## JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

# 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.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01536470

JAMA. 2017;318(14):1346-1357. doi:10.1001/jama.2017.14172 Published online September 27, 2017.



Supplemental content

+ CME Quiz at jamanetwork.com/learning

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).

iama.com

he number of patients undergoing major surgery worldwide is growing with advancements in treating disease.<sup>1</sup> However, many patients still die or experience severe perioperative complications.<sup>2</sup>

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.<sup>3-6</sup> 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,<sup>6,7</sup> mean arterial pressure less than 60 mm Hg,<sup>4</sup> and a reduction of 30% to 50% from baseline are common treatment thresholds used in clinical practice,<sup>7,8</sup> highlighting the lack of consensus. Current guidelines from the American College of Cardiology and the American Heart Association<sup>9</sup> 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,<sup>10,11</sup> 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.<sup>4,5,8,12</sup> Consensus guidelines in the context of critical illness have suggested adjusting blood pressure targets to premorbid values.<sup>13</sup> 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.

### 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 Anesthesiolo-

#### **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.

gists physical status of class II or higher, had a preoperative acute kidney injury risk index<sup>14</sup> 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<sup>2</sup> 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,<sup>15</sup> for any decrease in SBP below 80 mm Hg or lower than 40% from the patient's reference value.<sup>7</sup> 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,<sup>16,17</sup> 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<sup>18</sup> (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<sup>19</sup>), 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  $\leq$ 14), and coagulation (Sequential Organ Failure Assessment [SOFA]<sup>20</sup> subscore  $\geq$ 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<sup>21</sup>; 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<sup>22</sup>), 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  $\geq$ 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 a level of .05, assuming an event rate of 40% in the composite outcome in the standard treatment group.<sup>14,21,23,24</sup> 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.<sup>25</sup> 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  $\chi^2$  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,<sup>26</sup> 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.<sup>27</sup> 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, Effects of Individualized Blood Pressure Management on Postoperative Organ Dysfunction

#### Figure 1. Flow of Participants Through the Study



<sup>a</sup> 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.

<sup>b</sup> 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 <sup>a</sup>	65.9 (7.8)	66.4 (8.1)
ASA physical status class, No. (%) <sup>b</sup>		
II	62 (42.2)	54 (37.2)
	84 (57.1)	89 (61.4)
≥IV	1 (0.7)	2 (1.4)
Acute kidney injury risk index class, No. (%) <sup>c</sup>		
	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 <sup>d</sup>		
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 <sup>e</sup>		
Overall, median (IQR), mL/min/1.73 m <sup>2</sup>	88.0 (71.6-105.1)	87.8 (71.0-103.3)
Among those with estimated GFR <60 mL/min/1.73 m <sup>2</sup> , median (IQR), mL/min/1.73 m <sup>2</sup>	46.1 (43.6-54.6)	50.8 (43.8-55.6)
Estimated GFR <60 mL/min/1.73 m <sup>2</sup> , No. (%)	20 (13.7)	17 (11.9)
Digit Symbol Substitution Test score at inclusion, mean (SD) <sup>f</sup>	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.

 <sup>a</sup> 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.

- <sup>b</sup> 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.
- <sup>c</sup> 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.<sup>14</sup> Patients with a risk index of class III or higher (≥4 risk factors) were eligible for participation.
- <sup>d</sup> The patient's resting blood pressure was used as the reference.
- <sup>e</sup> 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.
- <sup>f</sup> 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



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, -4.0to 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 <u>targeting</u> an <u>individualized</u> SBP, as <u>compared</u> with a <u>standard</u> management approach, resulted in significantly <u>lower</u> rates of <u>organ dysfunction after surgery</u>. Patients assigned to <u>individualized</u> 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<sup>a</sup>

Variable	<mark>Individualized</mark> 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 <sup>2</sup>			
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 <sup>b</sup>			
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. (%) <sup>c</sup>	64 (44.8)	63 (45.0)	.97
Duration of surgery, median (IQR), min <sup>d</sup>	260 (170-365)	280 (200-375)	.08
Planned location following surgery, No. (%)			
Surgical ward	48 (32.7)	41 (28.3)	
High-dependency care unit <sup>e</sup>	81 (55.1)	84 (57.9)	.71
Intensive care unit	18 (12.2)	20 (13.8)	

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

- <sup>a</sup> Detailed data on intraoperative procedures are given in eTable 1 in Supplement 2.
- <sup>b</sup> 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.
- <sup>c</sup> Nine patients (4 in the individualized treatment group and 5 in the standard treatment group) were missing data on use of epidural analgesia.
- <sup>d</sup> Duration of surgery is the time between skin incision and closure of the incision.

<sup>e</sup> 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<sup>28</sup> and is a leading cause of morbidity and mortality even in patients with normal baseline renal function.<sup>29</sup> Early postoperative cognitive dysfunction and confusion are common after major surgery and are associated with prolonged recovery after surgery and higher postoperative mortality.<sup>30,31</sup>

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

Variable	Individualized Treatment (n = 147)	Standard Treatment	Between-Group Absolute Difference,	Unadjusted Relative Risk	DValue	Adjusted Relative Risk	DValue
Variable Primary Outcome	(n = 147)	(n = 145)	% (95% CI)	(95% CI)	P Value	(95% CI) <sup>a</sup>	P value
Primary composite outcome, No. (%) <sup>b</sup>	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. (%) <sup>c</sup>							
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) <sup>c</sup>	1.5 (1.3 to 1.7)	1.6 (1.4 to 1.7)			.62		.61
Acute kidney injury according to RIFLE criteria, No. (%) <sup>d</sup>							
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)	0.24 (0.16 += 0.74)	007	0.24 (0.16 += 0.75)	007
Altered consciousness, No. (%) <sup>e</sup>	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	2 ( 2 + 10)	1 44 (0 60 + - 2 01)		1 47 (0 07 1 0 02)	07
Coagulation SOFA score $\geq 2$ , 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
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
Dow 1	1 (0, 2)	1 (0 2)			21		26
Day 1	1 (0-3)	1 (0-3)			.31		.30
Day Z	1 (0-2)	2 (0-3)			.19		.21
Ddy /	12 (9 9)	0 (0-1)	$-7(-15 \pm 0)$	0.56 (0.20 to 1.06)	.00	$0.55(0.20 \pm 0.104)$	.00
Severe censis or centic chock	13 (8.8)	13 (9.0)	-7(-15(00))	0.30(0.23 to 1.00)	.07	$1.01(0.49 \pm 0.211)$	.07
No. (%)	15 (0.0)	15 (5.0)	0(0107)	0.55 (0.47 to 2.05)	.57	1.01 (0.45 to 2.11)	.57
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. (%) <sup>9</sup>	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 neart 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
or infarction, No. (%)	0	1 (0.7)					
Suroke, NO. (%)	0	0					
Surgical complications, No. (%)	22 (15 7)	26 (24.0)	0 ( 10 +- 0)	0.62 (0.20 + 1.00)	05	0.02 (0.40 + 0.00)	0.4
Surgical site infection	23 (15.7)	36 (24.8)	-9 (-18 to U)	0.78 (0.39 to 1.00)	.05	0.03 (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"	24 (16.3)	25 (17.2)	-1 (-9 t0 8)	0.95 (0.57 to 1.58)	.83	0.92 (0.57 to 1.50)	./4
Death at day 30, No. (%)	9 (6.1)	8 (5.5)	1 (-4 to 6)	1.11 (0.44 to 2.80)	دة.	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 <sup>i</sup>	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: IOR. interguartile				E			

range: RIFLE, risk, injury, failure, loss, and end-stage kidney injury; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.

