Blood Transfusion for Gastrointestinal Bleeding

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Gastrointestinal bleeding accounts for more than 450,000 hospitalizations annually in the United States[1] and is a frequent indication for red-cell transfusion. Blood transfusions are given to 43% of patients hospitalized with upper gastrointestinal bleeding in the United Kingdom[2] and to 21% of patients hospitalized with lower gastrointestinal bleeding in the United States.[3]

Transfusion practices for patients with gastrointestinal bleeding have fluctuated over the past 100 years. Avoidance of transfusions early in the 20th century, owing to concern that increased blood pressure would induce rebleeding, gave way to more liberal use of transfusions,[4] and a hemoglobin threshold for transfusion of 10 g per deciliter was recommended up to the early 2000s.[5] On the basis of more recent data, current guidelines for the management of gastrointestinal bleeding have returned to a restrictive transfusion strategy, recommending a hemoglobin threshold of 7 g per deciliter.[6,7] Meta-analyses of randomized trials of restrictive transfusion thresholds as compared with liberal transfusion thresholds show no significant differences in 30-day mortality, length of hospital stay, or rates of adverse events and largely exclude the possibility of a clinical benefit with a liberal transfusion strategy.[8,9] However, only 0 to 1% of the patients in these analyses had acute gastrointestinal bleeding, which raises concerns about the generalizability of these results to patients with gastrointestinal bleeding.

The important study by Villanueva et al. in this issue of the *Journal*[10] provides long-awaited evidence to guide practice and justify current recommendations for the management of upper gastrointestinal bleeding. A hemoglobin threshold for transfusion of 7 g per deciliter, as compared with a threshold of 9 g per deciliter, was associated with a significant 45% relative-risk reduction in 45-day mortality. On the basis of the results of this study, 25 patients would have to be treated according to a restrictive transfusion strategy rather than a liberal transfusion strategy to avert one additional death at 45 days. The decrease in mortality was accounted for primarily by fewer deaths from bleeding that could not be successfully controlled. Significant reductions with the restrictive strategy were also seen in the rates of further bleeding, transfusion reactions, and cardiac events and in the length of hospital stay.

Largely on the basis of results from studies in animals, a restrictive transfusion strategy is commonly used for patients with variceal bleeding to prevent rebound increases in portal pressure, and Villanueva et al. suggest that the benefit of the restrictive transfusion strategy was seen mainly in patients with portal hypertension. However, subgroup analyses performed by the authors do not support a conclusion that the benefit differed between patients with and those without portal hypertension. No formal test of interaction was provided, but hazard ratios for further bleeding and for death were similar in the overall group and in subgroups with cirrhosis, esophageal varices, or peptic ulcer, with closely overlapping confidence intervals.

Although the results of the study by Villanueva et al. apply to a broad group of patients with upper gastrointestinal bleeding, modification of the transfusion threshold may be considered in specific subpopulations, such as patients with hypotension due to severe bleeding and patients with cardiovascular disease. Hemoglobin values early in the course of acute bleeding are minimally decreased and, in patients with substantial intravascular volume depletion, markedly overestimate the "true" hemoglobin level that will be seen after fluid resuscitation and equilibration. Approximately 30% of the patients in the study by Villanueva et al. had "hypovolemic shock," defined as a systolic blood pressure of <100 mm Hg and a heart rate of >100 beats per minute). Multivariable analysis showed that a restrictive transfusion strategy significantly decreased further bleeding, even after adjustment of the analysis for hypovolemic shock. However, the analysis of mortality was not adjusted for hypovolemic shock, results were not provided for patients with more marked hypotension (e.g., systolic blood pressure <80 or 90 mm Hg), and patients with massive bleeding were excluded from the study. Until more data are available, it may be reasonable to give transfusions to patients with marked hypotension due to bleeding before

the hemoglobin reaches 7 g per deciliter in order to forestall the drop to levels well below 7 g per deciliter that would occur with fluid resuscitation alone.

There is also uncertainty regarding the need for a higher transfusion threshold in patients with cardiovascular disease, and evidence is available from populations without gastrointestinal bleeding. Subgroup analyses of data from patients with cardiovascular disease in two previous large, randomized trials of a restrictive transfusion strategy as compared with a liberal transfusion strategy revealed no increased risk with restrictive hemoglobin thresholds of 7 g per deciliter and 8 g per deciliter.[11,12] Current guidelines recommend considering transfusion when the hemoglobin level falls to 8 g per deciliter or when cardiovascular symptoms develop in hemodynamically stable patients with preexisting cardiovascular disease.[9]

A final question is whether a restrictive transfusion strategy has attributes that provide benefit for patients with gastrointestinal bleeding beyond that seen in other populations. Randomized trials involving patients without gastrointestinal bleeding have not shown significant improvements in most clinically important outcomes with a restrictive transfusion strategy as compared with a liberal transfusion strategy.[8,9] In contrast, the study by Villanueva et al. shows superiority in key outcomes, such as bleeding and mortality.[10] Lower splanchnic blood flow or pressure and less impairment in coagulation may explain, at least in part, the significant reductions in bleeding and bleeding-related deaths seen with a restrictive transfusion strategy in patients with gastrointestinal bleeding.

