EDITORIAL

Transfusion Threshold of 7 g per Deciliter — The New Normal

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Holst and colleagues[1] now provide definitive evidence in the *Journal* that a restrictive approach to blood transfusion not only reduced blood use by half but also did not cause harm to 998 critically ill patients with septic shock. It has been 15 years since the publication of the results of the Transfusion Requirements in Critical Care (TRICC) trial in the *Journal*.[2] In that Canadian Critical Care Trial Group study, 838 critically ill patients were randomly assigned to receive blood transfusions on the basis of a threshold of 7 g per deciliter or 10 g per deciliter while also agreeing to undergo transfusion 1 unit at a time. Much like the results of the Transfusion Requirements in Septic Shock (TRISS) trial by Holst et al., approximately 50% less blood was administered in the restrictive-strategy group than in the liberal-strategy group. In contrast to this latest trial, overall trends and all the secondary analyses suggested that a liberal transfusion strategy may have resulted in increased mortality, increased rates of pulmonary edema, and increased rates of organ failure.

In our 2012 Cochrane review of transfusion thresholds, we identified 19 randomized clinical trials involving 6264 patients.[3] A restrictive transfusion strategy was associated with more than one third fewer transfusions, without any apparent harm among a variety of patient populations including patients with perioperative care, those with cardiac surgery, and those with gastrointestinal hemorrhage. We did not identify any additional studies involving critically ill adults. However, a trial of transfusion in pediatric critical care patients included in the review also showed a dramatic decrease in blood transfusions with the adoption of a restrictive transfusion threshold, without increased rates of organ failure.[4]

Since the last Cochrane update, the results of four new trials involving critical care patients have been published,[5-7] including the results of a trial by Peake et al. now published in the *Journal*.[8] None have shown improved survival with a liberal transfusion strategy. Two trials evaluated early goal-directed therapy versus usual care in patients with septic shock. The Protocolized Care for Early Septic Shock (ProCESS) trial[7] included 1341 patients with severe sepsis and septic shock, and the Australasian Resuscitation in Sepsis Evaluation (ARISE) trial compared 1600 patients with septic shock who received either usual care or early goal-directed therapy.[8] The early goal-directed therapy groups in these two trials included several interventions guided by an algorithm that was based on continuous central venous oxygen saturations first promoted by Rivers et al.[9] The clinical protocols of the two trials included a transfusion threshold of a hematocrit of 30% when central venous oxygen saturations remained below 70%. There were no differences in overall mortality at 90 days despite the fact that twice the number of patients in the goal-directed groups as in the usual-care groups were administered blood.

Even in patients with major gastrointestinal hemorrhage, Villanueva and colleagues found an absolute decrease in mortality of 4 percentage points when patients were transfused with the use of a restrictive transfusion strategy.[10] On the basis of the results of this study, a liberal transfusion strategy would result in a number needed to be harmed of 25.

We believe it has become abundantly clear that a transfusion threshold of 7 g per deciliter should become the new normal, recommended in all critically ill patients, including those with severe sepsis and septic shock. To speed up adoption, we should ensure that clinical practice

guidelines are rapidly updated with new information. Indeed, most transfusion guidelines have already been updated,[11-14] but this is not so for sepsis guidelines.

The Surviving Sepsis Campaign has been effective in promoting best practices. Among its many recommendations, the guideline advised on transfusion strategies. In the 2012 edition, the authors recommended adopting a transfusion threshold of 7 g per deciliter on the basis of the results of the TRICC trial and reports in cardiac surgery (evidence base for the recommendation,[15] grade 1B [moderate recommendation and evidence]).[13] However, the recommendation begins with the statement, "Once hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic coronary artery disease, we recommend . . . ." This clause effectively allows clinicians to exclude most critically ill patients in the midst of any form of resuscitation from adopting a more restrictive approach to transfusion, in large part using the results of the trial by Rivers et al. as justification. With all the exceptions and citing the vague notion of hypoperfusion, the current guidance would suggest that the default option is to administer blood at a high transfusion threshold — perhaps because a liberal transfusion threshold is still considered safer, either by default or long-standing tradition.