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

<sup>b</sup> 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.

 $^{\rm c}$  The SIRS score (range, O [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<sub>2</sub> less than 32 mm Hg.

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.

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

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

<sup>g</sup> Tracheal intubation for reoperation because of surgical complications was not considered a reintubation.

<sup>h</sup> Anastomotic leakage of the gastrointestinal tract.

<sup>i</sup> 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  $\geq 2$  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.<sup>14,24</sup> 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 <u>risk</u> of acute <u>kidney</u> injury,<sup>29</sup> respiratory failure,<sup>32</sup> sepsis, and death.<sup>33,34</sup>

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.<sup>9</sup> 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<sup>35</sup>; 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 <u>10-mm Hg reduction</u> in <u>SBP</u> below 80 mm Hg<sup>6</sup> or a <u>5-mm</u> Hg reduction in mean arterial pressure <u>below 70 mm</u> Hg is associated with adverse outcomes.<sup>4,5</sup> 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 onequarter 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.<sup>36</sup> 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.<sup>15,37</sup> Moreover, phenylephrine is a selective  $a_1$ -adrenergic agonist with a greater risk of negative effects on cardiac output,<sup>38</sup> in contrast to ephedrine or norepinephrine, which have  $\beta$ -adrenergic activity.<sup>37,39</sup> 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.<sup>4,5</sup> 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.

#### **ARTICLE INFORMATION**

Accepted for Publication: August 30, 2017.

**Published Online:** September 27, 2017. doi:10.1001/jama.2017.14172

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 Lvon-1. Hospices Civils de Lvon. 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, 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. Obtained funding: Futier, Julia. Administrative, technical, or material support: Futier, Lefrant, Guinot, Godet, Cuvillon, Leone, Piriou, Julia, Bazin, Jaber. Supervision: Futier, Godet, Bertran, Julia, Constantin, Jaber. Conflict of Interest Disclosures: All authors have

completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Futier reported receiving consulting fees from Edwards Lifesciences and Dräger; lecture fees from Dräger, GE Healthcare, Fresenius Kabi, and Fisher and Paykel Healthcare; and travel reimbursement from Fisher and Paykel Healthcare. Dr Leone reported receiving personal fees from LFB and

jama.com

Julia, Imhoff, Constantin, Pereira, Jaber,

Augettant and nonfinancial support from MSD. Dr Julia reported being an inventor on a patent owned by Aguettant. Dr Bazin reported receiving honoraria for expertise from General Electric, Ambu, and MSD and a grant from General Electric. No other disclosures were reported.

**Funding/Support:** This study was funded by the University Hospital of Clermont-Ferrand and was supported in part by a grant from Aguettant.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The steering committee designed the study, vouches for protocol adherence, and made the decision to submit the manuscript for publication. All drugs used in the study were purchased from the manufacturers, who had no role in the study.

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)

Additional Contributions: We thank all the patients who participated in the study; the clinical and research staff at all trial sites, without whose assistance the INPRESS study would never have been completed; and the monitors of the trial. Dominique Morand (Direction de la Recherche Clinique, Centre Hospitalier Universitaire Clermont-Ferrand) coordinated the monitoring of the trial and Mervyn Singer, MD (Bloomsbury Institute of Intensive Care Medicine, University College London), provided valuable advice during the preparation of the manuscript; they received no compensation.

#### REFERENCES

1. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet*. 2008;372(9633):139-144.

2. Haynes AB, Weiser TG, Berry WR, et al; Safe Surgery Saves Lives Study Group. A surgical safety checklist to reduce morbidity and mortality in a global population. *N Engl J Med.* 2009;360(5):491-499.

3. Devereaux PJ, Sessler DI, Leslie K, et al; POISE-2 Investigators. Clonidine in patients undergoing noncardiac surgery. *N Engl J Med*. 2014;370(16): 1504-1513.

4. Walsh M, Devereaux PJ, Garg AX, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology*. 2013;119(3):507-515.

5. Sun LY, Wijeysundera DN, Tait GA, Beattie WS. Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. *Anesthesiology*. 2015;123(3):515-523.

 Monk TG, Bronsert MR, Henderson WG, et al. Association between intraoperative hypotension and hypertension and 30-day postoperative mortality in noncardiac surgery. *Anesthesiology*. 2015;123(2):307-319.

 Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. *Anesthesiology*. 2007;107(2):213-220.

8. Salmasi V, Maheshwari K, Yang D, et al. Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery: a retrospective cohort analysis. *Anesthesiology*. 2017;126(1):47-65.

9. Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130(24):e278-e333.

**10**. Palmer BF. Renal dysfunction complicating the treatment of hypertension. *N Engl J Med*. 2002;347 (16):1256-1261.

**11**. Strandgaard S, Olesen J, Skinhoj E, Lassen NA. Autoregulation of brain circulation in severe arterial hypertension. *Br Med J*. 1973;1(5852):507-510.

12. van Waes JA, van Klei WA, Wijeysundera DN, van Wolfswinkel L, Lindsay TF, Beattie WS. Association between intraoperative hypotension and myocardial injury after vascular surgery. *Anesthesiology*. 2016;124(1):35-44.

**13.** Brochard L, Abroug F, Brenner M, et al; ATS/ERS/ESICM/SCCM/SRLF Ad Hoc Committee on Acute Renal Failure. An official ATS/ERS/ESICM/ SCCM/SRLF statement: prevention and management of acute renal failure in the ICU patient: an international consensus conference in intensive care medicine. *Am J Respir Crit Care Med.* 2010;181(10):1128-1155.

14. Kheterpal S, Tremper KK, Heung M, et al. Development and validation of an acute kidney injury risk index for patients undergoing general surgery: results from a national data set. *Anesthesiology*. 2009;110(3):505-515.

**15**. Glick D. The autonomic nervous system. In: Miller RD, ed. *Miller's Anesthesia*. 8th ed. Philadelphia, PA: Elsevier; 2015:346-386.

**16.** Vallet B, Blanloeil Y, Cholley B, Orliaguet G, Pierre S, Tavernier B; Société française d'anesthésie et de réanimation. Guidelines for perioperative haemodynamic optimization [in French]. *Ann Fr Anesth Reanim*. 2013;32(6):454-462.

**17**. Vincent JL, Pelosi P, Pearse R, et al. Perioperative cardiovascular monitoring of high-risk patients: a consensus of 12. *Crit Care*. 2015;19:224.

**18**. Bone RC, Balk RA, Cerra FB, et al; ACCP/SCCM Consensus Conference Committee, American College of Chest Physicians/Society of Critical Care Medicine. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest.* 1992;101(6):1644-1655.

19. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative Workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8(4):R204-R212.

**20**. Vincent JL, Moreno R, Takala J, et al; Working Group on Sepsis-Related Problems, European Society of Intensive Care Medicine. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med*. 1996;22(7):707-710.

**21**. Talmor M, Hydo L, Barie PS. Relationship of systemic inflammatory response syndrome to organ dysfunction, length of stay, and mortality in critical surgical illness: effect of intensive care unit resuscitation. *Arch Surg.* 1999;134(1):81-87.

