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Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock

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ABSTRACT

BACKGROUND

Blood transfusions are frequently given to patients with septic shock. However, the benefits and harms of different hemoglobin thresholds for transfusion have not been established.

METHODS

In this multicenter, parallel-group trial, we randomly assigned patients in the intensive care unit (ICU) who had septic shock and a hemoglobin concentration of 9 g per deciliter or less to receive 1 unit of leukoreduced red cells when the hemoglobin level was 7 g per deciliter or less (lower threshold) or when the level was 9 g per deciliter or less (higher threshold) during the ICU stay. The primary outcome measure was death by 90 days after randomization.

RESULTS

We analyzed data from 998 of 1005 patients (99.3%) who underwent randomization. The two intervention groups had similar baseline characteristics. In the ICU, the lower-threshold group received a median of 1 unit of blood (interquartile range, 0 to 3) and the higher-threshold group received a median of 4 units (interquartile range, 2 to 7). At 90 days after randomization, 216 of 502 patients (43.0%) assigned to the lower-threshold group, as compared with 223 of 496 (45.0%) assigned to the higher-threshold group, had died (relative risk, 0.94; 95% confidence interval, 0.78 to 1.09; P=0.44). The results were similar in analyses adjusted for risk factors at baseline and in analyses of the per-protocol populations. The numbers of patients who had ischemic events, who had severe adverse reactions, and who required life support were similar in the two intervention groups.

CONCLUSIONS

Among patients with septic shock, mortality at 90 days and rates of ischemic events and use of life support were similar among those assigned to blood transfusion at a higher hemoglobin threshold and those assigned to blood transfusion at a lower threshold; the latter group received fewer transfusions. (Funded by the Danish Strategic Research Council and others; TRISS ClinicalTrials.gov number, NCT01485315.)

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Blood transfusions are frequently given to patients with septic shock.[1-4] Some of these transfusions are given to patients who are bleeding, but many nonbleeding patients also undergo transfusion.[5]

The recommendations of the Surviving Sepsis Campaign regarding blood transfusion in patients with septic shock are complex and include a recommendation for transfusion to maintain a hematocrit of more than 30% in the presence of hypoperfusion in the first 6 hours.[6] After that, the transfusion threshold should be a hemoglobin level of less than 7 g per deciliter, aiming at levels between 7 g and 9 g per deciliter in patients who do not have myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic coronary artery disease.[6] However, there are limited data supporting these recommendations,[6] and many clinicians may not follow them.[4,7] New trial data have been published recently,[8] and the use of a high hemoglobin threshold for transfusion may be at least questioned as part of an early resuscitation protocol for patients with septic shock.

Blood transfusion has been associated with increased mortality in subgroups of critically ill patients, both in cohort studies and in randomized trials,[9-12] but there have also been cohort studies in which transfusion was associated with improved survival,[13] including among patients with sepsis.[14] In some studies, nonleukoreduced blood was used, which may have influenced the results. Given the lack of efficacy data, in addition to concerns about safety, we conducted the Transfusion Requirements in Septic Shock (TRISS) trial to evaluate the effects on mortality of leukoreduced blood transfusion at a lower versus a higher hemoglobin threshold among patients with septic shock who are in the intensive care unit (ICU).

METHODS

TRIAL DESIGN AND OVERSIGHT

After the approvals from ethics committees and data-protection agencies were obtained, patients in 32 general ICUs in Denmark, Sweden, Norway, and Finland underwent screening and randomization between December 3, 2011, and December 26, 2013. Written informed consent was obtained from all the patients or their legal surrogates before or after enrollment. In all cases, consent was obtained from the patient when possible. If consent was withdrawn or not granted, we asked the patient or surrogate for permission to continue registration of trial data and to use these data in the analyses. The protocol, including details regarding trial conduct and the statistical analysis plan, has been published previously[15] and is available with the full text of this article at NEJM.org. The management committee (see the Supplementary Appendix, available at NEJM.org) designed the trial and vouches for the adherence of the study to the protocol and for the accuracy of the data and the analyses. The members of the management committee wrote the drafts of the manuscript and made the decision to submit the manuscript for publication. The funders had no role in the design of the protocol, the trial conduct, or the analyses or reporting of the data.

This trial was a multicenter, stratified, parallel-group, clinical trial. Randomization was performed with the use of a centralized computer-generated assignment sequence, with stratification according to study site and the presence or absence of active hematologic cancer, because these characteristics may influence outcome.[16,17] Patients with septic shock were randomly assigned in a 1:1 ratio, with the use of permuted blocks of varying sizes of 6, 8, or 10, to blood transfusion at the higher hemoglobin threshold or the lower hemoglobin threshold. Treatment assignments were concealed from the investigators assessing mortality, the data and safety monitoring committee, and the trial statistician. The conduct of the trial and the safety of the participants were overseen by the data and safety monitoring committee, which performed an interim analysis after 500 patients had been followed for 90 days. The trial data were monitored by staff from the coordinating center.

TRIAL PATIENTS

We screened patients 18 years of age or older who were in the ICU, fulfilled the criteria for septic shock,[18] and had a blood concentration of hemoglobin of 9 g per deciliter or less as measured by means of valid point-of-care testing (see the Supplementary Appendix). The reasons for the exclusion of some patients are shown in Figure 1 and listed in the Supplementary Appendix.

