randomization method and allocation concealment. The investigators neglected to present any assessment of quality of included trial or risk of bias.

The statistical power of this meta-analysis to detect an effect on RRT was limited by a very low event rate resulting both from incomplete data and inadequate follow-up. RRT data were not available for 57% of the patients in the meta-analysis, and follow-up was for 5 days or less in most included studies. The median reported time to HES-induced acute renal failure is 16 days,[12] therefore, many events were undoubtedly missed. Consequently, only 14 total RRT events were observed in this meta-analysis corresponding to 2.6% of the patients with available RRT data. In contrast, there were 672 RRT events in the meta-analysis of six RCTs corresponding to 8.3% of the patients.[5] Furthermore, that meta-analysis was devoid of heterogeneity (I^2, 0%) indicating, contrary to the contention of the Martin *et al.*, that RRT is not a highly variable endpoint in RCTs.

No mechanistic basis is suggested by the investigators for reduced renal risk in surgical patients. The nephrotoxicity of HES is associated with storage in renal tubular cells and osmotic nephrosis.[13] It is unclear why surgical patients should be less susceptible to such renal storage of HES and consequent impairment of renal function.

This meta-analysis fails to provide convincing evidence that surgical patients are at low risk of HES 130/0.4–induced renal injury. Rather, it highlights the lack of high-quality data on the safety of perioperative HES 130/0.4 infusion. Such data would be needed before it can be determined whether HES 130/0.4 might have a role to play for fluid management in surgery.

Christian J. Wiedermann, M.D., Central Hospital of Bolzano, Bolzano, Italy. christian.wiedermann@asbz.it

References

1. Wiedermann CJ: Hydroxyethyl starch—Can the safety problems be ignored? Wien Klin Wochenschr 2004; 116:583–94
2. Zarychanski R, Abou-Setta AM, Turgeon AF, Houston BL, McIntyre L, Marshall JC, Fergusson DA: Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: A systematic review and meta-analysis. JAMA 2013; 309:678–88
3. Perel P, Roberts I, Ker K: Colloids *versus* crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 2013; 2:CD000567
4. Wiedermann CJ, Joannidis M: Increased mortality after infusion of "modern" hydroxyethyl starch. Swiss Med Wkly 2013; 143:w13747
5. Gattas DJ, Dan A, Myburgh J, Billot L, Lo S, Finfer S; CHEST Management Committee: Fluid resuscitation with 6% hydroxyethyl starch (130/0.4 and 130/0.42) in acutely ill patients: Systematic review of effects on mortality and treatment with renal replacement therapy. Intensive Care Med 2013; 39:558–68
6. Haase N, Perner A, Hennings LI, Siegemund M, Lauridsen B, Wetterslev M, Wetterslev J: Hydroxyethyl starch 130/0.38-0.45 *versus* crystalloid or albumin in patients with sepsis: Systematic review with meta-analysis and trial sequential analysis. BMJ 2013; 346:f839
7. Patel A, Waheed U, Brett SJ: Randomised trials of 6% tetrastarch (hydroxyethyl starch 130/0.4 or 0.42) for severe sepsis reporting mortality: Systematic review and meta-analysis. Intensive Care Med 2013; 39:811–22
8. Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Åneman A, Madsen KR, Møller MH, Elkjær JM, Poulsen LM, Bendtsen A, Winding R, Steensen M, Berezowicz P, Søe-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjældgaard A-L, Fabritius ML, Mondrup F, Pott FC, Møller TP, Winkel P, Wetterslev J: Hydroxyethyl starch 130/0.4 *versus* Ringer's acetate in severe sepsis. N Engl J Med 2012; 367:124–34
9. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent JL, Moreno R; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup: Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 41:580–37
10. Martin C, Jacob M, Vicaut E, Guidet B, Van Aken H, Kurz A: Effect of waxy maize-derived hydroxyethyl starch 130/0.4 on renal function in surgical patients. Anesthesiology 2013; 118:387–94
11. Wilkes MM, Navickis RJ: Patient survival after human albumin administration. A meta-analysis of randomized, controlled trials. Ann Intern Med 2001; 135:149–64
12. Schortgen F, Lacherade JC, Bruneel F, Cattaneo I, Hemery F, Lemaire F, Brochard L: Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: A multicentre randomised study. Lancet 2001; 357:911–6
13. Cittanova ML, Leblanc I, Legendre C, Mouquet C, Riou B, Coriat P: Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. Lancet 1996; 348:1620–2

(Accepted for publication May 24, 2013.)

In Reply:

We thank Drs. Groeneveld *et al.* and Widermann for their interesting comments on our article.[1] Groeneveld *et al.* made a remark that in CHEST trial, the temporal effects of serum creatinine increase became apparent only between days 1 and 4. Yet the increase was from ±110 to ±116 μM, which is certainly not clinically relevant. Serum creatinine or creatinine clearance are not perfect biomarkers for renal injury, but no other marker is universally accepted in the field even though many have been studied. Although the CHEST trial[2] might be a landmark study, it was conducted in patients in intensive care unit, and we purposely excluded this patient population from our meta-analysis. In the CHEST trial[2] only 1,574 of 6,742 patients were randomized after elective surgery (the type of patients we evaluated). When such patients were admitted to intensive care units, it was probably because they suffered intraoperative complications, which may have put them at higher risk of delayed renal complications.

