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Transfusion Strategies for Acute Upper Gastrointestinal Bleeding

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ABSTRACT

BACKGROUND

The hemoglobin threshold for transfusion of red cells in patients with acute gastrointestinal bleeding is controversial. We compared the efficacy and safety of a restrictive transfusion strategy with those of a liberal transfusion strategy.

METHODS

We enrolled 921 patients with severe acute upper gastrointestinal bleeding and randomly assigned 461 of them to a restrictive strategy (transfusion when the hemoglobin level fell below 7 g per deciliter) and 460 to a liberal strategy (transfusion when the hemoglobin fell below 9 g per deciliter). Randomization was stratified according to the presence or absence of liver cirrhosis.

RESULTS

A total of 225 patients assigned to the restrictive strategy (51%), as compared with 61 assigned to the liberal strategy (14%), did not receive transfusions ($P < 0.001$). The probability of survival at 6 weeks was higher in the restrictive-strategy group than in the liberal-strategy group (95% vs. 91%; hazard ratio for death with restrictive strategy, 0.55; 95% confidence interval [CI], 0.33 to 0.92; $P = 0.02$). Further bleeding occurred in 10% of the patients in the restrictive-strategy group as compared with 16% of the patients in the liberal-strategy group ($P = 0.01$), and adverse events occurred in 40% as compared with 48% ($P = 0.02$). The probability of survival was slightly higher with the restrictive strategy than with the liberal strategy in the subgroup of patients who had bleeding associated with a peptic ulcer (hazard ratio, 0.70; 95% CI, 0.26 to 1.25) and was significantly higher in the subgroup of patients with cirrhosis and Child–Pugh class A or B disease (hazard ratio, 0.30; 95% CI, 0.11 to 0.85), but not in those with cirrhosis and Child–Pugh class C disease (hazard ratio, 1.04; 95% CI, 0.45 to 2.37). Within the first 5 days, the portal-pressure gradient increased significantly in patients assigned to the liberal strategy ($P = 0.03$) but not in those assigned to the restrictive strategy.

CONCLUSIONS

As compared with a liberal transfusion strategy, a restrictive strategy significantly improved outcomes in patients with acute upper gastrointestinal bleeding. (Funded by Fundació Investigació Sant Pau; ClinicalTrials.gov number, NCT00414713.)

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ACUTE UPPER GASTROINTESTINAL BLEEDING is a common emergency condition associated with high morbidity and mortality.¹ It is a frequent indication for red-cell transfusion, because acute blood loss can decrease tissue perfusion and the delivery of oxygen to tissues. Transfusion may be lifesaving in patients with massive exsanguinating bleeding. However, in most cases hemorrhage is not so severe, and in such circumstances the safest and most effective transfusion strategy is controversial.^{2,3}

Restricted transfusion strategies may be appropriate in some settings. Controlled trials have shown that for critically ill patients, a restrictive transfusion strategy is at least as effective as a liberal strategy, while substantially reducing the use of blood supplies.^{4,5} However, these studies excluded patients with gastrointestinal bleeding. Observational studies and small controlled trials have suggested that transfusion may be harmful in patients with hypovolemic anemia,^{6,7} even in those with gastrointestinal bleeding.⁸⁻¹² Furthermore, studies in animals suggest that transfusion can be particularly harmful in patients with bleeding from portal hypertensive sources, since restitution of blood volume after hemorrhage can lead to a rebound increase in portal pressure, which is associated with a risk of rebleeding.¹²⁻¹⁴

We performed a randomized, controlled trial in which we assessed whether a restrictive threshold for red-cell transfusion in patients with acute gastrointestinal bleeding was safer and more effective than a liberal transfusion strategy that was based on the threshold recommended in guidelines at the time the study was designed.^{15,16}

METHODS

STUDY OVERSIGHT

From June 2003 through December 2009, we consecutively enrolled patients with gastrointestinal bleeding who were admitted to Hospital de la Santa Creu i Sant Pau in Barcelona. Written informed consent was obtained from all the patients or their next of kin, and the trial was approved by the institutional ethics committee at the hospital. The protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org. No commercial support was involved in the study. All the authors vouch for the integrity and the accuracy of the analysis

and for the fidelity of the study to the protocol. No one who is not an author contributed to the manuscript.

SELECTION OF PATIENTS

Patients older than 18 years of age who had hematemesis (or bloody nasogastric aspirate), melena, or both, as confirmed by the hospital staff, were considered for inclusion. Patients were excluded if they declined to undergo a blood transfusion. Additional exclusion criteria were massive exsanguinating bleeding; an acute coronary syndrome, symptomatic peripheral vasculopathy, stroke, transient ischemic attack, or transfusion within the previous 90 days; a recent history of trauma or surgery; lower gastrointestinal bleeding; a previous decision on the part of the attending physician that the patient should avoid specific medical therapy; and a clinical Rockall score of 0 with a hemoglobin level higher than 12 g per deciliter. The Rockall score is a system for assessing the risk of further bleeding or death among patients with gastrointestinal bleeding; scores range from 0 to 11, with a score of 2 or lower indicating low risk and scores of 3 to 11 indicating increasingly greater risk.