It is time to adopt a transfusion threshold of 7 g per deciliter as the standard of care. To help promote this perspective, we suggest a substantial shift in the Surviving Sepsis Campaign guidelines. This may be easily accomplished with the use of the same recommendation without any of the caveats. Given the many new studies, we would also endorse upgrading the evidence base for the recommendation to 1A (strong recommendation and evidence).

Evidence stills remains weak in patients with an acute coronary syndrome. It may yet be proved that this distinct group of patients benefits from higher hemoglobin concentrations (9 or 10 g per deciliter).[14] Oxygen delivery to the myocardium is flow-dependent since the heart extracts a high percentage of oxygen, and myocardial ischemia may be precipitated by low hemoglobin concentrations.

The TRISS trial and two negative trials of early goal-directed therapy were unable to detect any benefit from the use of a liberal transfusion threshold. Although certainty would be nice, less is proving to be the safer option.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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ORIGINAL ARTICLE

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

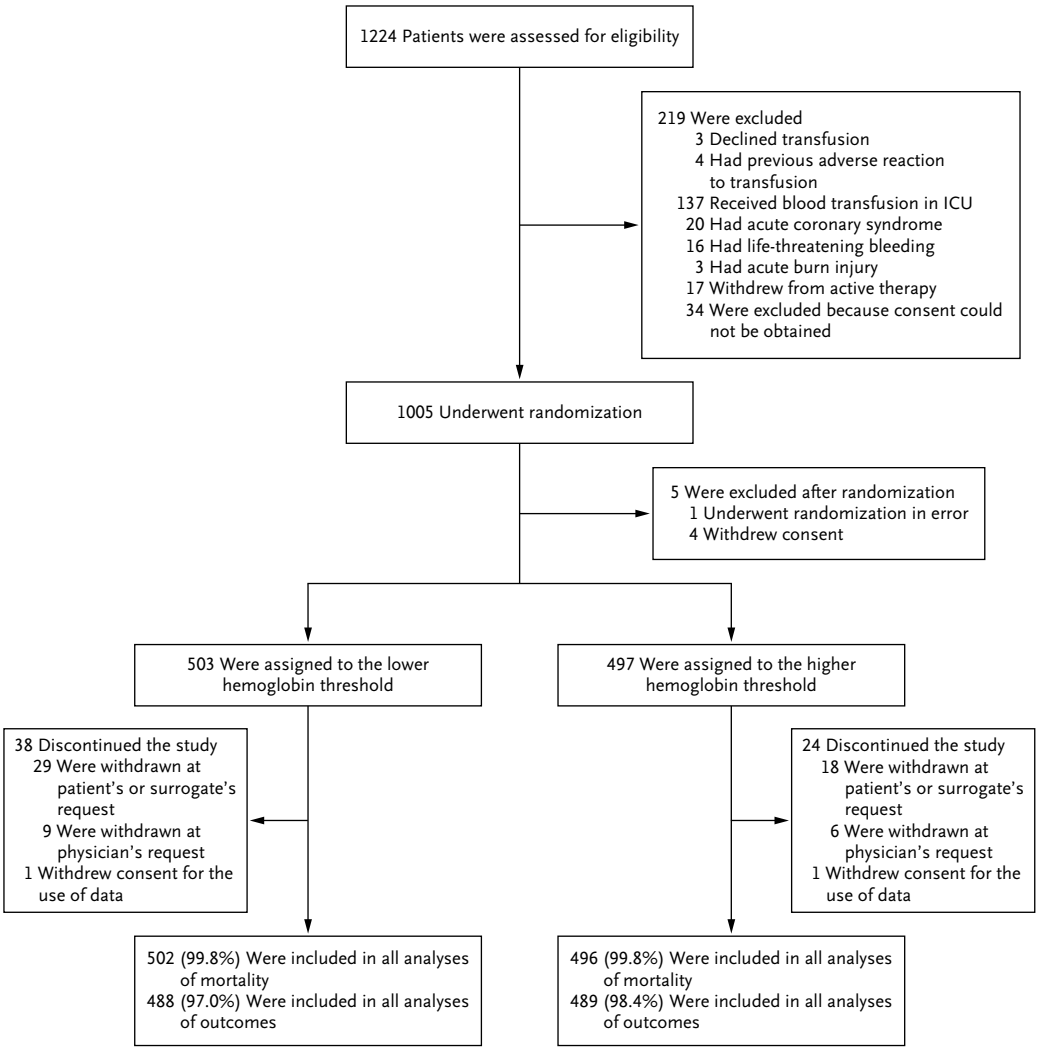


Figure 1. Assessment, Randomization, and Follow-up.

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 sep-

tic 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.

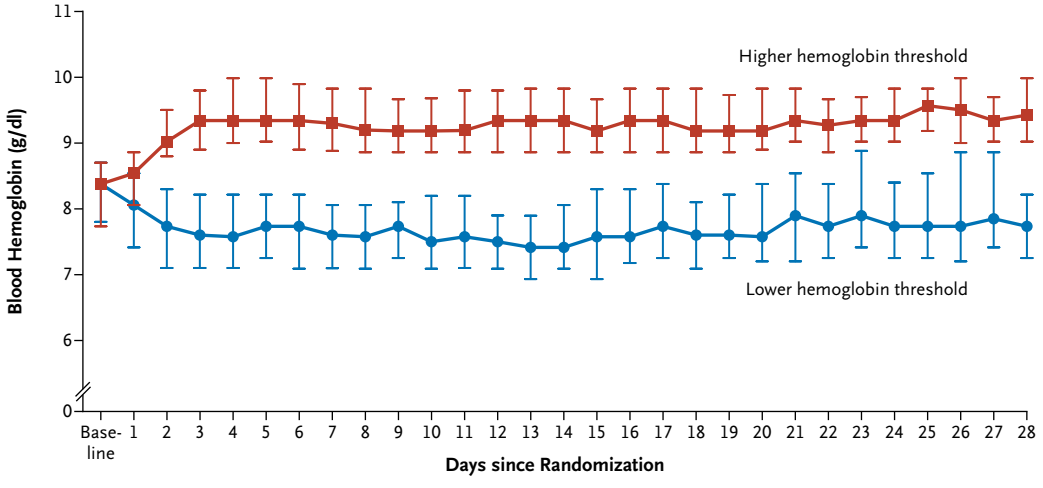


Figure 2. Blood Hemoglobin Levels in Patients in the ICU at Baseline and after Randomization.

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

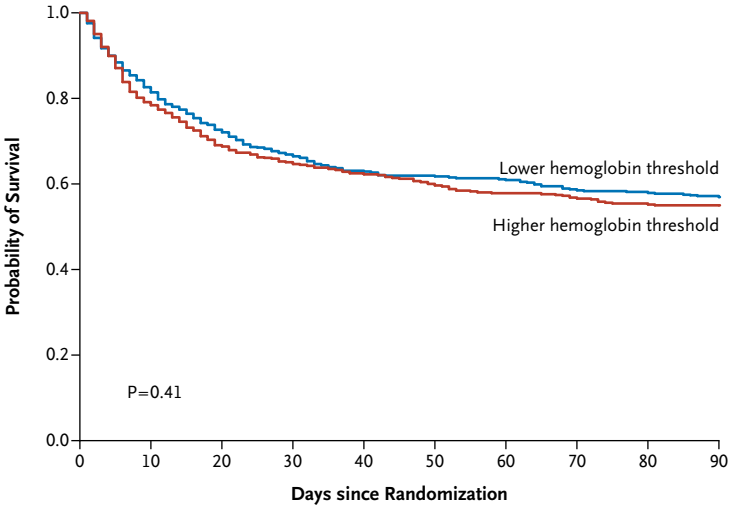
* CI denotes confidence interval.
† Logistic-regression analyses were adjusted for the stratification variables (study site and presence or absence of hematologic cancer). The results of the unadjusted outcome analyses are provided in Table S11 in the Supplementary Appendix.
‡ A total of 21 patients — 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

