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Effect of Individualized vs Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery
A Randomized Clinical Trial

Emmanuel Futier, MD, PhD; Jean-Yves Lefrant, MD, PhD; Pierre-Gregoire Guinot, MD, PhD; Thomas Godet, MD, PhD; Emmanuel Lorne, MD; Philippe Cuvillon, MD, PhD; Sebastien Bertran, MD; Marc Leone, MD, PhD; Bruno Pastene, MD; Vincent Piriou, MD, PhD; Serge Molliex, MD, PhD; Jacques Albanese, MD, PhD; Jean-Michel Julia, MD; Benoit Tavernier, MD, PhD; Etienne Imhoff, MD; Jean-Etienne Bazin, MD, PhD; Jean-Michel Constantin, MD, PhD; Bruno Pereira, PhD; Samir Jaber, MD, PhD; for the INPRESS Study Group

IMPORTANCE Perioperative hypotension is associated with an increase in postoperative morbidity and mortality, but the appropriate management strategy remains uncertain.

OBJECTIVE To evaluate whether an individualized blood pressure management strategy tailored to individual patient physiology could reduce postoperative organ dysfunction.

DESIGN, SETTING, AND PARTICIPANTS The Intraoperative Norepinephrine to Control Arterial Pressure (INPRESS) study was a multicenter, randomized, parallel-group clinical trial conducted in 9 French university and nonuniversity hospitals. Adult patients (n = 298) at increased risk of postoperative complications with a preoperative acute kidney injury risk index of class III or higher (indicating moderate to high risk of postoperative kidney injury) undergoing major surgery lasting 2 hours or longer under general anesthesia were enrolled from December 4, 2012, through August 28, 2016 (last follow-up, September 28, 2016).

INTERVENTIONS Individualized management strategy aimed at achieving a systolic blood pressure (SBP) within 10% of the reference value (ie, patient's resting SBP) or standard management strategy of treating SBP less than 80 mm Hg or lower than 40% from the reference value during and for 4 hours following surgery.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of systemic inflammatory response syndrome and dysfunction of at least 1 organ system of the renal, respiratory, cardiovascular, coagulation, and neurologic systems by day 7 after surgery. Secondary outcomes included the individual components of the primary outcome, durations of ICU and hospital stay, adverse events, and all-cause mortality at 30 days after surgery.

RESULTS Among 298 patients who were randomized, 292 patients completed the trial (mean [SD] age, 70 [7] years; 44 [15.1%] women) and were included in the modified intention-to-treat analysis. The primary outcome event occurred in 56 of 147 patients (38.1%) assigned to the individualized treatment strategy vs 75 of 145 patients (51.7%) assigned to the standard treatment strategy (relative risk, 0.73; 95% CI, 0.56 to 0.94; P = .02; absolute risk difference, −14%, 95% CI, −25% to −2%). Sixty-eight patients (46.3%) in the individualized treatment group and 92 (63.4%) in the standard treatment group had postoperative organ dysfunction by day 30 (adjusted hazard ratio, 0.66; 95% CI, 0.52 to 0.84; P = .001). There were no significant between-group differences in severe adverse events or 30-day mortality.

CONCLUSIONS AND RELEVANCE Among patients predominantly undergoing abdominal surgery who were at increased postoperative risk, management targeting an individualized systolic blood pressure, compared with standard management, reduced the risk of postoperative organ dysfunction.

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Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The INPRESS Study Group investigators are listed at the end of this article.

Corresponding Author: Emmanuel Futier, MD, PhD, Département de Médecine Périopératoire, Anesthésie Réanimation, Hôpital Estaing, 1 place Lucie Aubrac, 63003 Clermont-Ferrand, France (efutier@chu-clermontferrand.fr).

Section Editor: Derek C. Angus, MD, MPH, Associate Editor, *JAMA* (angusdc@upmc.edu).

The number of patients undergoing major surgery worldwide is growing with advancements in treating disease.[1] However, many patients still die or experience severe perioperative complications.[2]

Hemodynamic instability is common during surgery. There is accumulating evidence that intraoperative hypotension is associated with injury to heart, kidney, and brain and an increased likelihood of mortality in high-risk patients.[3-6] However, intraoperative hypotension is a preventable risk factor as arterial pressure is modifiable using intravenous fluids and/or vasopressors. There is no consensus regarding optimal blood pressure target thresholds to support perfusion of critical organs during surgery. Systolic blood pressure (SBP) less than 80 mm Hg,[6,7] mean arterial pressure less than 60 mm Hg,[4] and a reduction of 30% to 50% from baseline are common treatment thresholds used in clinical practice,[7,8] highlighting the lack of consensus. Current guidelines from the American College of Cardiology and the American Heart Association[9] in the setting of noncardiac surgery recommend individualizing care for surgical patients with associated comorbidities. In patients with preexisting hypertension, the autoregulatory capacity of the brain and kidneys is likely impaired,[10,11] thus rendering organs more susceptible to ischemia at low blood pressure. Accordingly, higher blood pressure targets tailored to individual patient physiology may be preferable for such high-risk patients.[4,5,8,12] Consensus guidelines in the context of critical illness have suggested adjusting blood pressure targets to premorbid values.[13] However, trial data are lacking for an individualized strategy in the surgical setting.

This multicenter, randomized, stratified clinical trial involving high-risk surgical patients sought to determine whether a strategy of targeting individualized systolic blood pressure, tailored to the patient's usual value, would reduce organ dysfunction as compared with standard practice.

Key Points

Question Does a strategy based on individualized blood pressure management reduce postoperative complications among high-risk patients undergoing major abdominal surgery?

Findings In this randomized clinical trial involving 292 patients, most of whom underwent abdominal surgery, an individualized management strategy of targeting a systolic blood pressure within 10% of the patient's normal resting value, compared with standard practice, resulted in significantly lower rates of postoperative organ dysfunction (38.1% vs 51.7%, respectively).

Meaning Among patients undergoing abdominal surgery, an individualized blood pressure management strategy during surgery tailored to individual patient physiology may improve postoperative outcomes.

Methods

Study Design

This was an investigator-initiated, multicenter, stratified, parallel-group randomized clinical trial conducted in 9 French university and nonuniversity hospitals. The trial protocol was approved for all centers on January 5, 2011, by the ethics committee at the Clermont-Ferrand University Hospital. Written informed consent was obtained from each patient before randomization and surgery. The trial protocol and the statistical analysis plan are available in Supplement 1. An independent data and safety monitoring committee oversaw the study conduct and reviewed blinded safety data.

Study Participants

Patients were assessed for eligibility on the eve of their surgery. Patients were eligible for participation if they were aged 50 years or older, were scheduled to undergo surgery under general anesthesia with an expected duration of 2 hours or longer, had an American Society of Anesthesiologists physical status of class II or higher, had a preoperative acute kidney injury risk index[14] of class III or higher, and did not meet any exclusion criteria. The acute kidney injury risk index ranges from I to V, with higher classes indicating a higher risk of postoperative acute kidney injury (eAppendix in Supplement 2). Patients were excluded if they had severe uncontrolled hypertension (SBP ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg); had chronic kidney disease (glomerular filtration rate <30 mL/min/1.73 m^2 or requiring renal replacement therapy for end-stage renal disease); had acute or decompensated heart failure or acute coronary syndrome; had preoperative sepsis or were already receiving norepinephrine infusion; required renal vascular surgery; or were enrolled in another study. Detailed exclusion criteria are listed in the eAppendix in Supplement 2.