INTERVENTION

Enrolled patients were given single units of cross-matched, prestorage leukoreduced red cells suspended in a saline–adenine–glucose–mannitol

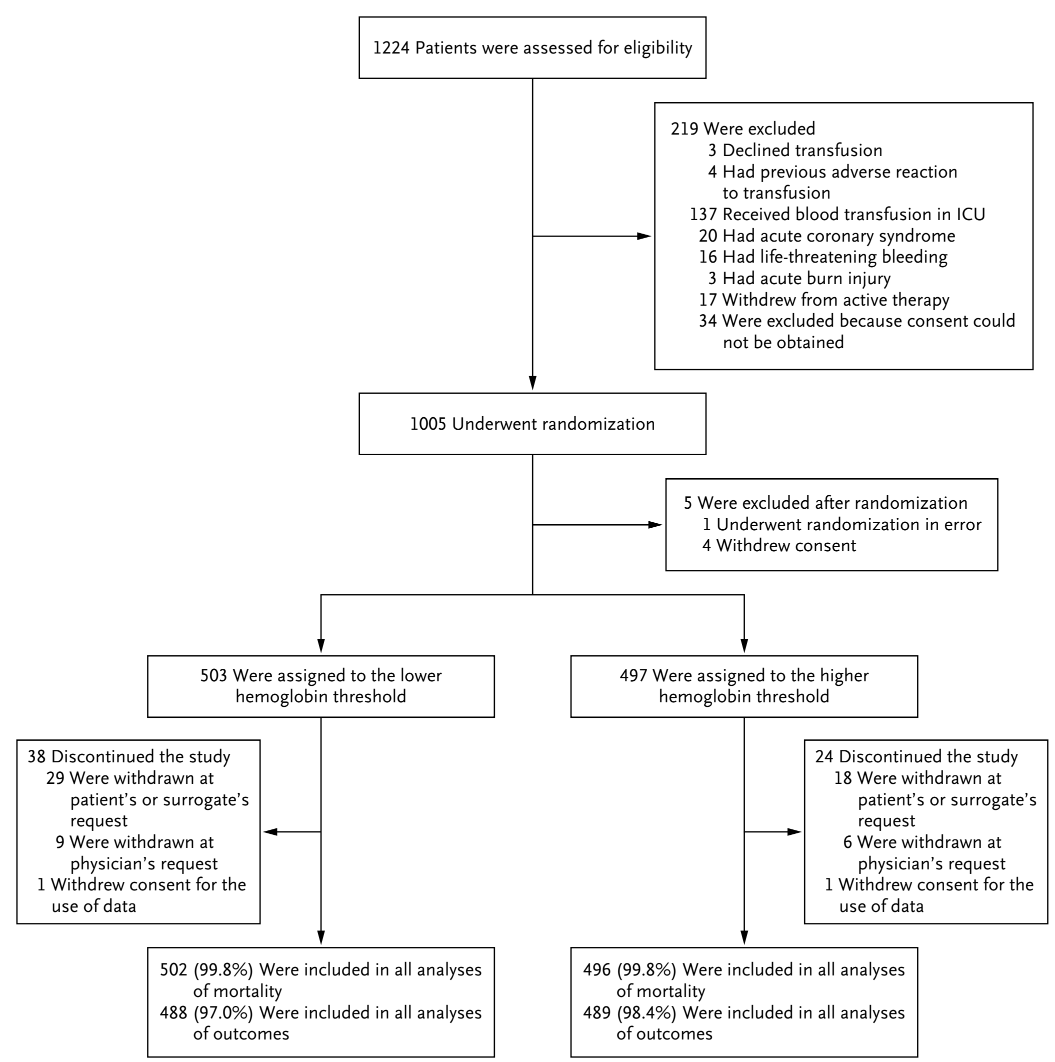

Figure 1. Assessment, Randomization, and Follow-up.

Patients were excluded if they had undergone randomization in this study previously, if there were medical reasons, if they had received a blood transfusion during the current intensive care unit (ICU) admission, if there was a documented wish not to receive a transfusion, or if informed consent could not be obtained. A total of 15 patients met two exclusion criteria. One patient was excluded immediately after randomization when it was determined that an inclusion criterion had not been met, and 4 were excluded because consent was withdrawn during the trial. Thereafter, 5 additional patients underwent randomization in order for the study to obtain the full sample. All the patients who withdrew from the trial at their own request or at a surrogate's request allowed the use of their data, but 14 patients or surrogates in the lower-threshold group (hemoglobin level, ≤7 g per deciliter) and 7 in the higher-threshold group (hemoglobin level, ≤9 g per deciliter) did not want further data registered except for mortality data, which were obtained from national registries. The process data (hemoglobin assessments and numbers of transfusions and temporary protocol suspensions and protocol violations) and some of the secondary-outcome data for these patients are missing.

solution when the blood concentration of hemoglobin had decreased to the assigned transfusion threshold (≤7 g per deciliter [lower threshold] or ≤9 g per deciliter [higher threshold]). These levels of hemoglobin have frequently been used as thresholds for transfusion in patients with septic shock.[15] Hemoglobin concentrations were reassessed within 3 hours after termination of the transfusion or before the initiation of another transfusion. The intervention period was the entire ICU stay, to a maximum of 90 days after randomization.