22. Levy MM, Fink MP, Marshall JC, et al; International Sepsis Definitions Conference. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Med*. 2003; 29(4):530-538.

23. Pittet D, Rangel-Frausto S, Li N, et al. Systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock: incidence, morbidities and outcomes in surgical ICU patients. *Intensive Care Med.* 1995;21(4):302-309.

24. Haga Y, Beppu T, Doi K, et al. Systemic inflammatory response syndrome and organ dysfunction following gastrointestinal surgery. *Crit Care Med*. 1997;25(12):1994-2000.

25. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay: a randomised, controlled trial [ISRCTN38797445]. *Crit Care*. 2005;9(6):R687-R693.

**26**. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702-706.

27. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika*. 1988; 75(4):800-802. doi:10.1093/biomet/75.4.800

**28**. Bihorac A, Yavas S, Subbiah S, et al. Long-term risk of mortality and acute kidney injury during hospitalization after major surgery. *Ann Surg.* 2009;249(5):851-858.

**29**. O'Connor ME, Kirwan CJ, Pearse RM, Prowle JR. Incidence and associations of acute kidney injury after major abdominal surgery. *Intensive Care Med*. 2016;42(4):521-530.

**30**. Moller JT, Cluitmans P, Rasmussen LS, et al; International Study of Post-Operative Cognitive Dysfunction (ISPOCD) Investigators. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. *Lancet*. 1998;351(9106):857-861.

**31**. Monk TG, Weldon BC, Garvan CW, et al. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology*. 2008;108(1): 18-30.

**32**. Jaber S, Lescot T, Futier E, et al; NIVAS Study Group. Effect of noninvasive ventilation on tracheal reintubation among patients with hypoxemic respiratory failure following abdominal surgery: a randomized clinical trial. *JAMA*. 2016;315(13): 1345-1353.

**33.** Moore LJ, Moore FA, Todd SR, Jones SL, Turner KL, Bass BL. Sepsis in general surgery: the 2005-2007 national surgical quality improvement program perspective. *Arch Surg.* 2010;145(7): 695-700.

**34**. Wakeam E, Hyder JA, Jiang W, Lipsitz SA, Finlayson S. Risk and patterns of secondary

complications in surgical inpatients. *JAMA Surg.* 2015;150(1):65-73.

**35**. Asfar P, Meziani F, Hamel JF, et al; SEPSISPAM Investigators. High versus low blood-pressure target in patients with septic shock. *N Engl J Med.* 2014;370(17):1583-1593.

**36.** Dalfino L, Giglio MT, Puntillo F, Marucci M, Brienza N. Haemodynamic goal-directed therapy and postoperative infections: earlier is better: a systematic review and meta-analysis. *Crit Care*. 2011;15(3):R154.

**37**. Mets B. Should norepinephrine, rather than phenylephrine, be considered the primary vasopressor in anesthetic practice? *Anesth Analg.* 2016;122(5):1707-1714.

**38**. Thiele RH, Nemergut EC, Lynch C III. The physiologic implications of isolated alpha(1) adrenergic stimulation. *Anesth Analg*. 2011;113(2): 284-296.

**39**. Hiltebrand LB, Koepfli E, Kimberger O, Sigurdsson GH, Brandt S. Hypotension during fluid-restricted abdominal surgery: effects of norepinephrine treatment on regional and microcirculatory blood flow in the intestinal tract. *Anesthesiology*. 2011;114(3):557-564.

Concept and design: Baggett. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Baggett. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Baggett, Berkowitz, Fung. Obtained funding: Baggett. Administrative, technical, or material support: Baggett. Supervision: Baggett.

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Baggett reported receiving royalty payments from *UpToDate* for authorship of a topic review on the health care of homeless people in the United States. No other disclosures are reported.

**Funding/Support:** This study was supported by grants K23DA034008 from the National Institute on Drug Abuse (Dr Baggett), K23DK109200 from the National Institute of Diabetes and Digestive and Kidney Diseases (Dr Berkowitz), R01HS025378 from the Agency for Healthcare Research and Quality (Dr Fung), and by the Massachusetts General Hospital Department of Medicine Transformative Scholars Program (Baggett).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

**Disclaimer:** The study content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, the Agency for Healthcare Research and Quality, or Massachusetts General Hospital.

1. Health Resources and Services Administration. 2016 Health center data. https://bphc.hrsa.gov/uds/datacenter.aspx. Accessed November 1, 2017.

2. Health Resources and Services Administration. Health Center Patient Survey. https://bphc.hrsa.gov/datareporting/research/hcpsurvey/index.html. Accessed November 2, 2017.

3. National Health Care for the Homeless Council. What is the official definition of homelessness? https://www.nhchc.org/faq/official-definition-homelessness/. Accessed August 22, 2017.

4. Montgomery AE, Fargo JD, Kane V, Culhane DP. Development and validation of an instrument to assess imminent risk of homelessness among veterans. *Public Health Rep.* 2014;129(5):428-436.

 Kushel MB, Gupta R, Gee L, Haas JS. Housing instability and food insecurity as barriers to health care among low-income Americans. J Gen Intern Med. 2006;21(1):71-77.

6. National Alliance to End Homelessness. The state of homelessness in America. https://endhomelessness.org/homelessness-in-america/homelessness -statistics/state-of-homelessness-report/. Accessed November 15, 2017.

#### **COMMENT & RESPONSE**

## Organ Dysfunction After Surgery in Patients Treated With Individualized or Standard Blood Pressure Management

**To the Editor** In a randomized clinical trial,<sup>1</sup> Dr Futier and colleagues assessed the effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction. We had concerns regarding the blood pressure goals that were established for the subgroup of patients that was assigned to the standard blood pressure group.

The authors chose to treat a systolic blood pressure (SBP) less than 80 mm Hg or less than 40% from a patient's resting blood pressure. However, it has been well described in the literature and is standard practice to maintain the intraoperative blood pressures within 20% of the patient's best estimate of preoperative blood pressure.<sup>2</sup> Only in healthy patients has a 25% to 35% decrease in blood pressure from immediate preoperative baseline values been found acceptable.<sup>3</sup> In a recent analysis,<sup>4</sup> maintaining intraoperative pressures below 20% of preoperative values was associated with myocardial and kidney injury. Thus, the authors' decision to allow the blood pressures to drop to less than 40% of preoperative values in the standard group might have predisposed these patients to a higher likelihood of postoperative organ dysfunction. The patient population studied by the authors had a high risk of perioperative complications and exposing these patients to a lower blood pressure threshold than what is standard practice might have artificially skewed the data in favor of the individualized blood pressure group.

The other concern we had was that patients in the standard group received a higher volume of crystalloid administration during surgery (2000 mL vs 1500 mL) compared with the individualized blood pressure group. Administration of a higher volume of fluids during the intraoperative period can be associated with worse postoperative outcomes.<sup>5</sup> The difference in fluid administration during the intraoperative period between the 2 groups could also have affected the postoperative outcomes.

Kunal Karamchandani, MD Zyad J. Carr, MD Anthony Bonavia, MD

Author Affiliations: Penn State Milton S. Hershey Medical Center, Anesthesiology and Perioperative Medicine, Hershey, Pennsylvania.

**Corresponding Author:** Kunal Karamchandani, MD, Department of Anesthesiology and Perioperative Medicine, H187, Penn State Health Milton S. Hershey Medical Center, 500 University Dr, Hershey, PA 17033 (kkaramchandani@pennstatehealth.psu.edu).

