchen, Germany) that has been validated against transpulmonary thermodilution.[26] Mean arterial blood pressure was maintained between 65 and 90 mm Hg using norepinephrine (the first-line vasopressor to treat intraoperative hypotension in our institution).

Control group (routine management)

Subjects allocated to the routine management group were treated as per anaesthesiologist preference. Routine management in our institution for patients eligible for study inclusion constitutes general anaesthesia maintained with inhaled sevoflurane and repeated boluses of sufentanil with or without neuraxial regional anaesthesia. Typically, blood pressure is monitored with an arterial catheter. Crystalloid or colloid fluid was used to maintain normovolaemia. Cardiac index monitoring was available on request. Mean arterial blood pressure was maintained above 65 mm Hg, with norepinephrine used as the first-line vasopressor. Clinical staff was unaware that these subjects participated in a trial.

Primary outcome

The primary outcome was a composite of major complications (i.e. severe complications defined according to the European Perioperative Clinical Outcome definitions[27]) or death within 30 days after surgery. The clinical outcomes of myocardial ischaemia, limb ischaemia, and bowel infarction were not prespecified as part of the composite, but were additionally included. Myocardial ischaemia might occur without the diagnosis of myocardial infarction. Limb ischaemia and bowel infarction were included as part of the composite based on the previous literature on similar trials.[7]

