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ORIGINAL ARTICLE

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Bleeding and risk of death with hydroxyethyl starch in severe sepsis: post hoc analyses of a randomized clinical trial

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Abstract *Purpose:* We aimed to characterize the degree and clinical importance of bleeding in patients treated with hydroxyethyl starch (HES). *Methods:* In post hoc analyses, we examined the associations between fluid assignment, hemostatic variables, bleeding events, transfusions, and death among 798 patients with severe sepsis randomized to fluid resuscitation with HES 130/0.42 versus Ringer's acetate. We used Cox regression analysis adjusted for fluid assignment and baseline characteristics. *Results:* Overall, 93 (23 %) patients assigned to HES versus 60 (15 %) patients assigned to Ringer's acetate bled in the ICU (relative risk (RR) 1.55; 95 % CI 1.16–2.08; $P = 0.003$). Of these, 38 and 25 (RR 1.52; 95 % CI 0.94–2.48; $P = 0.09$), respectively, had severe bleeding (intracranial or concomitant transfusion with three units of red blood cells). Most patients bled in the first days after randomization when most trial fluid was given. The hazards ratios for occurrence of any bleeding and severe bleeding in patients treated with HES versus Ringer's acetate were 1.70 (95 % CI 1.23–2.36; $P = 0.001$) and 1.55 (95 % CI 0.93–2.56; $P = 0.09$), respectively. The adjusted hazard ratios for death among patients with any bleeding and severe bleeding compared to those without bleeding were 1.36 (95 % CI 1.04–1.79; $P = 0.03$) and 1.74 (95 % CI 1.20–2.53; $P = 0.004$), respectively. *Conclusions:* In post hoc analyses of patient with severe sepsis, treatment with HES increased the risk of bleeding which was associated with increased risk of death. HES-induced bleeding complications may negatively affect outcome in patients with severe sepsis.

Keywords Hydroxyethyl starch · Sepsis · Coagulopathy · Bleeding · Mortality

Introduction

Hydroxyethyl starch (HES) was the most commonly used colloid in a recent worldwide point prevalence study of resuscitation in intensive care units (ICU) [1]. Systematic reviews report that HES affects hemostasis more than other fluids, but most clinical trials in these reviews assessed the former high molecular weight HES in surgical patients [2–4]. Thus, the degree of hemostatic impairment in patients with sepsis with the currently used HES with low molecular weight (130,000 Da) and substitution ratio of approximately 0.4 (range 0.38–0.45) is unknown, and whether such impairment affects patient important outcomes is yet to be elucidated.

We previously reported that patients with severe sepsis assigned to fluid resuscitation with 6 % HES 130/0.42

versus Ringer's acetate had increased risk of death, bleeding, and of being transfused with red blood cells [5]. However, the last two were not originally protocolized outcomes. On the basis of these results, the results from similar trials and meta-analyses [6–10], the European Medicines Agency's Pharmacovigilance Risk Assessment Committee recently recommended suspending marketing authorizations for all HES solutions, and the US Food and Drug Administration issued a boxed warning against the use of HES in critically ill patients and those at high risk of bleeding [11, 12].

To better understand the results of our trial, we analyzed the trial database to further explore the relationships between type of trial fluid, hemostatic variables (international normalized ratio (INR) and platelet count), bleeding events, transfusions, and mortality.

Methods

Study oversight

The present study is a post hoc analysis of the Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial database. The trial protocol, the statistical analysis plan and primary trial results were previously published [5, 13]. The trial was approved by the medicines agencies, ethical committees, and data protection agencies in Denmark, Norway, Finland, and Iceland prior to randomization of the first patient. Informed consent was obtained prior to randomization from all participants or their legal substitutes according to national legislation. Independently of funding agencies, the authors designed the study, analyzed the data, wrote the manuscript, and made the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the reported data.