**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Futier E, Lefrant JY, Guinot PG, et al; INPRESS Study Group. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. *JAMA*. 2017;318(14):1346-1357.

2. Ng JL, Chan MT, Gelb AW. Perioperative stroke in noncardiac, nonneurosurgical surgery. *Anesthesiology*. 2011;115(4):879-890.

**3**. Soo JC, Lacey S, Kluger R, Silbert BS. Defining intra-operative hypotension: a pilot comparison of blood pressure during sleep and general anaesthesia. *Anaesthesia*. 2011;66(5):354-360.

4. Salmasi V, Maheshwari K, Yang D, et al. Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery: a retrospective cohort analysis. *Anesthesiology*. 2017;126(1):47-65.

5. Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einav S, Matot I. Effect of intraoperative fluid management on outcome after intraabdominal surgery. *Anesthesiology*. 2005;103(1):25-32.

To the Editor Dr Futier and colleagues performed a study to evaluate the effects of targeting perioperative blood pressure based on patients' individual preoperative blood pressures compared with standard practice.<sup>1</sup> However, methodological issues raise questions about the results. The authors did not simply compare 2 groups with different perioperative blood pressure goals. Rather, they compared the outcomes of 2 completely different blood pressure management strategies.

First, the intervention group was managed with norepinephrine infusions to achieve blood pressure goals, whereas the standard group was managed with ephedrine boluses to achieve more liberal blood pressure goals. The authors supported this decision by stating that norepinephrine and ephedrine both act on  $\alpha$ - and  $\beta$ -adrenergic receptors to produce their clinical effects, but the fact remains that these are 2 very different medications. For example, norepinephrine is a directacting sympathomimetic amine, whereas ephedrine acts primarily via an indirect mechanism.<sup>2</sup> Using norepinephrine infusions to control blood pressure in both groups would have eliminated this unnecessary confounding.

Second, blood pressures were only recorded every 10 minutes, although standards from the American Society of Anesthesiologists recommend measuring blood pressure at least every 5 minutes.<sup>3</sup> Thus, unrecorded hypotension may have persisted for significant periods between blood pressure readings. Patients receiving vasopressor boluses would be expected to experience more blood pressure instability than those receiving vasopressor infusions. Without more frequent blood pressure recordings, the specifics of this instability remain unknown.

## Kelsey Mitchell, MD Douglas Adams, MD Stephen M. McHugh, MD

Author Affiliations: University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

**Corresponding Author**: Stephen M. McHugh, MD, Department of Anesthesiology, University of Pittsburgh School of Medicine, Ste M205, 5230 Centre Ave, Pittsburgh, PA 15232 (mchughsm@upmc.edu).

**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Futier E, Lefrant JY, Guinot PG, et al; INPRESS Study Group. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. *JAMA*. 2017;318(14):1346-1357.

 Ziegler MG, Lake CR, eds. Frontiers of Clinical Neuroscience. Baltimore, MD: Williams & Wilkins; 1984.

3. American Society of Anesthesiologists. Standards for basic anesthetic monitoring. https://www.asahq.org/~/media/Sites/ASAHQ/Files/Public /Resources/standards-guidelines/standards-for-basic-anesthetic-monitoring .pdf. Accessed January 5, 2018.

To the Editor A randomized clinical trial comparing a standard blood pressure management regimen vs individualized therapy in patients undergoing major surgery suggested that individualized goals could reduce postoperative organ dysfunction.<sup>1</sup> Unfortunately, the conclusions of the Intraoperative Norepinephrine to Control Arterial Pressure (INPRESS) study are not fully supported by the data.

The study was based on the premise that global blood pressure targets neglect the individual variation in baseline blood pressure (as exhibited by the SDs reported in Table 1 of the article<sup>1</sup>) and place patients at risk for relative hypotension. Yet when patients were randomized to global or individualized blood pressure targets, the between-group difference in SBP was only 6.5 mm Hg (95% CI, 3.8-9.2). Although this difference was statistically significant, in the context of the wide range of pressures exhibited in Figure 2,<sup>1</sup> this difference appears trivial. Contrast this with the Sepsis and Mean Arterial Pressure Trial in which critically ill patients were randomized to 2 mean arterial pressure targets, and a sharp physiologic distinction between groups was observed.<sup>2</sup>

*P* values less than .05 are often accepted as "truth." But even with properly conducted statistical analysis, the risk of incorrectly rejecting the null hypothesis remains as high as 5%. One strategy for mitigating that risk is simply asking whether there is a chain of logic that connects the intervention to the result. Unfortunately, it is not uncommon for investigators to conclude that their intervention was a success based on clinical outcome measures, even when the intervention had no detectable effect on the underlying physiology.<sup>3,4</sup>

In the case of the INPRESS study, the data do not allow this connection to be made. Missing is a report of the SBP indexed to baseline—if the intervention achieved a meaningful physiologic effect, the individualized therapy group should have maintained SBPs closer to baseline. Only then can it safely be concluded that therapy targeted to individual baseline blood pressure improves outcomes. Conversely, if SBPs indexed to baseline were almost identical between groups, it is hard to understand how one strategy could be superior.

#### Robert H. Thiele, MD

Author Affiliation: Department of Anesthesiology, University of Virginia School of Medicine, Charlottesville.

Corresponding Author: Robert H. Thiele, MD, University of Virginia, PO Box 800710, Charlottesville, VA 22908-0710 (rht7w@virginia.edu).

**Conflict of Interest Disclosures:** The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Futier E, Lefrant JY, Guinot PG, et al; INPRESS Study Group. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. *JAMA*. 2017;318(14):1346-1357.

2. Asfar P, Meziani F, Hamel JF, et al; SEPSISPAM Investigators. High versus low blood-pressure target in patients with septic shock. *N Engl J Med*. 2014;370(17): 1583-1593.

3. Pölönen P, Ruokonen E, Hippeläinen M, Pöyhönen M, Takala J. A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. *Anesth Analg.* 2000;90(5):1052-1059.

4. Jansen TC, van Bommel J, Schoonderbeek FJ, et al; LACTATE study group. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med*. 2010;182(6): 752-761.

To the Editor Dr Futier and colleagues<sup>1</sup> concluded that management targeting an individualized SBP minimized the risk of postoperative organ dysfunction compared with standard management. The authors used a composite primary outcome. Composite outcomes should include components that are of comparable severity and occur with similar frequency.<sup>2</sup> It was not appropriate to combine the less severe and more common RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) stage risk with the more severe and less common myocardial infarction, nor a Glasgow Coma Scale score of 14 or less with stroke. The incidence of acute kidney dysfunction was relatively large, so that it overwhelmed the other components of the composite primary outcome and effectively became the primary outcome.

In interventional trials, all groups should be treated equally, apart from the experimental and control treatments to ensure that any differences in the outcome can be attributed to effects of the study intervention.<sup>3</sup> In this study, the individualized treatment group received more than 1 intervention compared with the standard treatment group. The individualized treatment group targeted an SBP within 10% of the patient's resting SBP, whereas the standard treatment group targeted an SBP less than 80 mm Hg or lower than 40% from the patient's resting SBP. Different medications (norepinephrine vs ephedrine) and different methods of administration (continuous intravenous infusion vs intravenous boluses) were used. Each of these co-interventions may be responsible for the differences in the outcome of the study. It would be more appropriate if both groups received either intravenous boluses of ephedrine or, as mentioned in the limitations, continuous intravenous infusion norepinephrine. Interpretation is further complicated by the fact that 38 patients (26.2%) in the standard treatment group required rescue therapy with norepinephrine to achieve the target SBP.