STUDY DESIGN

Immediately after admission, patients were randomly assigned to a restrictive transfusion strategy or a liberal transfusion strategy. Randomization was performed with the use of computer-generated random numbers, with the group assignments placed in sealed, consecutively numbered, opaque envelopes. Randomization was stratified according to the presence or absence of liver cirrhosis and was performed in blocks of four. Cirrhosis was diagnosed according to clinical, biochemical, and ultrasonographic findings.

In the restrictive-strategy group, the hemoglobin threshold for transfusion was 7 g per deciliter, with a target range for the post-transfusion hemoglobin level of 7 to 9 g per deciliter. In the liberal-strategy group, the hemoglobin threshold for transfusion was 9 g per deciliter, with a target range for the post-transfusion hemoglobin level of 9 to 11 g per deciliter. In both groups, 1 unit of red cells was transfused initially; the hemoglobin level was assessed after the transfusion, and an additional unit was transfused if the hemoglobin level was below the

threshold value. The transfusion protocol was applied until the patient's discharge from the hospital or death. The protocol allowed for a transfusion to be administered any time symptoms or signs related to anemia developed, massive bleeding occurred during follow-up, or surgical intervention was required. Only prestorage leukocyte-reduced units of packed red cells were used for transfusion. The volume of a unit ranged from 250 to 320 ml, with a hematocrit of approximately 60%.

Hemoglobin levels were measured after admission and again every 8 hours during the first 2 days and every day thereafter. Hemoglobin levels were also assessed when further bleeding was suspected.

TREATMENTS AND FOLLOW-UP

All the patients underwent emergency gastroscopy within the first 6 hours. When endoscopic examination disclosed a nonvariceal lesion with active arterial bleeding, a nonbleeding visible vessel, or an adherent clot, patients underwent endoscopic therapy with injection of adrenaline plus multipolar electrocoagulation or application of endoscopic clips. Patients with peptic ulcer received a continuous intravenous infusion of omeprazole (80 mg per 10-hour period after an initial bolus of 80 mg) for the first 72 hours, followed by oral administration of omeprazole.

When portal hypertension was suspected, a continuous intravenous infusion of somatostatin (250 μ g per hour) and prophylactic antibiotic therapy with norfloxacin or ceftriaxone were administered at the time of admission and continued for 5 days. Bleeding esophageal varices were also treated with band ligation or with sclerotherapy, and gastric varices with injection of cyanoacrylate. In patients with variceal bleeding, portal pressure was measured within the first 48 hours and again 2 to 3 days later to assess the effect of the transfusion strategy on portal hypertension. Portal pressure was estimated with the use of the hepatic venous pressure gradient (HVPG), as described elsewhere.¹⁷

OUTCOME MEASURES AND DEFINITIONS

The primary outcome measure was the rate of death from any cause within the first 45 days. Secondary outcomes included the rate of further bleeding and the rate of in-hospital complications.

Further bleeding was defined as hematemesis or fresh melena associated with hemodynamic instability (systolic blood pressure of <100 mm Hg; pulse rate of >100 beats per minute, or both) or a fall in hemoglobin level of 2 g per deciliter or more within a 6-hour period. Further bleeding was considered to indicate therapeutic failure; if the bleeding involved nonvariceal lesions, the patient underwent repeat endoscopic therapy or emergency surgery, whereas in the case of further variceal bleeding, transjugular intrahepatic portosystemic shunting (TIPS) was considered.

Complications were defined as any untoward events that necessitated active therapy or prolonged hospitalization. Side effects were considered to be severe if the health or safety of the patient was endangered.

STATISTICAL ANALYSIS

We estimated that with 430 patients in each group, the study would have the power to detect a between-group difference in mortality of at least 5 percentage points, assuming 10% mortality in the liberal-strategy group (on the basis of results of previous trials with standard care^{1,3,18}), with the use of a two-tailed test and with alpha and beta values of 0.05 and 0.2, respectively. The statistical analysis was performed according to the intention-to-treat principle. Standard tests were used for comparisons of proportions and means. Continuous variables are expressed as means and standard deviations. Actuarial probabilities were calculated with the use of the Kaplan–Meier method and were compared with the use of the log-rank test. A Cox proportional-hazards regression model was used to compare the two transfusion-strategy groups with respect to the primary and secondary end points, with adjustment for baseline risk factors (see the Supplementary Appendix, available at NEJM.org). The hazard ratios and their 95% confidence intervals were calculated. Data were censored at the time an end-point event occurred, at the patient's last visit, or at the end of the 45-day follow-up period, whichever occurred first. Prespecified subgroup analyses were performed to assess the efficacy of transfusion strategies according to the source of bleeding (lesions related to portal hypertension or peptic ulcer). All P values are two-tailed. Calculations were performed with the use of the SPSS statistical package, version 15.0 (SPSS).

