

# Effect of Waxy Maize-derived Hydroxyethyl Starch 130/0.4 on Renal Function in Surgical Patients

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## ABSTRACT

**Background:** The aim of this meta-analysis was to evaluate renal safety with the active substance of the latest generation of waxy maize-derived hydroxyethyl starch in surgical patients. The authors focused on prospective, randomized, controlled studies that documented clinically relevant variables with regard to renal effects of waxy maize-derived hydroxyethyl starch 130/0.40.

**Materials and methods:** The authors carefully searched for all available prospective, randomized studies and evaluated the greatest delta from baseline values in renal safety variables

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## What We Already Know about This Topic

- The use of hydroxyethyl starches has been associated with nephrotoxicity and increase in mortality in the critically ill
- The renal safety of modern hydroxyethyl starches 130/0.40 in nonseptic surgical patients remains unclear

## What This Article Tells Us That Is New

- In a meta-analysis of 17 randomized studies (n = 1,230) evaluating renal safety of waxy maize-derived hydroxyethyl starches 130/0.40 in surgical patients no evidence for renal dysfunction was observed

(serum creatinine values, calculated creatinine clearance, incidence of renal replacement therapy, and acute renal failure). The authors included 17 studies that analyzed patients (n = 1,230) undergoing a variety of surgical procedures.

**Results:** For maximum serum creatinine values, the effect size estimate was 0.068 (95% CI = -0.227 to 0.362),  $P = 0.65$ . For calculated creatinine clearance values, pooled risk difference was 0.302 (95% CI = -0.098 to 0.703),  $P = 0.14$ . For incidence of acute renal failure, pooled risk difference was 0.0003 (95% CI = -0.018 to 0.019),  $P = 0.98$ . For incidence of renal replacement therapy, pooled risk difference was -0.003 (95% CI = -0.028 to 0.022),  $P = 0.85$ .

**Conclusions:** The authors found no evidence for renal dysfunction caused by modern waxy maize-derived hydroxyethyl starch 130/0.40 in surgical patients.

**H**YDROXYETHYL starches (HES) are colloidal solutions used for prevention and treatment of hypovolemia. During the past decades, the molecular weight and molar substitution (proportion of hydroxyethylated glucose subunits) of these molecules have been optimized, leading to an average molecular weight of approximately 130 kDa and a molar substitution of approximately 0.4. Between the different generations of starches there are clear clinical differences in terms of coagulation effects<sup>1-6</sup> or effects on renal function.<sup>7,8</sup> Nevertheless, it has recently been suggested to exclude starches from volume resuscitation in the critically ill patient.<sup>9</sup> This led to great uncertainty about general use of

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HES, especially in European countries where many clinicians routinely use HES preparations to stabilize cardiac preload.

The clinical trials that have raised concerns about the renal safety of HES<sup>10–14</sup> showed a higher frequency of acute renal failure (ARF) and some even higher mortality in critically ill patients, using different isotonic and hypertonic HES preparations. A retrospective trial<sup>15</sup> and two prospective randomized studies<sup>16,17</sup> performed with waxy maize-derived HES 130/0.40 in intensive care unit patients found no significant signs of renal dysfunction or differences in mortality.

Several reviews and meta-analyses have addressed the safety of HES before. But first, most analyses did not usually take into account different HES generations and the raw material.<sup>1,18</sup>

Second, within the latest meta-analyses<sup>19–21</sup> two also focused on HES 130 but did not differentiate between the products derived from waxy maize and potato.<sup>20,21</sup> Also, they included surgical patients and/or critically ill or septic patients. Currently, many small studies in surgery supporting HES 130/0.4 face a small number of relatively large studies in critically ill patients, which showed negative effects. Thus, one might argue that surgical studies were just underpowered to show the adverse effects observed in the critically ill. To test this hypothesis, the current meta-analysis evaluates renal safety with the most modern HES 130/0.40 derived from waxy maize in nonseptic, surgical patients.

We evaluated studies that reported renal effects of waxy maize-derived HES 130/0.40. Furthermore, we included only prospective, randomized interventional studies and analyzed the largest changes from baseline values in renal safety variables within these studies.

## Materials and Methods

### Eligibility Criteria

We selected only prospective, randomized controlled trials and included all available surgical procedures to achieve as much generalizability of our results as possible.

Inclusion criteria for eligible studies were:

- 1) The use of waxy maize-derived HES 130/0.40, the latest (third) generation starches, in at least one intervention group. Due to the heavy imbalance in study evidence and proven differences of the products<sup>22–24</sup> we refrained from including data about HES 130/0.42.
- 2) Reporting on one of the following variables as primary endpoint, secondary endpoint or safety data:
- 3) Blood urea, serum creatinine, calculated creatinine clearance, glomerular filtration rate,  $\alpha$ 1-microglobulin, neutrophil gelatinase-associated lipocalin, N-acetyl- $\beta$ -(D)-glucosaminidase, Risk, Injury, Failure, Loss, End stage kidney disease classification<sup>25</sup>, Acute Kidney Injury Network classification, or ARF.

- 4) The use of a colloidal or crystalloidal solution other than HES 130/0.40 in one intervention group of the study as a control. Studies conducted exclusively in septic or critically ill patients were excluded.