Study participants

This randomized trial with concealed allocation and blinding recruited 798 patients with severe sepsis in ICUs in 26 hospitals in Denmark, Norway, Finland, and Iceland in 2010 and 2011. Eligible patients fulfilled the criteria for severe sepsis and needed fluid resuscitation as judged by the treating clinician. We excluded patients undergoing renal replacement therapy or having intracranial bleeding. A detailed description of inclusion and exclusion criteria can be found in the main publication of the 6S trial [5]. Patients were randomly assigned to fluid resuscitation with either 6 % HES 130/0.42 in Ringer's acetate (Tetraspan 6 %, B Braun, Melsungen, Germany) or Ringer's acetate (Sterofundin ISO, B Braun) to a maximum daily dose of 33 ml per kg ideal body weight per day followed by Ringer's acetate if needed. Randomization was stratified according to the presence or absence of shock, the presence or absence of active hematologic cancer, and admission to a university or non-university hospital. The trial design was pragmatic so fluid resuscitation was at the discretion of the treating clinicians, and no other part of the treatment was protocolized or standardized among the participating ICUs. The intervention period lasted until discharge from the ICU to a maximum of 90 days.

At baseline we collected data on demographics and clinical characteristics. Daily recordings during the entire admission to the ICU included bleeding events (see supplementary material for a case record form) and transfusions of red blood cells, platelets, and fresh frozen plasma. The lowest hemoglobin levels, the highest INR, and the lowest platelet count were registered in the first 5 days. Time of death was registered for all patients to a maximum follow-up of 90 days. Observation for bleeding stopped at the time of discharge from the ICU.

Severe bleeding was defined as intracranial bleeding or bleeding with concomitant transfusion of three units of red blood cells.

Statistical analyses

We examined the influence of the trial fluid on time to any bleeding and on time to severe bleeding using proportional hazards methods (Cox regression analysis), where patients were censored at discharge from the ICU, death, or 90 days whichever came first. If patients were discharged from the ICU to a general ward and readmitted to the ICU, the time between two such ICU admissions was included as observation time with no events. We calculated unadjusted hazard ratios and hazard ratios adjusted for the stratification variables [14], and the following other baseline characteristics: surgery prior to ICU admission or not, HES given in the 24 h prior to randomization or not, simplified acute physiology score (SAPS) II [15], sepsis-related organ failure assessment (SOFA) score [16], platelet count, and INR.

We then assessed the relationship between any bleeding or severe bleeding and mortality within 90 days with Cox regression analysis where occurrence of bleeding was included as a time-dependent covariate. To further examine whether bleedings contributed to the excess mortality observed with HES, we performed a Cox regression analysis of time to death according to trial fluid assignment with and without censoring of patients with bleedings.

Risk factors for any bleeding and severe bleeding were identified with the use of univariate and multivariate logistic regression analysis. Covariates were included in the multivariate model if the P value was less than 0.10 in the univariate analysis.

The time courses of the lowest hemoglobin level, highest INR, and lowest platelets count during the first 5 days after randomization were analyzed as the difference between the intervention groups in area under the curve and using a mixed model taking into consideration repeated measurements made in the same patient.

In all analyses we used multiple imputation of missing variables according to the recommendations of the Patient-Centered Outcomes Research Institute and Shafer [17, 18].

Author and statistician P.W. performed the analyses in SPSS 18 and SAS 9.2. A two-sided P value of less than 0.05 was considered to indicate statistical significance.

Results

Study participants

The modified intention-to-treat population comprised 798 patients with severe sepsis in the ICU (Table 1). The median (interquartile range, IQR) observation period for bleeding (time from randomization to discharge from the ICU) was 6 (3–15) days in the HES group and 7 (3–15) days in the Ringer's acetate group.

Intervention

Overall, 779 patients (98 %) received trial fluid. Most trial fluid was given in the first 3 days (Table S1 in the supplementary material). The median cumulative volume during the entire ICU admission was 3,000 ml (IQR 1,507–5,100) in the HES group and 3,000 (IQR 2,000–5,750) in the Ringer's group ($P = 0.20$) corresponding to 44 and 47 ml/kg ideal body weight, respectively ($P = 0.18$).