RESULTS

STUDY PATIENTS

During the study period, 2372 patients were admitted to the hospital for gastrointestinal bleeding and 1610 were screened. Of these, 41 declined to participate and 648 were excluded; among the reasons for exclusion were exsanguinating bleeding requiring transfusion (in 39 patients) and a low risk of rebleeding (329 patients) (Fig. 1). A total of 921 patients underwent randomization and 32 withdrew or were withdrawn by the investigators after randomization (see Fig. 1 for details), leaving 444 patients in the restrictive-strategy group and 445 in the liberal-strategy group for the intention-to-treat analysis. The baseline characteristics were similar in the two groups (Table 1). A total of 277 patients (31%) had cirrhosis, and the baseline characteristics of the patients in this subgroup were similar in the two transfusion-strategy groups (Table 1). Bleeding was due to peptic ulcer in 437 patients (49%) and to esophageal varices in 190 (21%) (Table 1).

HEMOGLOBIN LEVELS AND TRANSFUSION

The hemoglobin concentration at admission was similar in the two groups (Table 2). The lowest hemoglobin concentration within the first 24 hours was significantly lower in the restrictive-strategy group than in the liberal-strategy group, as was the daily hemoglobin concentration until discharge ($P < 0.001$). The percentage of patients in whom the lowest hemoglobin level was less than 7 g per deciliter was higher in the restrictive-strategy group than in the liberal-strategy group. The hemoglobin concentration at 45 days was similar in the two groups.

A total of 225 patients (51%) in the restrictive-strategy group, as compared with 61 patients (14%) in the liberal-strategy group, received no transfusion ($P < 0.001$). The mean (\pm SD) number of units transfused was significantly lower in the restrictive-strategy group than in the liberal-strategy group (1.5 ± 2.3 vs. 3.7 ± 3.8 , $P < 0.001$), and a violation of the transfusion protocol occurred more frequently in the restrictive-strategy group (in 39 patients [9%] vs. 15 patients [3%], $P < 0.001$) (Table 2). The percentage of patients who received a transfusion of fresh-frozen plasma, the percentage of patients who received a transfusion of platelets, and the total amount of fluid administered were similar in the two groups.

MORTALITY

Mortality at 45 days was significantly lower in the restrictive-strategy group than in the liberal-strategy group: 5% (23 patients) as compared with 9% (41 patients) ($P = 0.02$) (Fig. 2). The risk of death was virtually unchanged after adjustment for baseline risk factors for death (hazard ratio with restrictive strategy, 0.55; 95% confidence interval [CI], 0.33 to 0.92) (Table S4 in the Supplementary Appendix). Among all patients with cirrhosis, the risk of death was slightly lower in the restrictive-strategy group than in the liberal-strategy group (Fig. 2). In the subgroup of patients with cirrhosis and Child–Pugh class A or B disease, the risk of death was significantly lower among patients in the restrictive-strategy group than among those in the liberal-strategy group, whereas in the subgroup of patients with cirrhosis and Child–Pugh class C disease, the risk was similar in the two groups. Among patients with bleeding from a peptic ulcer, the risk of death was slightly lower with the restrictive strategy than with the liberal strategy.

Death was due to unsuccessfully controlled bleeding in 3 patients (0.7%) in the restrictive-strategy group and in 14 patients (3.1%) in the liberal-strategy group ($P = 0.01$). Death was caused by complications of treatment in 3 patients (2 in the liberal-strategy group and 1 in the restrictive-strategy group). In the remaining 44 patients (19 in the restrictive-strategy group and 25 in the liberal-strategy group), hemorrhage was controlled and death was due to associated diseases.

FURTHER BLEEDING

The rate of further bleeding was significantly lower in the restrictive-strategy group than in the liberal-strategy group: 10% (45 patients), as compared with 16% (71 patients) ($P = 0.01$) (Table 3). The risk of further bleeding was significantly lower with the restrictive strategy after adjustment for baseline risk factors for further bleeding (hazard ratio, 0.68; 95% CI, 0.47 to 0.98) (Table S4 in the Supplementary Appendix). In addition, the length of hospital stay was shorter in the restrictive-strategy group than in the liberal-strategy group.

In the subgroup of patients with cirrhosis, the risk of further bleeding was lower with the restrictive transfusion strategy than with the liberal transfusion strategy among patients with Child–Pugh class A or B disease and was similar

in the two groups among patients with Child–Pugh class C disease (Table 3). Among patients with bleeding from esophageal varices, the rate of further bleeding was lower in the restrictive-strategy group than in the liberal-strategy group (11% vs. 22%, $P=0.05$). Rescue therapy with balloon tamponade or with transjugular intrahepatic portosystemic shunt was required less frequently in the restrictive-strategy group than in the liberal-strategy group.