In the event that life-threatening bleeding or ischemia developed while a patient was in the ICU or a patient required the use of extracorporeal membrane oxygenation, the patient could receive a transfusion at a hemoglobin threshold decided by the attending doctor. The attending doctor decided when the patient again was to receive a transfusion at the assigned hemoglobin threshold. After the unmasking of trial data showing harm from hydroxyethyl starch,[3] we recommended against the use of all starch products in trial patients. All other interventions were at the discretion of the clinicians, including transfusion during surgery and after ICU discharge.

OUTCOME MEASURES

The primary outcome measure was death by 90 days after randomization. Secondary outcome measures were the use of life support (defined as the use of vasopressor or inotropic therapy, mechanical ventilation, or renal-replacement therapy) at days 5, 14, and 28 after randomization[19]; the number of patients with serious adverse reactions while in the ICU (allergic reaction, hemolysis, transfusion-associated acute lung injury, or transfusion-associated circulatory overload) (see the Supplementary Appendix); the number of patients with ischemic events while in the ICU, which included cerebral ischemia (identified from the results of imaging), acute myocardial ischemia (defined by symptoms, electrocardiographic signs, or elevated biomarker levels resulting in an intervention), intestinal ischemia (as observed during endoscopic examination or surgery), or limb ischemia (defined as clinical signs resulting in an intervention) (for full definitions, see the Supplementary Appendix); the percentage of days alive without vasopressor or inotropic therapy, mechanical ventilation, or renal-replacement therapy in the 90 days after randomization; and the percentage of days alive and out of the hospital in the 90 days after randomization. Data for the outcome measures were obtained by TRISS trial investigators or their delegates from patient files and national and regional registries for the entire 90-day follow-up period.

STATISTICAL ANALYSIS

We calculated that we would need to enroll 1000 patients for the trial to have 80% power to show mortality at 90 days that was 9 percentage points lower in the lower-threshold group than in the higher-threshold group, at a two-sided alpha level of 5%, assuming a mortality in the higher-threshold group of 45% (estimated from two previous cohorts).[20,21] The estimated difference of 9 percentage points was derived from the 20% reduction in relative risk observed with a restrictive versus liberal transfusion strategy in the subgroup of patients with severe infection in the Transfusion Requirements in Critical Care (TRICC) trial.[9] During our trial, 5 patients were excluded after randomization (4 patients did not allow the use of their data, and 1 did not have sepsis, which was realized immediately after randomization). A total of 5 additional patients underwent randomization in order for the study to obtain the full sample (Fig. 1).

An author who was the statistician for the study and who was unaware of the study-group assignments performed all the analyses according to International Conference on Harmonisation Good Clinical Practice guidelines[22] and the statistical analysis plan.[15] We performed the primary analyses in the intention-to-treat population, which included all the patients who underwent randomization, except for those whose data were deleted from the database during the trial (i.e., the 5 patients, noted above, who were excluded after randomization) and after the trial (2 patients who withdrew consent for the use of their data) (Fig. 1). In the per-protocol populations, we excluded patients who had one or more bleeding or ischemic episodes or one or more major protocol violations (see the Supplementary Appendix).[22]

In the primary analyses (including the analysis of the primary outcome measure), we compared data between the two groups by means of logistic-regression analysis for binary outcome measures with adjustment for the stratification variables (study site and presence or absence of active hematologic cancer),[23] and we converted odds ratios to relative risks.[24] We also performed unadjusted chi-square testing for binary outcome measures and Wilcoxon signed-rank testing for rate and ordinal data. We compared the primary outcome in the per-protocol populations and in prespecified subgroups defined according to the presence or absence of chronic cardiovascular disease (i.e., any history of myocardial infarction, any history of stable or unstable angina pectoris, previous treatment with nitrates, percutaneous coronary intervention, coronary-artery bypass grafting or noncoronary vascular interventions, any history of chronic heart failure [defined as New York Heart Association class III or IV], or any history of cerebral infarction or transitory cerebral ischemia), an age of 70 years or younger versus an age older than 70 years, and a Simplified Acute Physiology Score (SAPS) II above 53 versus 53 or lower at baseline (with the score calculated from 17 variables and ranging from 0 to 163, with higher scores indicating higher severity of disease) and used multiple logistic-regression analyses in the intention-to-treat population to adjust for differences in prespecified risk factors at baseline. Details regarding the handling of missing data are provided in the Supplementary Appendix. We performed all analyses using SAS software, version 9.3 (SAS Software), and SPSS software, version 17.0 (SPSS). A two-sided P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

TRIAL POPULATION

We obtained 90-day vital status for 998 patients (99.3%), including 502 in the lower-threshold group and 496 in the higher-threshold group (Fig. 1). The characteristics of the patients at baseline were similar in the two groups (Table 1, and Table S1 in the Supplementary Appendix). A total of 29 of 488 patients (5.9%) in the lower-threshold group and 11 of 489 (2.2%) in the higher-threshold group had the protocol temporarily suspended (P=0.004) (Table S2 in the Supplementary Appendix).

HEMOGLOBIN CONCENTRATIONS, BLOOD PRODUCTS, AND CIRCULATORY VARIABLES

The median value of the lowest concentration of hemoglobin in the 24 hours before randomization was 8.4 g per deciliter in both intervention groups. After randomization, the daily lowest concentrations of hemoglobin differed between the two groups (P<0.001) (Fig. 2). Additional details regarding hemoglobin assessments are provided in Table S3 in the Supplementary Appendix.