More confidence would be achieved if both the intentionto-treat and per-protocol analyses were performed and reached the same conclusions.<sup>4</sup> A per-protocol analysis was mentioned as being planned in the protocol but not reported in the article.

#### Mahmoud Daoud, MD

Author Affiliation: Department of Anesthesia, Prince Sultan Military Medical City, Riyadh, Kingdom of Saudi Arabia.

**Corresponding Author:** Mahmoud Daoud, MD, Department of Anesthesia, Prince Sultan Military Medical City, Makkah Al Mukarramah Branch Road, Sulaimaniyah, Riyadh 11159, Kingdom of Saudi Arabia (mahmouddaoud@gmail.com).

**Conflict of Interest Disclosures:** The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Futier E, Lefrant JY, Guinot PG, et al; INPRESS Study Group. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. *JAMA*. 2017;318(14):1346-1357.

2. Tomlinson G, Detsky AS. Composite end points in randomized trials: there is no free lunch. *JAMA*. 2010;303(3):267-268.

**3**. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586.

**4**. Gupta SK. Intention-to-treat concept: a review. *Perspect Clin Res.* 2011;2(3): 109-112.

To the Editor In a recent study, individualized perioperative blood pressure management compared with standard care in the setting of major surgery was found to reduce the risk of postoperative organ dysfunction.<sup>1</sup> Although the study was hypothesis generating, the manner and rigor with which reference or normal resting blood pressure was obtained warrants further explanation.

Resting blood pressure from the preoperative anesthesiology consultation was used as the reference value and, if unavailable, the blood pressure measurement recorded on a surgical ward the day before surgery, while the patient was supine, was used. Clearly, these values may vary widely. Basing the intervention of keeping the SBP within 10 mm Hg of the normal resting value obtained with a nonuniform method of measurement may affect the internal validity of the results. Furthermore, international guidelines recognize that preoperative blood pressure management should be rigorous and evaluated in the context of historical blood pressures taken in a primary care setting.<sup>2</sup> In this trial, in which greater than 65% of patients were taking an antihypertensive medication at baseline, such an approach would have been particularly valuable.

The data suggest that individualized blood pressure management can improve postoperative surgical outcomes. However, fundamental questions remain regarding the validity of the individualized therapeutic blood pressure targets. Were multiple blood pressure measurements taken in the preoperative clinic and averaged? Were these measurements obtained in the supine position? Was blood pressure obtained by a manual auscultatory method or via an oscillometric blood pressure machine? The answers to these questions will reveal the trust that should be placed in each patient's normal resting value and consequently the trust that should be placed in the trial's results. Reproducibility and accuracy when measuring blood pressure are critical.

#### Luke J. Laffin, MD Michael R. Laffin, MD

Author Affiliations: Section of Cardiology, University of Chicago Medicine, Chicago, Illinois (L. J. Laffin); Department of Surgery, University of Alberta, Edmonton, Alberta, Canada (M. R. Laffin).

**Corresponding Author:** Luke J. Laffin, MD, University of Chicago Medicine, 5841 S Maryland Ave, MC 6080, Chicago, IL 60637 (luke.laffin@uchospitals.edu).

**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Futier E, Lefrant JY, Guinot PG, et al; INPRESS Study Group. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. *JAMA*. 2017;318(14):1346-1357.

2. Hartle A, McCormack T, Carlisle J, et al. The measurement of adult blood pressure and management of hypertension before elective surgery: joint guidelines from the Association of Anaesthetists of Great Britain and Ireland and the British Hypertension Society. *Anaesthesia*. 2016;71(3):326-337.

In Reply Dr Karamchandani and colleagues suggest that exposing patients in the standard treatment group to a blood pressure threshold level lower than what is generally accepted may have predisposed patients to organ dysfunction. However, although there is accumulating evidence that intraoperative blood pressure is associated with outcomes, the goals for blood pressure are not well supported by robust evidence and there are few data to support any specific threshold.

Karamchandani and colleagues also raise concerns about a possible effect of a between-group difference in intraoperative crystalloid administration. The mean difference in crystalloid administration during surgery between the 2 groups was 355 mL (95% CI, 138-572). Although patients who developed the primary outcome received more crystalloids (mean difference, 434 mL; 95% CI, 218-650), intraoperative crystalloid

administration was not associated with the primary outcome (adjusted relative risk, 1.29; 95% CI, 0.95-1.77), nor was the cumulative volume of fluids (eTable 2 in the Supplement).

Dr Mitchell and colleagues are concerned about blood pressure recordings at 10-minute intervals. Blood pressure was monitored continuously during surgery but hemodynamic data were collected at 10-minute intervals. As a result, the possibility of substantial variations in blood pressure between measurements points, and the possibility of longer durations of hypotensive events in the standard treatment group, cannot be excluded.

Dr Thiele questions the relevance of the overall small but statistically significant between-group difference in mean SBP and its connection to outcomes. Whether a higher threshold of statistical significance should be used in clinical research merits further debate. We agree, however, that in the INPRESS study, the risk of incorrectly rejecting the null hypothesis was as high as 2%. Thiele also suggests we report blood pressure indexed to baseline. We disagree given the stress-induced variability between baseline and usual blood pressure values both within and between patients commonly observed in clinical practice.<sup>1</sup>

Dr Daoud raises concern about the relative weights of each component of the composite primary outcome. Although the positive effect on the composite end point was mainly driven by statistically significant differences in renal dysfunction and altered consciousness with the individualized strategy, additional analysis with each individual component was also performed, as recommended,<sup>2</sup> and adjustment was made for multiple testing.

Mitchell and colleagues and Daoud point out the possible effects of a co-intervention of different vasopressor agents in addition to different blood pressure thresholds on study outcomes, and they suggest that use of norepinephrine instead of ephedrine in the standard treatment group would have eliminated this unnecessary confounding. Norepinephrine is rarely used to treat hypotension in general surgical patients, and data on its efficacy and safety have not been extensively studied in this context.<sup>3</sup> Nevertheless, we agree that an independent effect of the vasopressor agent on outcome cannot be excluded, in particular because norepinephrine may exert venoconstrictive effects on venous capacitance vessels leading to an increase in venous return and cardiac preload.<sup>4</sup> However, in the trial, no between-group differences were noted in the cardiac index or the cumulative volume of fluids. In the per-protocol analysis (including patients who required norepinephrine because of persistent hypotension), the primary outcome occurred in 28 patients (74%) in the standard treatment group vs 53 patients (38%) in the individualized treatment group (adjusted relative risk, 0.53; 95% CI, 0.40-0.72; P < .001).

Drs L. J. Laffin and M. R. Laffin raise concerns about the standardization and accuracy of blood pressure measurements to define resting values. We agree on the difficulty of defining resting blood pressures, especially when 60% of patients taking antihypertensive drugs had treatment discontinuation prior to surgery and 15% had emergency procedures. However, extensive measures were taken to minimize

the risk of variability, and blood pressures documented in the patient medical record were used as the reference value in most cases.