Study Interventions

Eligible patients were assigned in a 1:1 ratio to either a standard or individualized treatment strategy. The resting blood pressure from the preoperative anesthesiology consultation was obtained from the patient medical record and used as the reference value. If this was unavailable, the blood pressure measurement recorded by a nurse of the surgical ward the day before surgery, while the patient was in supine position, was used as the reference value. In the standard treatment group, patients received intravenous ephedrine administered in 6-mg boluses (for a maximum dose not exceeding 60 mg), as recommended,[15] for any decrease in SBP below 80 mm Hg or lower than 40% from the patient's reference value.[7] In the individualized treatment group, SBP was targeted to remain within ±10% of the reference value using a continuous infusion of norepinephrine. Norepinephrine was diluted as 2.5 mg in 250 mL of 0.9% saline. The infusion rate of norepinephrine was adjusted according to a dedicated table (eAppendix in Supplement 2). In both groups, lactated Ringer solution was infused intravenously at a rate of 4 mL/kg per hour to satisfy maintenance fluid requirements. Additional fluids were given based on a protocolized hemodynamic algorithm,[16,17] using 6% hydroxyethyl starch (molecular weight of 130 kDa, substitution ratio of 0.4) in 0.9% saline administered in 250-mL boluses to achieve and

maintain a maximal value of stroke volume (eAppendix in Supplement 2). In the individualized treatment group, a reduction in the norepinephrine infusion rate was recommended in the case of severe bradycardia (heart rate <40 beats/min). In the standard treatment group, if SBP remained below the target value after a maximum dose of 60 mg of ephedrine, the use of norepinephrine was permitted as rescue therapy. Group assignment was not modified, and data analysis was conducted on a modified intention-to-treat basis. The intervention period lasted from anesthesia induction to 4 hours after completion of surgery. With the exception of the interventions described earlier, decisions regarding all other aspects of patient care during and after surgery were at the discretion of the attending physician according to local expertise and clinical practice. To avoid extremes of practice, invasive blood pressure measurement through a radial catheter was required. Additional details are given in the trial protocol in Supplement 1.

Study Outcomes

The primary outcome was a composite of systemic inflammatory response syndrome[18] (SIRS) and at least 1 organ system dysfunction for the renal (defined by a risk, injury, failure, loss, and end-stage kidney injury [RIFLE] stage of risk or higher[19]), respiratory (need for invasive or noninvasive ventilation for respiratory failure), cardiovascular (acute cardiac failure or myocardial ischemia or infarction), neurologic (stroke or altered consciousness, defined as a Glasgow Coma Scale score ≤14), and coagulation (Sequential Organ Failure Assessment [SOFA][20] subscore ≥2 points in the coagulation component) systems occurring by day 7 after surgery. The occurrence and severity of organ dysfunctions were assessed at least once daily and at the time of follow-up evaluation.

The prespecified secondary outcomes included the individual components of the primary composite outcome; changes in hemodynamic variables; the SOFA score on days 1, 2, and 7; the SIRS score[21]; postoperative complications; durations of intensive care unit and hospital stay; and all-cause mortality at 30 days after surgery. Postoperative complications within 30 days after surgery were defined as infectious complications (sepsis, severe sepsis, and septic shock using the 2001 International Sepsis Definitions[22]), respiratory complications (hypoxemia, pneumonia, need for noninvasive or invasive mechanical ventilation for respiratory failure, acute respiratory distress syndrome), neurologic complications (stroke, altered consciousness), cardiovascular complications (cardiac arrhythmia, acute heart failure, myocardial infarction), and surgical complications (anastomotic leak, surgical site infection, reoperation). Adverse events included severe bradycardia (ie, heart rate <40 beats/min) and major bleeding (ie, transfusion of ≥4 units of red blood cells). More details of these definitions are provided in the trial protocol in Supplement 1. Other end points not reported in this article are listed in the eAppendix in Supplement 2.

Randomization and Blinding

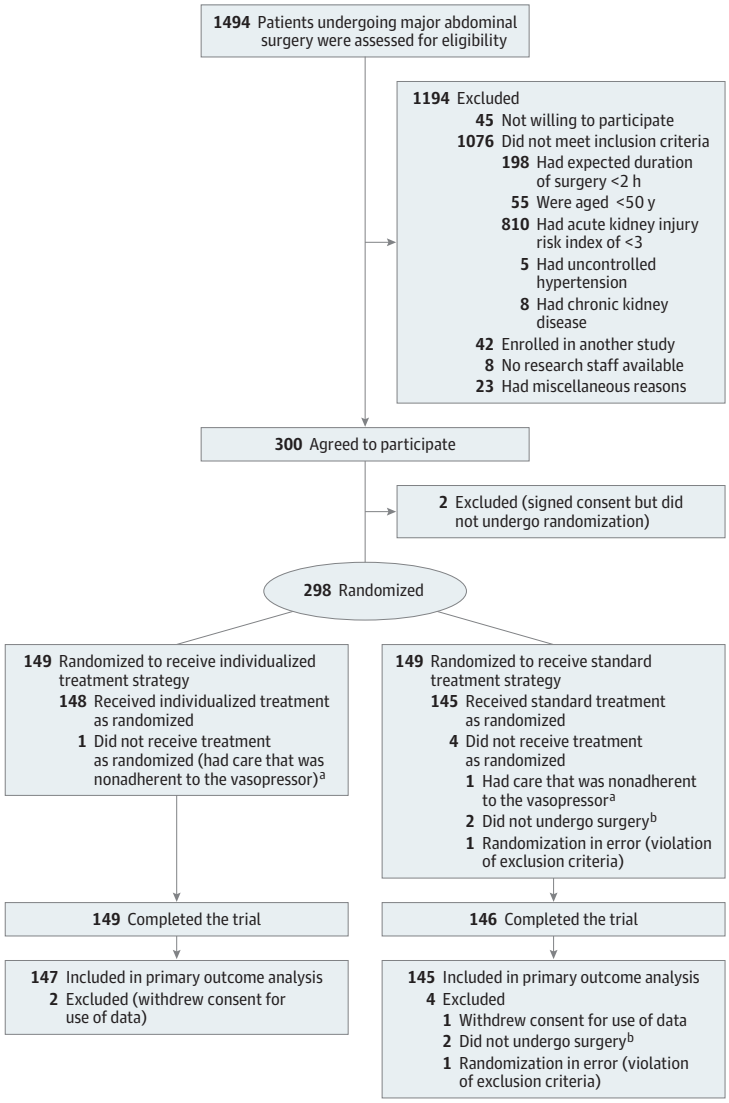
Enrollment, randomization (1:1 allocation ratio), and data collection were performed using a dedicated, secure, web-based system. Randomization was performed with the use of a minimization algorithm and stratified according to study site, urgency of surgery, and surgical site (abdominal or nonabdominal surgery). Although the research staff members who collected data during surgery could not be blinded to group assignments, much attention was given to ensuring strict blinding during the follow-up period and during data collection. The medical team who provided care during the postoperative period (ie, in the intensive care unit and the surgical ward), investigators, patients, the statistician, and the data and safety monitoring committee were unaware of the group assignments. Outcomes were verified according to predefined criteria by the principal investigator or designee at each site. Automated validation checks included plausibility ranges and cross-checks between data fields. Further data checks were performed centrally and through source data verification.