During the trial period, a total of 1545 blood transfusions were given in the lower-threshold group and 3088 transfusions in the higher-threshold group (P<0.001). The median cumulative number of blood transfusions after randomization was 1 unit (interquartile range, 0 to 3) in the lower-threshold group and 4 (interquartile range, 2 to 7) in the higher-threshold group (P<0.001). A total of 176 patients (36.1%) in the lower-threshold group did not undergo transfusion in the ICU, as compared with 6 (1.2%) in the higher-threshold group (P<0.001). Details regarding blood products, bleeding, cointerventions, fluid volumes and balances, and circulatory assessments are provided in Tables S4 through S9 in the Supplementary Appendix. The numbers of protocol violations differed significantly between the two groups (Table S10 in the Supplementary Appendix).

OUTCOMES

At 90 days after randomization, 216 patients (43.0%) in the lower-threshold group and 223 (45.0%) in the higher-threshold group had died (relative risk, 0.94; 95% confidence interval, 0.78 to 1.09; P=0.44) (Table 2 and Fig. 3, and Table S11 in the Supplementary Appendix). We obtained similar results in the analyses that were adjusted for prespecified baseline risk factors and in the per-protocol analyses (Table S12 in the Supplementary Appendix). The prespecified subgroup analyses showed no significant heterogeneity in the effect of the transfusion threshold on mortality at 90 days between patients with and those without chronic cardiovascular disease, patients 70 years of age or younger and those older than 70 years of age, and patients with a SAPS II of 53 or less and those with a SAPS II of more than 53 at baseline (Fig. 3).

A total of 7.2% of the patients in the lower-threshold group, as compared with 8.0% in the higher-threshold group, had one or more ischemic events in the ICU (Table 2, and Tables S13 and S14 in the Supplementary Appendix, which include the numbers of patients with myocardial ischemia and ischemia of other anatomical sites). One patient had a serious adverse reaction to transfusion (Table 2, and Table S13 in the Supplementary Appendix). The use of life support at days 5, 14, and 28 was similar in the two intervention groups (Table 2, and Tables S11 and S13 in the Supplementary Appendix), as were the percentages of days alive without vasopressor or inotropic therapy, without mechanical ventilation, and without renal-replacement therapy and the percentage of days alive and out of the hospital (Table 2).

DISCUSSION

In this international, multicenter, partially blinded, randomized trial involving patients with septic shock who were in the ICU, we observed no significant differences in mortality at 90 days, in the numbers of patients with ischemic events or with severe adverse reactions, in the use of life support, or in the numbers of days alive and out of the hospital between the group of patients who underwent transfusion at a lower hemoglobin threshold and the group of those who underwent transfusion at a higher hemoglobin threshold. Similar results were observed in subgroups of patients with chronic cardiovascular disease, with older age, or with greater disease severity. The patients in the lower-threshold group received 50% fewer units of blood than those in the higher-threshold group, and 36% of the patients in the lower-threshold group did not undergo transfusion in the ICU, as compared with 1% of the patients in the higher-threshold group.

Our results are consistent with those obtained in the TRICC trial, which assessed a lower versus higher hemoglobin threshold for blood transfusion in a broad population of adult patients in the ICU.[9] In that trial, there were no significant differences in mortality at 30 days in the full trial population (the primary outcome) or among patients 55 years of age or older or

Table 1. Characteristics of the Trial Patients at Baseline.*

Characteristic	Lower Hemoglobin Threshold (N=502)	Higher Hemoglobin Threshold (N=496)
Age — yr		
Median	67	67
Interquartile range	57–73	58–75
Male sex — no. (%)	272 (54.2)	259 (52.2)
Chronic cardiovascular disease — no. (%)†	75 (14.9)	66 (13.3)
Chronic lung disease — no. (%)‡	111 (22.1)	102 (20.6)
Hematologic cancer — no. (%)	39 (7.8)	36 (7.3)
Admission to a university hospital — no. (%)	323 (64.3)	324 (65.3)
Surgery during index hospitalization — no. (%)		
Emergency	191 (38.0)	217 (43.8)
Elective	59 (11.8)	53 (10.7)
Source of ICU admittance — no. (%)		
Emergency department	90 (17.9)	79 (15.9)
General ward	268 (53.4)	257 (51.8)
Operating or recovery room	113 (22.5)	121 (24.4)
Other ICU	31 (6.2)	39 (7.9)
Source of sepsis — no. (%)§		
Lungs	267 (53.2)	259 (52.2)
Abdomen	206 (41.0)	198 (39.9)
Urinary tract	58 (11.6)	61 (12.3)
Soft tissue	59 (11.8)	59 (11.9)
Other	50 (10.0)	47 (9.5)
Positive culture from blood or sterile site	188 (37.5)	160 (32.3)
Interval from ICU admission to randomization — hr		
Median	23	20
Interquartile range	7–50	7–43
SAPS II¶		
Median	51	52
Interquartile range	42–62	44–64

Table 1. (Continued.)