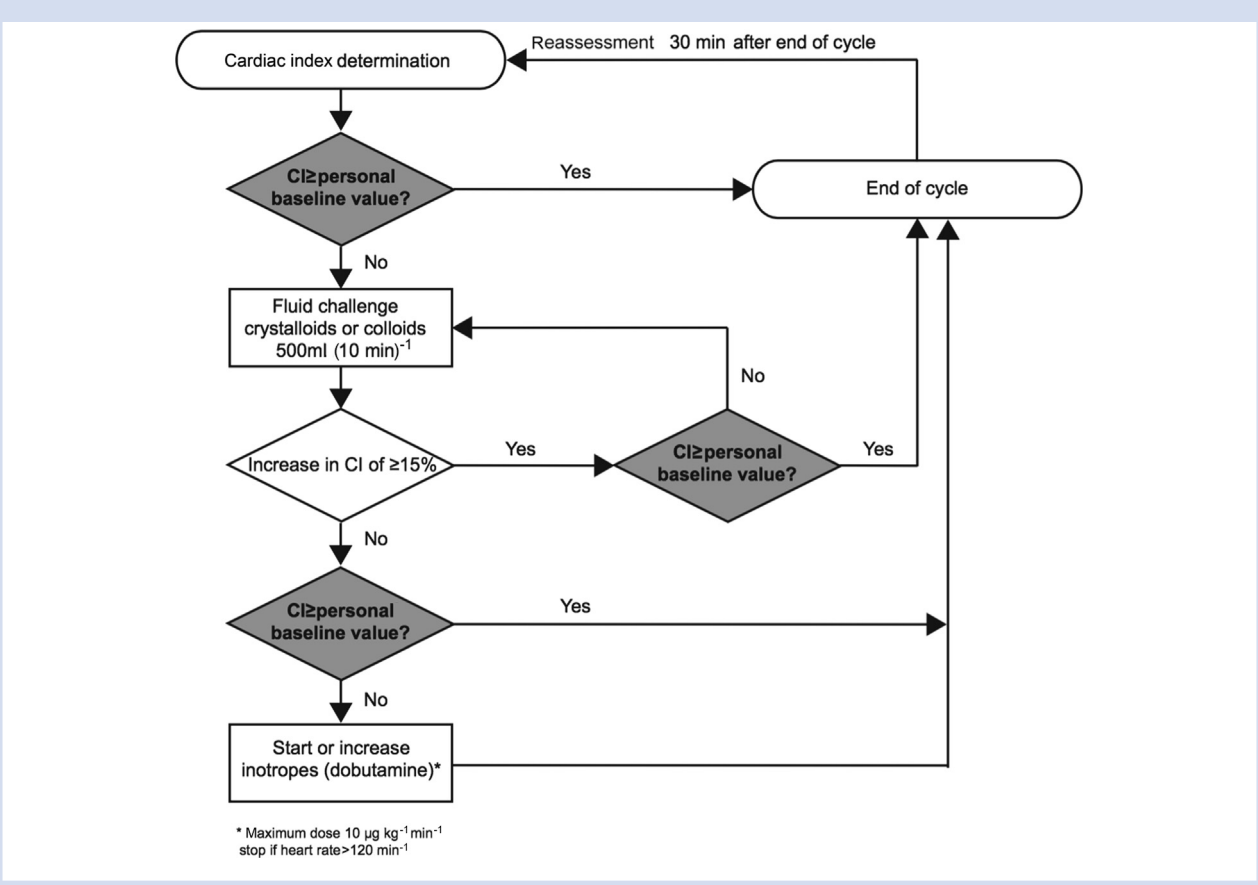

Fig. 1. Treatment algorithm in the personalised management group. Norepinephrine was used to keep the mean arterial blood pressure between 65 and 90 mm Hg. CI, cardiac index.

Secondary outcomes

Secondary study endpoints were as follows:

(i) Postoperative complications defined in the postoperative morbidity survey (POMS)[28] at postoperative Days 3, 7, 14, and 30, using electronic health records or telephone follow-up
(ii) Hospital length of stay
(iii) All-cause mortality at Day 90, assessed by contacting the subject, relatives, or the primary care physician by telephone
(iv) Neurocognitive function: subjects completed a patient health depression questionnaire (Patient Health Questionnaire-9[29]) and four neuropsychological tests before surgery and after postoperative Day 3. The tests were the California Verbal Learning Test for the assessment of memory, the Stroop Colour–Word Interference Test to measure attention and cognitive speed, the Trail Making Tests A and B for capturing cognitive processing speed and flexibility, and an examination of fine motor skills (Supplementary Tables S3 and S4). All tests were performed in a standardised way by the same investigator, and parallel versions were applied.
(v) Systemic inflammation, as reflected by arginine derivatives at Day 3 (Supplementary Table S5) as measures of nitric oxide (NO) metabolic pathway (blood samples were collected immediately before and 3 days after surgery)

Statistical analysis

Statistical analyses for the primary endpoint were performed according to the intention-to-treat principle. For comparison of categorical data of the primary endpoint, the χ^2 test was used. For the analysis of the secondary endpoints, we used statistical tests for independent samples (parametric or non-parametric tests for continuous data, and χ^2 test for categorical data). All-cause mortality up to 90 days after the surgical procedure was analysed by the Kaplan–Meier method, and the log rank test for statistical significance was applied. For continuous variables, the mean with standard deviation is presented for normally distributed data and medians with inter-quartile ranges for non-normally distributed data. For categorical variables, the number and percentage of patients are shown. For the comparison of baseline patient characteristic variables between the personalised and routine management groups, we calculated absolute standardised differences.[30] All statistical analyses were performed using the statistical software package R version 3.1.2 (R Core Team [2014]; R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org).

Sample size calculation

Around 50% of subjects sustain complications after similar surgery.[11] We estimated that 94 patients per group would provide 80% power for detecting an absolute reduction in the primary composite outcome from 50% to 30% at an alpha level of 5%. We therefore planned to enrol 188 subjects without interim analyses. The statistical analysis plan was included in the full trial protocol that was approved by the ethics committee before enrolment of the first study subject. The statistical analysis plan was not publically accessible before the completion of data collection.

Results

Subject characteristics

From May 2016 to June 2017, 188 subjects were randomised (Fig. 2). The two groups were similar with respect to subject characteristics and baseline risk factors, although the duration of surgery was longer in subjects assigned to routine management (Table 1). A detailed overview of the types of surgery is provided in Supplementary Table S1. The total amount of administered fluids, blood loss, urine output, and intraoperative use of vasopressors were similar between each group (Table 2).

Adherence to intervention

Cardiac index was monitored in >99% of the subjects assigned to personalised management and 20% of the subjects assigned to routine management. In 43% of subjects, the first measured cardiac index at the beginning of surgery was equal or higher than the preoperative personal cardiac index value. In 85% of the personalised management group subjects, cardiac index was maintained above the personal target cardiac index for >90% of the duration of surgery. In the personalised management group, non-adherence to protocol occurred in 9% of patients; typically, non-adherence consisted of additional fluid administration although the cardiac index target was already reached.

Primary outcome: complications and mortality

The primary outcome occurred in 29.8% (28/94) of subjects in the personalised management group, compared with 55.3% (52/94) of subjects in the routine management group (relative risk: 0.54, 95% confidence interval [CI]: 0.38 to 0.77; absolute risk reduction: −25.5%, 95% CI: −39.2% to −11.9%; $P<0.001$) (Table 3). Infection was the component that contributed most to differences in the composite incidence. One subject assigned to the personalised management group and five assigned to the routine management group died within 30 days after surgery ($P=0.097$).