### Search Strategy

We searched PubMed for studies with the following terms in all fields: HES 130, HES 130/0.4, and one of the terms “creatinine,” “renal function,” “renal failure,” or “renal replacement therapy.” Because many randomized, controlled trials might not be listed in common databases,<sup>26</sup> we performed an additional manual search *via* the Fresenius Kabi study tracking system, using the same search terms. This approach yielded 10 further studies. All studies found in addition to the initial search were also listed in PubMed.\*\*

### Study Selection and Data Extraction

The selection criteria mentioned above were developed and studies screened by all authors. The inclusion and exclusion criteria for retrieved studies were *a priori* jointly discussed and agreed upon. The study flow diagram is shown in figure 1. The initial search *via* PubMed resulted in 48 hits. A manual search using the Fresenius Kabi tracking system yielded 10 additional studies.

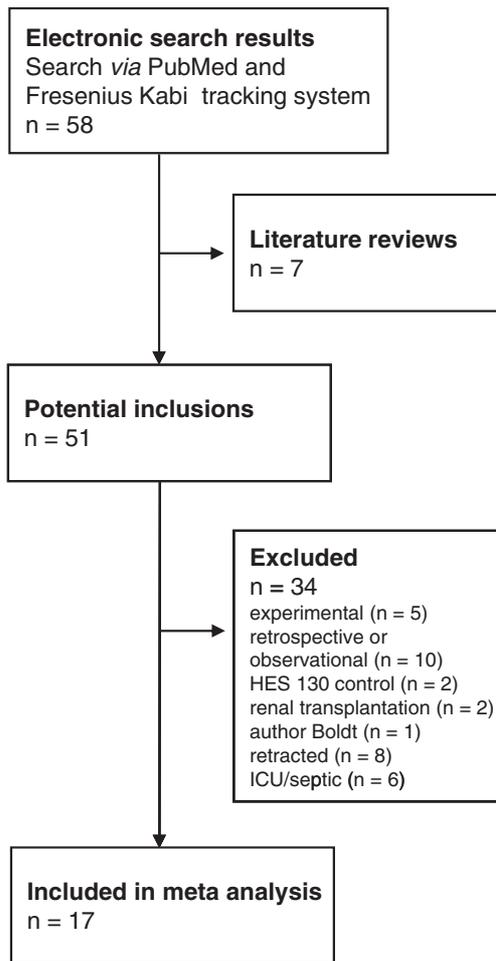
Thirty-four publications had to be excluded as they were conducted on critically ill patients (*e.g.*, sepsis, trauma,  $n = 6$ ), review articles ( $n = 7$ ), experimental studies ( $n = 5$ ) (*e.g.*, using MP4OX, which is an experimental drug with an unknown safety profile [ $n = 2$ ]<sup>27,28</sup>), retrospective or observational without control group ( $n = 10$ ), or without adequate control group (comparison of 2 HES 130/0.4) ( $n = 2$ ).<sup>29,30</sup> In addition, we excluded studies in kidney transplant patients ( $n = 2$ ),<sup>31</sup> because effects of kidney transplantation on creatinine will very likely mask any effects of HES as creatinine values typically improve after a transplant. Thus, we avoided introducing a falsely positive signal for HES by excluding these studies. We also excluded a nonretracted study published by Boldt<sup>32</sup> due to the retraction of nearly all other relevant studies from this author. For an overview of all included studies and numbers of patients see table 1.

Data were extracted from the individual studies and, in addition to the variables mentioned above, intensive care unit length of stay, hospital length of stay, and mortality were recorded, if available. For renal function, we extracted baseline values for each variable as well as the highest or lowest value after HES administration. This indicated the greatest impact on renal function, independent of the point in time it had been recorded.

Calculated creatinine clearance was directly measured in two studies<sup>33,34</sup> but not specified in the others. Thus, we expect that most of the data presented are calculated or estimated creatinine clearances.

ARF was defined according to Risk, Injury, Failure, Loss, End stage kidney disease<sup>25</sup> criteria when available. In case Risk, Injury, Failure, Loss, End stage kidney disease classification was not reported, the definition of ARF was considered according

\*\* Or at [www.clinicaltrials.gov](http://www.clinicaltrials.gov). Accessed December 20, 2012.



**Fig. 1.** Study flow diagram. HES = hydroxyethyl starch; ICU = intensive care unit.

to the definition mentioned in the original article. This definition may vary slightly from one publication to another.

### Statistical Analysis

All values extracted from the individual studies were transformed to mean values and SD. If mean value and SD were not reported, they were estimated from median values and ranges, or interquartile ranges.<sup>35</sup> If studies included more than one control group,<sup>34,36</sup> the respective data were pooled (weighted estimate). Two studies did not provide a baseline value for serum creatinine<sup>36</sup> or blood urea.<sup>37,38</sup> Nevertheless, the respective highest or lowest values were included in the meta-analysis. We calculated the effect size using the nonbiased method proposed by Hedges and Olkin.<sup>39</sup> Finally, the effect size for continuous variables or relative risk for binary variables was pooled *via* a meta-analysis with random effects based on DerSimonian-Laird using the Statdirect software (StatDirect Ltd., Altrincham, United Kingdom). Begg-Mazumdar and Egger variables were used for testing bias within publications. Heterogeneity was estimated by the  $I^2$  index proposed by Higgins and Thomson.<sup>40</sup>  $P$  values were

two-tailed and a  $P$  value of less than 0.05 was considered as statistically significant.