A baseline hepatic hemodynamic study was performed in 86 patients in the restrictive-strategy group and in 89 in the liberal-strategy group, and it was repeated 2 to 3 days later in 74 and 77 patients, respectively, to assess changes. Patients in the liberal-strategy group had a significant increase in the mean hepatic venous pressure gradient between the first hemodynamic study and the second (from 20.5 ± 3.1 mm Hg to 21.4 ± 4.3 mm Hg, $P=0.03$). There was no significant change in mean hepatic venous pressure gradient in the restrictive-strategy group during that interval.

Among patients with bleeding from a peptic ulcer, there was a trend toward a lower risk of further bleeding in the restrictive-strategy group (Table 3). Emergency surgery to control further bleeding was required less frequently in the restrictive-strategy group than in the liberal-strategy group (2% vs. 6%, $P=0.04$).

ADVERSE EVENTS

The overall rate of complications was significantly lower in the restrictive-strategy group than in the liberal-strategy group (40% [179 patients] vs. 48% [214 patients], $P=0.02$), as was the rate of serious adverse events (Table S5 in the Supplementary Appendix). Transfusion reactions and cardiac events, mainly pulmonary edema, occurred more frequently in the liberal-strategy group (Table 3). The rates of other adverse events, such as acute kidney injury or bacterial infections, did not differ significantly between the groups (Table S5 in the Supplementary Appendix).

DISCUSSION

We found that among patients with severe acute upper gastrointestinal bleeding, the outcomes were significantly improved with a restrictive transfusion strategy, in which the hemoglobin threshold was 7 g per deciliter, as compared with

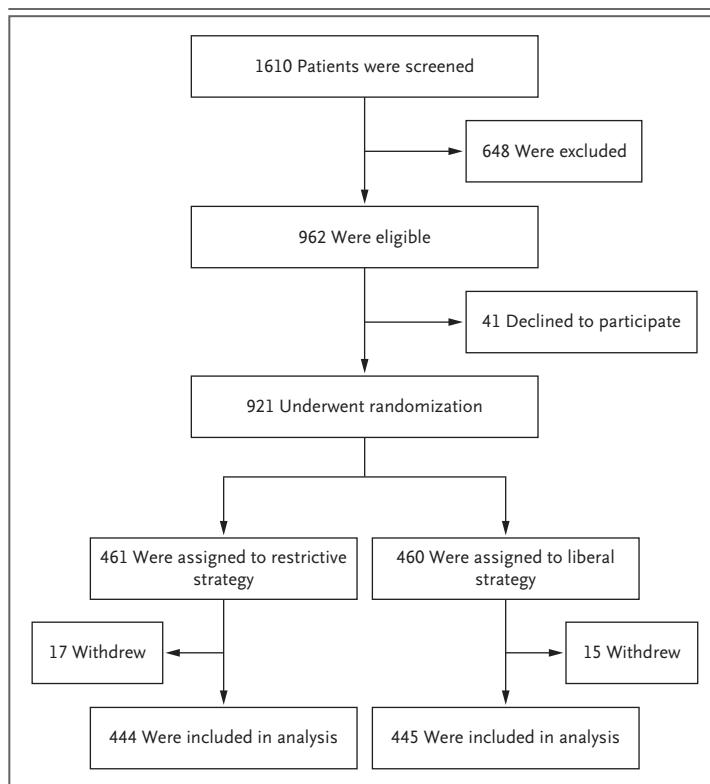


Figure 1. Screening, Randomization, and Follow-up.

During the study period, 1610 patients with gastrointestinal bleeding were screened, and 648 patients were excluded. The reasons for exclusion included massive exsanguinating bleeding requiring transfusion before randomization (39 patients) and a low risk of rebleeding (329 patients). A low risk of rebleeding was defined as a clinical Rockall score of 0 and hemoglobin levels higher than 12 g per deciliter. (The Rockall score is a system for assessing the risk of further bleeding or death among patients with gastrointestinal bleeding; scores range from 0 to 11, with higher scores indicating greater risk.) Patients were also excluded if they declined blood transfusion (14 patients); other exclusion criteria were an acute coronary syndrome (58), symptomatic peripheral vasculopathy (12), stroke or transient ischemic attack (7), or transfusion (10) within the previous 90 days; lower gastrointestinal bleeding (51); pregnancy (3); a recent history of trauma or surgery (41); a decision by the attending physician that the patient should avoid medical therapy (9); or inclusion in this study within the previous 90 days or inclusion more than twice (75). A total of 921 patients underwent randomization, of whom 32 were withdrawn: 23 were found to be ineligible, 5 had major protocol violations, and 4 decided to withdraw from the study.

a liberal transfusion strategy, in which the hemoglobin threshold was 9 g per deciliter. The most relevant finding was the improvement in survival rates observed with the restrictive transfusion strategy. This advantage was probably related to a better control of factors contributing to death, such as further bleeding, the need for rescue therapy, and serious adverse events. All these factors were significantly reduced with the restric-