Secondary endpoints

POMS-defined postoperative complication

There were fewer subjects with at least one POMS-defined postoperative complication in the personalised management group than in the routine management group at postoperative Days 3 and 7 (there were no significant differences at postoperative Days 14 and 30) (detailed results are provided in Supplementary Table S2).

Hospital length of stay/90-day mortality

Hospital lengths of stay and 90 day mortality (Fig. 3) were similar in each group.

Neurocognitive testing

A detailed description of the preoperative and postoperative neuropsychological test battery results is provided in Supplementary Table S4. The California Verbal Learning Test

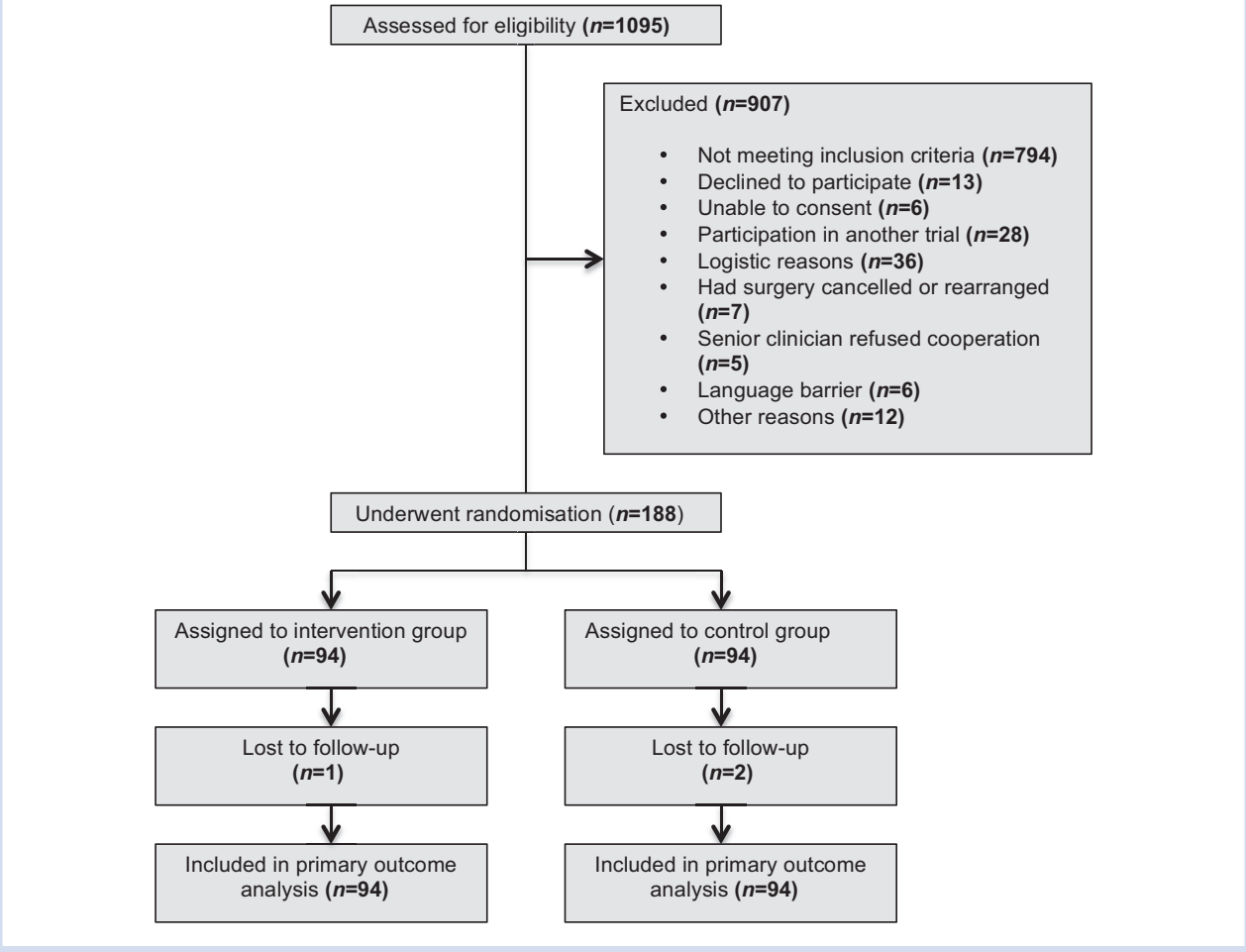

Fig. 2. CONSORT (Consolidated Standards of Reporting Trials) participant flow. Flow diagram illustrating patient enrolment and reasons for exclusion.