### Results

In total, 17 studies were included in the analysis. These comprised patients undergoing elective surgical procedures like cardiopulmonary bypass,<sup>37,38,41,42</sup> cardiac surgery,<sup>2,3,43–45</sup> other surgical procedures,<sup>33,34,36,46–49</sup> or liver transplantation.<sup>50</sup> Most studies provided data about serum creatinine or calculated creatinine clearance, whereas other variables like neutrophil gelatinase-associated lipocalin or  $\beta$ -acetyl- $\beta$ -(D)-glucosaminidase were reported only rarely. The extracted extreme values for serum creatinine occurred on average 2 days after surgery. None of our funnel plots showed significant heterogeneity. The bias indicators for serum creatinine extreme values were  $-0.099$  (0.5906) for Kendall tau (Begg-Mazumdar) and  $0.735$  (95% CI =  $-5.395$  to  $3.925$ );  $P = 0.74$  for the Egger bias indicator. We found no significant difference for the effect of waxy maize-derived HES 130/0.40 on serum creatinine as compared with the respective controls for baseline (pooled  $d+ = -0.021$  [95% CI =  $-0.261$  to  $0.219$ ],  $P = 0.86$ ,  $I^2 = 68.5\%$  [95% CI =  $35.8$  to  $80.9\%$ ]) and for extreme values (pooled  $d+ = 0.068$  [95% CI =  $-0.227$  to  $0.362$ ],  $P = 0.65$ ,  $I^2 = 79.8\%$  [95% CI =  $65.2$  to  $86.6\%$ ]) (fig. 2, A and B). Two studies differed in their results: for Tiryakioglu *et al.*,<sup>38</sup> the HES group showed significantly higher serum creatinine values 24 h after the procedure ( $97 \pm 9$  to  $124 \pm 21$   $\mu\text{mol/l}$ ). In Gallandat-Huet *et al.*,<sup>2</sup> the serum creatinine concentration did not differ significantly between the study groups. Yet it increased slightly in the HES 130 group ( $96 \pm 14$  to  $109 \pm 17$   $\mu\text{mol/l}$ ), whereas it decreased in the HES 200 control ( $98 \pm 14$  to  $94 \pm 21$   $\mu\text{mol/l}$ ).

In terms of ARF ( $n = 701$ , fig. 3), none of the selected studies showed a significant difference in risk. The pooled risk difference for random effects was  $0.0003$  (95% CI =  $-0.018$  to  $0.019$ ),  $P = 0.98$ ,  $I^2 = 0\%$  (95% CI =  $0$ – $56.3\%$ ). We did not find significant differences between HES and control groups for calculated creatinine clearance ( $n = 344$ ), urea ( $n = 390$ ), mortality ( $n = 834$ ), and the need for renal replacement therapy ( $n = 531$ ) (table 2). Furthermore, there was no significant difference in intensive care unit or hospital length of stay ( $n = 723$  and  $940$  respectively, table 2).

### Discussion

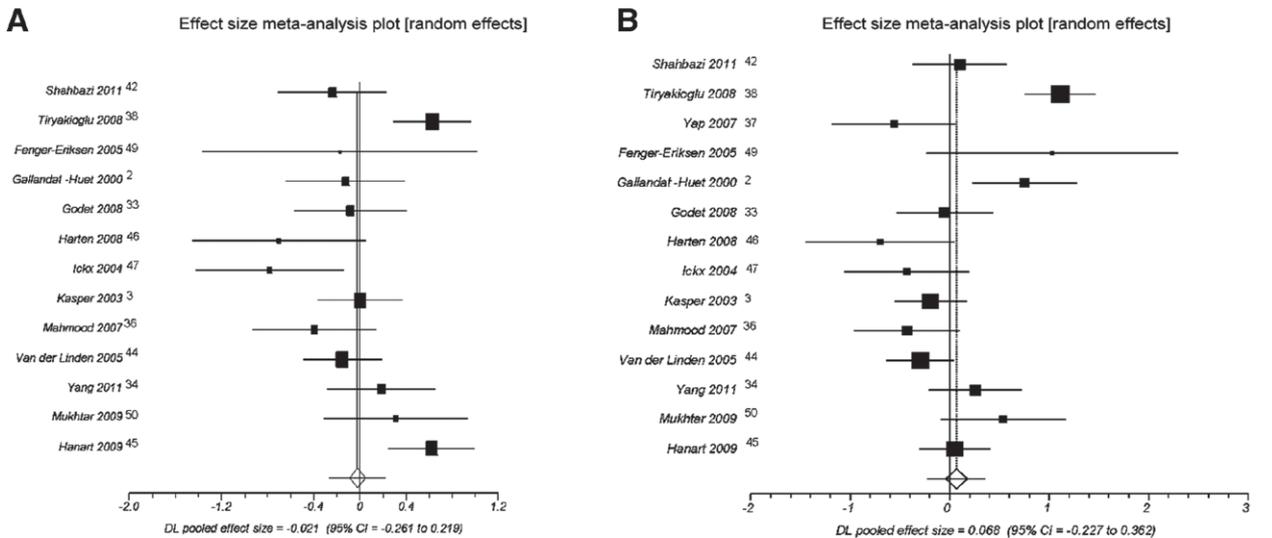
The present meta-analysis on the renal effects of third-generation waxy maize-derived hydroxyethyl starch 130/0.40 shows no evidence for renal impairment caused by this colloidal solution in surgical patients.