Characteristic	Restrictive Strategy (N=444)	Liberal Strategy (N=445)	P Value
In-hospital bleeding — no. (%)†	20 (5)	30 (7)	0.19
Rockall score‡	5.3±2.0	5.4±1.7	0.18
Source of bleeding — no./total no. (%)			
Peptic ulcer	228/444 (51)	209/445 (47)	0.20
Location			0.95
Gastric	76/228 (33)	71/209 (34)	
Duodenal	143/228 (63)	131/209 (63)	
Stomal	9/228 (4)	7/209 (3)	
Stigmata			0.93
Active bleeding	35/228 (15)	33/209 (16)	
Visible vessel	127/228 (56)	119/209 (57)	
Gastroesophageal varices	101/444 (23)	109/445 (24)	0.58
Mallory–Weiss tears	25/444 (6)	30/445 (7)	0.49
Erosive gastritis or esophagitis	38/444 (9)	29/445 (7)	0.26
Neoplasms	16/444 (4)	20/445 (4)	0.50
Other	36/444 (8)	48/445 (11)	
Cirrhosis — no. (%)	139 (31)	138 (31)	0.94
Alcoholic cause — no./total no. (%)	63/139 (45)	62/138 (45)	0.49
Child–Pugh class — no./total no. (%)§			0.57
A	37/139 (27)	30/138 (22)	
B	76/139 (55)	79/138 (57)	
C	26/139 (19)	29/138 (21)	
HVPG — mm Hg¶	20.1±4.4	20.6±5.2	0.61
Causes of bleeding — no./total no. (%)			
Esophageal varices	93/139 (67)	97/138 (70)	0.60
Gastric varices	8/139 (6)	12/138 (9)	0.36
Peptic lesions	21/139 (15)	18/138 (13)	0.73

* Plus–minus values are means ±SD.

† Among patients with in-hospital bleeding, 16 (7 in the restrictive-strategy group and 9 in the liberal-strategy group) were admitted to the intensive care unit with sepsis or for pressure support.

‡ The Rockall score is a system for assessing the risk of further bleeding or death among patients with gastrointestinal bleeding; scores range from 0 to 11, with higher scores indicating higher risk.

§ Child–Pugh class A denotes good hepatic function, class B intermediate function, and class C poor function. The mean Model for End-Stage Liver Disease (MELD) score among patients in all Child–Pugh classes (on a scale from 6 to 40, with higher values indicating more severe liver disease) was 11.9±7 in the restrictive-strategy group and 12.1±6 in the liberal-strategy group (P=0.95).

¶ Portal pressure was measured with the use of the hepatic venous pressure gradient (HVPG), which is the difference between the wedged and free hepatic venous pressures. Measurements were performed within the first 48 hours in 175 patients with variceal bleeding (86 in the restrictive-strategy group and 89 in the liberal-strategy group).

tive strategy. Our results are consistent with those from previous observational studies and randomized trials performed in other settings, which have shown that a restrictive transfusion strategy did not increase,^{5,19} and even de-

creased,^{4,20} the mortality observed with a liberal transfusion strategy.

Current international guidelines recommend decreasing the hemoglobin threshold level for transfusion in patients with gastrointestinal

Table 2. Hemoglobin Levels, Transfusions, and Cointerventions.*

Variable	Restrictive Strategy (N = 444)	Liberal Strategy (N = 445)	P Value
Hemoglobin level — g/dl			
At admission	9.6±2.2	9.4±2.4	0.45
Lowest value during hospital stay	7.3±1.4	8.0±1.5	<0.001
At discharge†	9.2±1.2	10.1±1.0	<0.001
At day 45	11.6±1.7	11.7±1.8	0.67
Patients with lowest hemoglobin <7 g/dl — no. (%)	202 (45)	81 (18)	<0.001
Patients with lowest hemoglobin >9 g/dl — no. (%)	55 (12)	67 (15)	0.28
Red-cell transfusion			
Any — no. of patients (%)	219 (49)	384 (86)	<0.001
Units transfused — no.			
Total‡	671	1638	<0.001
Mean/patient	1.5±2.3	3.7±3.8	<0.001
Median	0	3	<0.001
Range	0–19	0–36	
During index bleeding§	1.2±1.8	2.9±2.2	<0.001
Transfusion not adjusted to hemoglobin level — no. of patients (%)¶	35 (8)	12 (3)	0.001
Major protocol violation — no. of patients (%)	39 (9)	15 (3)	<0.001
Duration of storage of red cells — days**			0.95
Median	15	15	
Range	1–40	1–42	
Fresh-frozen plasma transfusion — no. of patients (%)††	28 (6)	41 (9)	0.13
Platelet transfusion — no. of patients (%)‡‡	12 (3)	19 (4)	0.27
Crystalloids administered within first 72 hr — ml	5491±3448	5873±4087	0.19
Receipt of colloids — no. of patients (%)	86 (19)	93 (21)	0.62

* Plus-minus values are means ±SD.