for assessment of memory and the Trail Making Tests A and B for cognitive processing speed and flexibility were similar in each group. The processing speed in the Stroop Colour–Word Interference Test, a measure of attention and cognitive speed, was faster in the personalised management group than in the routine management group (6.0 [1.75] min *vs* 6.8 [2.3] min; $P=0.04$). Fine motor skills were also significantly better in patients in the personalised management group compared with patients in the routine management group (postoperative left-hand line tracing: lower number [34 {13} *vs* 40 {15}; $P=0.02$] and shorter duration of errors [4.6 {2.4} s *vs* 6.5 {3.3} s; $P<0.001$]).

Systemic inflammation

Preoperative and postoperative levels of biomarkers of NO metabolism were similar in each group. The detailed results for all blood analyses are provided in Supplementary Table S5.

Discussion

In this randomised clinical trial in high-risk patients undergoing major abdominal surgery, personalised haemodynamic management, which targeted each individual's baseline cardiac index value at rest using fluids and dobutamine, reduced a composite outcome of major postoperative complications or death within 30 days after surgery, compared with routine management.

We used the patient's personal baseline cardiac index value at rest as the intraoperative haemodynamic target. Haemodynamic variables show large inter-individual variability, and reference ranges for cardiac chamber sizes and cardiac function depend on the patient's characteristics and biometric factors.[15,31–33] We observed a wide range of baseline cardiac index values. This supports the hypothesis that targeting the patient's personal baseline cardiac index value results in markedly different target values than using population-derived normal values. In a previous multicentre randomised trial on postoperative goal-directed therapy, it was demonstrated that achieving a patient's individual preoperative oxygen delivery value in the postoperative phase was associated with less morbidity (although this was not affected by the use of an oxygen delivery targeted strategy).[34]

Innovative noninvasive monitoring technologies now enable patients' baseline cardiac index values to be assessed

Table 1 Clinical characteristics before surgery

Baseline subject characteristics*				
Characteristic	**Total (*n*=188)**	**Personalised group (*n*=94)**	**Routine group (*n*=94)**	**Standardised differences**
Age, mean (SD), yr				
Age (yr)	63 (14)	63 (14)	63 (14)	0.000
<65	94 (50)	45 (48)	49 (52)	0.040
≥65	94 (50)	49 (52)	45 (48)	0.040
Sex				
Male	114 (61)	54 (57)	60 (64)	0.057
Female	74 (39)	40 (43)	34 (36)	0.065
Height, mean (SD), cm	173.2 (9.2)	173.4 (9.9)	172.9 (8.4)	0.054
Weight, mean (SD), kg	76.1 (17.9)	76.1 (18.8)	76.2 (17.1)	0.006
Preoperative cardiac index, mean (SD), L min^{-1} m^{-2}	3.01 (0.62)	2.98 (0.66)	3.05 (0.58)	0.113
Baseline risk factors†				
Renal impairment	47 (25)	22 (23)	25 (27)	0.040
Risk factor for cardiac or respiratory disease	92 (49)	45 (48)	47 (50)	0.020
Immunosuppression	90 (48)	45 (48)	45 (48)	0.000
Liver impairment	3 (2)	1 (1)	2 (2)	0.052
Age ≥80 yr	13 (7)	7 (7)	6 (6)	0.023
Abdominal surgery procedure category				
General surgery	117 (62)	59 (63)	58 (62)	0.009
Urological surgery	22 (12)	6 (6)	16 (17)	0.201
Gynaecological surgery	24 (13)	16 (17)	8 (9)	0.136
Aortic surgery	25 (13)	13 (14)	12 (13)	0.017
American Society of Anesthesiologists physical status				
2	25 (13)	11 (12)	14 (15)	0.053
3	136 (73)	69 (73)	67 (73)	0.018
4	25 (13)	14 (15)	11 (12)	0.051
Patient Health Questionnaire-9 score,‡ mean (SD) (points)	6.8 (5.1)	7 (5.4)	6.5 (4.8)	0.098