Statistical Analysis

We calculated that a sample of 268 patients would provide the trial with 95% power to detect an absolute difference of 20% with respect to the primary outcome, at a 2-sided α level of .05, assuming an event rate of 40% in the composite outcome in the standard treatment group.[14,21,23,24] The choice of 20% as expected difference in the primary outcome was based on the effect size observed in an earlier study in high-risk surgical patients.[25] To account for potential protocol deviations and withdrawal of consent, the recruitment target was 300 patients. An independent data and safety monitoring committee performed a blinded and planned interim analysis after enrollment of 50% of patients using the Lan-DeMets method to evaluate adverse events. There was no stopping rule for efficacy when considering the primary outcome. The committee recommended that the study be continued.

All analyses were conducted before the randomization code was broken, in line with the International Conference on Harmonization Good Clinical Practice guidelines. All the analyses were performed on data from the modified intention-to-treat population, which included all randomly assigned participants who initiated the study intervention and did not withdraw consent for the use of their data. An unadjusted χ^2 test was used for the primary outcome analysis. Multiple logistic mixed regression analysis was used to identify relevant baseline covariates associated with the primary outcome, in addition to the stratification variables (center treated as a random effect). Adjusted analyses were performed with the use of robust Poisson generalized linear model regression,[26] including a random effect to account for center effect, and are presented as relative risks with 95% confidence intervals. Results for the primary outcome are additionally reported as absolute risk reductions with 95% confidence intervals. The Hochberg procedure was used to adjust for multiple testing of components of the composite primary outcome.[27] A random-effects model was used to model longitudinal differences in SBP between treatment groups, taking into account between- and within-patient variability, in addition to center effect. Kaplan-Meier curves were plotted for organ dysfunction for renal, respiratory,

Figure 1. Flow of Participants Through the Study



[a] Two patients (1 per group) had care adherent to the assigned systolic blood pressure target but nonadherent to the vasopressor; they were included in the analysis of the group to which they were assigned.

[b] Two patients did not undergo surgery (surgery cancelled) and did not receive the study intervention.

cardiovascular, neurologic, and coagulation systems and compared by marginal Cox model. Follow-up time was censored at 30 days following surgery. The time to organ dysfunction was analyzed using a marginal Cox proportional hazards model with results reported as hazard ratios with 95% confidence intervals, and proportional hazard assumption verified using the Schoenfeld test and plotting residuals. As less than 5% of data were missing, handling of missing data was not applied. We did not compensate for dropouts caused by the withdrawal of consent or surgery cancellations after randomization. With the exception of the components of the composite primary outcome, no adjustment was made for multiple comparisons; therefore, secondary outcomes should be considered exploratory. All hypothesis tests were 2-sided, and $P < .05$ was considered to indicate statistical significance. The statistical analysis was conducted using Stata software version 13.0 (StataCorp LP).

Results

Study Population

During the study period from December 4, 2012, through August 28, 2016, a total of 1494 patients were screened for eligibility, and 298 patients were ultimately enrolled and randomized (**Figure 1**). Last follow-up was September 28, 2016. Data on the primary outcome were available for 292 patients (mean [SD] age, 70 [7] years; 44 [15.1%] women; 147 patients in the individualized treatment group and 145 patients in the standard treatment group) who completed the trial and were included in the modified intention-to-treat analysis. Two patients (1 per group) had care adherent with the assigned SBP target but not with the vasopressor, and were included in the analysis of the group to which they were assigned. The 2 groups were well balanced at baseline (**Table 1**; eTable 1 in

Table 1. Baseline Characteristics of Patients

Characteristic	Individualized Treatment (n = 147)	Standard Treatment (n = 145)
Age		
Overall, mean (SD), y	69.7 (7.1)	70.0 (7.5)
Among those aged ≥70 y, mean (SD), y	75.6 (4.3)	76.1 (4.8)
≥70 y, No. (%)	71 (48.3)	73 (50.3)
Male, No. (%)	125 (85.0)	123 (84.8)
Height, mean (SD), cm	170.7 (7.4)	171.3 (7.6)
Predicted body weight, mean (SD), kg[a]	65.9 (7.8)	66.4 (8.1)
ASA physical status class, No. (%)[b]		
II	62 (42.2)	54 (37.2)
III	84 (57.1)	89 (61.4)
≥IV	1 (0.7)	2 (1.4)
Acute kidney injury risk index class, No. (%)[c]		
III	76 (51.7)	71 (49.0)
IV	51 (34.7)	52 (35.9)
V	20 (13.6)	22 (15.1)
Reference blood pressure, mean (SD), mm Hg[d]		
Systolic	135.4 (20.2)	135.3 (17.1)
Diastolic	75.1 (11.6)	77.4 (12.1)
Preexisting conditions, No. (%)		
Chronic arterial hypertension	120 (81.6)	120 (82.8)
Chronic heart failure	26 (17.7)	38 (26.2)
Ischemic heart disease	20 (13.6)	32 (22.1)
Renal impairment	28 (19.1)	17 (11.7)
Diabetes mellitus	77 (52.4)	73 (50.3)
Type of surgery, No. (%)		
Abdominal	138 (93.9)	140 (96.6)
Nonabdominal	9 (6.1)	5 (3.4)
Urgency of surgical procedure, No. (%)		
Elective	124 (84.4)	123 (84.8)
Emergency	23 (15.6)	22 (15.2)
Medication use, No. (%)		
Antihypertensive		
Overall	100 (68.0)	97 (66.9)
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	71 (48.2)	72 (49.6)
Medications not taken within 24 h prior to surgery	61 (61.0)	58 (59.8)
Diuretic	24 (16.3)	20 (13.8)
Antidiabetic	72 (49.0)	68 (46.9)
Serum creatinine at inclusion, mean (SD), mg/dL	0.93 (0.30)	0.93 (0.34)
Estimated GFR[e]		
Overall, median (IQR), mL/min/1.73 m^2	88.0 (71.6-105.1)	87.8 (71.0-103.3)
Among those with estimated GFR <60 mL/min/1.73 m^2, median (IQR), mL/min/1.73 m^2	46.1 (43.6-54.6)	50.8 (43.8-55.6)
Estimated GFR <60 mL/min/1.73 m^2, No. (%)	20 (13.7)	17 (11.9)
Digit Symbol Substitution Test score at inclusion, mean (SD)[f]	30.4 (13.1)	29.3 (12.4)

Abbreviations: ASA, American Society of Anesthesiologists; GFR, glomerular filtration rate; IQR, interquartile range.