Characteristic	Lower Hemoglobin Threshold (N=502)	Higher Hemoglobin Threshold (N=496)
SOFA score‖		
Median	10	10
Interquartile range	8–12	8–12
Renal-replacement therapy — no. (%)**	68 (13.5)	53 (10.7)
Mechanical ventilation — no. (%)††	345 (68.7)	350 (70.6)

* None of the differences between the two groups were significant (P≥0.05). Additional details regarding baseline characteristics are provided in Table S1 in the Supplementary Appendix. The lower hemoglobin threshold was defined as a hemoglobin level of 7 g per deciliter or less, and the higher hemoglobin threshold as a hemoglobin level of 9 g per deciliter or less. ICU denotes intensive care unit.

† Patients were considered to have chronic cardiovascular disease if they had any history of myocardial infarction, stable or unstable angina pectoris, chronic heart failure (defined as New York Heart Association class III or IV), cerebral infarction or transitory cerebral ischemia, previous treatment with nitrates, percutaneous coronary intervention, coronary-artery bypass grafting, or noncoronary vascular interventions.

‡ Patients were considered to have chronic lung disease if they had any history of chronic obstructive pulmonary disease, asthma or other chronic lung disease, or any treatment with a drug indicated for chronic lung disease.

§ Some patients had more than one source of infection. Other sources of sepsis included a vascular catheter, meningitis, or endocarditis or were unclear.

¶ The Simplified Acute Physiology Score (SAPS) II[25] was assessed in the 24 hours before randomization. The SAPS II is calculated from 17 variables and ranges from 0 to 163, with higher scores indicating higher severity of disease. One or two of the 17 variables were missing for 77 patients in the higher-threshold group and for 99 in the lower-threshold group, so their values were not included here.

‖ The Sepsis-Related Organ Failure Assessment (SOFA)[26] score was assessed in the 24 hours before randomization. The SOFA grades organ failure, with subscores ranging from 0 to 4 for each of six organ systems (cerebral, circulation, pulmonary, hepatic, renal, and coagulation). The aggregated score ranges from 0 to 24, with higher scores indicating more severe organ failure. One variable was missing for 51 patients in the higher-threshold group and for 64 in the lower-threshold group, so their values were not included here.

** Renal-replacement therapy was defined as therapy for acute or chronic kidney failure at randomization.

†† Mechanical ventilation was defined as invasive or noninvasive ventilation in the 24 hours before randomization.

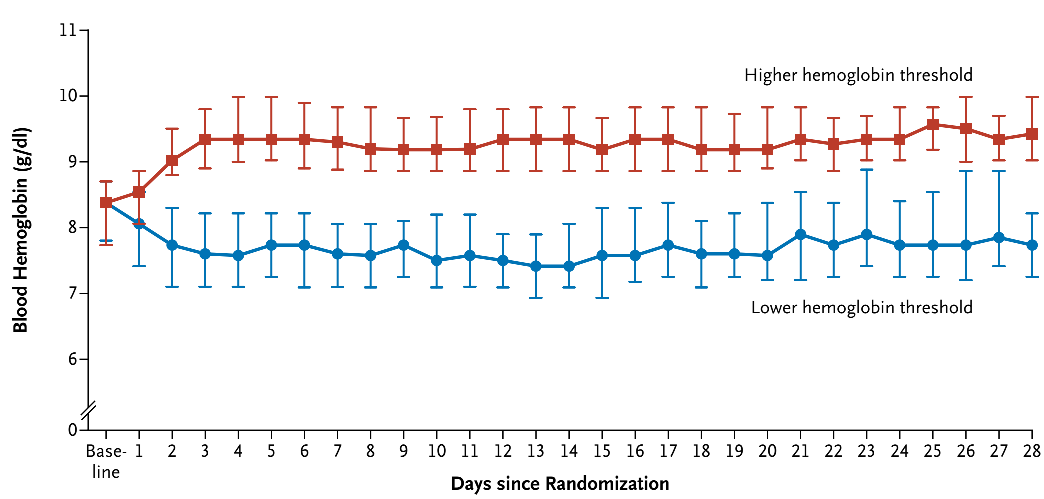

Figure 2. Blood Hemoglobin Levels in Patients in the ICU at Baseline and after Randomization.

The graphs show the median daily lowest levels of blood hemoglobin in the lower-threshold group and the higher-threshold group. Baseline values were the lowest blood hemoglobin level measured in the 24 hours before randomization. Day 1 was defined as the time of randomization to the end of that day and lasted a median of 15 hours in the lower-threshold group and 14 hours in the higher-threshold group. The I bars indicate the 25th and 75th percentiles.

Table 2. Primary and Secondary Outcome Measures.*

Outcome	Lower Hemoglobin Threshold	Higher Hemoglobin Threshold	Relative Risk (95% CI)	P Value
Primary outcome: death by day 90 — no./total no. (%)	216/502 (43.0)	223/496 (45.0)	0.94 (0.78–1.09)	0.44†
Secondary outcomes‡				
Use of life support — no./total no. (%)§				
At day 5	278/432 (64.4)	267/429 (62.2)	1.04 (0.93–1.14)	0.47†
At day 14	140/380 (36.8)	135/367 (36.8)	0.99 (0.81–1.19)	0.95†
At day 28	53/330 (16.1)	64/322 (19.9)	0.77 (0.54–1.09)	0.14†
Ischemic event in the ICU — no./total no. (%)¶	35/488 (7.2)	39/489 (8.0)	0.90 (0.58–1.39)	0.64‖
Severe adverse reaction — no./total no. (%)**	0/488	1/489 (0.2)	—	1.00
Alive without vasopressor or inotropic therapy — mean % of days††	73	75	—	0.93
Alive without mechanical ventilation — mean % of days††	65	67	—	0.49
Alive without renal-replacement therapy — mean % of days††	85	83	—	0.54
Alive and out of the hospital — mean % of days††	30	31	—	0.89

* CI denotes confidence interval.