## Emmanuel Futier, MD, PhD Bruno Pereira, PhD Samir Jaber, MD, PhD

Author Affiliations: Hôpital Estaing, Centre Hospitalier Universitaire Clermont-Ferrand, Clermont-Ferrand, France (Futier); Centre Hospitalier Universitaire Clermont-Ferrand, Direction de la Recherche Clinique, Clermont-Ferrand, France (Pereira); Hôpital Saint-Eloi, Centre Hospitalier Universitaire Montpellier, Montpellier, France (Jaber).

**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).

**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Futier reported receiving consulting fees from Edwards Lifesciences and Dräger; lecture fees from Dräger, GE Healthcare, Fresenius Kabi, and Fisher and Paykel Healthcare; and travel reimbursement from Fisher and Paykel Healthcare. No other disclosures were reported.

1. van Klei WA, van Waes JA, Pasma W, et al. Relationship between preoperative evaluation blood pressure and preinduction blood pressure: a cohort study in patients undergoing general anesthesia. *Anesth Analg.* 2017;124(2):431-437.

2. Irony TZ. The "utility" in composite outcome measures: measuring what is important to patients. *JAMA*. 2017;318(18):1820-1821.

**3**. Mets B. Should norepinephrine, rather than phenylephrine, be considered the primary vasopressor in anesthetic practice? *Anesth Analg.* 2016;122(5):1707-1714.

**4**. Monnet X, Jabot J, Maizel J, Richard C, Teboul JL. Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients. *Crit Care Med.* 2011;39(4):689-694.

## **Authorship Credit for Large Clinical Trials**

To the Editor Drs Mentzelopoulos and Zakynthinos outlined the goals for maintaining the academic integrity of research in a Viewpoint.<sup>1</sup> However, the current structure of promotions in most academic settings discourages rather than promotes collaboration. This current structure is not good for clinical research, as it perpetuates, rather than helps to resolve, the continuing problem that the majority of clinical trials are relatively small, single-site studies<sup>2</sup> that may be underpowered and of questionable significance and potential to advance medicine. In clinical research involving human participants, high statistical variability is frequently seen. Thus, high-quality, meaningful research usually means large sample sizes. Except in rare cases, this requires collaboration among large groups of researchers. Under the present criteria for academic promotion at many universities, whereby investigators are heavily rewarded for either first or last authorship and promoted based largely on individual rather than collaborative efforts, the motivation to participate in large collaborative efforts is markedly diminished.

Clinical trials represent the central means by which preventive, diagnostic, and therapeutic interventions are evaluated.<sup>2</sup> Pharmaceutical industry-sponsored clinical trials represent an important line of therapeutic research, and the large majority of new clinical treatments achieve approval by the US Food and Drug Administration through industrysponsored trials. The state of clinical trials in mental health is

## Letters

#### **COMMENT & RESPONSE**

## Additional Factors Regarding Clinical Outcomes of General Anesthesia and Conscious Sedation for Acute Ischemic Stroke

**To the Editor** Simonsen et al<sup>1</sup> concluded that general anesthesia (GA) did not influence infarct growth compared with conscious sedation in endovascular-treated patients with acute stroke. This is an interesting study that addresses topical questions. However, we would like to point out some limitations.

The authors used infarct growth, which was determined by magnetic resonance imaging scans that were obtained before endovascular treatment (EVT) and 2 to 3 days after EVT, as a primary end point. Before imaging biomarkers, such as final infarct volume and infarct growth, are used as surrogate for clinical end points, a mediation analysis must establish the causal pathway between intervention and mediator and between mediator and clinical outcome.<sup>2</sup> However, infarct growth that is associated with a clinical outcome is complex and the clinical benefit may not be explained by changes in infarct growth solely.<sup>3</sup> Although posttreatment infarct volume is described as a strong predictor that is associated with functional outcome in patients with acute stroke, infarct volume is not (completely) causally related (mediating) to functional outcome at 90 days.<sup>3,4</sup> As long as it is unclear as to which proportion of functional outcome is explained by infarct volume or prevention of infarct growth, it should not be reported as a surrogate imaging end point.

The authors mentioned several physiological and procedural considerations that cause differences in outcome between both anesthetic approaches (ie, patient movement, a time increase that is associated with intubation, and blood pressure drops). This study shows 2 findings regarding these considerations. First, in opposition to the current literature, patients undergoing GA for EVT had better functional outcomes despite the higher rates of low blood pressure. Second, technical success, which was defined as a successful reperfusion (thrombosis in cerebral infarction  $\ge$  2b) of EVT was greater in the GA group. However, no explanation was given for the latter finding. Additionally, GA was compared with conscious sedation in this randomized clinical trial, although a comparison with treatment effect regarding local anesthesia at the groin puncture site only remains.

In conclusion, interpreting infarct growth as a surrogate marker for clinical outcome should be done with great care. Further research on the influences of different types of anesthetic management on EVT in patients with acute stroke is still warranted.

Kars C. J. Compagne, BSc Rob A. van de Graaf, MD Aad van der Lugt, MD, PhD

Author Affiliations: Department of Radiology and Nuclear Medicine, Erasmus University Medical Center, Rotterdam, the Netherlands (Compagne, van de Graaf, van der Lugt); Department of Neurology, Erasmus University Medical Center, Rotterdam, the Netherlands (Compagne, van de Graaf).

**Corresponding Author**: Kars C. J. Compagne, BSc, Department of Radiology, Erasmus University Medical Center. PO Box 2040 3000 CA, Rotterdam, the Netherlands (c.compagne@erasmusmc.nl).

Published Online: July 16, 2018. doi:10.1001/jamaneurol.2018.1844

**Conflict of Interest Disclosures:** The Erasmus University Medical Center Rotterdam received funds from Stryker for consultations by AvdL outside the submitted work. No other disclosures are reported.

1. Simonsen CZ, Yoo AJ, Sørensen LH, et al. Effect of general anesthesia and conscious sedation during endovascular therapy on infarct growth and clinical outcomes in acute ischemic stroke: a randomized clinical trial. *JAMA Neurol*. 2018;75(4):470-477. doi:10.1001/jamaneurol.2017.4474

2. Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. *Stat Med.* 1989;8(4):431-440. doi:10.1002/sim.4780080407

3. Al-Ajlan FS, Al Sultan AS, Minhas P, et al; REVASCAT Investigators. Posttreatment infarct volumes when compared with 24-hour and 90-day clinical outcomes: insights from the REVASCAT randomized controlled trial. *AJNR Am J Neuroradiol*. 2018;39(1):107-110. doi:10.3174/ajnr.A5463

4. Al-Ajlan FS, Goyal M, Demchuk AM, et al; ESCAPE Trial Investigators. Intra-arterial therapy and post-treatment infarct volumes: insights from the ESCAPE randomized controlled trial. *Stroke*. 2016;47(3):777-781.

To the Editor We applaud Simonsen et al<sup>1</sup> for performing a randomized clinical trial about the effect of general anesthesia (GA) and conscious sedation (CS) during endovascular therapy on infarct growth and clinical outcomes in acute ischemic stroke. Despite its equipoise, this study is important in the field because it reinforces the results of recent randomized clinical trials concerning GA safety in thrombectomy for acute ischemic stroke.<sup>2,3</sup>

While the authors focused on the aspect of arterial blood pressure with clear critical thresholds and protocolized management, we believe that 2 points concerning ventilatory management should be discussed.