Only three of the included studies showed a slight increase in serum creatinine to approximately  $124$   $\mu\text{mol/l}$ . With respect to calculated creatinine clearance, incidence of ARF and mortality, our results showed no significant differences for HES 130/0.40 and the respective comparators. However, especially data with regard to ARF are limited due to a low number of patients with ARF and different

**Table 1.** Overview of Studies with Surgery Patients (N = 1,230)

Study, Year	N (Total)	Clinical Setting	Comparator	Most Important Renal Parameter	Creatinine Data ( $\mu\text{mol/l}$ )*			
					HES 130 BL	HES 130 Worst	BL	Worst
Fenger-Eriksen <i>et al.</i> , 2005 <sup>49</sup>	11	Spine surgery	Isotonic saline	Serum creatinine	73 (54–89)	71 (64–75)	77 (50–98)	65 (51–72)
Gallandat-Huet <i>et al.</i> , 2000 <sup>2</sup>	59	Cardiac surgery	HES 200	Serum creatinine	96 $\pm$ 14	109 $\pm$ 17	98 $\pm$ 14	94 $\pm$ 21
Godet <i>et al.</i> , 2008 <sup>33</sup>	65	Vascular surgery	Gelatin solution	Serum creatinine, calculated creatinine clearance	108 $\pm$ 29	123 $\pm$ 62	111 $\pm$ 24	127 $\pm$ 62
Hanart <i>et al.</i> , 2009 <sup>45</sup>	119	Cardiac surgery	Human albumin	Serum creatinine	28 (24–34) (IQR)	27 (22–35) (IQR)	24 (21–28) (IQR)	26.5 (20–32) (IQR)
Harten <i>et al.</i> , 2008 <sup>46</sup>	29	Abdominal surgery	“Standard care”	Serum creatinine	85 (55–160)	85 (60–150)	100 (70–260)	95 (60–300)
Ickx <i>et al.</i> , 2004 <sup>47</sup>	40	Abdominal surgery	HES 200	Serum creatinine	93 $\pm$ 11	84 $\pm$ 17	102 $\pm$ 11	90 $\pm$ 11
Jover <i>et al.</i> , 2009 <sup>48</sup>	29	Abdominal laparoscopic surgery	Ringer solution	Calculated creatinine clearance	—	—	—	—
Kasper <i>et al.</i> , 2003 <sup>3</sup>	117	Cardiac surgery	HES 200	Serum creatinine	80 $\pm$ 18	88 $\pm$ 35	80 $\pm$ 18	97 $\pm$ 53
Lee <i>et al.</i> , 2011 <sup>43</sup>	106	Cardiac surgery	Isotonic saline	ARF	—	—	—	—
Mahmood <i>et al.</i> , 2007 <sup>36</sup>	62	Vascular surgery	Gelatin solution, HES 200	Serum creatinine	96 $\pm$ 1 (SEM)	95 $\pm$ 2 (SEM)	101 $\pm$ 2 (SEM)	138 $\pm$ 24 (SEM)
Mukhtar <i>et al.</i> , 2009 <sup>50</sup>	40	Liver transplantation	Human albumin	Serum creatinine, calculated creatinine clearance	97 $\pm$ 9	133 $\pm$ 31	93 $\pm$ 18	115 $\pm$ 34
Ooi <i>et al.</i> , 2009 <sup>41</sup>	90	Cardiopulmonary bypass	Gelatin solution	eGFR	—	—	—	—
Shabazi <i>et al.</i> , 2011 <sup>42</sup>	70	Cardiopulmonary bypass	Ringer solution	Serum creatinine, calculated creatinine clearance	85 $\pm$ 16	111 $\pm$ 31	88 $\pm$ 13	107 $\pm$ 40
Tiryakioglu <i>et al.</i> , 2008 <sup>38</sup>	140	Cardiopulmonary bypass	Ringer solution	Serum creatinine, calculated creatinine clearance	97 $\pm$ 9	124 $\pm$ 21	88 $\pm$ 18	97 $\pm$ 27
Van der Linden <i>et al.</i> , 2005 <sup>44</sup>	132	Cardiac surgery	Gelatin solution	Serum creatinine	93 $\pm$ 20	88 $\pm$ 27	96 $\pm$ 26	103 $\pm$ 65
Yang <i>et al.</i> , 2011 <sup>34</sup>	81	Liver surgery	Ringer solution, human albumin	Serum creatinine	78 $\pm$ 20	73 $\pm$ 22	RL: 77 $\pm$ 15HA: 73 $\pm$ 11	RL: 71 $\pm$ 18HA: 67 $\pm$ 16
Yap <i>et al.</i> , 2007 <sup>37</sup>	40	Cardiopulmonary bypass	Gelatin solution	Serum creatinine	—	96 $\pm$ 23	—	118 $\pm$ 51