† Logistic-regression analyses were adjusted for the stratification variables (study site and presence or absence of hematologic cancer). The results of the unadjusted outcome analyses are provided in Table S11 in the Supplementary Appendix.

‡ A total of 21 patients — 14 in the lower-threshold group and 7 in the higher-threshold group — did not wish to be included in the follow-up, so data regarding secondary outcome measures are missing for these patients.

§ Use of life support was defined as infusion of vasopressor or inotropic agents or the use of invasive or noninvasive mechanical ventilation or renal-replacement therapy on those days. The total number of patients decreased because patients died. See Table S13 in the Supplementary Appendix.

¶ An ischemic event in the ICU was defined as one or more events of acute myocardial, cerebral, intestinal, or limb ischemia. See Table S13 in the Supplementary Appendix.

‖ Logistic-regression analyses were adjusted for the presence of hematologic cancer. Adjustment according to study site was not possible, because there were zero events at four study sites.

** A severe adverse reaction was defined as allergic reaction, hemolysis, transfusion-associated acute lung injury, or transfusion-associated circulatory overload. See Table S13 in the Supplementary Appendix.

†† The mean percentage of days was calculated as the number of days without vasopressor, ventilator, or renal-replacement therapy, divided by the number of days alive during the 90-day follow-up period, or as the number of days out of the hospital, divided by the number of days alive during the 90-day follow-up period.

those with more severe disease; these two subgroups may best resemble our patients. Our results are also in line with those of a large trial involving high-risk patients after hip surgery, the Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) trial,[27] and the Cochrane meta-analysis of trials of transfusion thresholds, both of which support restrictive transfusion to reduce the use of blood in patients with preexisting cardiovascular disease.[28] An important exception is patients with acute myocardial infarction, who were excluded both from our trial and from the FOCUS trial.[27] Research is needed to assess the safety of lower hemoglobin thresholds for transfusion in these patients.[12]

The effect of transfusion thresholds on rates of myocardial infarction may have differed among the three trials. In the TRICC trial, significantly increased rates of myocardial infarction were observed with a higher transfusion threshold,[9] whereas the opposite was observed in the FOCUS trial and in our trial, although the numerical differences were not significant in either of these two trials.[27] In our trial, myocardial infarction was not a prespecified outcome measure (the data are provided in the Supplementary Appendix); we did not specify surveillance testing for myocardial ischemia in the protocol and may have missed some events. This may also have resulted in detection bias because the clinicians and investigators were not unaware of the intervention assignments.

We observed no harm with an excess transfusion of a median of 3 units of blood, a finding that is contrary to most of the observational data