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

[a] Predicted body weight was calculated as follows: 50 + 0.91 × [height in centimeters − 152.4] for men and 45.5 + 0.91 × [height in centimeters − 152.4] for women.

[b] The ASA physical status classification is a grading system for preoperative physical health assessment of surgical patients ranging from class I to V, with higher classes indicating more severe systemic disease: class I indicates a completely healthy, fit patient; II, a patient with mild systemic disease that does not limit physical activity; III, a patient with severe systemic disease; IV, a patient with severe systemic disease that is a constant threat to life; and V, a moribund patient who is not expected to live 24 hours with or without surgery. Patients with an ASA physical status of class II or higher were eligible for inclusion.

[c] The acute kidney injury risk index for postoperative kidney injury is a scoring system based on 9 independent preoperative risk factors, with higher classes indicating a higher risk of postoperative acute kidney injury.[14] Patients with a risk index of class III or higher (≥4 risk factors) were eligible for participation.

[d] The patient's resting blood pressure was used as the reference.

[e] The estimated GFR was calculated with the use of the 4-variable Modification of Diet in Renal Disease equation. Three patients (2 in the standard treatment group and 1 in the individualized treatment group) were missing data on estimated GFR.

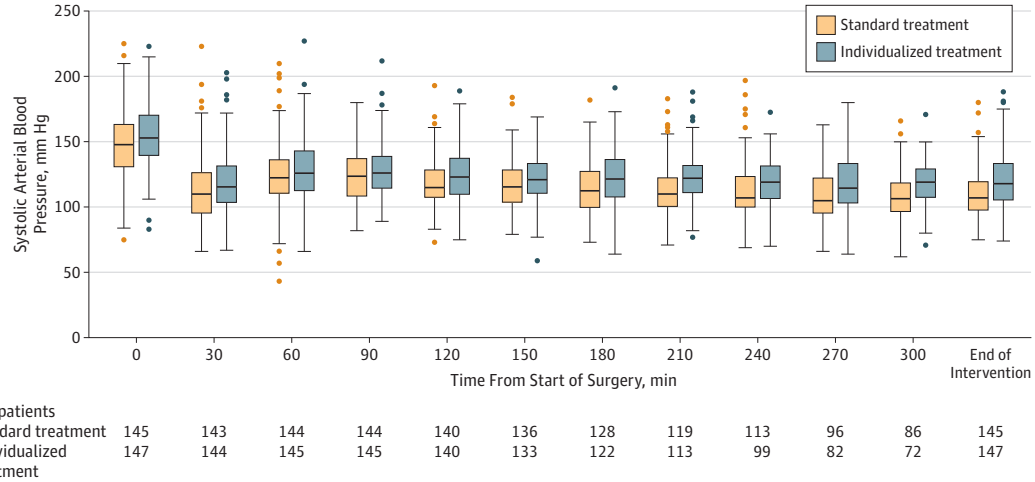
[f] The Digit Symbol Substitution Test is a standardized test that measures psychomotor speed and concentration, with higher scores denoting better cognitive function.

Supplement 2). Overall, 240 patients (82.2%) had chronic hypertension. Sixty-one of 100 patients (61.0%) in the individualized treatment group and 58 of 97 patients (59.8%) in the standard treatment group had discontinued their antihypertensive medication prior to surgery. Values for reference resting blood pressure were similar between study groups.

Blood Pressure and Intraoperative Management

Throughout surgery, the mean (SD) SBP was 123 (25) mm Hg in the individualized treatment group and 116 (24) mm Hg in the standard treatment group (**Figure 2**; eFigure 1 and eFigure 2 in Supplement 2); the between-group difference was 6.5 mm Hg (95% CI, 3.8-9.2). The cumulative volume of

Figure 2. Systolic Arterial Blood Pressure in the Individualized and Standard Treatment Groups Over the Intervention Period



No. of patients

Standard treatment	145	143	144	144	140	136	128	119	113	96	86	145
Individualized treatment	147	144	145	145	140	133	122	113	99	82	72	147

Systolic arterial blood pressures were higher in the individualized treatment group ($P < .001$ by random-effect model for the between-group comparison across the entire study intervention). The horizontal line in the center of each box indicates the median; bottom and top borders of the box, 25th and 75th percentiles, respectively; whiskers, 1.5 times the interquartile range (IQR); and circles, extreme outliers. The intervention period lasted from anesthesia induction to 4 hours after completion of surgery. The median (IQR) duration of surgery was 260 (170-365) minutes in the individualized treatment group and 280 (200-375) minutes in the standard treatment group. The median (IQR) duration of the intervention period was 423 (342-550) minutes in the individualized treatment group and 465 (390-600) minutes in the standard treatment group.

fluids infused over the intervention period and the cardiac index values were not significantly different between study groups (**Table 2**). Six patients (4.1%) in the individualized treatment group and 22 (15.2%) in the standard treatment group met SBP targets throughout the intervention period without any need for vasopressor (absolute difference, 11%; 95% CI, 4%-18%; $P = .001$). Thirty-eight patients (26.2%) in the standard treatment group required rescue therapy with norepinephrine to achieve the target SBP value because of persistent hypotension despite receiving ephedrine (Table 2).

Outcomes

A primary composite outcome event within the first 7 days after surgery was confirmed for 56 patients (38.1%) in the individualized treatment group and 75 patients (51.7%) in the standard treatment group (adjusted relative risk, 0.73; 95% CI, 0.56 to 0.94; $P = .02$), for an absolute risk difference of −14% (95% CI, −25% to −2%) (**Table 3**). The results of associated bivariable and multivariable analyses are provided in eTable 2 in Supplement 2. With the exception of the study group, none of the variables tested in the model were associated with the primary outcome.

Renal dysfunction (RIFLE stage of risk or higher) occurred in 48 patients (32.7%) in the individualized treatment group and 71 patients (49.0%) in the standard treatment group (absolute risk difference, −16%; 95% CI, −27% to −5%; adjusted relative risk, 0.70; 95% CI, 0.53 to 0.92; $P = .01$). Altered consciousness occurred in 8 patients (5.4%) in the individualized treatment group and 23 patients (15.9%) in the standard treatment group (absolute risk difference, −10%; 95% CI, −17% to −3%; adjusted relative risk, 0.34; 95% CI, 0.16 to 0.75; $P = .007$). There were no significant differences between groups in the other major components of the composite primary outcome (Table 3).

Fewer patients developed sepsis during the first 30 days after surgery in the individualized treatment group compared with the standard treatment group (22 patients [15.0%] vs 38 patients [26.2%], respectively; absolute risk difference, −11%; 95% CI, -20% to -2%; adjusted relative risk, 0.54; 95% CI, 0.34 to 0.86; $P = .009$). Sixty-eight patients (46.3%) in the individualized treatment group and 92 (63.4%) in the standard treatment group had postoperative organ dysfunction by day 30 (adjusted hazard ratio, 0.66; 95% CI, 0.52 to 0.84; $P = .001$) (**Figure 3**).