Transfusion with blood products

More patients in the HES group than in the Ringer's group received red blood cells [relative risk (RR) 1.28, 95 % CI 1.12–1.47, $P = 0.0004$]. The lowest hemoglobin levels, on days where patients received red blood cell transfusion, were approximately 8 g/dl in both intervention groups (Table S2 in the supplementary material). The number of patients who received fresh frozen plasma and platelets did not differ significantly between the groups (RR 1.13, 95 % CI 0.96–1.34, $P = 0.14$ and RR 1.21, 95 % CI 0.98–1.51, $P = 0.06$, respectively).

Time course of INR, hemoglobin level, and platelet count

Patients assigned to HES had lower hemoglobin and higher INR values than those assigned to Ringer's acetate. The differences were present during the first days after randomization and seemed to diminish towards day 5, but their clinical relevance was unclear. The platelet counts were not affected with statistical significance by the type of trial fluid (see figure in the supplementary material).

Bleeding events

Overall, 93 (23 %) patients assigned to HES versus 60 (15 %) patients assigned to Ringer's acetate bled in the ICU ($P = 0.003$). Of these, 38 and 25 patients, respectively, had severe bleeding ($P = 0.09$). In both groups most patients had their first bleeding episode within the first days after randomization (Fig. 1), but the longer the patient stayed in the ICU the higher the risk of bleeding (Table S3 in the supplementary material). Most frequently, the patients bled during surgery, from wounds, or from the upper gastrointestinal tract (Table S4 in the supplementary material). Once a patient bled, the median duration of the bleeding was 1 day in both groups (IQR 1–2). Blood loss was reported in very few patients who bled from the gastrointestinal tract, urinary tract, or airways, but was reported for most patients who bled during surgery and did not differ between the groups (HES group: 33 of 33 patients, median 1,650 ml, IQR 250–2,500; Ringer's group: 23 of 26 patients, median 1,000 ml, IQR 200–2,600; $P = 0.78$). More patients who had bleeding or severe bleeding received transfusions of red blood cells, fresh frozen plasma, or platelets, and transfused volumes were larger (all $P < 0.0001$ compared to patients without bleeding) (Tables 2 and S5 in the supplementary material). Cox regression analyses showed a statistically significant increased risk of any bleeding in patients assigned to HES versus Ringer's acetate both in the unadjusted and adjusted analyses (Fig. 1). Hazard ratio estimates for severe bleeding were comparable to those of any bleeding, but were not statistically significant (Fig. 1).

Risk factors for bleeding

Characteristics of patients with no bleeding, any bleeding, and severe bleeding are shown in Table 2. Admission to a university hospital, surgery prior to randomization, and assignment to fluid resuscitation with HES were all independent risk factors for bleeding (Table 3). For severe bleeding, assignment to HES was no longer an independent risk factor, but baseline platelet count appeared to be so.

Association between bleeding and mortality

During the 90-day follow-up period, 373 of the 798 patients (47 %) died including 299 of the 645 patients

Table 1 Baseline characteristics of the patients

	HES 130/0.42 ($N = 398$)	Ringer's acetate ($N = 400$)
Age in years, median (IQR)	66 (56–75)	67 (56–76)
Male sex, *N* (%)	239 (60)	244 (61)
Admitted to a university hospital, *N* (%)	194 (49)	188 (47)
Septic shock, *N* (%)[a]	336 (84)	337 (84)
Active hematologic cancer, *N* (%)	36 (9)	36 (9)
Surgery prior to ICU admission, *N* (%)[b]	131 (33)	146 (37)
SAPS II, median (IQR)[c]	50 (40–60)	51 (39–62)
SOFA score, median (IQR)[d]	7 (5–9)	7 (5–9)
INR, median (IQR)[e]	1.3 (1.2–1.6)	1.3 (1.1–1.6)
Platelet count in 10^9/l, median (IQR)[f]	197 (106–275)	189 (112–275)
Hemoglobin concentration in g/dl, median (IQR)	10.3 (8.9–11.9)	10.3 (8.9–11.9)
Transfusion prior to randomization, *N* (%)		
Red blood cells	71 (18)	65 (16)
Fresh frozen plasma	42 (11)	38 (10)
Platelets	25 (6)	22 (6)
Treatment with HES prior to randomization, *N* (%)	152 (38)	159 (40)
Time from ICU admission to randomization in hours, median (IQR)	3.7 (1.3–12.9)	4.0 (1.4–12.6)