*Data are presented as *n* (%) of patients unless otherwise indicated.
†Patients may have more than one risk factor.
‡Data available in 152 patients; scale ranges from 0 to 27 points; 1–4 points, minimal depressive disorder; 5–9 points, mild depressive disorder; 10–14 points, moderate depressive disorder; and 15–27 points, severe depressive disorder.
SD, standard deviation; ASA, American Society of Anesthesiologists.

before surgery. For preoperative cardiac index assessment, we used a finger-cuff technology validated for blood pressure[35,36] and cardiac output[22] measurements. For intraoperative measurement of cardiac index, we used pulse wave analysis of the arterial blood pressure waveform obtained with a radial arterial catheter. Using easy-to-apply monitoring technologies and a straightforward treatment algorithm has probably facilitated the high rate of adherence to the treatment protocol in the personalised management group.

Our study intervention markedly decreased the incidence of the primary endpoint in the personalised management group compared with the routine management group. This marked effect might be explained by the use of rigorous definitions of inclusion criteria that allowed identifying patients at particular high risk for postoperative complications after major abdominal surgery. Meta-analyses demonstrated that perioperative goal-directed haemodynamic therapy is particularly beneficial in high-risk surgical patients.[6,37] In addition, recent meta-analyses showed that perioperative goal-directed haemodynamic therapy only improves patient outcome if fluids and vasoactive agents are required per protocol[6] and cardiac output/cardiac index goals were applied.[38] Our treatment algorithm triggered the use of dobutamine in the personalised management group, whilst the amount of administered fluids and the use and dosage of norepinephrine were similar between groups. We observed that infectious complications occurred less frequently in patients allocated to receive personalised management. This is consistent with findings from previous meta-analyses showing that goal-directed haemodynamic therapy was associated with a reduction in infectious complications.[7,39]

Major abdominal surgery results in a systemic inflammatory response syndrome associated with an increased risk for infection and impaired microbicidal immunity.[40] Adequate oxygen tissue concentrations may promote immune competence and wound healing,[41,42] as neutrophils and alveolar macrophages depend on adequate oxygen tissue pressure.[43,44] Therefore, adequate perioperative oxygen delivery may be particularly important to avoid infectious complications, especially as major abdominal surgery is thought to be accompanied by an increased oxygen demand. Low tissue oxygen pressure is a known risk factor for surgical site infections,[45] a postoperative complication that was lower in patients receiving personalised management. Pathophysiologically reduced blood flow leads to hypoperfusion and consequently to an impairment of the mucosal immunological

Table 2 Clinical characteristics during the perioperative period

Clinical characteristics during the perioperative period				
Characteristic	**Total (n=188)**	**Personalised group (n=94)**	**Routine group (n=94)**	**Standardised differences**
Anaesthetic technique, n (%)				
Inhalational anaesthesia†	175 (93)	87 (93)	88 (94)	0.009
Total i.v. anaesthesia	12 (6)	7 (7)	5 (5)	0.048
Epidural anaesthesia (in addition to general anaesthesia)	127 (68)	64 (68)	63 (67)	0.009
Duration of surgery, mean (SD), min*	246 (101)	222 (85)	271 (109)	0.501
Cardiac index monitoring, n (%)*	112 (60)	93 (99)	19 (20)	0.724
Fluids, median (IQR), ml				
Crystalloids during surgery	2888 (2000–3883)	2730 (2000–3580)	3000 (2000–4000)	
Colloids during surgery	1000 (500–1500)	1000 (500–1500)	1000 (500–1500)	
Crystalloids+colloids during surgery	3250 (2182–4568)	3110 (2054–4408)	3500 (2500–5000)	
Packed red blood cells	840 (560–1120)	840 (560–1120)	840 (560–1330)	
Fresh frozen plasma	1320 (880–1760)	1540 (1100–4070)	1320 (880–1760)	
Platelets	300 (200–500)	500 (350–650)	300 (200–400)	
Albumin, g	25 (25–50)	25 (25–25)	31 (25–50)	
Total fluids	6000 (4090–8570)	5552 (4100–7438)	6000 (4080–9280)	
Blood loss	600 (200–1100)	500 (200–1000)	700 (300–1350)	
Urine output	435 (240–700)	450 (200–690)	420 (250–700)	
Fluid balance	2440 (1440–3995)	2384 (1500–3458)	2500 (1400–4230)	
Vasopressors and inotropes				
Use of vasopressor (norepinephrine) during surgery, n (%)	186 (99)	93 (99)	93 (100)	0.000
Hourly median (IQR) of norepinephrine dose during surgery ($\mu g\ kg^{-1}\ min^{-1}$)	0.12 (0.07–0.19)	0.11 (0.06–0.18)	0.14 (0.09–0.19)	
Use of inotrope (dobutamine) during surgery, n (%)*	46 (25)	36 (38)	10 (11)	0.326
Median cumulative dose (IQR) of dobutamine during surgery (mg)	27 (17–43)	27 (19–43)	18 (14–39)	
Actual location of care after surgery, n (%)				
PACU and normal ward	31 (16)	13 (14)	18 (19)	0.081
High-dependency unit Level 1	57 (30)	30 (32)	27 (29)	0.036
High-dependency unit Level 2	66 (35)	34 (36)	32 (34)	0.023
ICU	34 (18)	17 (18)	17 (18)	0.000