The median duration of hospital stay was 12 days (interquartile range [IQR], 7-19 days) in the individualized treatment group and 14 days (IQR, 7-23 days) in the standard treatment group (median difference, −2.0 days; 95% CI, −4.0 to 1.0; $P = .15$). The median duration of intensive care unit stay was 7 days (IQR, 3-11 days) in the individualized treatment group and 6 days (IQR, 2-14 days) in the standard treatment group (median difference, 1.0 day; 95% CI, −2.0 to 4.0; $P = .51$). There was no significant between-group difference in all-cause mortality within the 30-day follow-up period or in the rate of adverse events (Table 3).

Discussion

A strategy of targeting an individualized SBP, as compared with a standard management approach, resulted in significantly lower rates of organ dysfunction after surgery. Patients assigned to individualized treatment had significantly lower rates of clinically important outcomes, notably

Table 2. Clinical Management of Patients During the Intervention Period, Including During Surgery and for 4 Hours Following Surgery[a]

Variable	Individualized Treatment (n = 147)	Standard Treatment (n = 145)	*P* Value
Cumulative volume of crystalloid, median (IQR), mL	2275 (1600-3000)	2500 (1825-3225)	.09
During surgery	1500 (1000-2000)	2000 (1500-2500)	<.001
During 4 h following surgery	750 (500-1000)	600 (500-1000)	.54
Cumulative volume of colloid, median (IQR), mL	1000 (500-1500)	1000 (500-1750)	.25
During surgery	875 (500-1500)	1000 (500-1500)	.12
During 4 h following surgery	500 (300-500)	500 (400-1500)	.43
Use of blood products			
Patients, No. (%)	39 (26.5)	34 (23.4)	.54
No. of units/patient, mean (SD)	2.5 (1.4)	2.8 (1.7)	.28
Blood loss, median (IQR), mL	500 (200-925)	500 (200-837)	.63
Blood pressure, mean (SD), mm Hg			
Systolic			
Preinduction	153 (25)	148 (27)	.09
End of intervention period	120 (22)	110 (19)	<.001
Diastolic			
Preinduction	75 (14)	74 (13)	.61
End of intervention period	60 (10)	56 (9)	<.001
Mean arterial pressure			
Preinduction	103 (17)	101 (17)	.28
End of intervention period	81 (14)	75 (13)	<.001
Cardiac index, mean (SD), mL/min/m^2			
Baseline	2.5 (0.6)	2.5 (0.7)	.48
End of intervention period	3.0 (0.8)	3.1 (0.8)	.39
Vasoactive drug not needed, No. (%)	6 (4.1)	22 (15.2)	.001
Vasoactive drug dose during surgery[b]			
Norepinephrine			
Patients, No. (%)	140 (95.2)	38 (26.2)	
Dose, mean (SD), μg/kg/min	0.06 (0.14)	0.03 (0.03)	.03
Ephedrine			
Patients, No. (%)	1 (0.7)	122 (84.1)	
Dose, median (IQR), mg	NA	30 (15-48)	
Epidural analgesia, No. (%)[c]	64 (44.8)	63 (45.0)	.97
Duration of surgery, median (IQR), min[d]	260 (170-365)	280 (200-375)	.08
Planned location following surgery, No. (%)			
Surgical ward	48 (32.7)	41 (28.3)	.71
High-dependency care unit[e]	81 (55.1)	84 (57.9)	
Intensive care unit	18 (12.2)	20 (13.8)	

Abbreviations: IQR, interquartile range; NA, not applicable.

[a] Detailed data on intraoperative procedures are given in eTable 1 in Supplement 2.

[b] Thirty-eight patients in the standard treatment group required norepinephrine as rescue therapy for persistent hypotension (systolic blood pressure below the target range after the maximum dose of ephedrine was reached). Two patients (1 per group) had care that was nonadherent to the assigned vasopressor regimen and were analyzed in the group to which they were allocated.

[c] Nine patients (4 in the individualized treatment group and 5 in the standard treatment group) were missing data on use of epidural analgesia.

[d] Duration of surgery is the time between skin incision and closure of the incision.

[e] High-dependency care unit is a specially staffed and equipped unit providing intensive care (treatment and monitoring) at an intermediate clinical level for patients who are in a critically ill or unstable condition.

a lower risk for renal dysfunction and a lower risk for altered consciousness, than patients in the standard treatment group. There were no significant between-group differences for the other individual components of the composite primary outcome.

A particular feature of this trial was the use of a primary outcome that was a composite of SIRS and organ dysfunction with a possible synergism between the components. Postoperative acute kidney injury, which is mainly related to hypoperfusion and systemic inflammation, is associated with sepsis, coagulopathy, and mechanical ventilation[28] and is a leading cause of morbidity and mortality even in patients with normal baseline renal function.[29] Early postoperative cognitive dysfunction and confusion are common after major surgery and are associated with prolonged recovery after surgery and higher postoperative mortality.[30,31]

The observed effect of the individualized treatment strategy in this trial was lower than the anticipated absolute risk reduction of 20 percentage points. Although the expected rate of organ dysfunction in this study was consistent with those reported in surgical patients at the time the trial was designed, the composite event rate was slightly higher than