The values for the simplified acute physiology score (SAPS) II, sepsis-related organ failure assessment (SOFA) score, international normalized ratio (INR), platelet count, hemoglobin concentration, transfusions, and treatment with HES pertain to the 24 h prior to randomization

HES hydroxyethyl starch, *ICU* intensive care unit, *INR* international normalized ratio, *IQR* interquartile range

[a] Septic shock was defined as a mean arterial pressure of less than 70 mmHg, the need for ongoing treatment with vasopressors or inotropic agents, or a plasma lactate level of more than 4.0 mmol/l in the hour before randomization

[b] Surgery includes both elective and emergency surgery prior to the admission on the ICU

[c] SAPS II was calculated from 17 variables; scores range from 0 to 163, with higher scores indicating more severe disease. Data regarding 1 or 2 of the 17 variables were missing for 105 patients in the HES 130/0.42 group and 107 patients in the Ringer's acetate group

[d] The SOFA score includes subscores ranging from 0 to 4 for each of five components (circulation, lungs, liver, kidneys, and coagulation). Aggregated scores range from 0 to 20, with higher scores indicating more severe organ failure. The scoring was modified because cerebral failure was not assessed. One of the five subscores was missing for two patients in the HES 130/0.42 group

[e] INR was missing for 27 patients in the HES 130/0.42 group and 26 patients in the Ringer's acetate group

[f] Platelet counts were missing for two patients in the HES 130/0.42 group and two patients in the Ringer's acetate group

(46 %), who did not bleed in the ICU, and 74 of the 153 patients (48 %) with any bleeding. Of the 63 patients with severe bleeding, 34 (54 %) died. Mortality was highest among patients who stayed in the ICU for a shorter period (Table S6 in the supplementary material).

The hazard ratio for death was significantly increased among patients with any bleeding and severe bleeding compared to those who did not bleed in the ICU in both unadjusted and adjusted analyses (Fig. 2).

When patients with any bleeding were censored, the hazard ratio estimates for mortality in patients treated with HES versus Ringer's acetate were reduced (Table S7 in the supplementary material). The censoring of patients with severe bleeding did not change the estimates.

Discussion

The 6S trial is the first randomized clinical trial with adequate size to assess bleeding complications with HES in patients with severe sepsis. In post hoc analyses, treatment with 6 % HES 130/0.42 versus Ringer's acetate led to markedly increased risk of bleeding and transfusion with red blood cells. In multivariate analysis assignment to HES remained an independent risk factor for bleeding. This suggests that treatment with a low molecular weight HES results in clinically relevant coagulopathy and adds to previous concerns regarding the safety of HES in critically ill patients at high risk of bleeding.

In this pragmatic trial, we measured only few hemostatic variables and were unable to show clinically relevant alterations in hemostatic variables that could possibly link HES assignment to increased risk of bleeding. However, such a link has been provided by other studies. In a systematic review, HES 130/0.4 impaired coagulation to a greater extent than crystalloid and albumin in 19 of 24 retrieved studies [4]. The hypocoagulability was dose-dependent in in vitro studies and was detected in vivo after infusion of a relatively low HES dose of 28 ml/kg, which is well below the dose used in our trial. The degree of hypocoagulability has been suggested to depend on the molecular properties of the HES molecule [19, 20], but currently no study clearly show that the hemostatic alterations with the potato-derived HES 130/0.42 used in our trial should be different to those of maize-derived HES 130/0.4 [21, 22]. Thus, a causal relationship between HES treatment and increased