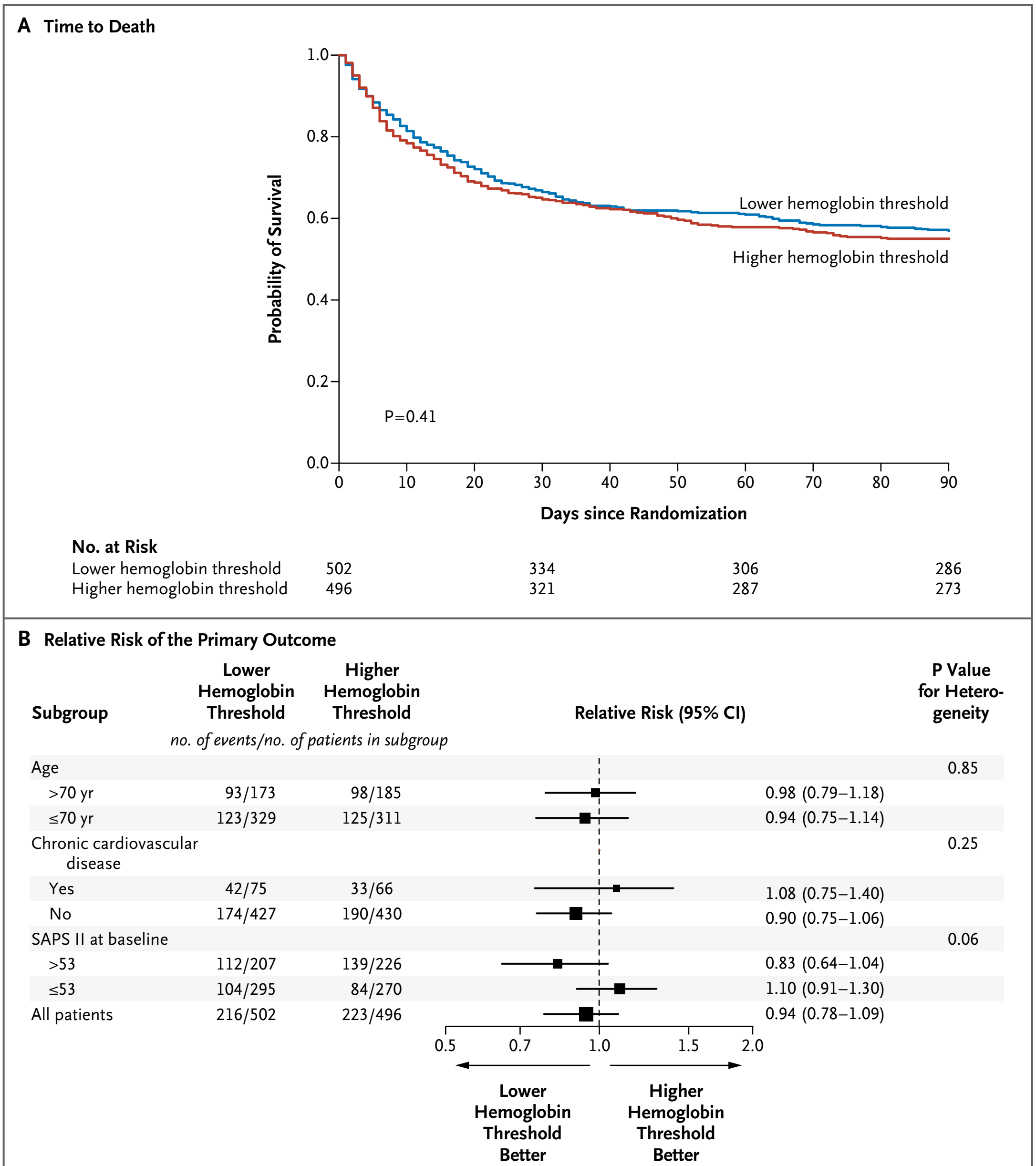

Figure 3. Time to Death and Relative Risk of Death at 90 Days.

Panel A shows the survival curves, with data censored at 90 days, in the two intervention groups in the intention-to-treat population. Kaplan–Meier analysis showed that the survival time did not differ significantly between the two groups (P=0.41 by Cox regression analysis, with adjustment for the stratification variables). Panel B shows the relative risks (black boxes) with 95% confidence intervals (horizontal lines) for the primary outcome measure of death by day 90 in the lower-threshold group, as compared with the higher-threshold group, among all the patients and in the three prespecified subgroups, as assessed by means of logistic-regression analysis, with adjustment for the stratification variables. The size of each black box is proportional to the size of the corresponding subgroup. Chronic cardiovascular disease was defined as any history of myocardial infarction, any history of stable or unstable angina pectoris, previous treatment with nitrates, percutaneous coronary intervention, coronary-artery bypass grafting or noncoronary vascular interventions, any history of chronic heart failure (defined as New York Heart Association class III or IV), or any history of cerebral infarction or transitory cerebral ischemia. The Simplified Acute Physiology Score (SAPS) II[25] is calculated from 17 baseline variables; scores range from 0 to 163, with higher scores indicating higher severity of disease. A total of 1 or 2 of the 17 variables were missing for 77 patients in the higher-threshold group and for 99 in the lower-threshold group. In this analysis, these missing variables were considered to be within the normal range, thereby not contributing to the composite SAPS II of these patients.

regarding transfusion in critically ill patients.[10] Whether this was due to the use of leukoreduced blood cannot be assessed, but results similar to ours were observed in the FOCUS trial, in which the majority of patients also received leukoreduced blood.[27] The safety of leukoreduced blood was challenged by the results of a trial involving patients with upper gastrointestinal bleeding, which showed increased mortality with liberal transfusion of this product.[11] Ongoing bleeding may have contributed to the increased mortality observed with liberal transfusion in that trial.[11] Thus the effects of leukoreduction on outcome are unclear, as they were a decade ago, as indicated in a 2004 meta-analysis of trial data on leukoreduced versus nonleukoreduced blood.[29]

The strengths of our trial include a low risk of bias, because group assignment at randomization was concealed, and the blinding of the assessors of mortality and the statistician to the assigned intervention. It is reasonable to assume that our results are generalizable, because patients were recruited both in university hospitals and in nonuniversity hospitals, and the majority of patients who underwent screening were included. The trial protocol was pragmatic, so routine practice was maintained except for the hemoglobin thresholds for transfusion. In addition, the characteristics of the patients and the outcome rates were similar to those observed in some recent trials involving patients with septic shock in the ICU.[3,19,30,31]

Our trial has limitations. First, the investigators, clinicians, and patients were aware of the study-group assignments, and we did not assess all the cointerventions. Because the trial was multicenter and large and used stratified randomization, it is unlikely that imbalance in concomitant interventions affected the results. Second, the confidence interval was relatively wide for the point estimate for mortality, so we cannot exclude a 9% relative increase or a 22% relative decrease in mortality at 90 days in the lower-threshold group versus the higher-threshold group. Third, we had limited power to detect differences in some other outcome measures (in particular, the ischemic events) and in some of the subgroup analyses (in particular, the subgroup defined according to the presence or absence of chronic cardiovascular disease).

We recorded only one serious adverse reaction to blood transfusion, but serious adverse reactions are rare events in general, and their frequencies are unknown among patients with septic shock in the ICU. We included some patients who had received a blood transfusion before ICU admission, and some patients had protocol suspensions and violations, which tended to reduce the difference between the two intervention groups. However, we found clear differences between the two groups in the hemoglobin levels and the numbers of transfusions, and the per-protocol analyses, which excluded patients who had protocol suspensions and violations, supported the primary analysis. Protocol suspensions and violations have been difficult to prevent in transfusion trials,[32,33] and when reported they appear to have occurred at frequencies similar to those observed in our trial.