Table 3. Primary and Secondary Outcomes and Adverse Events

Variable	Individualized Treatment (n = 147)	Standard Treatment (n = 145)	Between-Group Absolute Difference, % (95% CI)	Unadjusted Relative Risk (95% CI)	*P* Value	Adjusted Relative Risk (95% CI)[a]	*P* Value
Primary Outcome							
Primary composite outcome, No. (%)[b]	56 (38.1)	75 (51.7)	−14 (−25 to −2)	0.74 (0.57 to 0.95)	.02	0.73 (0.56 to 0.94)	.02
Secondary Outcomes							
Complications within 7 d							
SIRS							
No. (%)	108 (73.5)	105 (72.4)	1 (−9 to 11)	0.84 (0.65 to 1.10)	.20	1.01 (0.92 to 1.12)	.78
SIRS score, No. (%)[c]							
2	49 (33.3)	36 (24.8)	9 (−2 to 19)	1.18 (0.90 to 1.59)	.29	1.19 (0.89 to 1.59)	.25
≥3	59 (40.1)	69 (47.6)	−8 (−19 to 4)	0.84 (0.65 to 1.10)	.20	0.81 (0.64 to 1.02)	.07
Daily SIRS score, mean (95% CI)[c]	1.5 (1.3 to 1.7)	1.6 (1.4 to 1.7)			.62		.61
Acute kidney injury according to RIFLE criteria, No. (%)[d]							
Risk	23 (15.7)	36 (24.8)	−9 (−18 to 0)	0.63 (0.39 to 1.00)	.05	0.73 (0.47 to 1.14)	.17
Injury	16 (10.9)	26 (17.9)	−7 (−15 to 1)	0.61 (0.34 to 1.08)	.09	0.61 (0.34 to 1.08)	.09
Failure	9 (6.1)	9 (6.2)	0 (−6 to 5)	0.99 (0.40 to 2.41)	.98	0.97 (0.40 to 2.34)	.95
Use of renal replacement therapy, No. (%)	4 (2.7)	5 (3.5)	0 (−5 to 3)	0.79 (0.22 to 2.88)	.72	0.81 (0.22 to 2.97)	.76
Acute heart failure, No. (%)	1 (0.7)	0	1 (−1 to 2)				
Myocardial ischemia or infarction, No. (%)	0	1 (0.7)	−1 (−2 to 1)				
Altered consciousness, No. (%)[e]	8 (5.4)	23 (15.9)	−10 (−17 to −3)	0.34 (0.16 to 0.74)	.007	0.34 (0.16 to 0.75)	.007
Stroke, No. (%)	0	0					
Coagulation SOFA score ≥2, No. (%)	16 (11.0)	11 (7.6)	3 (−3 to 10)	1.44 (0.69 to 3.01)	.33	1.47 (0.07 to 2.23)	.07
Hypoxemia, No. (%)	21 (14.3)	33 (22.8)	−8 (−17 to 0)	0.63 (0.38 to 1.03)	.07	0.64 (0.40 to 1.03)	.07
Pneumonia, No. (%)	4 (2.7)	11 (7.6)	−5 (−10 to 0)	0.36 (0.12 to 1.10)	.07	0.36 (0.12 to 1.10)	.07
ARDS, No. (%)	7 (4.8)	7 (4.8)	0 (−5 to 5)	0.99 (0.35 to 2.74)	.98	0.98 (0.35 to 2.67)	.95
Reintubation, No. (%)	10 (6.8)	15 (10.3)	−4 (−10 to 3)	0.66 (0.31 to 1.42)	.28	0.66 (0.31 to 1.42)	.28
Need for noninvasive or invasive ventilation, No. (%)	25 (17.0)	36 (24.8)	−8 (−17 to 1)	0.68 (0.43 to 1.08)	.10	0.71 (0.45 to 1.11)	.13
SOFA score, median (IQR)[f]							
Day 1	1 (0-3)	1 (0-3)			.31		.36
Day 2	1 (0-2)	2 (0-3)			.19		.21
Day 7	0 (0-1)	0 (0-1)			.66		.68
Sepsis, No. (%)	13 (8.8)	23 (15.9)	−7 (−15 to 0)	0.56 (0.29 to 1.06)	.07	0.55 (0.29 to 1.04)	.07
Severe sepsis or septic shock, No. (%)	13 (8.8)	13 (9.0)	0 (−6 to 7)	0.99 (0.47 to 2.05)	.97	1.01 (0.49 to 2.11)	.97
Complications within 30 d							
Use of renal replacement therapy, No. (%)	6 (4.1)	7 (4.8)	0 (−5 to 4)	0.85 (0.29 to 2.46)	.76	0.85 (0.29 to 2.48)	.77
Pneumonia, No. (%)	6 (4.1)	16 (11.0)	−7 (−13 to −1)	0.37 (0.15 to 0.92)	.03	0.38 (0.15 to 0.93)	.03
ARDS, No. (%)	9 (6.1)	8 (5.5)	1 (−5 to 6)	1.11 (0.44 to 2.80)	.83	1.10 (0.44 to 2.75)	.84
Reintubation, No. (%)[g]	16 (10.9)	20 (13.8)	−3 (−10 to 5)	0.79 (0.43 to 1.46)	.45	0.79 (0.43 to 1.46)	.46
Need for noninvasive or invasive ventilation, No. (%)	28 (19.1)	40 (27.6)	−9 (−18 to 1)	0.69 (0.45 to 1.06)	.09	0.73 (0.48 to 1.11)	.14
Sepsis, No. (%)	22 (15.0)	38 (26.2)	−11 (−20 to −2)	0.57 (0.36 to 0.92)	.02	0.54 (0.34 to 0.86)	.009
Severe sepsis or septic shock, No. (%)	18 (12.2)	22 (15.2)	−3 (−11 to 5)	0.81 (0.45 to 1.44)	.47	0.81 (0.46 to 1.43)	.47
Acute heart failure, No. (%)	3 (2.0)	1 (0.7)	1 (−1 to 4)	2.96 (0.31 to 28.12)	.35	2.53 (0.25 to 25.08)	.43
Myocardial ischemia or infarction, No. (%)	0	1 (0.7)					
Stroke, No. (%)	0	0					
Surgical complications, No. (%)							
Surgical site infection	23 (15.7)	36 (24.8)	−9 (−18 to 0)	0.63 (0.39 to 1.00)	.05	0.63 (0.40 to 0.98)	.04
Surgical reoperation	23 (15.7)	29 (20.0)	−4 (−13 to 4)	0.78 (0.48 to 1.29)	.33	0.77 (0.47 to 1.26)	.30
Anastomotic leakage[h]	24 (16.3)	25 (17.2)	−1 (−9 to 8)	0.95 (0.57 to 1.58)	.83	0.92 (0.57 to 1.50)	.74
Death at day 30, No. (%)	9 (6.1)	8 (5.5)	1 (−4 to 6)	1.11 (0.44 to 2.80)	.83	1.11 (0.44 to 2.81)	.82

(continued)

Table 3. Primary and Secondary Outcomes and Adverse Events (continued)

Variable	Individualized Treatment (n = 147)	Standard Treatment (n = 145)	Between-Group Absolute Difference, % (95% CI)	Unadjusted Relative Risk (95% CI)	*P* Value	Adjusted Relative Risk (95% CI)[a]	*P* Value
Adverse Events							
No. (%)							
Severe bradycardia	16 (10.9)	16 (11.0)	0 (−7 to 7)	0.99 (0.51 to 1.90)	.97	0.97 (0.51 to 1.88)	.94
Major bleeding[i]	6 (15.4)	8 (23.5)	−8 (−17 to 1)	0.65 (0.25 to 1.70)	.38	0.68 (0.26 to 1.77)	.43

Abbreviations: ARDS, acute respiratory distress syndrome; IQR, interquartile range; RIFLE, risk, injury, failure, loss, and end-stage kidney injury; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.

[a] Adjustment was performed for stratification variables (study center, urgency of surgery, and surgical site), study group, and acute kidney injury risk index.

[b] The primary outcome was a composite of SIRS and at least 1 organ system dysfunction for the renal, respiratory, cardiovascular, coagulation, and neurologic systems by day 7 after surgery.

[c] The SIRS score (range, 0 [best] to 4 [worst]) assigns 1 point for each of the following parameters: temperature higher than 38°C or lower than 36°C, white blood cell count higher than 12 000/μL or lower than 4000/μL, heart rate higher than 90 beats/min, and respiratory rate higher than 20 breaths/min or $Paco_2$ less than 32 mm Hg.