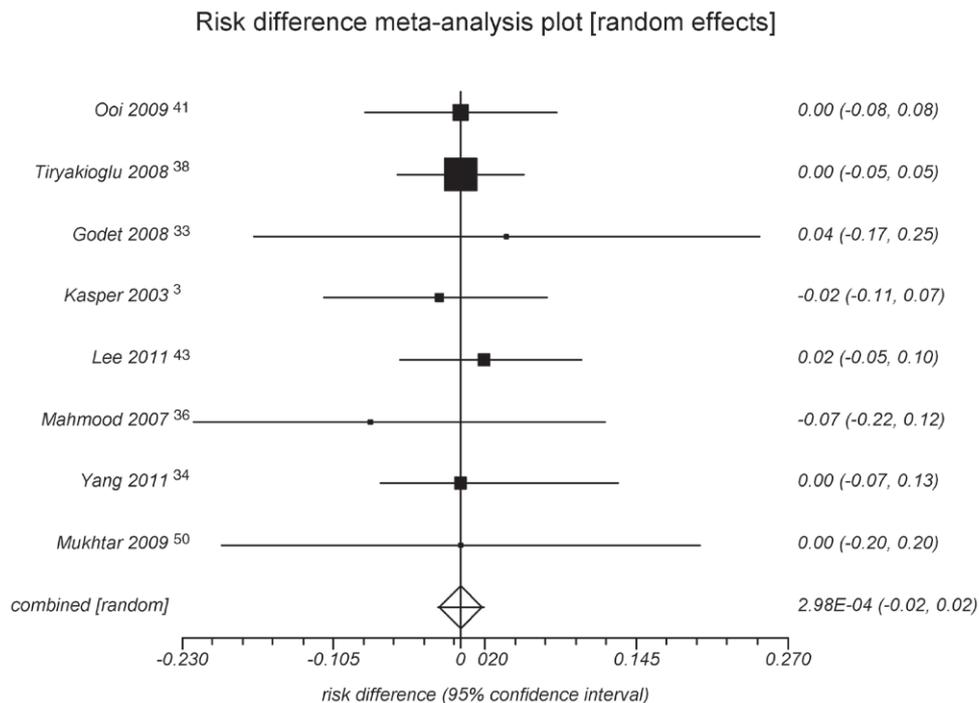
\* Values are expressed as mean  $\pm$  SD or median (range) if not stated differently (IQR = median + interquartile ranges, SEM = standard error of the mean). ARF = acute renal failure; BL = baseline; eGFR = estimated glomerular filtration rate; G = gelatin; HA = human albumin; HES = hydroxyethyl starch; RL = Ringer's lactate.



**Fig. 2.** Surgical patients. (A): Serum creatinine baseline values; random effect pooled  $d+ = -0.021$  (95% CI =  $-0.261$  to  $0.219$ ),  $Z$  (test  $d+$  differs from 0) =  $-0.172$ ,  $P = 0.86$ . (B): Serum creatinine extreme values; random effects (DerSimonian-Laird), pooled  $d+ = 0.068$ , (95% CI =  $-0.227$  to  $0.362$ ),  $Z$  (test  $d+$  differs from 0) =  $0.45$ ,  $P = 0.65$ . No significant differences were found between extreme values and baseline.  $d+$  effect size = difference; DL = DerSimonian-Laird; FK = Fresenius Kabi; HES = hydroxyethyl starch; N = number of patients.

definitions of ARF among the studies. The results of one study<sup>48</sup> for calculated creatinine clearance indicated a potentially positive effect of waxy maize-derived HES 130/0.40. However, in this study the clearance of the control group corresponding to the worst value for waxy maize-derived HES 130/0.40 was exceptionally low whereas it increased

for the HES group. Additionally, the number of patients in this study was very low; it was only 29. Within the last years, several other authors performed meta-analyses or literature reviews on safety aspects of HES. Unfortunately, no analysis so far has provided a stringent and transparent inclusion of the best available data sets about surgical patients only.



**Fig. 3.** Risk difference of acute renal failure; random effects (DerSimonian-Laird): Pooled risk difference =  $0.000298$  (95% CI =  $-0.018$  to  $0.019$ ),  $\text{Chi}^2$  (test risk difference differs from 0) =  $0.000992$  (df = 1),  $P = 0.98$ . No significant risk difference was found. df = degree of freedom.

**Table 2.** Results of the Meta-analysis

Parameter	Results (Model: Random Effects (DerSimonian-Laird))	
Calculated creatinine clearance (n = 344)	Baseline	Extreme value
	Pooled d+ = 0.302 (95% CI = -0.098 to 0.703) Z (test d+ differs from 0) = 1.482; P = 0.14 I <sup>2</sup> = 67.8% (95% CI = 0% to 85.4)	Pooled d+ = 0.783 (95% CI = -0.229 to 1.795) Z (test d+ differs from 0) = 1.517; P = 0.13 I <sup>2</sup> = 93.8% (95% CI = 88.9 to 95.9%)
Urea (n = 390)	Baseline	Extreme value
	Pooled d+ = -0.068 (95% CI = -0.371 to 0.236) Z (test d+ differs from 0) = -0.437; P = 0.66 I <sup>2</sup> = 12.3% (95% CI = 0% to 76.1)	Pooled d+ = -0.148 (95% CI = -1.077 to 0.782) Z (test d+ differs from 0) = -0.311; P = 0.76 I <sup>2</sup> = 94.3% (95% CI = 90.2 to 96.2%)
Renal replacement therapy (n = 531)	Pooled risk difference = -0.003 (95% CI = -0.028 to 0.022) Chi <sup>2</sup> (test risk difference differs from 0) = 0.037 (df=1); P = 0.85 I <sup>2</sup> = 0% (95% CI = 0 to 58.5%)	
ICU length of stay (n = 723)	Pooled d+ = 0.113 (95% CI = -0.172 to 0.398) Z (test d+ differs from 0) = 0.775; P = 0.44 I <sup>2</sup> = 80.1% (95% CI = 62.6% to 87.4)	
Hospital length of stay (n = 940)	Pooled d+ = 0.212 (95% CI = -0.035 to 0.46) Z (test d+ differs from 0) = 1.68; P = 0.09 I <sup>2</sup> = 73.9% (95% CI = 48.1 to 83.9%)	

ICU = intensive care unit.