A Time to Death



No. at Risk

Lower hemoglobin threshold	502	334	306	286
Higher hemoglobin threshold	496	321	287	273

B Relative Risk of the Primary Outcome

Subgroup	Lower Hemoglobin Threshold	Higher Hemoglobin Threshold	Relative Risk (95% CI)	P Value for Heterogeneity
	no. of events/no. of patients in subgroup			
Age				0.85
>70 yr	93/173	98/185	0.98 (0.79–1.18)	
≤70 yr	123/329	125/311	0.94 (0.75–1.14)	
Chronic cardiovascular disease				0.25
Yes	42/75	33/66	1.08 (0.75–1.40)	
No	174/427	190/430	0.90 (0.75–1.06)	
SAPS II at baseline				0.06
>53	112/207	139/226	0.83 (0.64–1.04)	
≤53	104/295	84/270	1.10 (0.91–1.30)	
All patients	216/502	223/496	0.94 (0.78–1.09)	

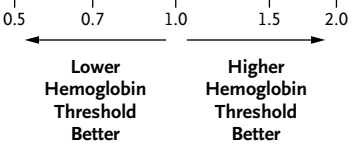


Figure 3. Time to Death and Relative Risk of Death at 90 Days.

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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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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CORRESPONDENCE

Hemoglobin Threshold for Transfusion in Septic Shock

TO THE EDITOR: Holst et al. (Oct. 9 issue)[1] found no significant differences in 90-day mortality and the rate of overt ischemic events between a lower and a higher hemoglobin threshold for transfusion in patients with septic shock. This study did not assess the occurrence of silent ischemic events that may have a substantial effect on long-term outcomes. Previous studies have shown that a low hemoglobin concentration is associated with silent cerebral ischemia in specific populations (e.g., patients with sickle cell anemia, those who require dialysis, and those with β-thalassemia).[2] In children with sickle cell anemia, silent cerebral infarction is associated with cognitive impairment and an increased risk of stroke. A recent controlled trial by DeBaun et al. showed that regular blood-transfusion therapy significantly reduced the incidence of recurrence of both silent and overt cerebral infarction in this group.[3] To rule out whether patients with septic shock who have a lower hemoglobin concentration are at risk for ischemic events such as silent cerebral ischemia and cognitive impairment, both brain imaging and cognitive-function tests after hospital discharge should be considered.

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1413474

TO THE EDITOR: The Transfusion Requirements in Septic Shock (TRISS) trial by Holst and colleagues showed no benefit from maintaining a hemoglobin level of at least 9 g per deciliter in patients with septic shock.

Physiologically, oxygen delivery is dependent on cardiac output, hemoglobin, arterial oxygen saturation, and partial pressure of oxygen, forming the rationale for the supportive measures used in the management of septic shock.[1,2] In practice, clinicians may use central venous oxygen saturation ($Scvo_2$) and lactate level as global markers of perfusion and their normalization as resuscitation goals.[3]

In the TRISS trial, at baseline, the median value of the lowest concentration of hemoglobin was approximately 8.4 g per deciliter, the lowest $Scvo_2$ was approximately 70%, and the highest lactate level was approximately 2.5 mmol per liter, suggesting adequate perfusion despite a low hemoglobin level in a substantial proportion of patients. It follows that further increasing the

THIS WEEK'S LETTERS

hemoglobin level with the use of red-cell transfusions in such patients would not result in meaningful improvement in perfusion (and thus clinical outcomes).

Before dismissing the potential value of increasing oxygen-carrying capacity by means of transfusions in patients with hypoperfusion, anemia, and septic shock, it seems prudent to confirm the consistency of inefficacy on the basis of baseline $Scvo_2$ (<70% vs. ≥70%) and lactate level (<4 mmol per liter vs. ≥4 mmol per liter). Could the authors present outcome data for these important subgroups?