[d] Acute kidney injury was assessed with the use of the 5-category RIFLE classification system. Because the loss and end-stage kidney injury categories are defined by durations of loss of kidney function longer than 7 days, they were not assessed as part of the complications within 7 days of surgery.

[e] Altered consciousness was defined as a Glasgow Coma Scale score of 14 or less (SOFA subscore of ≥1 point in the neurologic component).

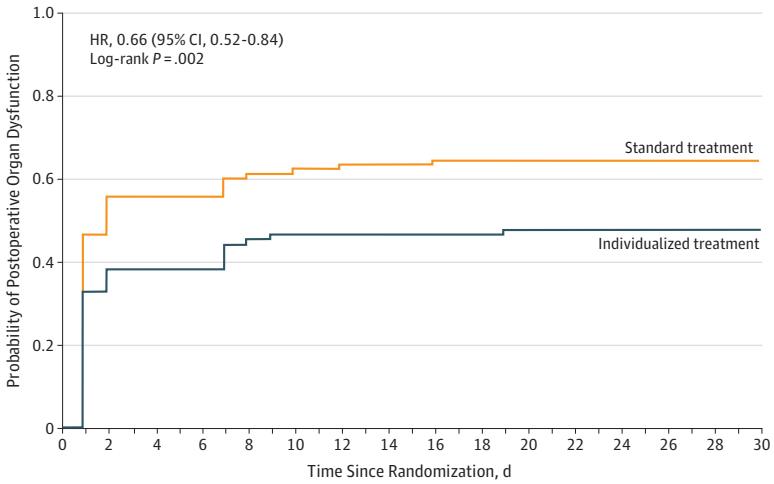
[f] Scores on the SOFA scale range from 0 to 4 for each organ system, with higher scores indicating more severe organ dysfunction.

[g] Tracheal intubation for reoperation because of surgical complications was not considered a reintubation.

[h] Anastomotic leakage of the gastrointestinal tract.

[i] Blood transfusion was required in 39 patients in the individualized treatment group and 34 patients in the standard treatment group.

Figure 3. Kaplan-Meier Estimates of the Probability of Postoperative Organ Dysfunction by Day 30 After Surgery



Organ dysfunction was assessed for renal (risk, injury, failure, loss, and end-stage kidney injury [RIFLE] stage of risk or higher), respiratory (need for invasive or noninvasive ventilation), cardiovascular (acute cardiac failure or myocardial ischemia or infarction), neurologic (stroke or altered consciousness), and coagulation (Sequential Organ Failure Assessment subscore ≥2 points in the coagulation component) systems. Data for patients who did not develop organ dysfunction were censored at 30 days after surgery. The adjusted hazard ratio (HR) for postoperative organ dysfunction in the individualized treatment group, as compared with the standard treatment group, was 0.66 (95% CI, 0.52-0.84; *P* = .001). The median follow-up duration was 30 days (interquartile range, 30-30 days) in the 2 treatment groups.

predicted.[14,24] This was due, at least in part, to the inclusion of a high-risk population; 49% of participants were aged 70 years or older, and 82% experienced chronic hypertension. Most patients underwent abdominal surgery, which is associated with an increased risk of acute kidney injury,[29] respiratory failure,[32] sepsis, and death.[33,34]

The issue of intraoperative blood pressure management has been debated for the past several years, a significant component of the controversy being the minimal acceptable blood pressure in anesthetized patients. The findings of this trial add to the evidence of benefits of personalizing care, especially in high-risk surgical patients.[9] To our knowledge, this is the first study to investigate the effects of individualizing blood pressure management according to patients' preoperative values, and the study differs from others that either examined the relationship between different blood pressure thresholds and outcome or used predefined fixed blood pressure targets. The recent SEPSISPAM trial found no mortality difference in patients with septic shock who underwent resuscitation targeting a mean arterial pressure of either 65 to 70 mm Hg or 80 to 85 mm Hg[35]; however, patients with chronic hypertension in the high target group had less kidney injury.

The overall between-group difference in mean SBP in the present trial was 6.5 mm Hg, although the possibility of larger variations in blood pressure between measurement points cannot be excluded. Large observational studies have suggested

that even brief exposure to a 10-mm Hg reduction in SBP below 80 mm Hg[6] or a 5-mm Hg reduction in mean arterial pressure below 70 mm Hg is associated with adverse outcomes.[4,5] According to the trial protocol, hemodynamic data were systematically recorded at 10-minute intervals, but the duration of hypotension events was not recorded. As approximately one-quarter of patients required rescue treatment for persistent hypotension in the standard treatment group, the possibility of a longer duration of hypotension cannot be excluded.

Major surgery is a significant risk factor for postoperative sepsis. In this study, postoperative sepsis was significantly less common in the individualized treatment group than in the standard treatment group, which might be related to improved tissue oxygenation and perfusion, thus rendering organs less susceptible to infection. However, the association between the arterial pressure treatment strategy and sepsis needs to be explored further and should be considered only as a hypothesis-generating concept for future research.

Protection against hypoperfusion relies primarily on maintaining adequate intravascular volume and organ perfusion pressure. One strength of this trial is the use in both groups of a protocolized hemodynamic algorithm to guide delivery of intravenous fluids and maximize stroke volume. Previous trials have suggested a lower incidence of organ dysfunction with goal-directed hemodynamic optimization during surgery.[36] In this trial, no between-group differences were noted in the cardiac index or in the cumulative volume of fluids. No association was found between the fluid composition and the primary outcome event.

This study has several limitations. The use of ephedrine as the first-line vasopressor for standard care, rather than other vasoactive drugs such as phenylephrine, was arbitrary but supported by literature.[15,37] Moreover, phenylephrine is a selective α_1-adrenergic agonist with a greater risk of negative effects on cardiac output,[38] in contrast to ephedrine or norepinephrine, which have β-adrenergic activity.[37,39] Although the use of norepinephrine rather than ephedrine in the standard treatment group might have enhanced the study design, data on the use of norepinephrine to manage arterial pressure in the operating room are relatively scarce. Furthermore, the efficacy and safety of intermittent intravenous boluses of norepinephrine, rather than continuous infusion, to treat a decrease in blood pressure have not been extensively studied. More than 80% of patients had chronic hypertension, and in these individuals, organ blood flow may become pressure dependent at higher blood pressure limits due to a possible rightward shift of the organ autoregulation curves. As discussed previously, the duration of hypotensive events was not recorded, and substantial variations in blood pressure between measurement points may have occurred. The minimum duration of hypotension to trigger harm is unclear, but a graded relationship between the duration of hypotension and postoperative acute kidney injury has previously been assumed.[4,5] Generalizability to populations not included in the trial, such as those with a lower risk of morbidity, remains to be evaluated. Moreover, use of the resting blood pressure as reference—which may not be available in daily care—rather than preinduction values may represent a meaningful difference with routine clinical practice. The intervention could not be blinded, but the risk of bias was minimized through online randomization to ensure the concealment of study group assignments, the use of validated criteria for the primary outcome that were not subject to observer bias, and health care workers conducting postoperative care who were unaware of the study assignments.