*P-value <0.001.
†Inhaled sevoflurane and repeated boluses of sufentanil.
IQR, inter-quartile range; SD, standard deviation; PACU, post anaesthesia care unit; ICU, intensive care unit.

response and disruption of the gut barrier.[46–48] A dysfunctional gut barrier may permit bacterial translocation into the bloodstream.[49] Personalised haemodynamic management aiming at optimising cardiac index and oxygen delivery may therefore limit gut barrier damage.[50]

Neurocognitive impairment after anaesthesia and surgery represents a significant public health concern.[51] We found that the processing speed in the Stroop Colour-Word Interference Test was superior in patients receiving personalised haemodynamic management. Recent studies imply that there is an association between perioperative haemodynamic management and postoperative neurocognitive function.[18,19] Those studies corroborate the assumption that optimising blood flow improves postoperative cognitive function in older and high-risk patients.[18,19] Intraoperative personalised haemodynamic management to optimise blood flow may thus be an appealing strategy to prevent delayed cognitive recovery in patients undergoing high-risk abdominal surgery.

We found no differences in biomarkers for NO metabolism between groups. NO is crucial in regulating vascular tone and blood flow to all organs. Direct measurement of NO is impossible because of its extremely short half-life. One possibility to estimate NO activity is indirect measurement of substrates of NO synthases (NOS) (L-arginine and homoarginine) and endogenous inhibitors of NOS (asymmetric dimethylarginine [ADMA] and symmetric dimethylarginine [SDMA]). Increasing concentrations of ADMA and SDMA are associated with poor outcome in patients with septic complications.[17] Moreover, in patients with chronic cardiovascular and renal disease, NOS inhibitors are related to disease severity. However, our findings did not support the hypothesis that personalised haemodynamic therapy altered NOS activity and vascular reactivity.

A strength of this study was the high rate of protocol adherence. Measuring baseline cardiac index before surgery and thus personalising intraoperative goal-directed therapy were feasible and accepted by patients and caregivers. Both the noninvasive pulse wave analysis method we used to assess the preoperative baseline value and the invasive pulse wave analysis method we used during surgery have been validated against clinical reference methods (indicator dilution methods).[22,26,52] However, there are no studies directly

