

relatively healthy (mainly American Society of Anesthesiologists status II) and young patients, and the incidence of postoperative ileus was lower than expected. This subgroup of patients probably has a higher risk of volume overload than tissue hypoperfusion, so a balanced fluid therapy generally should be sufficient to achieve outcomes. Recently, Tengberg *et al.* showed a statistically significant reduction in postoperative mortality in acute high-risk abdominal surgery by implementing enhanced recovery protocols with goal-directed hemodynamic therapy, based mainly on stroke volume optimization with colloids (15 vs. 22%;  $P = 0.005$ ).<sup>10</sup> This is consistent with a previous meta-analysis that showed a reduction in complications only in high-risk patients (relative risk 0.57; 95% CI, 0.41 to 0.78;  $P = 0.0005$ ).<sup>2</sup> In conclusion, future goal-directed hemodynamic therapy research should focus specifically on high-risk surgical patients, both within and outside enhanced recovery pathways.

### Competing Interests

Dr. Ripollés-Melchor received travel funding from Deltex Medical (Chichester, United Kingdom) and honoraria for lectures from Fresenius Kabi (Bad Homburg, Germany), Edwards Lifesciences (Irvine, California), Deltex Medical, and Merck Sharp & Dohme (Kenilworth, New Jersey). He is currently the Chief of Fluid Management section of Grupo Español de Rehabilitación Multimodal (GERM/ ERAS Spain Chapter; Zaragoza, Spain). Dr. Aldecoa declares no competing interests.

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### In Reply:

We would like to thank Bloomstone *et al.* for their important comments on our study.<sup>1</sup> We certainly agree with Bloomstone *et al.* that fluid responsiveness should not be confused with hypovolemia. Being a fluid responder does not necessarily mean requiring additional intravenous fluids. *Vice versa*, fluid responsiveness should be determined before volume expansion, when clinical signs of hypovolemia suggest that patients might require additional intravenous fluids. Identifying hypovolemic patients might be challenging, however, given that standard hemodynamic parameters or biologic markers used during surgery may not be specific enough, or may fail to identify hypovolemic patients in a timely fashion. Furthermore, the majority of studies evaluating the effectiveness of goal-directed fluid therapy on postoperative outcomes, including ours, include protocols that preemptively maximize stroke volume by administering bolus of fluids based on dynamic indices or on the stroke volume response to a fluid challenge, independent of the presence of clinical signs of hypovolemia. As Bloomstone *et al.* also reported in their referenced and important consensus statement, stroke volume maximization has been considered “the cornerstone of most goal-directed therapy protocols.”<sup>2</sup>

Although consensus statements and recommendations on perioperative fluid therapy (that we fully support) properly advocate to first determine whether “the patient requires hemodynamic support or augmentation of cardiovascular function”<sup>2</sup> or to contextualize the presence of fluid responsiveness (*i.e.*, is there a problem justifying additional fluid administration?),<sup>3</sup> and second, to establish the presence of fluid responsiveness,<sup>2,3</sup> it must be acknowledged that these recommendations are based on studies mainly adopting maximal stroke volume optimization protocols,<sup>4–7</sup> rather than protocols based on stroke volume optimization when ascertained clinically.

In our study, we decided to preemptively maximize stroke volume because splanchnic hypoperfusion occurs before clinical signs of hypovolemia are manifested, even when blood losses are minimal.<sup>8</sup> We believed that, in the absence of an accurate method or biologic marker to monitor splanchnic perfusion, preemptively maximizing stroke volume would have prevented occulted hypovolemia, and, therefore, minimized gastrointestinal dysfunction caused by splanchnic ischemia.

We would also like to thank Drs. Ripollés-Melchor and Aldecoa for their comments on our study.<sup>1</sup> We disagree, however, with Ripollés-Melchor and Aldecoa that a similar amount of fluid was administered the day of surgery; patients in the control group overall received significantly more fluids (2,370 ml *vs.* 1,535 ml,  $P < 0.001$ ), but less colloids (0 ml *vs.* 900 ml,  $P < 0.001$ ) than patients in the goal-directed fluid therapy group.<sup>1</sup> However, although a larger volume of colloids was infused in the goal-directed fluid therapy group, intravascular expansion might have been similar, possibly explaining why stroke volume and cardiac output, and probably splanchnic perfusion, were not statistically different between the two groups. In fact, it must be considered that the volume expanding effect of crystalloids infused during surgery and anesthesia is increased, while the volume expanding effect of colloid is reduced because of the inflammatory response associated with surgery.<sup>9</sup> On the other hand, the larger volume of crystalloid administered in the control group might not have caused enough bowel edema to impair bowel function significantly, as also indicated by a marginal weight gain (less than 2.5 kg) on day 1, and by a rapid recovery of weight balance on day 2. Avoidance of splanchnic hypoperfusion and the absence of significant bowel edema in both groups, together with the other considerations reported in the discussion of the manuscript,<sup>1</sup> might have contributed to the fact that we did not observe a lower incidence of primary postoperative ileus in the goal-directed fluid therapy group. Our findings also highlight the importance of judicious administration of intravenous fluids in the postoperative period to limit gastrointestinal dysfunction.<sup>10</sup> In fact, only 48% and 44% of patients in the goal-directed fluid therapy group and in the control group, respectively, continued to receive intravenous fluids after day 0, limiting the risk of bowel edema and subsequent delayed recovery of bowel function.