Conclusions

Among patients predominantly undergoing abdominal surgery who were at increased postoperative risk, management targeting an individualized systolic blood pressure, compared with standard management, reduced the risk of postoperative organ dysfunction.

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Author Affiliations: Département de Médecine Périopératoire, Université Clermont Auvergne, Centre national de la recherche scientifique, Inserm, Centre Hospitalier Universitaire Clermont-Ferrand, Clermont-Ferrand, France (Futier, Godet, Bazin, Constantin); Section d'Anesthésie and Département Anesthésie et Réanimation, Centre Hospitalier Universitaire Nîmes, Nîmes, France (Lefrant, Cuvillon, Bertran); Département Anesthésie et Réanimation, Centre Hospitalier Universitaire Amiens, Amiens, France (Guinot, Lorne); Service Anesthésie et Réanimation, Assistance Publique Hôpitaux de Marseille, Hôpital Nord, Université Aix Marseille, Marseille, France (Leone, Pastene); Service d'Anesthésie-Réanimation, Université Claude Bernard Lyon-1, Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, Lyon, France (Piriou, Imhoff); Département Anesthésie-Réanimation, Centre Hospitalier Universitaire Saint-Etienne, Saint-Étienne, France (Molliex); Service Anesthésie et Réanimation, Assistance Publique Hôpitaux de Marseille, Hôpital de la Conception, Marseille, France (Albanese); Anesthésie et Réanimation, Clinique du Parc, Castelnau-Le-Lez, France (Julia); Pôle Anesthésie-Réanimation, Centre Hospitalier Universitaire Lille, Lille, France (Tavernier); Biostatistic Unit, Centre Hospitalier Universitaire Clermont-Ferrand, Direction de la Recherche Clinique, Clermont-Ferrand, France (Pereira); Département Anesthésie et Réanimation B, Centre Hospitalier Universitaire Montpellier, Hôpital Saint-Eloi, and INSERM U-1046, Montpellier, France (Jaber).

Author Contributions: Drs Futier and Jaber had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Futier, Lefrant, Julia, Tavernier, Bazin, Constantin, Pereira, Jaber.
Acquisition, analysis, or interpretation of data: Futier, Lefrant, Guinot, Godet, Lorne, Cuvillon, Bertran, Leone, Pastene, Piriou, Molliex, Albanese, Julia, Imhoff, Constantin, Pereira, Jaber.
Drafting of the manuscript: Futier, Cuvillon, Leone, Tavernier, Pereira, Jaber.
Critical revision of the manuscript for important intellectual content: Futier, Lefrant, Guinot, Godet, Lorne, Bertran, Leone, Pastene, Piriou, Molliex, Albanese, Julia, Tavernier, Imhoff, Bazin, Constantin, Pereira, Jaber.
Statistical analysis: Pereira.
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Intraoperative Norepinephrine to Control Arterial Pressure (INPRESS) Study Group Investigators: The INPRESS Study Group investigators are as follows: *Steering Committee:* Emmanuel Futier, MD, PhD (principal investigator; Hôpital Estaing, Centre Hospitalier Universitaire Clermont-Ferrand), Jean-Yves Lefrant, MD, PhD (project scientist; Centre Hospitalier Universitaire Nîmes, l'Hôpital Carémeau), Samir Jaber, MD, PhD (project scientist; Centre Hospitalier Universitaire Montpellier, Hôpital Saint-Eloi), Jean-Michel Julia, MD (project scientist; Clinique du Parc), Jean-Etienne Bazin, MD, PhD (chair; Centre Hospitalier Universitaire Clermont-Ferrand), and Jean-Michel Constantin, MD, PhD (vice chair; Centre Hospitalier Universitaire Clermont-Ferrand); *Scientific Committee:* Emmanuel Futier, MD, PhD (Hôpital Estaing, Centre Hospitalier Universitaire Clermont-Ferrand), Samir Jaber, MD, PhD (Centre Hospitalier Universitaire Montpellier, Hôpital Saint-Eloi), Jean-Yves Lefrant, MD, PhD (Centre Hospitalier Universitaire Nîmes, l'Hôpital Carémeau), Marc Leone, MD, PhD (Assistance Publique Hôpitaux de Marseille, Hôpital Nord), Matthieu Biais, MD, PhD (Centre Hospitalier Universitaire de Bordeaux, Hôpital Pellegrin), and Benoit Tavernier, MD, PhD (Centre Hospitalier Universitaire Lille); *Trial Management Committee:* Emmanuel Futier, MD, PhD, Jean-Yves Lefrant, MD, PhD, and Samir Jaber, MD, PhD; *Trial Monitoring and Research Coordinators:* Dominique Morand, Christine Rolhion, and Justine Bourdier (Direction de la Recherche Clinique, Centre Hospitalier Universitaire Clermont-Ferrand); *Data and Safety Monitoring Committee:* Karim Asehnoune, MD, PhD (Nantes, France), Catherine Paugam-Burtz, MD, PhD (Assistance Publique Hôpitaux de Paris, Paris, France), and Nicolas Molinari, PhD (biostatistician; Montpellier, France); *Statistical and Data Coordination:* Bruno Pereira, PhD; *Writing Committee:* Emmanuel Futier, MD, PhD, Samir Jaber, MD, PhD, and Jean-Michel Constantin, MD, PhD; and *INPRESS Participating Clinical Centers:* Hôpital Estaing, Centre Hospitalier Universitaire Clermont-Ferrand (Antoine Petit, MD, Sebastien Christophe, MD, Marie Vignaud, MD, Oana Cherbis, MD, Adeline Gerard, MD, and Emmanuel Futier, MD, PhD), Hospices Civils de Lyon, Centre Hospitalier Lyon Sud (Vincent Piriou, MD, PhD, Etienne Imhoff, MD, Camille Parent, MD, and Aline Steghens, MD), Assistance Publique Hôpitaux de Marseille, Hôpital Nord (Marc Leone, MD, PhD, Marie-France Brunier Mercier, MD, Malik Haddam, MD, Ludovic Richiardone, MD, Clement Brun, MD, and Remy Bardin, MD), Assistance Publique Hôpitaux de Marseille, Hôpital de la Conception (Jacques Albanese, MD, PhD), Clinique du Parc (Matthieu Ponrouch, MD, and Jean-Michel Julia, MD), Centre Hospitalier Universitaire Saint-Etienne (Serge Molliex, MD, PhD), Centre Hospitalier Universitaire Nîmes, l'Hôpital Carémeau (Jean-Yves Lefrant, MD, PhD, Philippe Cuvillon, MD, PhD, and Sebastien Bertran, MD), Institut du Cancer Val d'Aurelle, Montpellier (Gilles Leclerc, MD, and Christian Popescu Horatiu, MD), and Centre Hospitalier Universitaire Amiens (Emmanuel Lorne, MD, PhD, Pierre-Gregoire Guinot, MD, PhD, Bruno de Broca, MD, and Marc-Olivier Fischer, MD, PhD).

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