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

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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.¹

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,² 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.³ Nevertheless, we agree that an independent effect of the vasopressor agent on outcome cannot be excluded, in particular because norepinephrine may exert vasoconstrictive effects on venous capacitance vessels leading to an increase in venous return and cardiac preload.⁴ 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.

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