First, in the discussion of their article, the authors emphasized the potential influence of ventilatory parameters in stroke outcomes, and especially hypercapnia, that could enhance cerebral blood flow in ischemic penumbra. Indeed, blood carbon dioxide (CO<sub>2</sub>) tension is a major determinant of cerebral blood flow and could be best modulated during GA under mechanical ventilation. This parameter seems to have been strictly monitored in both arms of the trial with an aim of normoventilation in GA, as postulated in the published protocol and in the supplemental content of the article.<sup>4</sup> We are therefore surprised that no data were published in the article on end tidal CO<sub>2</sub> or the arterial partial pressure of CO<sub>2</sub>. These parameters could partially explain the overall results.

Second, CS is defined by the American Society of Anesthesiologists as a moderate sedation/analgesia that is a "drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous

jamaneurology.com

ventilation is adequate. Cardiovascular function is usually maintained.<sup>75</sup> It seems that no clinical parameter was used to evaluate the conduction of CS, which could be highly variable between practitioners. One could imagine that some patients undergoing CS were treated with an inadequate sedation level that could affect outcomes, notably via ventilatory parameters, such as oxygenation or carbon dioxide tension. Oxygenation parameters, such as pulse oxymetry, were also not mentioned in the study results.

## Russell Chabanne, MD Emmanuel Futier, MD, PhD

Author Affiliations: Department of Perioperative Medicine, Centre Hospitalier Universitaire Clermont-Ferrand, Clermont-Ferrand, France.

**Corresponding Author:** Russell Chabanne, MD, Department of Perioperative Medicine, Centre Hospitalier Universitaire Clermont-Ferrand, Clermont-Ferrand, France, 58 Rue Montalembert, 63003 Clermont-Ferrand Cedex 1, France (rchabanne@chu-clermontferrand.fr).

#### Published Online: July 16, 2018. doi:10.1001/jamaneurol.2018.1847

**Conflict of Interest Disclosures:** Drs Chabanne and Futier received grants from the French Ministry of Health (Projet Hospitalier de Recherche Clinique Interrégional 2016) to conduct the ongoing Anesthesia Management in Endovascular Therapy for Ischemic Stroke (AMETIS) trial (NCT03229148). They received no funding for this Letter to the Editor. Dr Futier received consulting fees from Edwards Lifesciences and Dräger; lecture fees from Dräger, GE Healthcare, Fresenius Kabi, and Fisher and Paykel Healthcare; and travel reimbursements from Fisher and Paykel Healthcare.

1. Simonsen CZ, Yoo AJ, Sørensen LH, et al. Effect of general anesthesia and conscious sedation during endovascular therapy on infarct growth and clinical outcomes in acute ischemic stroke: a randomized clinical trial. *JAMA Neurol.* 2018;75(4):470-477. doi:10.1001/jamaneurol.2017.4474

2. Schönenberger S, Uhlmann L, Hacke W, et al. Effect of conscious sedation vs general anesthesia on early neurological improvement among patients with ischemic stroke undergoing endovascular thrombectomy: a randomized clinical trial. *JAMA*. 2016;316(19):1986-1996. doi:10.1001/jama.2016.16623

 Löwhagen Hendén P, Rentzos A, Karlsson JE, et al. General anesthesia versus conscious sedation for endovascular treatment of acute ischemic stroke: the AnStroke Trial (Anesthesia During Stroke). *Stroke*. 2017;48(6):1601-1607. doi:10.1161/STROKEAHA.117.016554

 4. Simonsen CZ, Sørensen LH, Juul N, et al. Anesthetic strategy during endovascular therapy: general anesthesia or conscious sedation? (GOLIATH—General or Local Anesthesia in Intra Arterial Therapy) A single-center randomized trial. *Int J Stroke*. 2016;11(9):1045-1052. doi:10.1177 /1747493016660103

5. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. A report by the American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. *Anesthesiology*. 1996;84(2):459-471. doi:10.1097/00000542-199602000-00029

In Reply We thank Chabanne and Futier for the relevant question concerning ventilator parameters in the General or Local Anesthesia in Intra Arterial Therapy (GOLIATH) trial. Unfortunately, it was not possible for us to obtain periprocedural arterial blood gas parameters because of resource constraints. However, we have recently reported the end tidal carbon dioxide (EtCO<sub>2</sub>) levels in the general anesthesia (GA) arm (4.4 kPa; interquartile range, 4.2-4.8 kPa).<sup>1</sup> Taking the normal arterial to EtCO<sub>2</sub> gradient into account, our data indicate a normoventilation, which was the intention in the study protocol. The EtCO<sub>2</sub> levels were not measured in the conscious sedation (CS) arm.

It is true that no objective measure was used to monitor the level of CS or GA. Generally, anesthetic drugs are administered

according to a patient response. In the GOLIATH trial, the level of sedation was monitored according to institutional guidelines that primarily focused on patient responses to verbal commands and airway monitoring. The main objectives of CS for endovascular treatment are to minimize involuntary patient movements and pain and maintain a patent airway. Individual patients respond differently to sedatives and often different drug dosages have to be administered to obtain a similar sufficient level of sedation in 2 different patients. Thus, we believe that monitoring the level of sedation according to an objective measure has only academic interest. The drug doses administered in the CS arm have also recently been published and provide information on the level of sedation.<sup>1</sup>

We appreciate the insights of Compagne et al regarding their objection to the use of infarct growth as a surrogate end point; we are also aware of the recent studies that use a formal mediation analysis to show a weaker than expected contribution of posttreatment ischemic lesion volume to longterm functional outcomes.<sup>2</sup> Indeed, this finding might explain why the clinical outcomes between the trial arms were significantly different, whereas infarct growth was not. The greater statistical power displayed by our clinical end point is another argument against infarct volume as a potential surrogate. When the GOLIATH trial was designed, the aforementioned mediation analyses were not published, and based on the literature at the time, infarct growth was the best choice for a surrogate end point. Nevertheless, the biological rationale for the interventions we do in acute stroke (ie, achieving greater revascularization, treating faster, and avoiding blood pressure drops) remains preventing infarct growth. In this light, this trial provides important data regarding the mechanisms by which the anesthetic regimen might influence the acute evolution of stroke and the response to intervention.

With respect to the higher rate of successful reperfusion in the GA group, we proposed in our article's Discussion<sup>3</sup> that it might have been related to decreased patient movement. Although most stroke patients can be safely and effectively treated while undergoing CS, it is clear that there are some patients for whom excessive movement can pose a major impediment to the neurointerventionist. As we also concluded, this finding is in opposition to the retrospective literature but agrees with other randomized clinical trials.

## Claus Z. Simonsen, MD, PhD Albert J. Yoo, MD, PhD Mads Rasmussen, MD, PhD

Author Affiliations: Department of Neurology, Aarhus University Hospital, Aarhus, Denmark (Simonsen); Division of Neurointervention, Texas Stroke Institute, Dallas-Fort Worth (Yoo); Department of Anesthesiology and Intensive Care-North, Section of Neuroanesthesia, Aarhus University Hospital, Aarhus, Denmark (Rasmussen).

**Corresponding Author:** Claus Z. Simonsen, MD, PhD, Department of Neurology, Aarhus University Hospital, Norrebrogade 44, Aarhus 8000, Denmark (clasim@rm.dk).