† The average difference in the daily hemoglobin level between the restrictive-strategy group and the liberal-strategy group was 1.0±1.3 g per deciliter, from the time of admission to discharge.

‡ Included are all red-cell transfusions received from the time of admission to discharge.

§ This category refers to the units of red cells transfused before further bleeding.

¶ Transfusions were administered in 31 patients (26 in the restrictive-strategy group and 5 in the liberal-strategy group) because of symptoms or signs (defined as tachycardia, chest pain, or signs of severe hypoxemia) in 14 patients (8 in the restrictive-strategy group and 6 in the liberal-strategy group) because of massive bleeding, and in 2 patients (1 in each group) because of surgery.

|| In the restrictive-strategy group, 39 patients without signs or symptoms, massive bleeding, or surgery received a transfusion when the hemoglobin level was higher than 7 g per deciliter. In the liberal-strategy group, 15 patients with a hemoglobin level lower than 9 g per deciliter did not receive a transfusion.

** Red cells were stored for up to 42 days. At least 1 unit stored for more than 14 days was administered in 141 of the 219 patients in the restrictive-strategy group (64%) and 253 of the 384 patients in the liberal-strategy group (66%) who received a transfusion.

†† Included are all patients who received a transfusion of fresh-frozen plasma from the time of admission to discharge.

‡‡ Included are all patients who received a transfusion of platelets from the time of admission to discharge.

bleeding, from 10 g per deciliter^{15,16} to 7 g per deciliter.^{3,21} A reduction in the number of transfusions performed may have accounted for the reduction in mortality from gastrointestinal bleed-

ing that has been observed in recent years.^{22,23} However, current guidelines are based on findings from trials of transfusion triggers involving critically ill patients with normovolemic anemia