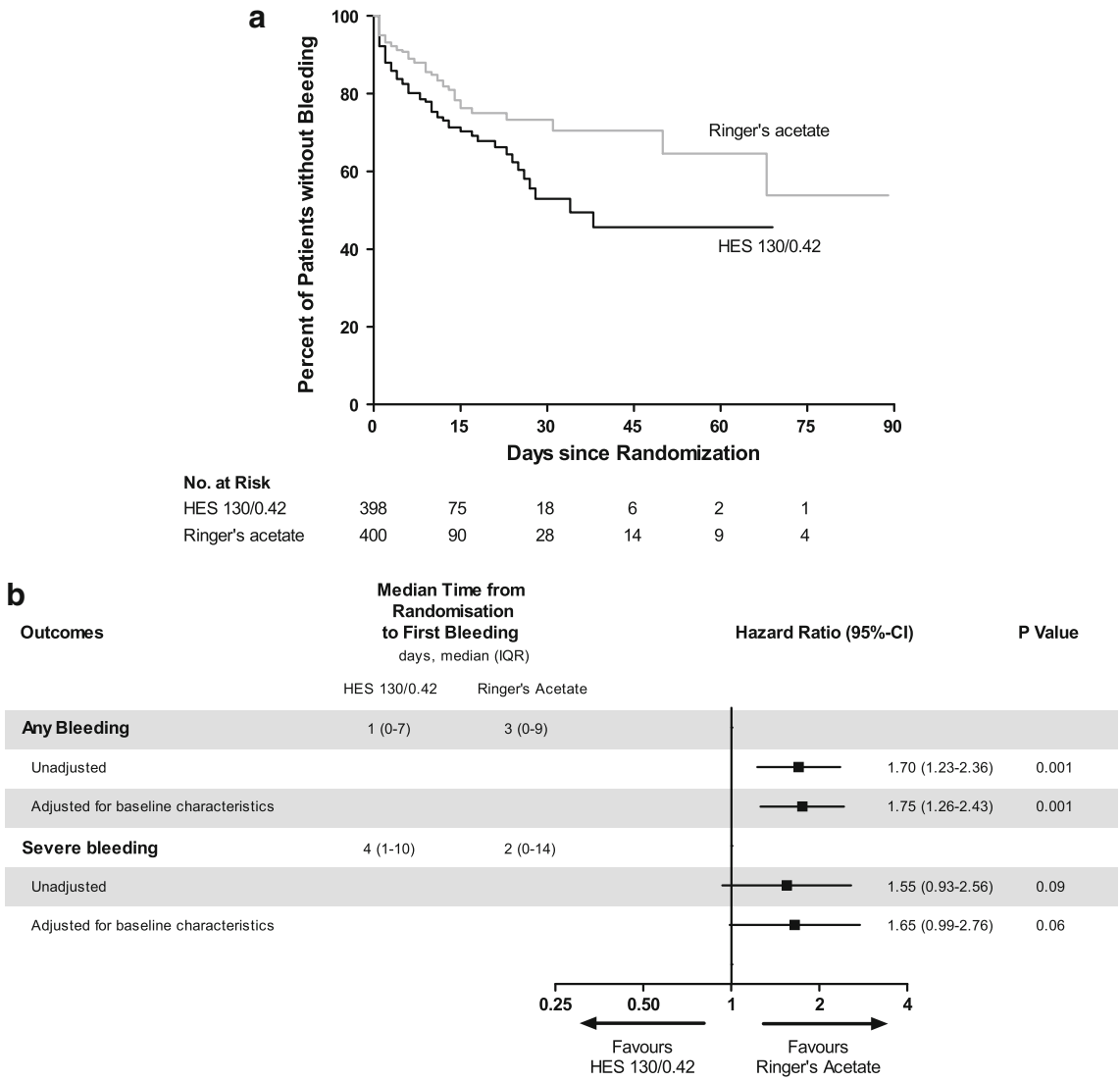

Fig. 1 Time to bleeding and hazard ratio for bleeding and severe bleeding according to trial fluid assignment. **a** Kaplan–Meier curves of time to bleeding censored at death, discharge from the intensive care unit, or at 90 days whichever came first for the two intervention groups. Kaplan–Meier analysis showed that the time to bleeding differed significantly between the groups ($P = 0.001$). **b** Hazard ratios with 95 % confidence intervals for bleeding and severe bleeding according to trial fluid assignment. Severe bleeding was defined as an intracranial bleeding or bleeding with concomitant transfusion with three units of red blood cells

risk of bleeding seems plausible in the light of other studies, and the fact that most patients bled in the first days after randomization, when most trial fluid was given, underlines the likely relationship between HES and bleeding.