In conclusion, patients with septic shock who underwent transfusion at a hemoglobin threshold of 7 g per deciliter, as compared with those who underwent transfusion at a hemoglobin threshold of 9 g per deciliter, received fewer transfusions and had similar mortality at 90 days, use of life support, and number of days alive and out of the hospital; the numbers of patients with ischemic events and severe adverse reactions to blood in the ICU were also similar in the two intervention groups.

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REFERENCES

1. Zarychanski R, Doucette S, Fergusson D, et al. Early intravenous unfractionated heparin and mortality in septic shock. Crit Care Med 2008;36:2973-9.

2. Labelle A, Juang P, Reichley R, et al. The determinants of hospital mortality among patients with septic shock receiving appropriate initial antibiotic treatment. Crit Care Med 2012;40:2016-21.

3. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.4 versus Ringer's acetate in severe sepsis. N Engl J Med 2012;367:124-34. [Erratum, N Engl J Med 2012;367:481.]

4. Rosland RG, Hagen MU, Haase N, et al. Red blood cell transfusion in septic shock — clinical characteristics and outcome of unselected patients in a prospec-

tive, multicentre cohort. Scand J Trauma Resusc Emerg Med 2014;22:14.
5. Haase N, Wetterslev J, Winkel P, Perner A. Bleeding and risk of death with hydroxyethyl starch in severe sepsis: post hoc analyses of a randomized clinical trial. Intensive Care Med 2013;39:2126-34.
6. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013;39:165-228.
7. Reade MC, Huang DT, Bell D, et al. Variability in management of early severe sepsis. Emerg Med J 2010;27:110-5.
8. The ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014;370:1683-93.
9. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 1999; 340:409-17. [Erratum, N Engl J Med 1999; 340:1056.]
10. Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. Crit Care Med 2008;36:2667-74. [Erratum, Crit Care Med 2008;36:3134.]
11. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013;368:11-21. [Erratum, N Engl J Med 2013;368:2341.]
12. Chatterjee S, Wetterslev J, Sharma A, Lichstein E, Mukherjee D. Association of blood transfusion with increased mortality in myocardial infarction: a meta-analysis and diversity-adjusted study sequential analysis. JAMA Intern Med 2013;173:132-9.
13. Vincent JL, Sakr Y, Sprung C, Harboe S, Damas P, Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators. Are blood transfusions associated with greater mortality rates? Results of the Sepsis Occurrence in Acutely Ill Patients study. Anesthesiology 2008;108:31-9.
14. Park DW, Chun BC, Kwon SS, et al. Red blood cell transfusions are associated with lower mortality in patients with severe sepsis and septic shock: a propensity-matched analysis. Crit Care Med 2012;40:3140-5.
15. Holst LB, Haase N, Wetterslev J, et al. Transfusion requirements in septic shock (TRISS) trial — comparing the effects and safety of liberal versus restrictive red blood cell transfusion in septic shock — patients in the ICU: protocol for a randomised controlled trial. Trials 2013;14:150.
16. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med 2006;34:344-53.
17. Reinikainen M, Karlsson S, Varpula T, et al. Are small hospitals with small intensive care units able to treat patients with severe sepsis? Intensive Care Med 2010;36:673-9.
18. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864-74.
19. Heyland DK, Muscedere J, Drover J, Jiang X, Day AG, Canadian Critical Care Trials Group. Persistent organ dysfunction plus death: a novel, composite outcome measure for critical care trials. Crit Care 2011;15:R98.
20. Carlsen S, Perner A, East Danish Septic Shock Cohort Investigators. Initial fluid resuscitation of patients with septic shock in the intensive care unit. Acta Anaesthesiol Scand 2011;55:394-400.
21. Smith SH, Perner A. Higher vs. lower fluid volume for septic shock: clinical characteristics and outcome in unselected patients in a prospective, multicenter cohort. Crit Care 2012;16:R76.
22. ICH Steering Committee. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH Harmonised Tripartite Guideline for Statistical Principles for Clinical Trials. 3rd ed. Richmond, UK: Brookwood Medical, 1998.
23. Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. Stat Med 2012;31:328-40.
24. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998;280:1690-1.
25. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 1993; 270:2957-63. [Erratum, JAMA 1994;271:1321.]
26. Vincent JL, Moreno R, Takala J, et al. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996; 22:707-10.
27. Carson JL, Terrin ML, Noveck H, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med 2011;365:2453-62.
28. Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev 2012;4:CD002042.
29. Fergusson D, Khanna MP, Tinmouth A, Hébert PC. Transfusion of leukoreduced red blood cells may decrease postoperative infections: two meta-analyses of randomized controlled trials. Can J Anaesth 2004;51:417-24.
30. Asfar P, Meziani F, Hamel J-F, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med 2014;370:1583-93.
31. Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med 2014;370:1412-21.
32. Walsh TS, Boyd JA, Watson D, et al. Restrictive versus liberal transfusion strategies for older mechanically ventilated critically ill patients: a randomized pilot trial. Crit Care Med 2013;41:2354-63.
33. Rohde JM, Dimcheff DE, Blumberg N, et al. Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis. JAMA 2014;311:1317-26.