Table 3 Primary outcome

Results for the primary outcome						
Outcome	**Total, *n* (%) (*n*=188)**	**Personalised group, *n* (%) (*n*=94)**	**Routine group, *n* (%) (*n*=94)**	**Standardised differences**	**P-value**	**Relative risk (95% CI)**
Composite of predefined major postoperative complications and mortality at Day 30 after surgery	80 (43)	28 (30)	52 (55)	0.268	<0.001	0.54 (0.38–0.77)
Single outcome measures[†]						
Mortality	6 (3)	1 (1)	5 (5)	0.158	0.1	0.2 (0.02–1.68)
Myocardial ischaemia or infarction	0	0	0	0.000	NA	NA
Arrhythmia	7 (4)	3 (3)	4 (4)	0.033	0.68	0.73 (0.17–3.19)
Cardiac arrest	5 (3)	2 (2)	3 (3)	0.039	0.63	0.65 (0.11–3.82)
Limb ischaemia	1 (1)	1 (1)	0	0.073	0.32	NA
Cardiogenic pulmonary oedema	1 (1)	0	1 (1)	0.103	0.31	NA
Deep vein thrombosis	0	0	0	0.000	NA	NA
Pulmonary embolism	2 (1)	2 (2)	0	0.104	0.16	NA
Acute respiratory distress syndrome	1 (1)	0	1 (1)	0.103	0.31	NA
Gastrointestinal bleeding	1 (1)	1 (1)	0	0.073	0.32	NA
Bowel infarction	0	0	0	0.000	NA	NA
Anastomotic breakdown	7 (4)	4 (4)	3 (3)	0.031	0.72	1.31 (0.30–5.67)
Paralytic ileus	2 (1)	0	2 (2)	0.147	0.15	NA
Acute kidney injury[‡]	15 (8)	5 (5)	10 (11)	0.118	0.17	0.49 (0.17–1.38)
Infection, source uncertain	5 (3)	2 (2)	3 (3)	0.039	0.63	0.65 (0.11–3.82)
Delirium	13 (7)	5 (5)	8 (9)	0.074	0.37	0.61 (0.21–1.80)
Urinary tract infection	8 (4)	1 (1)	7 (8)	0.209	0.03	0.14 (0.02–1.11)
Surgical site infection	37 (20)	13 (14)	24 (26)	0.169	0.04	0.53 (0.29–0.98)
Laboratory-confirmed blood stream infection	11 (6)	6 (6)	5 (5)	0.025	0.78	1.17 (0.37–3.72)
Hospital-acquired pneumonia	17 (9)	10 (11)	7 (8)	0.061	0.47	1.40 (0.56–3.52)
Postoperative haemorrhage	3 (2)	2 (2)	1 (1)	0.046	0.57	1.96 (0.18–21.22)
Stroke	2 (1)	0	2 (2)	0.147	0.15	NA

[†]Some patients developed more than one complication.
[‡]Kidney Disease Improving Global Outcomes guidelines Stage 1 or higher (Stage 1: serum creatinine 1.5–1.9 times baseline value within 7 days or ≥27 μmol L^{-1} (0.3 mg dl^{-1}) increase within 48 h).
CI, confidence interval; NA, not applicable

comparing the two pulse wave analysis methods with each other.

This single-centre trial has several limitations. The unanticipated differences in duration of surgery between the groups may explain the difference in postoperative complications. Because of the relatively small sample size, we were unable to adjust for the possible impact of the duration of surgery on the study outcomes. A further limitation was the mode of randomisation; a centralised randomisation system has advantages over the envelope-based randomisation that was used in our study.[53] We cannot compare episodes of hypotension between groups as we did not systematically record blood pressure values in the routine management group. The patient's cardiac index value at rest might not necessarily be a useful surrogate for the cardiac index needed during high-risk surgery, in the face of trauma and systemic inflammation. In addition, only a minority of patients in the routine management group had advanced haemodynamic monitoring; therefore, we are not able to provide a full comparison of cardiac index values. We do not generally recommend the approach of using two different devices. This was a pragmatic randomised controlled clinical trial using noninvasively assessed personal cardiac index at rest as a haemodynamic target during surgery. The study ideally needs repeating with either two devices that have been previously compared or with the same device. In the personalised management group, anaesthesiologists, surgeons, nurses, and investigators could not be blinded because of the mandatory use of cardiac index monitoring and the haemodynamic treatment algorithm. Further, the clinicians treating the personalised management