Published Online: July 16, 2018. doi:10.1001/jamaneurol.2018.1850

**Conflict of Interest Disclosures:** Dr Yoo reports receiving research grant support from Penumbra Inc and Neuravi Inc; consulting fees from Cerenovus Inc, Genentech, and Stryker; and equity ownership in Insera Therapeutics Inc. No other disclosures are reported.

1. Rasmussen M, Espelund US, Juul N, et al. The influence of blood pressure management on neurological outcome in endovascular therapy for acute ischaemic stroke. Br J Anaesth. 2018;120(6):1287-1294. doi:10.1016/j.bja.2018 01039

2. Al-Ajlan FS, Al Sultan AS, Minhas P, et al; REVASCAT Investigators. Posttreatment infarct volumes when compared with 24-hour and 90-day clinical outcomes: insights from the REVASCAT randomized controlled trial. AJNR Am J Neuroradiol. 2018;39(1):107-110. doi:10.3174/ajnr.A5463

3. Simonsen CZ, Yoo AJ, Sørensen LH, et al. Effect of general anesthesia and conscious sedation during endovascular therapy on infarct growth and clinical outcomes in acute ischemic stroke: a randomized clinical trial. JAMA Neurol. 2018;75(4):470-477. doi:10.1001/jamaneurol.2017.4474

#### **Retinoids and Amyotrophic Lateral Sclerosis**

To the Editor We read with great interest the article by Rosenbohm and colleagues.<sup>1</sup> They conducted a case-control study and reported that retinol-binding protein 4 had an inverse association with both risk for amyotrophic lateral sclerosis (ALS) and disease prognosis. Although we agree with the relevance of the reported results and their interpretation, we would like to comment on 2 issues that might also correlate with these findings.

First, as the authors indicated in the study, growing evidence shows disturbances in energy metabolism levels in patients with ALS who may experience a shift from glucose to lipid metabolism as the main energy source.<sup>2</sup> Interestingly, ALS is a very complex syndrome from a genotypic and phenotypic perspective. In this line, it has been postulated that causes of the disease could vary depending on the clinical form.<sup>2</sup> In their article,<sup>1</sup> Rosenbohm et al reported that 97 (33.6%), 91 (31.5%), and 73 (25.3%) of the patients had lumbar, bulbar, and cervical onset, respectively, but they did not include this grouping category in the analysis of retinolbinding protein 4 levels.<sup>1</sup> In our opinion, because some pathogenic features, as well as several clinical conditions, such as diet, might differ between bulbar and spinal ALS, it would have been interesting to have considered this, for it would might provide further insight into the pathogenesis of the different disease forms.

The second issue refers to the potential therapeutic role of retinoids. Because of the absence of an effective modifying disease therapy, there is a pressing need to search for new therapies for ALS. We previously showed that the retinoid agonist bexarotene has clear neuroprotective associations in ALS murine models.<sup>3</sup> Traditionally, there are important difficulties in translating basic experimental findings into patients with ALS.<sup>4</sup> However, the study by Rosenbohm et al<sup>1</sup> provides further support for the implication of retinoids in ALS. Also, in line with this concept, Nieves et al<sup>5</sup> conducted a study to evaluate the association between nutrients and ALS course in more than 300 patients with ALS at the initial stages of the disease. Interestingly, it was reported that patients who have caroteneenriched diets exhibited a better prognosis.<sup>5</sup> Altogether, these studies suggest that retinoid pathway activation by bexarotene or other retinoids might be considered in a clinical trial for patients with ALS.

Javier Riancho, MD, PhD Francisco J. Gil-Bea, PhD

Author Affiliations: Department of Neurology, Hospital Sierrallana-Instituto de Investigación Sanitaria, Centro Investigación Biomédica en Red Enfermedades (CIBERNED), Santander, Spain (Riancho): Neurosciences Area, Biodonostia Health Research Institute, CIBERNED, Torrelavega, Spain (Gil-Bea); Department of Neurology, University Hospital Donostia, Biodonostia Health Research Institute, CIBERNED, San Sebastián, Spain (López de Munaín); Department of Neurosciences, University of the Basque Country Universidad del Pais Vasco/ Euskal Herriko Unibertsitatea, CIBERNED, San Sebastián, Spain (López de Munaín).

Corresponding Author: Javier Riancho, MD, PhD, Service of Neurology. Hospital Sierrallana-Instituto de Investigación Sanitaria, Barrio de Ganzo, s/n, 39300, Torrelavega, Spain (javier.riancho86@gmail.com).

Published Online: August 13, 2018. doi:10.1001/jamaneurol.2018.2242

#### Conflict of Interest Disclosures: None reported.

1. Rosenbohm A, Nagel G, Peter RS, et al; ALS Registry Study Group. Association of serum retinol-binding protein 4 concentration with risk for and prognosis of amyotrophic lateral sclerosis. JAMA Neurol. 2018;75(5):600-607. doi:10.1001/jamaneurol.2017.5129

2. Zufiría M, Gil-Bea FJ, Fernández-Torrón R, et al. ALS: A bucket of genes, environment, metabolism and unknown ingredients. Prog Neurobiol. 2016;142: 104-129. doi:10.1016/i.pneurobio.2016.05.004

3. Riancho J, Ruiz-Soto M, Berciano MT, Berciano J, Lafarga M. Neuroprotective effect of bexarotene in the SOD1(G93A) mouse model of amyotrophic lateral sclerosis. Front Cell Neurosci. 2015;9:250. doi:10.3389/fncel.2015.00250

4. Ittner LM, Halliday GM, Kril JJ, Götz J, Hodges JR, Kiernan MC. FTD and ALS-translating mouse studies into clinical trials. Nat Rev Neurol. 2015;11(6): 360-366. doi:10.1038/nrneurol.2015.65

5. Nieves JW, Gennings C, Factor-Litvak P, et al; Amyotrophic Lateral Sclerosis Multicenter Cohort Study of Oxidative Stress (ALS COSMOS) Study Group. Association between dietary intake and function in amyotrophic lateral sclerosis. JAMA Neurol. 2016;73(12):1425-1432. doi:10.1001/jamaneurol.2016.3401

In Reply We appreciate the comments of Riancho et al on our article<sup>1</sup> investigating the association of retinol-binding protein 4 (RBP4) concentrations with the amyotrophic lateral sclerosis (ALS) risk and prognosis in the ALS registry Swabia. In their letter, they pointed out important clinical aspects and suggested that the causes of the disease could vary depending on the clinical characteristics of ALS and should be considered.

In response to their first comment, we have now analyzed RBP4 values by clinical subgroup of ALS (Table). In the case-control study, which included 289 ALS cases and 504 controls, the geometric mean of RBP4 values was different among the various categories of ALS onset site. Notably, ALS cases with a thoracic onset had the lowest mean values. In addition, concentrations in patients with ALS with bulbar, cervical, and thoracic onset were statistically significantly lower than in the controls. This observation is consistent with the suggestion that ALS subgroups may differ by genotype and phenotype.<sup>2</sup> As others have, we observed worse survival rates in bulbar vs spinal forms of ALS,<sup>3</sup> and the former also had comparatively low RBP4 values in this analysis (Table).

We agree also with Riancho et al that there is pressing need to search for new therapies for ALS. As stated in the Discussion section of our article,<sup>1</sup> the replication of our results in other, ideally prospective, observational studies of sufficient size and the further elucidation of the possible causal role of retinoids in ALS will justify establishing clinical trials to further clarify the role of retinoids as a target for

jamaneurology.com

Adolfo López de Munaín, MD, PhD