A very extensive meta-analysis on HES by Dart *et al.*<sup>18</sup> addressed the question of renal safety. Yet, it did not take into account the existence of differences between HES generations and pooled data for all HES preparations, concentrations, and different oncotic properties. It is thus not surprising that this review article—like others before—highlights the negative effects of some very old starches like HES 650. Unfortunately, the authors extend their results to all HES. Additionally, the analysis was dominated by the VISEP trial,<sup>13</sup> in which critically ill patients received a hyperoncotic 10% HES 200/0.5, whereas the vast majority of studies with colloids used isooncotic preparations. Groeneveld *et al.*<sup>19</sup> distinguished between different HES generations. Still this analysis has several limitations: First, the incidence of ARF and the need for renal replacement therapy were the primary outcome. Yet, as discussed before, the definitions of ARF varied largely among studies. Renal replacement therapy is also subject of controversy, because the decision when to start it differs considerably among studies and centers and is generally not defined by the study protocol. Therefore, this specific outcome is highly variable among studies. Second, the included data were incomplete. Notably, three available studies<sup>38,41,50</sup> and several others regarding nonrenal outcomes were not taken into account.

Another recent analysis by Hartog *et al.*<sup>20</sup> also extensively reviewed the literature on HES 130/0.40. However, with regard to renal outcome, the authors considered only a limited number of trials and excluded several others by using criteria that seem to be weakly defined. Most important, data from small trials were classified as “random findings” and, therefore, excluded from the analysis. This seems questionable as the main merit of a meta-analysis or a literature

review is its ability to gain evidence from pooling small studies that fulfill basic requirements in study design.

The most recent review article in critically ill patients was published by Gattas *et al.*,<sup>21</sup> and critically it analyzed whether the recent retraction of studies by Boldt<sup>34</sup> substantially changed the evidence concerning clinical use of HES 130/0.40. In fact, the authors found that this was not the case. Gattas *et al.* only considered studies reporting the need for renal replacement therapy and urine output and concluded that there were insufficient data to draw definite conclusions about the renal safety of HES 130/0.40.

Our meta-analysis includes all available randomized controlled trials analyzing waxy maize-derived HES 130/0.40 effects on renal safety in elective surgical patients. We chose serum creatinine as our main outcome as this was available in all studies. Furthermore, monitoring serum creatinine, as well as changes in serum creatinine, has been reported to be a valid and sensitive variable in predicting patient outcome.<sup>25,51</sup> As with all clinical markers, serum creatinine has inherent limitations that might not reflect small but long-term damages that could become relevant after repeated or very high dose administration of HES.

The present meta-analysis includes the comparison of waxy maize-derived HES 130/0.40 to various control solutions, including products that are known as being safe for renal function like crystalloid solutions. For subanalysis of data comparing waxy maize-derived HES 130/0.40 with, for example, crystalloids or specific colloids, the number of patients is too small to draw meaningful conclusions. The estimates of heterogeneity (*I*<sup>2</sup>) between studies may represent substantial heterogeneity, which should be kept in mind when interpreting the data. Given the range of different

settings and comparators analyzed for this meta-analysis, this is not surprising and is a trait that has even been reported even for many Cochrane meta-analyses.

We are also aware that our analysis does not allow the drawing of any conclusions about critically ill patients.

A limitation of any meta-analysis as of ours potentially is sample size and power of the study. Also, not all variables used to assess renal function were available in all the analyzed studies. Furthermore, our findings cannot be extrapolated to the use of hypertonic HES,<sup>52</sup> the use in patients undergoing kidney transplantation<sup>53</sup> even if waxy maize-derived HES is used during the resuscitation of the donors and the recipients.

In summary, our meta-analysis provides evidence that there is currently no verifiable association between the administration of waxy maize-derived HES 130/0.40 and changes of serum creatinine and calculated creatinine clearance or the incidence of ARF in patients undergoing surgical procedures.