The HES molecule likely interferes with fibrinogen/fibrin polymerization and reduces platelet function as well as von Willebrand factor, which may explain why we did not detect large differences in INR and platelet count between the two intervention groups [4].

The only other trial in critically ill patients with data on bleeding did not find any association between HES 130/0.4 vs. saline and bleeding rates and coagulopathy in patients with severe sepsis, which may be due to differences in bleeding registration, less sick patients, fluid dosing, or lack of statistical power [23]. Neither the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial [6] nor the Crystalloid versus Hydroxyethyl Starch Trial (CHEST) [7] registered bleeding events, but both trials reported increased use of red blood cell transfusion—a finding that is consistent with our trial and a meta-analysis of HES 130/0.4 and HES 130/0.42 in sepsis [24]. Whether the increased use of red blood cells in patients treated with HES is a consequence of bleeding, hemodilution, or other disease processes is unknown.

Table 2 Characteristics of patients with no bleeding, any bleeding, and severe bleeding in the ICU

	No bleeding ($n = 645$)	Any bleeding ($n = 153$)	Severe bleeding ($n = 63$)
Baseline			
Assignment to HES 130/0.42	305 (47)	93 (61)	38 (60)
Admitted to a university hospital *N* (%)	291 (45)	91 (59)	41 (65)
Surgery prior to ICU admission *N* (%)	206 (32)	71 (46)	33 (52)
Septic shock *N* (%)	538 (83)	135 (88)	55 (87)
Active hematological cancer *N* (%)	53 (8)	19 (12)	9 (14)
Treatment with HES in the 24 h prior to randomization, *N* (%)	254 (39)	57 (37)	26 (41)
SAPS II, median (IQR)	50 (39–60)	53 (41–63)	53 (42–67)
SOFA score, median (IQR)	7 (5–9)	8 (6–10)	7 (6–10)
INR, median (IQR)	1.3 (1.1–1.6)	1.4 (1.2–1.7)	1.4 (1.2–1.8)
Platelet count in 10^9/l, median (IQR)	198 (116–279)	154 (81–246)	150 (69–244)
Post-randomization			
Transfusions *N* (%)			
Red blood cells	290 (46)	130 (86)	62 (98)[a]
Fresh frozen plasma	134 (21)	88 (60)	53 (85)
Platelets	67 (11)	69 (47)	39 (64)
Mortality at 90 days *N* (%)	299 (46)	74 (48)	34 (54)

The 798 patients in the 6S trial were divided into the 'no bleeding' and 'any bleeding' groups according to whether they had a bleeding in the intensive care unit after randomization. The 'severe bleeding' group included the subgroup of bleeding patients who had bleeding with concomitant transfusion of three units of red blood cells or intracranial bleeding

HES hydroxyethyl starch, *ICU* intensive care unit, *SAPS* simplified acute physiology score, *SOFA* sepsis-related organ failure assessment, *INR* International normalized ratio

[a] One patient had intracranial bleeding and did not receive blood transfusion

Table 3 Results of uni- and multivariate analysis for potential risk factors at baseline for subsequent bleeding or severe bleeding