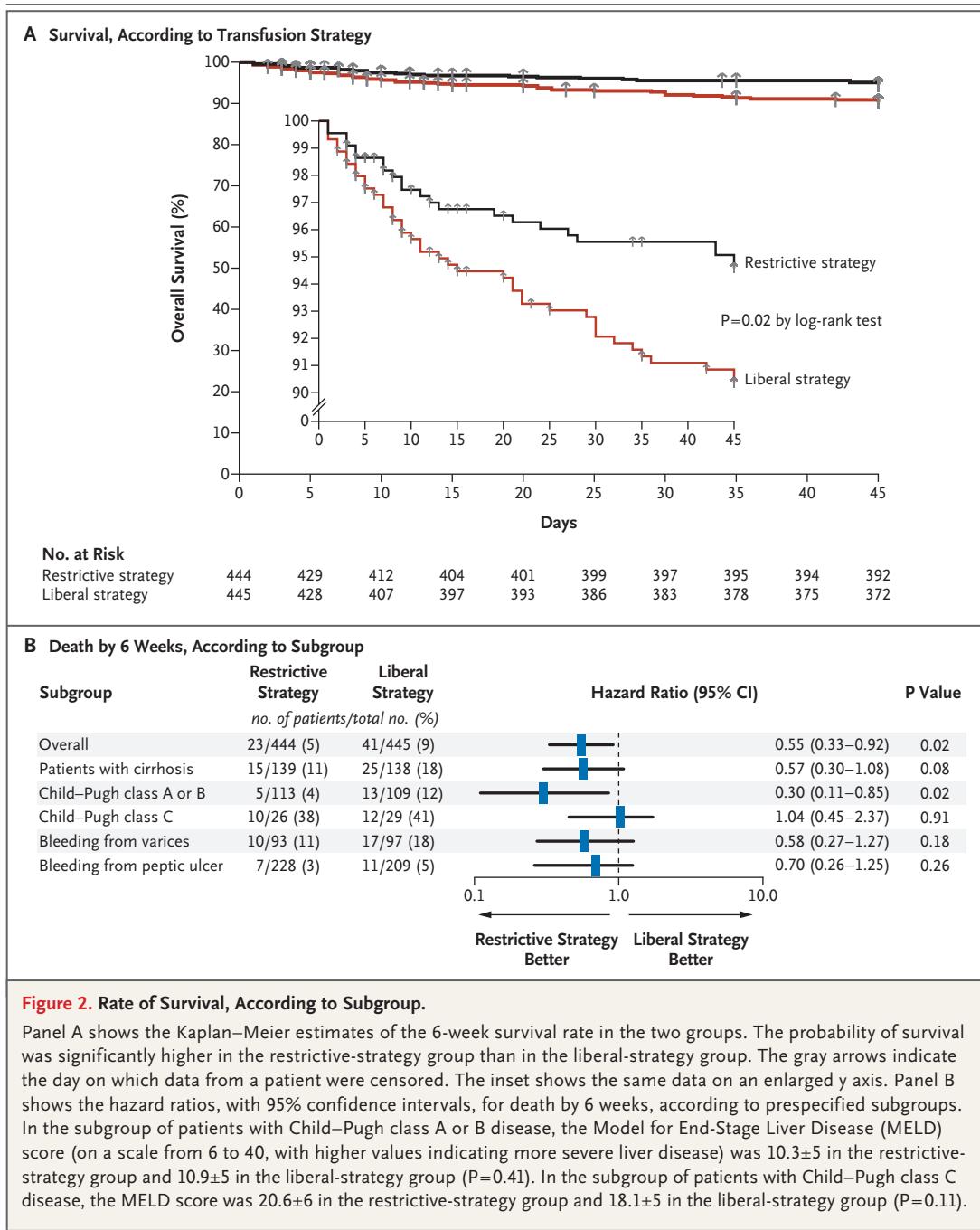


Figure 2. Rate of Survival, According to Subgroup.

Panel A shows the Kaplan–Meier estimates of the 6-week survival rate in the two groups. The probability of survival was significantly higher in the restrictive-strategy group than in the liberal-strategy group. The gray arrows indicate the day on which data from a patient were censored. The inset shows the same data on an enlarged y axis. Panel B shows the hazard ratios, with 95% confidence intervals, for death by 6 weeks, according to prespecified subgroups. In the subgroup of patients with Child–Pugh class A or B disease, the Model for End-Stage Liver Disease (MELD) score (on a scale from 6 to 40, with higher values indicating more severe liver disease) was 10.3 ± 5 in the restrictive-strategy group and 10.9 ± 5 in the liberal-strategy group ($P=0.41$). In the subgroup of patients with Child–Pugh class C disease, the MELD score was 20.6 ± 6 in the restrictive-strategy group and 18.1 ± 5 in the liberal-strategy group ($P=0.11$).

— trials from which patients with acute bleeding have been excluded.^{4,5} Transfusion requirements may be different for patients with acute hemorrhage due to factors such as hemodynamic instability or rapid onset of anemia to extremely low hemoglobin levels. The current study addressed the effects of transfusion in this setting. Previous observational studies and small

controlled trials have supported the use of a restrictive transfusion strategy for patients with gastrointestinal bleeding.^{8–11} Our results, which are consistent with the results from those studies, showed that a restrictive strategy significantly reduced the rates of factors related to therapeutic failure such as further bleeding and the need for rescue therapy, as well as reducing the length of

Table 3. Study Outcomes.*

Outcome	Restrictive Strategy (N=444)	Liberal Strategy (N=445)	Hazard Ratio with Restrictive Strategy (95% CI)	P Value
Death from any cause within 45 days — no. (%)	23 (5)	41 (9)	0.55 (0.33–0.92)	0.02
Further bleeding — no. of patients/total no. (%)				
Overall	45/444 (10)	71/445 (16)	0.62 (0.43–0.91)	0.01
Patients with cirrhosis	16/139 (12)	31/138 (22)	0.49 (0.27–0.90)	0.02
Child–Pugh class A or B	12/113 (11)	23/109 (21)	0.53 (0.27–0.94)	0.04
Child–Pugh class C	4/26 (15)	8/29 (28)	0.58 (0.15–1.95)	0.33
Bleeding from esophageal varices	10/93 (11)	21/97 (22)	0.50 (0.23–0.99)	0.05
Rescue therapies				
Balloon tamponade	3/139 (2)	11/138 (8)		0.03
TIPS	6/139 (4)	15/138 (11)		0.04
Patients with bleeding from peptic ulcer	23/228 (10)	33/209 (16)	0.63 (0.37–1.07)	0.09
Rescue therapies				
Second endoscopic therapy	20/228 (9)	26/209 (12)		0.21
Emergency surgery	4/228 (2)	12/209 (6)		0.04
No. of days in hospital	9.6±8.7	11.5±12.8		0.01
Adverse events — no. (%)†				
Any‡	179 (40)	214 (48)	0.73 (0.56–0.95)	0.02
Transfusion reactions	14 (3)	38 (9)	0.35 (0.19–0.65)	0.001
Fever	12 (3)	16 (4)	0.74 (0.35–1.59)	0.56
Transfusion-associated circulatory overload	2 (<1)	16 (4)	0.06 (0.01–0.45)	0.001
Allergic reactions	1 (<1)	6 (1)	0.16 (0.02–1.37)	0.12
Cardiac complications§	49 (11)	70 (16)	0.64 (0.43–0.97)	0.04
Acute coronary syndrome¶	8 (2)	13 (3)	0.61 (0.25–0.49)	0.27
Pulmonary edema	12 (3)	21 (5)	0.56 (0.27–1.12)	0.07
Pulmonary complications	48 (11)	53 (12)	0.89 (0.59–1.36)	0.67
Acute kidney injury	78 (18)	97 (22)	0.78 (0.56–1.08)	0.13
Stroke or transient ischemic attack	3 (1)	6 (1)	0.49 (0.12–2.01)	0.33
Bacterial infections	119 (27)	135 (30)	0.87 (0.63–1.21)	0.41

* Plus–minus values are means ±SD. TIPS denotes transjugular intrahepatic portosystemic shunt.