Our study was not designed to determine the effect of goal-directed fluid therapy on overall complications, but to determine whether goal-directed fluid therapy could specifically reduce primary postoperative ileus after colorectal surgery in the context of an Enhanced Recovery Program. However, a secondary analysis pooling all data of the 128 patients included in the study was performed (submitted with the original manuscript<sup>1</sup> and available to reviewers only). The results of univariate and multivariate regression analysis, including all perioperative factors and hemodynamic variables (stroke volume, stroke volume

index, cardiac output, cardiac index, mean arterial pressure, and oxygen delivery index less than  $400 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  at the beginning and end of surgery) that could potentially increase the risk of primary postoperative ileus, did not reveal any significant association with primary postoperative ileus (multivariate regression analysis, model statistic: discriminative power area under the curve = 0.753; Hosmer-Lemeshow goodness of fit test:  $P = 0.280$ ). Similarly, we could not identify any perioperative factor or hemodynamic value independently associated with 30-day postoperative complications (multivariate regression analysis, model statistic: discriminative power area under the curve = 0.738; Hosmer-Lemeshow goodness of fit test:  $P = 0.664$ ).

We agree with Ripollés-Melchor and Aldecoa that the value of goal-directed fluid therapy has been proven mainly in high-risk surgical patients,<sup>11,12</sup> and not in the context of an Enhanced Recovery Program.<sup>13</sup> As recommended by consensus statements and others,<sup>2,3,14</sup> it should not be used in low-risk surgical patients, providing that rational and evidence-based physiologic principles are followed to guide fluid therapy.<sup>15</sup> Finally, we believe that future studies are warranted to better define “high-risk” patients and surgical procedures, because this definition varies significantly among the studies evaluating the impact of goal-directed fluid therapy on postoperative outcomes. Similarly, more research is needed to determine if extending goal-directed fluid therapy to the postoperative period could improve outcomes, especially considering that on surgical floors a large proportion of patients still receive bolus of intravenous fluids, based mainly on the evaluation of inaccurate signs of hypovolemia and fluid responsiveness.

### Competing Interests

Deltex Medical Ltd. (Chichester, United Kingdom) loaned the esophageal doppler monitor to Dr. Baldini. Dr. Baldini's academic research funding was used to purchase the esophageal doppler probes. Dr. Baldini received travel funding and consulting fees from Edwards Lifesciences Inc. (Mississauga, Ontario, Canada). The other authors declare no competing interests.

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## Statin Therapy before Cardiac Surgery: Neutral or Detrimental Effects?

To the Editor:

We read the interesting large retrospective study by Komatsu *et al.* on preoperative chronic statin use in patients undergoing coronary artery bypass grafting, valve surgery, or combined procedures.<sup>1</sup> Chronic statin therapy was associated with no significant difference in prolonged mechanical ventilation, pneumonia, in-hospital mortality, neurologic outcome, and length of intensive care unit or hospital stay,<sup>1</sup> suggesting neutral effects on postoperative clinical outcome.

It would be interesting to know the incidence of acute kidney injury after surgery in the study by Komatsu *et al.*<sup>1</sup> It is well known that postoperative acute kidney injury is crucial in patients' postoperative course and is associated with higher mortality rate.<sup>2</sup> Two large, high-quality, randomized placebo-controlled trials were recently published, respectively, in the *New England Journal of Medicine* and *JAMA*. Zheng *et al.*<sup>3</sup> randomly assigned 1,922 cardiac surgery patients to receive perioperative rosuvastatin or placebo, started 1 to 8 days before surgery, and the authors found that perioperative statins did not prevent postoperative atrial fibrillation or perioperative myocardial damage, but acute kidney injury was more common in patients receiving rosuvastatin. Billings *et al.*<sup>4</sup> randomized 617 patients to high-dose perioperative atorvastatin or placebo, started the day before surgery, and found increased acute kidney injury in statin-naïve patients with chronic kidney disease. A recent systematic review and meta-analysis of randomized controlled trials with low risk of bias found that perioperative statin therapy was associated with an increased incidence of postoperative acute kidney injury as compared with placebo, with 314 of 1,318 patients (23.82%) in the statin group having acute kidney injury *versus* 262 of 1,319 patients (19.86%) in the placebo group (odds ratio 1.26 [95% CI, 1.05 to 1.52];  $P = 0.01$ ).<sup>5</sup> Notably, a trend toward increased mortality was noted in the statin group: 9 of 1,318 (0.68%) patients died in the statin group *versus* 2 of 1,319 (0.15%) in the placebo group (odds ratio 1.26 [95% CI, 1.05 to 1.52];  $P = 0.06$ ).<sup>5</sup> Since the trials included in the meta-analysis randomized patients to a short course of preoperative statin regimen (between 1 and 7 days), we would like to ask Komatsu *et al.* for further data regarding length of preoperative statin therapy and, if available, a stratification according to it (*e.g.*, short-term *vs.* long-term statins administration).

In conclusion, there is growing high-quality evidence<sup>3–5</sup> that suggests not administering statins in the days before cardiac surgery. Statins in the days before cardiac surgery are not

This letter was sent to the author of the original article referenced above, who did not respond.—Evan D. Kharasch, M.D., Ph.D., Editor-in-Chief