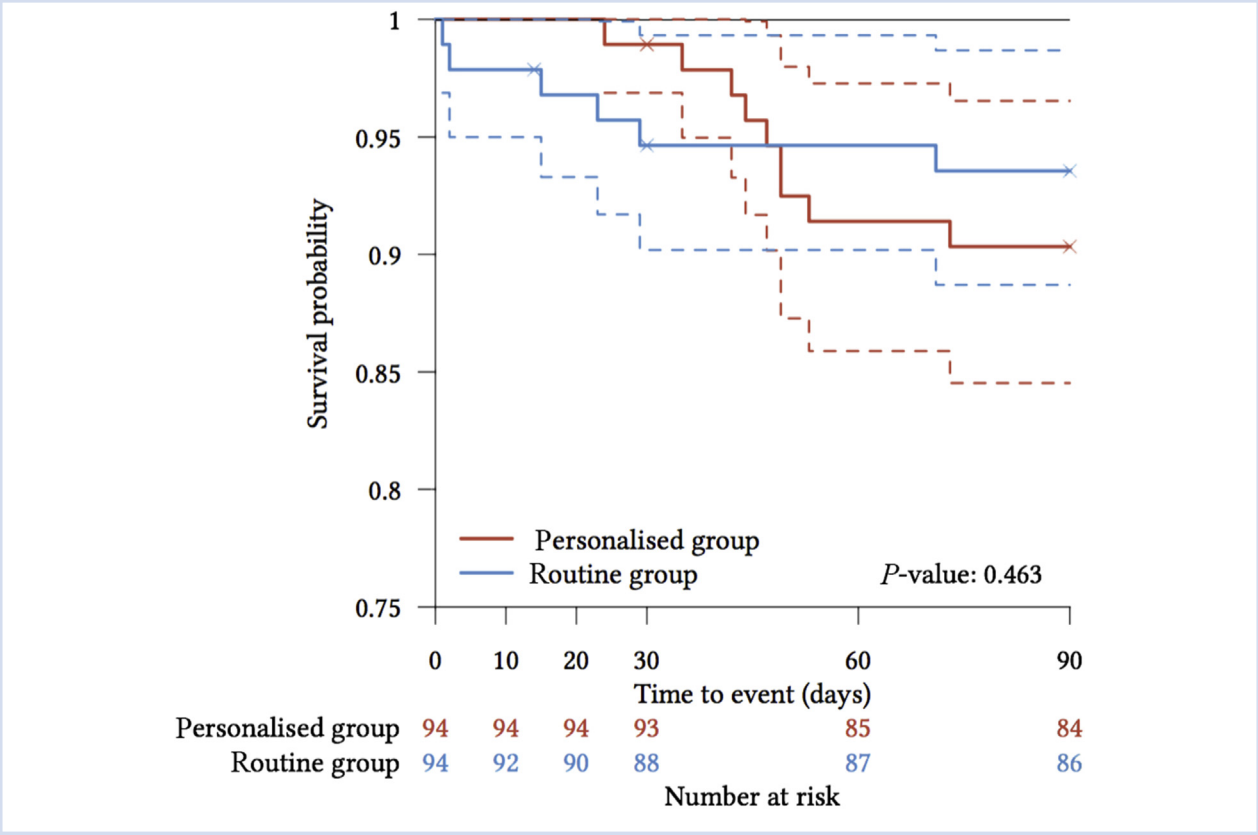

Fig. 3. Survival probability up to 90 days after surgery. Kaplan–Meier plot and 95% confidence intervals for the personalised management and routine management groups for the event 'death' are shown.

group patients were supervised by the study investigators. This implies the possibility that more global aspects of clinical care (e.g. management of intraoperative blood pressure) contributed to the differences in outcomes. It cannot be excluded that the use of a more structured approach to intraoperative fluid management *per se* instead of targeting the personal baseline cardiac index decreased postoperative complications. Finally, we cannot prove that the improvement in outcome in patients in the personalised management group is caused by targeting the exact value of the patients' personal baseline cardiac index or simply by increasing cardiac index at all.

In conclusion, in high-risk patients undergoing major abdominal surgery, personalised haemodynamic management (targeting the personal baseline cardiac index at rest using fluids and dobutamine) reduces a composite outcome of major postoperative complications or death within 30 days after surgery compared with routine management.

Authors' contributions

Study conception/design: JYN, BS
Data acquisition: JYN, OD, ML, CS
Data analysis/interpretation: all authors.
Statistical analysis: GS, JYN, BS
Drafting of article: JYN, BS
Critical revision of article for important intellectual content: all authors.
JYN and BS had full access to all of the data in the study, and are responsible for the integrity of the data and the accuracy of the data analysis.

Declarations of interest

JYN has received refunds of travel expenses from CNSystems Medizintechnik GmbH (Graz, Austria). BS collaborates with PULSION Medical Systems SE (Feldkirchen, Germany) as a member of the medical advisory board, and has received institutional restricted research grants, honoraria for giving lectures, and refunds of travel expenses from PULSION Medical Systems SE. BS has received research support, honoraria for giving lectures, and honoraria for consulting from Edwards Lifesciences (Irvine, CA, USA). BS has received institutional restricted research grants, honoraria for giving lectures, and refunds of travel expenses from CNSystems Medizintechnik GmbH. BS has received institutional restricted research grants, honoraria for consulting, and refunds of travel expenses from Tensys Medical Inc. (San Diego, CA, USA). BS has received institutional restricted research grants from Retia Medical LLC (Valhalla, NY, USA). BS has received honoraria for giving lectures from Philips Medizin Systeme Böblingen GmbH (Böblingen, Germany). DAR was a member of the medical

advisory board of PULSION Medical Systems SE. All other authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.04.094.

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