† Patients may have had more than one type of adverse event.

‡ Included are all patients who had at least one adverse event during the study period.

§ This category includes patients with acute coronary syndrome, pulmonary edema, or arrhythmias.

¶ Unstable angina developed in 13 patients (8 in the restrictive-strategy group and 5 in the liberal-strategy group), and myocardial infarction occurred in 8 patients (all in the liberal-strategy group).

stay in the hospital. These harmful effects of transfusion may be related to an impairment of hemostasis. Transfusion may counteract the splanchnic vasoconstrictive response caused by hypovolemia, inducing an increase in splanchnic blood flow and pressure that may impair the formation of clots.^{24,25} Transfusion may also induce abnormalities in coagulation properties.^{8,10}

Concerns about transfusion have been raised primarily with respect to patients who have cirrhosis with portal hypertension. Experimental studies have shown that restitution of blood volume can induce rebound increases in portal pressure that may precipitate portal hypertensive-related bleeding.^{12–14} Clinical studies have also shown that transfusion increases portal pressure

during acute variceal bleeding, an increase that may be prevented with somatostatin.¹⁷ In keeping with these observations, we found that the beneficial effect of a restrictive transfusion strategy with respect to further bleeding was observed mainly in patients with portal hypertension. We also observed that despite treatment with somatostatin, patients in the liberal-strategy group had a significant increase in portal pressure during acute variceal bleeding that was not observed in patients in the restrictive-strategy group. This may have accounted for the higher rate of further bleeding with the liberal strategy.

We found a reduction in the rate of complications with the restrictive transfusion strategy. This finding is consistent with results from a previous trial involving critically ill adults.⁴ However, conflicting results have been shown in other settings.^{5,19} Several factors, such as coexisting conditions or age, may account for this discrepancy. Cardiac complications, particularly pulmonary edema, occurred more frequently with the liberal transfusion strategy, both in the current study and in the trial that involved critically ill adults.⁴ The higher level of cardiac complications may indicate a higher risk of circulatory overload associated with a liberal transfusion strategy. Other effects of transfusion, such as transfusion-related immunomodulation,²⁶ may increase the risk of complications or death. These are unlikely to have occurred in the current study given the similar incidence of bacterial infections in the two groups and the universal use of prestorage leukocyte-reduced red cells. Adverse outcomes have also been associated with long storage time of transfused blood.²⁷ In our study, the storage time was similar in the two groups. However, the median duration of storage was 15 days, and storage lesions become apparent after about 14 days.²⁸ Therefore, the fact that there were more transfusions of blood with these long storage times in the liberal-strategy group may have contributed to the worse outcome. Further research is needed to determine whether the use of newer blood may influence the results with respect to the transfusion strategy. We found that a restrictive transfusion strategy significantly decreased the number of units transfused and the percentage of patients who received no transfusions — findings that were also seen in previous trials.^{4,5,19}

The goal of red-cell transfusions is to improve

the delivery of oxygen to tissues. The safest and most effective transfusion strategy depends not only on the hemoglobin trigger level but also on factors such as coexisting conditions, age, and hemodynamic status.^{1,3} Consequently, we allowed transfusions to be performed at the discretion of attending physicians when symptoms related to anemia developed, when massive bleeding occurred, or when surgical intervention was required. Transfusions that were not adjusted to the hemoglobin level and violations of the transfusion protocol occurred more often in the restrictive-strategy group than in the liberal-strategy group. However, both these deviations from the protocol occurred in less than 10% of cases.

Our trial has several limitations. First, the results cannot be generalized to all patients with acute gastrointestinal bleeding. Patients with a low risk of rebleeding were not included in this study. However, these patients are less likely to require a transfusion. Patients with massive exsanguinating hemorrhage were also excluded from this trial because red-cell transfusion may be lifesaving for them. However, only a minority of eligible patients were excluded for this reason. Second, because we compared two transfusion strategies, the study was not blinded, and this may have introduced a bias. It is unlikely that bias was introduced, however, owing to the objective definition of the primary outcome and the use of a randomized design with concealed assignments.

In summary, we found that a restrictive transfusion strategy, as compared with a liberal transfusion strategy, improved the outcomes among patients with acute upper gastrointestinal bleeding. The risk of further bleeding, the need for rescue therapy, and the rate of complications were all significantly reduced, and the rate of survival was increased, with the restrictive transfusion strategy. Our results suggest that in patients with acute gastrointestinal bleeding, a strategy of not performing transfusion until the hemoglobin concentration falls below 7 g per deciliter is a safe and effective approach.

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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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