Variable	Any bleeding				Severe bleeding			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Odds ratio (95 % CI)	*P* value	Odds ratio (95 % CI)	*P* value	Odds ratio (95 % CI)	*P* value	Odds ratio (95 % CI)	*P* value
Assignment to HES 130/0.42	1.73 (1.21–2.48)	0.003	1.80 (1.25–2.60)	0.002	1.58 (0.81–2.68)	0.09	1.64 (0.96–2.80)	0.07
Admitted to a university hospital	1.79 (1.25–2.55)	0.002	1.49 (1.03–2.17)	0.04	2.15 (1.26–3.69)	0.005	1.76 (1.01–3.06)	0.047
Surgery prior to ICU admission	1.85 (1.29–2.64)	0.001	1.93 (1.32–2.81)	0.001	2.21 (1.32–3.72)	0.003	2.28 (1.32–3.92)	0.003
Septic shock	1.49 (0.88–2.54)	0.14	–	–	1.30 (0.60–2.80)	0.50	–	–
Active hematologic cancer	1.58 (0.91–2.76)	0.11	–	–	1.78 (0.85–3.77)	0.13	–	–
Treatment with HES in the 24 h prior to randomization	0.91 (0.64–1.32)	0.63	–	–	1.11 (0.66–1.87)	0.70	–	–
Square root of SAPS II[a]	1.15 (0.97–1.37)	0.11	–	–	1.19 (0.92–1.53)	0.22	–	–
Square root of SOFA score[a]	1.52 (1.09–2.10)	0.01	1.36 (0.93–1.98)	0.11	1.43 (0.89–2.29)	0.14	–	–
Transformed INR[b]	1.36 (0.85–2.15)	0.20	–	–	1.57 (0.85–2.92)	0.16	–	–
Logarithm of platelet count[a]	0.83 (0.69–0.98)	0.04	0.88 (0.72–1.09)	0.24	0.80 (0.63–1.01)	0.07	0.77 (0.60–1.00)	0.048

Factors included in the multivariate analyses were those with *P* values less than 0.10 in the univariate analysis. Missing data were imputed using multiple imputation. For binary outcomes the reference group was those without the risk factor

HES hydroxyethyl starch, *ICU* intensive care unit

[a] The odds ratio is per 1-unit increase in the transformed variable

[b] INR was transformed as the lowest value of either the natural logarithm of INR or 2.12. The odds ratio is per 1-unit increase in the transformed variable

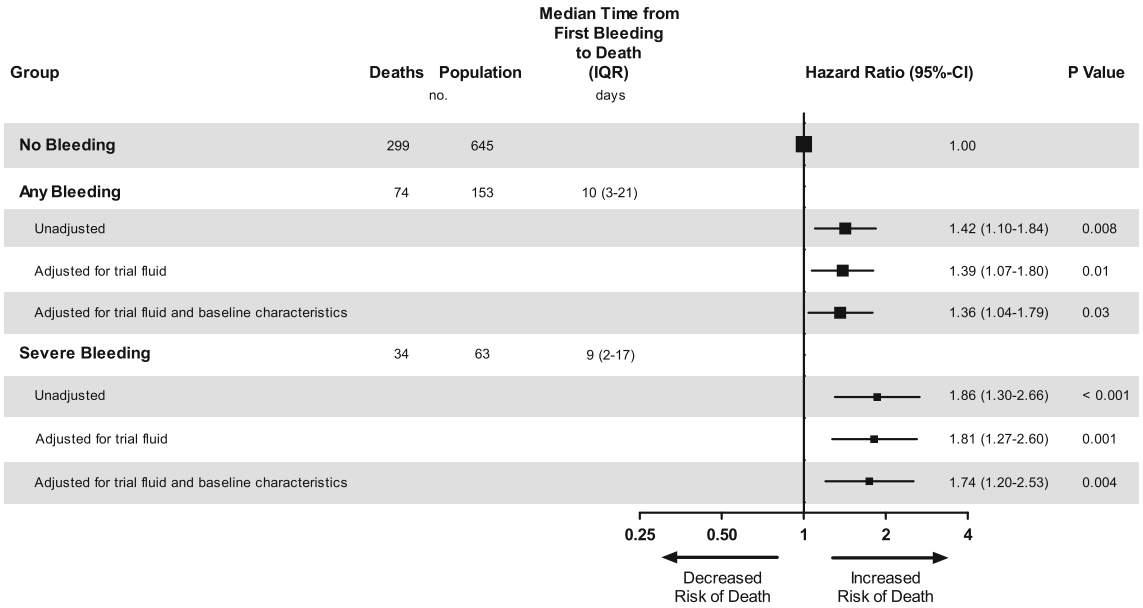

Fig. 2 Hazard ratio for death according to occurrence of bleeding or severe bleeding. Severe bleeding was defined as intracranial bleeding or bleeding with concomitant transfusion with three units of red blood cells