We do not think that the comparison of our work with the meta-analysis by Zarychanski *et al.*[3] is adequate. This

meta-analysis has included very heterogeneous groups of patients, including severely ill patients in intensive care units, many of them with different forms of shock including septic shock. Such a population is at high risk of organ dysfunction, including acute kidney failure, and cannot be compared with elective surgical patients. Also, we do not think that our meta-analysis is comparable with analysis by Gattas *et al.*[4] In this meta-analysis, the studies showing a higher risk for the need of renal replacement therapy (fig 3, top panel[4]) were all conducted in patients in intensive care unit, with only one exception (Nagpal *et al.*). In the middle panel of figure 3 of our article,[1] trials conducted in surgical patients are presented. These trials were not associated with a higher risk of renal replacement therapy (risk ratio, 0.46; 95% CI, 0.10–2.05; $P = 0.794$). Therefore both meta-analyses either are inadequate to address the clinical question that we wanted to address or found comparable evidence.

Surgical patients were also evaluated by Van Der Linden *et al.*[5]. In their meta-analysis, 2,139 patients treated with tetrastarches were compared with 2,390 patients treated with a comparator. From 39 trials, the authors concluded that tetrastarches used during surgery did not induce adverse renal effects as assessed by changes in serum creatinine or need for renal replacement therapy. The authors reported 21 studies documenting serum creatinine or creatinine clearance after administration of 130/0.4 starch or other tested fluids. One thousand five patients were given a tetrastarch and 1,051 patients were given a comparator. The period for which creatinine was reported covered up to 14 days after administration. All but three studies showed no difference in peak creatinine concentration. Two studies found a statistically better outcome for the tetrastarch. The authors concluded that they could not detect a hint for an adverse signal after the use of modern starch in surgical patients.[5] The risk of excessive bleeding was out of the scope of our meta-analysis, but the results of the Van Der Linden meta-analysis are reassuring with this regard. Every meta-analysis can only be as reliable as the data available. In this way, it is in fact limited, and this point was emphasized at the end of our discussion. But, even though only two of the trials in the meta-analysis were primarily designed to evaluate the renal effect of hydroxyethyl starch 130/0.4, this side effect of colloids was well known since long and thus was an integral safety parameter in all of these trials.

We are confident that our conclusions are meaningful today and can hold in the light of upcoming evidence. Although Groeneveld *et al.* point out that a retrospective analysis has found an association between hydroxyethyl starch 130/0.4 and renal replacement therapy, we would like to draw the readers' attention to a recently published prospective randomized study in patients undergoing abdominal surgery by Feldheiser *et al.*[6] demonstrating that a stringent treatment algorithm and an adequate monitoring results in better hemodynamic stability and reduced need for fresh-frozen plasma. This study included a 3-month follow-up and measured the sensitive renal marker neutrophil gelatinase-associated lipocalin. If older studies might not provide the evidence, we would wish for today, this is also true for all studies that did not use rigorous protocols to identify patients who were in need of volume therapy.

Claude Martin, M.D.,* Matthias Jacob, M.D., Eric Vicaut, M.D., Bertrand Guidet, M.D., Hugo Van Aken, M.D., Ph.D., Andrea Kurz, M.D. *CHU Nord, Assistance Publique-Hôpitaux de Marseille, Marseille, France. claude.martin@ap-hm.fr

References

1. Martin C, Jacob M, Vicaut E, Guidet B, Van Aken H, Kurz A: Effect of waxy maize-derived hydroxyethyl starch 130/0.4 on renal function in surgical patients. Anesthesiology 2013; 118:387–94
2. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SA; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group: Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012; 367:1901–11
3. Zarychanski R, Abou-Setta AM, Turgeon AF, Houston BL, McIntyre L, Marshall JC, Fergusson DA: Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: A systematic review and meta-analysis. JAMA 2013; 309:678–88
4. Gattas DJ, Dan A, Myburgh J, Billot L, Lo S, Finfer S; CHEST Management Committee: Fluid resuscitation with 6% hydroxyethyl starch (130/0.4 and 130/0.42) in acutely ill patients: Systematic review of effects on mortality and treatment with renal replacement therapy. Intensive Care Med 2013; 39:558–68
5. Van Der Linden P, James M, Mythen M, Weiskopf RB: Safety of modern starches used during surgery. Anesth Analg 2013; 116:35–8
6. Feldheiser A, Pavlova V, Bonomo T, Jones A, Fotopoulou C, Sehouli J, Wernecke KD, Spies C: Balanced crystalloid compared with balanced colloid solution using a goal-directed haemodynamic algorithm. Br J Anaesth 2013; 110:231–40

(Accepted for publication May 24, 2013.)

Epidural and Continuous Wound Infusion in Enhanced Recovery Protocols

To the Editor:

I read with interest the article by Jouve *et al.*[1] comparing epidural analgesia with continuous wound infusion of local anaesthetic after fast-track colorectal surgery, and I would like to commend the authors on their thorough methodology.

An important aspect of this trial is the management of patients within an enhanced recovery program, and the authors cite consensus recommendations, which guided to their management decisions.[2] There are two areas that I feel the authors did not strictly adhere to the enhanced recovery recommendations. First, the consensus group