## References

- Westphal M, James MF, Kozek-Langenecker S, Stocker R, Guidet B, Van Aken H: Hydroxyethyl starches: Different products—different effects. *ANESTHESIOLOGY* 2009; 111:187–202
- Gallandat Huet RC, Siemons AW, Baus D, van Rooyen-Butijn WT, Haagenaars JA, van Oeveren W, Bepperling F: A novel hydroxyethyl starch (Voluven) for effective perioperative plasma volume substitution in cardiac surgery. *Can J Anaesth* 2000; 47:1207–15
- Kasper SM, Meinert P, Kampe S, Görg C, Geisen C, Mehlhorn U, Diefenbach C: Large-dose hydroxyethyl starch 130/0.4 does not increase blood loss and transfusion requirements in coronary artery bypass surgery compared with hydroxyethyl starch 200/0.5 at recommended doses. *ANESTHESIOLOGY* 2003; 99:42–7
- Langeron O, Doelberg M, Ang ET, Bonnet F, Capdevila X, Coriat P: Voluven, a lower substituted novel hydroxyethyl starch (HES 130/0.4), causes fewer effects on coagulation in major orthopedic surgery than HES 200/0.5. *Anesth Analg* 2001; 92:855–62
- Gandhi SD, Weiskopf RB, Jungheinrich C, Koorn R, Miller D, Shangraw RE, Prough DS, Baus D, Bepperling F, Warltier DC: Volume replacement therapy during major orthopedic surgery using Voluven (hydroxyethyl starch 130/0.4) or hetastarch. *ANESTHESIOLOGY* 2007; 106:1120–7
- Kozek-Langenecker SA: Benefits of fluid therapy on the hemostatic system of intensive care patients. *J Coagul Disorders* 2010; 2:41–8
- Jungheinrich C, Scharpf R, Wargenau M, Bepperling F, Baron JF: The pharmacokinetics and tolerability of an intravenous infusion of the new hydroxyethyl starch 130/0.4 (6%, 500 mL) in mild-to-severe renal impairment. *Anesth Analg* 2002; 95:544–51
- Blasco V, Leone M, Antonini F, Geissler A, Albanèse J, Martin C: Comparison of the novel hydroxyethylstarch 130/0.4 and hydroxyethylstarch 200/0.6 in brain-dead donor resuscitation on renal function after transplantation. *Br J Anaesth* 2008; 100:504–8
- Reinhart K, Perner A, Sprung CL, Jaeschke R, Schortgen F, Johan Groeneveld AB, Beale R, Hartog CS; European Society of Intensive Care Medicine: Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients. *Intensive Care Med* 2012; 38:368–83
- 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
- Bayer O, Reinhart K, Sakr Y, Kabisch B, Kohl M, Riedemann NC, Bauer M, Settmacher U, Hekmat K, Hartog CS: Renal effects of synthetic colloids and crystalloids in patients with severe sepsis: A prospective sequential comparison. *Crit Care Med* 2011; 6:1–8
- Schortgen F, Girou E, Deye N, Brochard L; CRYCO Study Group: The risk associated with hyperoncotic colloids in patients with shock. *Intensive Care Med* 2008; 34:2157–68
- Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K; German Competence Network Sepsis (SepNet): Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008; 358:125–39
- 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, Søj-Jensen P, Bestle M, Strand K, Wiis J, White JO, Thornberg KJ, Quist L, Nielsen J, Andersen LH, Holst LB, Thormar K, Kjældgaard AL, Fabritius ML, Mondrup F, Pott FC, Møller TP, Winkel P, Wetterslev J; 6S Trial Group; Scandinavian Critical Care Trials Group: Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012; 367:124–34
- Boussekey N, Darmon R, Langlois J, Alfandari S, Devos P, Meybeck A, Chiche A, Georges H, Leroy O: Resuscitation with low volume hydroxyethylstarch 130 kDa/0.4 is not associated with acute kidney injury. *Crit Care* 2010; 14:R40
- Guidet B, Martinet O, Boulain T, Philippart F, Poussel JF, Maizel J, Forceville X, Feissel M, Hasselmann M, Heininger A, Van Aken H: Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study. *Crit Care* 2012; 16:R94
- 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
- Dart AB, Mutter TC, Ruth CA, Taback SP: Hydroxyethyl starch (HES) versus other fluid therapies: Effects on kidney function. *Cochrane Database Syst Rev* 2010; 20:CD007594
- Groeneveld AB, Navickis RJ, Wilkes MM: Update on the comparative safety of colloids: A systematic review of clinical studies. *Ann Surg* 2011; 253:470–83
- Hartog CS, Kohl M, Reinhart K: A systematic review of third-generation hydroxyethyl starch (HES 130/0.4) in resuscitation: Safety not adequately addressed. *Anesth Analg* 2011; 112:635–45
- Gattas DJ, Dan A, Myburgh J, Billot L, Lo S, Finfer S; CHEST Management Committee: Fluid resuscitation with 6% hydroxyethyl starch (130/0.4) in acutely ill patients: An updated systematic review and meta-analysis. *Anesth Analg* 2012; 114:159–69
- Jamnicki M, Zollinger A, Seifert B, Popovic D, Pasch T, Spahn DR: The effect of potato starch derived and corn starch derived hydroxyethyl starch on in vitro blood coagulation. *Anaesthesia* 1998; 53:638–44
- Lehmann G, Marx G, Förster H: Bioequivalence comparison between hydroxyethyl starch 130/0.42/6: 1 and hydroxyethyl starch 130/0.4/9: 1. *Drugs R D* 2007; 8:229–40
- Sommermeier K, Cehc F, Schossow R: Differences in chemical structures between waxy maize- and potato starch-based hydroxyethyl starch volume therapeutics. *Transfus Altern Transfus Med* 2007; 9:127–33