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1413474

TO THE EDITOR: Holst et al. conclude that there are no significant differences in terms of mortality and rates of ischemic events and use of life support when considering different hemoglobin thresholds in patients with septic shock. Despite these results, the authors overlooked a well-known factor that could bias the efficacy of red-cell transfusion: the age of the blood. The storage lesion of red cells (functional and structural changes in the preserved cells) affects the erythrocyte deformability and capability of adhesion to endothelium, as well as the nitric oxide–mediated vasodilatory response, and triggers a proinflammatory state.[1] Hassan et al. found an association between the amount of older blood (>14 days of storage) that trauma victims received and the risk of complicated sepsis and death.[2] In addition, a recent study showed an association between transfusion of old, stored blood and acute lung injury in patients with sepsis.[3] Our group highlighted the inefficacy of red cells stored for more than 19 days in the improvement of cerebral oxygenation.[4] Therefore, taking into account that most red cells are stored for more than 20 days, we consider it essential that studies consider the age of the blood in order to elucidate its effect on transfusion efficacy.

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1413474

THE AUTHORS REPLY: Beerepoot and Vogt make the point that we did not assess silent ischemic events in the TRISS trial. This issue may be important because transfusion may reduce silent cerebral infarction in children with sickle cell disease.[1] Our trial was pragmatic and was not designed to assess silent ischemic events. The statistical analysis plan includes preplanned outcome analyses of health-related quality of life after 1 year of follow-up of the last enrolled patient.[2] These data may indicate whether there are differences in cognitive function between the lower-threshold group and the higher-threshold group in our trial.

Turgeon and Harder speculate that some patients enrolled in the TRISS trial were unlikely to benefit from improved perfusion by blood transfusion, as indicated by baseline values of hemoglobin, $Scvo_2$, and lactate. We tested the effects of two hemoglobin thresholds (7 vs. 9 g per deciliter) because these were frequent triggers

for transfusion in our clinical setting.[3] The benefit of using the lactate level and $Scvo_2$ to initiate and guide early resuscitation, including transfusion, in patients with septic shock may be questioned after the results of recent randomized trials.[4,5] As compared with the high-quality data from these trials, the results of any post hoc subgroup analyses that we may do are less valid.

Gordillo-Escobar et al. speculate that the age of blood and storage lesion could bias the results of our trial. Transfusion practice in patients with septic shock was not based on the age of blood at the TRISS trial sites. These factors may be important, and data from ongoing randomized trials will help us to understand whether the age of blood affects the outcome of critically ill patients (Standard Issue Transfusion versus Fresher Red Blood Cell Use in Intensive Care [TRANSFUSE] trial [ClinicalTrials.gov number, NCT01638416] and the Age of Blood Evaluation [ABLE] trial [Current Controlled Trials number, ISRCTN44878718]).

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Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1413474

Inhaled Glucocorticoids and COPD Exacerbations

TO THE EDITOR: In the Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management (WISDOM) study, Magnussen et al. (Oct. 2 issue)[1] report that the withdrawal of inhaled glucocorticoids had no significant effect on exacerbations in patients with severe chronic obstructive pulmonary disease (COPD), a finding that prompted them to cast doubts about the use of these drugs in such patients. We are concerned about this conclusion because the follow-up of less than 1 year was probably not long enough to assess exacerbations, given that such events occur with an average frequency of 1.3 to 2 per year. In addition, there was a definite trend toward an increase in severe exacerbations after glucocorticoid withdrawal ($P=0.08$), which we think conveys an important warning. Perhaps, patients with stage 3 disease (according to the Global Initiative for Chronic Obstructive Lung Disease [GOLD] criteria) should be analyzed separately from those with stage 4 disease to see whether they have different responses.[2,3] The most worrisome findings were the significant dose- and time-dependent loss of forced expiratory volume in 1 second (FEV_1) and deterioration in quality of life after the withdrawal of inhaled corticosteroids.

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TO THE EDITOR: Magnussen and colleagues report that stepwise withdrawal of inhaled glucocorticoids had no adverse effect on exacerbation frequency in patients with severe COPD. The decision to exclude from this study patients with no