The clinical implications of HES-induced coagulopathy and bleeding are less clear, but we found a strong association between bleeding and death in the 6S trial. To determine whether HES-induced coagulopathy and bleeding contributed to the overall increased mortality observed with HES, we calculated hazard ratios for death according to trial fluid assignment with censoring of patients with bleeding. We then observed a lower hazard ratio compared to that of the analysis of all patients, which suggested that patients with bleeding contributed to the excess mortality in the HES group. When patients with severe bleeding were censored, the hazard ratio estimates for death with HES remained unchanged, but there were relatively few patients with severe bleeding making these results uncertain.

Our study design cannot prove causality between bleeding and mortality, but a causal relationship is possible because bleeding may lead not only to imminent death, but also ischemia and organ injury, which later may translate into multiorgan failure and death [25]. In addition, the ability to sustain life in the ICU may explain late death after early complications [26]. In line with this, another ICU trial found a similar timely relationship between hypoglycemic events and death in the ICU [27]. Moreover, bleeding patients received more red blood cell transfusions, which may have late adverse effects [28].

Alternatively, the association between bleeding and death is confounded by other disease processes that increase the risk of death. Previous findings that HES treatment results in increased inflammation and release of inflammatory mediators [29, 30], which is closely linked to coagulopathy in sepsis [31], support the hypothesis that bleeding is a marker of increased inflammation with HES and not a direct cause of death.

Another explanation is that the longer the patients stayed in the ICU, the higher the risk of death and of being observed with bleeding. In our trial, patients who stayed longer in the ICU did have higher risk of bleeding, but mortality did not increase correspondingly, so our data do not support this hypothesis.

Our results come with some limitations. Most analyses presented in this paper were planned post hoc and as such cannot be considered confirmative. Even though we tested multiple outcomes, we refrained from adjusting *P* values for this type of multiplicity as the likely correlation between outcomes made exact correction impossible. Thus, *P* values close to 0.05 should be interpreted with caution. Owing to early deaths the results were likely subject to some degree of survival bias. Other limitations were related to the pragmatic trial design where administration of trial fluid, blood products transfusion, and other interventions were at the discretion of the clinician [32–35]. We did not collect detailed clinical data to evaluate the decisions made by the clinicians, but hemoglobin triggers for transfusion were comparable between the groups. Neither did we collect detailed laboratory data on coagulation. On the other hand, the simplistic pragmatic design allowed us to evaluate the effect of HES in clinical practice on bleeding complications in a large number of ICU patients at high risk of bleeding. The blinded design and the large sample size reduced the probability of imbalance in co-interventions. The registration of bleeding may have been prone to some subjectivity, and bleeding must have been visible and of a

certain volume to be observed clinically. Thus, minor or occult bleeding may not have been detected. Furthermore, we were unable to detect bleeding events after ICU discharge.

In conclusion, in post hoc analyses of a pragmatic randomized clinical trial patients with severe sepsis resuscitated with HES 130/0.42 had increased risk of bleeding, which was associated with increased risk of death. HES-induced bleeding complications may negatively affect outcome in patients with severe sepsis.

Conflicts of interest A.P. was the sponsor-investigator of the Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial and J.W. and N.H. were members of the steering committee. The 6S trial was funded by the Danish Research Council, the Rigshospitalet Research Council, and the Scandinavian Society of Anaesthesiology and Intensive Care Medicine (the ACTA Foundation). B Braun Medical delivered trial fluid to all sites free of charge. Neither the funders nor B Braun Medical had an influence on the protocol, trial conduct, data analyses, or reporting of the 6S trial. A.P. is head of research in his department, which receives research funds from Fresenius Kabi, Germany, Cosmed, Italy, and BioPorto Diagnostics, Denmark. B Braun Medical has covered his travel expenses for presenting 6S trial data at the German Anaesthetic Congress 2012. A.P. has received honoraria from Ferring Pharmaceuticals and LFB. P.W. declares that he has no conflict of interests.

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