25. 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:R204-12
26. Wieland LS, Robinson KA, Dickersin K: Understanding why evidence from randomised clinical trials may not be retrieved from Medline: comparison of indexed and non-indexed records. *BMJ* 2012; 344:d7501
27. van der Linden P, Gazdzik TS, Jahoda D, Heylen RJ, Skowronski JC, Pellar D, Kofranek I, Górecki AZ, Fagrell B, Keipert PE, Hardiman YJ, Levy H; 6090 Study Investigators: A double-blind, randomized, multicenter study of MP4OX for treatment of perioperative hypotension in patients undergoing primary hip arthroplasty under spinal anesthesia. *Anesth Analg* 2011; 112:759-73
28. Olofsson CI, Górecki AZ, Dirksen R, Kofranek I, Majewski JA, Mazurkiewicz T, Jahoda D, Fagrell B, Keipert PE, Hardiman YJ, Levy H; Study 6084 Clinical Investigators: Evaluation of MP4OX for prevention of perioperative hypotension in patients undergoing primary hip arthroplasty with spinal anesthesia: A randomized, double-blind, multicenter study. *ANESTHESIOLOGY* 2011; 114:1048-63
29. Base EM, Standl T, Lassnigg A, Skhirtladze K, Jungheinrich C, Gayko D, Hiesmayr M: Efficacy and safety of hydroxyethyl starch 6% 130/0.4 in a balanced electrolyte solution (Volulyte) during cardiac surgery. *J Cardiothorac Vasc Anesth* 2011; 25:407-14
30. Kulla M, Weidhase R, Lampl L: Hydroxyethyl starch 6% 130/0.42 in acetate-buffered Ringer's solution as a part of a balanced-volume resuscitation in abdominal surgery. *Anästhesiologie* 2008; 49:7-18
31. Wu Y, Wu AS, Wang J, Tian M, Jia XY, Rui Y, Yue Y: Effects of the novel 6% hydroxyethyl starch 130/0.4 on renal function of recipients in living-related kidney transplantation. *Chin Med J* 2010; 123:3079-83
32. Boldt J, Lehmann A, Römpert R, Haisch G, Isgro F: Volume therapy with a new hydroxyethyl starch solution in cardiac surgical patients before cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2000; 14:264-8
33. Godet G, Lehot JJ, Janvier G, Steib A, De Castro V, Coriat P: Safety of HES 130/0.4 (Voluven®) in patients with preoperative renal dysfunction undergoing abdominal aortic surgery: A prospective, randomized, controlled, parallel-group multicentre trial. *Eur J Anaesthesiol* 2008; 25:986-94
34. Yang J, Wang WT, Yan LN, Xu MQ, Yang JY: Alternatives to albumin administration in hepatocellular carcinoma patients undergoing hepatectomy: An open, randomized clinical trial of efficacy and safety. *Chin Med J* 2011; 124:1458-64
35. Hozo SP, Djulbegovic B, Hozo I: Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005; 5:13
36. Mahmood A, Gosling P, Vohra RK: Randomized clinical trial comparing the effects on renal function of hydroxyethyl starch or gelatine during aortic aneurysm surgery. *Br J Surg* 2007; 94:427-33
37. Yap WW, Young D, Pathi V: Effects of gelatine and medium molecular weight starch as priming fluid in cardiopulmonary bypass—a randomized controlled trial. *Perfusion* 2007; 22:57-61
38. Tiryakioglu O, Yildiz G, Vural H, Goncu T, Ozyazicioglu A, Yavuz S: Hydroxyethyl starch versus Ringer solution in cardiopulmonary bypass prime solutions (a randomized controlled trial). *J Cardiothorac Surg* 2008; 3:45
39. Hedges LV, Olkin I: Statistical methods for meta-analysis. London, Academic Press, 1985
40. Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21:1539-58
41. Ooi JS, Ramzisham AR, Zamrin MD: Is 6% hydroxyethyl starch 130/0.4 safe in coronary artery bypass graft surgery? *Asian Cardiovasc Thorac Ann* 2009; 17:368-72
42. Shahbazi S, Zeighami D, Allahyary E, Alipour A, Esmaeeli MJ, Ghanele M: Effect of colloid versus crystalloid administration of cardiopulmonary bypass prime solution on tissue and organ perfusion. *Iran Cardiovasc Res J* 2011; 5:24-31
43. Lee JS, Ahn SW, Song JW, Shim JK, Yoo KJ, Kwak YL: Effect of hydroxyethyl starch 130/0.4 on blood loss and coagulation in patients with recent exposure to dual antiplatelet therapy undergoing off-pump coronary artery bypass graft surgery. *Circ J* 2011; 75:2397-402
44. Van der Linden PJ, De Hert SG, Deraedt D, Cromheecke S, De Decker K, De Paep R, Rodrigus I, Daper A, Trenchant A: Hydroxyethyl starch 130/0.4 versus modified fluid gelatin for volume expansion in cardiac surgery patients: The effects on perioperative bleeding and transfusion needs. *Anesth Analg* 2005; 101:629-34, table of contents
45. Hanart C, Khalife M, De Villé A, Otte F, De Hert S, Van der Linden P: Perioperative volume replacement in children undergoing cardiac surgery: Albumin versus hydroxyethyl starch 130/0.4. *Crit Care Med* 2009; 37:696-701
46. Harten J, Crozier JE, McCreath B, Hay A, McMillan DC, McArdle CS, Kinsella J: Effect of intraoperative fluid optimisation on renal function in patients undergoing emergency abdominal surgery: A randomised controlled pilot study (ISRCTN 11799696). *Int J Surg* 2008; 6:197-204
47. Ickx BE, Bepplerling F, Melot C, Schulman C, Van der Linden PJ: Plasma substitution effects of a new hydroxyethyl starch HES 130/0.4 compared with HES 200/0.5 during and after extended acute normovolaemic haemodilution. *Br J Anaesth* 2003; 91:196-202
48. Jover JL, García JP, Martínez C, Espí A, Gregori E, Almagro J: [Hydroxyethyl starch to protect renal function in laparoscopic surgery]. *Rev Esp Anesthesiol Reanim* 2009; 56:27-30
49. Fenger-Eriksen C, Hartig Rasmussen C, Kappel Jensen T, Anker-Møller E, Heslop J, Frøkiaer J, Tønnesen E: Renal effects of hypotensive anaesthesia in combination with acute normovolaemic haemodilution with hydroxyethyl starch 130/0.4 or isotonic saline. *Acta Anaesthesiol Scand* 2005; 49:969-74
50. Mukhtar A, Aboufetoouh F, Obayah G, Salah M, Emam M, Khater Y, Akram R, Hoballah A, Bahaa M, Elmeteini M, Hamza A: The safety of modern hydroxyethyl starch in living donor liver transplantation: A comparison with human albumin. *Anesth Analg* 2009; 109:924-30
51. Kim KE, Onesti G, Ramirez O, Brest AN, Swartz C: Creatinine clearance in renal disease. A reappraisal. *Br Med J* 1969; 4:11-4
52. Kerbaul F, Rondelet B, Bénas V, Grisoli D, De Waroquier A, Fesler P, Fusai T, Brimiouille S: Hypertonic saline hydroxyethylstarch restores right ventricular-arterial coupling after normovolemic hemodilution in piglets. *ANESTHESIOLOGY* 2011; 115:136-43
53. 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