(10% HES 200/0.5) has shown relevant differences on renal function and integrity in the preclinical setting.[3] The safety of 6% HES 130/0.4 with regard to renal function in the perioperative setting was confirmed by clinical studies and a recent meta-analysis.[4,5] As a result, one pharmaceutical company has stopped the production of high-molecular HES in 2013 (Fresenius Kabi Germany). Moreover, in our department, the use of starches other than 6% HES 130/0.4 was already abandoned in 2001 for the above-mentioned reasons. It is therefore surprising that in the present database of Cleveland hospitals, more than 50% of the analyzed patients were treated with high-molecular HES despite the fact that low-molecular preparations have been available since 1999. With respect to this, the clinical relevance of the present study appears to be limited. Finally, the title of the article does not specify the type of starch that was analyzed and is therefore misleading. This is especially true because several recent publications in Anesthesiology highlighted the important differences between HES preparations.[4,6]

With regard to the quality of the propensity-matched analysis, many variables that may serve as potential confounders were numerically higher in the colloid group, even though the predefined level of absolute standard difference was not exceeded. These include intraoperative fluid amounts, intraoperative hypotension, intraoperative blood loss, duration of surgery, blood transfusion, and vasopressor use, which were all higher in the matched colloid as compared with the crystalloid group. It therefore appears that the colloid group was *a priori* at a higher risk of developing acute kidney injury as compared with the crystalloid group. Such intrinsic differences in patient characteristics may hardly be compensated by sophisticated statistical analysis. Finally, despite the known fundamental differences between the various HES preparations,[6] high-molecular HES and waxy maize-derived and potato-derived tetrastarches are not adequately differentiated in the Discussion section.

In summary, the present article investigates a fluid that is known to be unsuitable for modern perioperative care, despite starches with a better renal safety profile are available for perioperative use. Relevant baseline differences may limit valid conclusions from the present dataset.

Competing Interests

The authors declare no competing interests.

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In Reply:

We appreciate Dr. Raghunathan's and Dr. Van Aken's interest in our recent article.[1] Our analysis was based on approximately 29,000 propensity-matched patients who were or were not given intraoperative 6% hydroxyethyl starch (HES) 670/0.75. As Raghunathan *et al.* note, we did not match on intraoperative factors such as hypotension, vasopressor use, and transfusions, and these factors were thus unbalanced. However, we adjusted for hypotension—an obvious confounder—in our subsequent multivariable analysis. A second propensity match that includes all intraoperative factors except vasopressor use and transfusions produced nearly identical results, a roughly 22% increase in the odds of acute kidney injury.

We chose to consider vasopressor use and transfusions to be mediators in our primary analysis "based on our assumption that the administration of hetastarch is mainly triggered by blood loss and that the administration of transfusions and vasopressors happens thereafter and thus might not influence the decision to administer colloids. Thus, vasopressor use and blood transfusions might be mediators."

However, we recognize that vasopressor use and transfusions could also be confounders or (perhaps most likely) both confounders and mediators. We therefore conducted and presented sensitivity analyses in which various factors were considered to be either confounders or mediators. Whereas the conclusion of our primary analysis was that hetastarch administration increases the odds of acute kidney injury approximately 21%, the increases were no longer statistically significant when transfusions or the combination of transfusions and vasopressor use were included as confounding factors. We note, though, that among the eight sensitivity analyses presented in our article, all others remained statistically significant and had roughly comparable treatment effects. Difficulty distinguishing confounders from

mediators, and the fact that some factors are surly both, is one of the many reasons why the results of large trials are more reliable than the retrospective analyses.

Raghunathan *et al.* suggest using calendar time as an instrumental variable for clinician decision making on HES usage in an environment of changing Food and Drug Administration regulations. Study patients' had noncardiac surgeries between January 2005 and September 2012; during this time period, regulatory changes might have affected overall HES usage. Therefore, we intentionally propensity-matched patients on the year of surgery to make sure most of the times we compared surgeries close in time to each other. Although, among nonmatched patients, the proportion of those receiving HES decreased in years 2011 and 2012 compared to previous years.

Ertmer and Van Aken are also concerned that unadjusted confounding may have contributed to our conclusion that 6% HES 670/0.75 promotes acute renal injury, which would suggest that the product is actually safe. Curiously, they then express surprise that high-molecular-weight starches, which they claim to be "unsuitable for modern perioperative care," are still used at the Cleveland Clinic. It is not just at the Clinic. The high-molecular-weight starch we used remains by far the most commonly used plasma expander in the United States, even after Food and Drug Administration approval of low-molecular-weight starches in December 2007.

Continued use of 6% HES 670/0.75 is hardly unreasonable. There is little previous evidence that the intraoperative use is harmful and there has never been a large trial comparing high- and low-molecular-weight starches. Ertmer and Van Aken cite a meta-analysis to support their assertion that low-molecular-weight starches are safer than higher-molecular preparations.[2] However, that study did not compare low-molecular-weight starches to 6% HES 670/0.75, the preparation we used. In fact, a more recent meta-analysis in cardiac surgical patients who presumably are at high risk for acute kidney injury concludes that "no reliable analysis for separate hetastarch generations compared to albumin, gelatin, or crystalloids was possible."[3]

In summary, retrospective analyses are complicated by factors that are not clearly confounders or mediators. As illustrated by the comparison between our primary and sensitivity analyses, the distinction matters and can profoundly influence conclusions—and is one reason why randomized trials are so important. No large study has compared high- and low-molecular-weight starches; whether one is safer than the other for perioperative use thus remains unclear. In the mean time, the conclusion that 6% HES 670/0.75 is "unsuitable for modern perioperative care" seems premature.

Competing Interests

The authors declare no competing interests.

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Tracheal Tube Obstruction Assessed by Computed Tomography

To the Editor:

In a very elegant bench-to-bedside investigation, Mietto *et al.*[1] studied the secretion-induced cross-sectional area (CSA) reductions of tracheal tubes (TTs) in intensive care unit patients. Using *ex vivo* high-resolution computed tomography (CT) scans, extubated TTs showed a minimum CSA 25 ± 4% lower than new and nonused TTs; using *in vivo* standard clinical chest CT scans of selected patients, 6 of 20 intubated TTs showed measurable secretions with a CSA reduction of 24 ± 4% and an absolute reduction of 1.5 ± 0.4 mm in the anteroposterior diameter of TTs.

One main finding in the *ex vivo* CT scans was that CSA progressively decreased from oral to lung end of used TTs, suggesting that increases in the resistance to airflow that could result in higher ventilatory pressures and greater work of breathing are mainly caused by retained secretions at that end of TTs. However, TTs may bend and even "kink" in the part located in the neck and oral region, depending on the tube quality and the number of days it is in use, among other factors. Although this by itself could reduce the inner diameter of TTs, it will certainly increase the impact of secretions on resistance to airflow at this part of TTs. Because of design of the study, the *in vivo* CT scans did not allow Mietto *et al.* to review the extrathoracic part of TT, as neck and oral cavity were not included in the standard clinical chest CT scans.

I agree with the authors that the impact of retained secretions within the TT lumen is of greater clinical importance than often recognized and that CT scanning could be a useful tool for early detection of secretion-induced CSA reductions. But then we may need to deviate a little from the standard clinical chest CT scan by including the neck and oral cavity.

This letter was sent to the author of the original article referenced above, who declined to respond.