In conclusion, the study by Villanueva et al. provides important evidence to guide clinical practice. Most patients with upper gastrointestinal bleeding, with or without portal hypertension, should have blood transfusions withheld until the hemoglobin level drops below 7 g per deciliter.

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

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Polycythemia Vera, the Hematocrit, and Blood-Volume Physiology

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Marchioli et al.[1] report in the *Journal* that a hematocrit target of less than 45% for therapeutic phlebotomy reduces the risk of thrombosis in patients with polycythemia vera. In the genomic era, readers may question attention given to a measurement as mundane as the hematocrit, but this study resolves a half-century of debate about the role of phlebotomy in polycythemia vera and has ramifications for diagnosis and management.

Polycythemia vera is a unique myeloproliferative disorder in which there is overproduction of morphologically normal erythrocytes, granulo-

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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 65 assigned to the liberal strategy (15%), 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 μg 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 (±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).

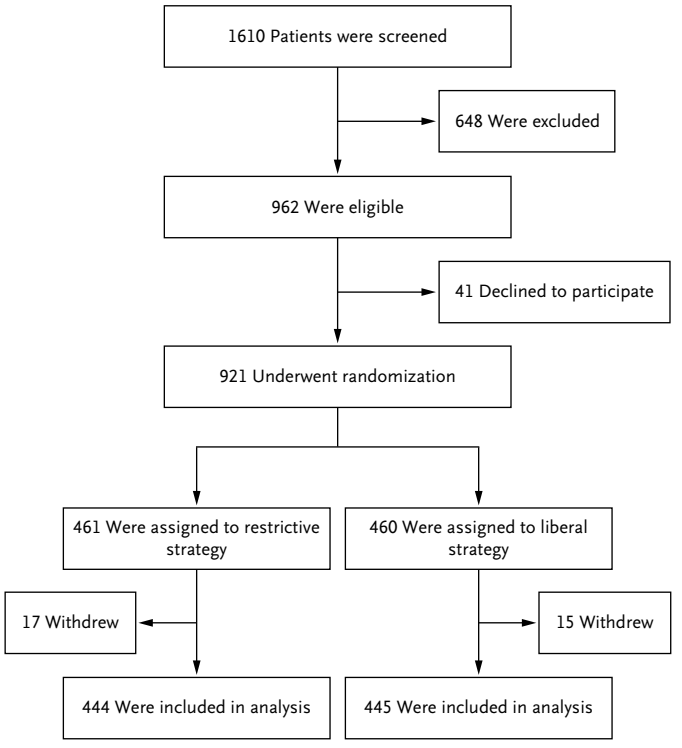


Figure 1. Screening, Randomization, and Follow-up.

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.

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 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-

Table 1. Baseline Characteristics of the Patients.*

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 decreased,[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

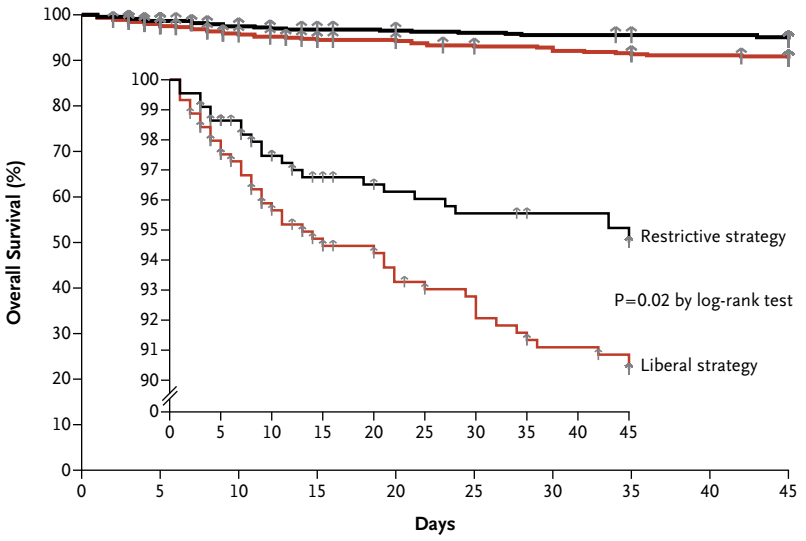
Table 2. Hemoglobin Levels, Transfusions, and Cointerventions.*

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 bleeding 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

A Survival, According to Transfusion Strategy



No. at Risk

Restrictive strategy	444	429	412	404	401	399	397	395	394	392
Liberal strategy	445	428	407	397	393	386	383	378	375	372

B Death by 6 Weeks, According to Subgroup

Subgroup	Restrictive Strategy	Liberal Strategy	Hazard Ratio (95% CI)	P Value
	no. of patients/total no. (%)			
Overall	23/444 (5)	41/445 (9)	0.55 (0.33–0.92)	0.02
Patients with cirrhosis	15/139 (11)	25/138 (18)	0.57 (0.30–1.08)	0.08
Child–Pugh class A or B	5/113 (4)	13/109 (12)	0.30 (0.11–0.85)	0.02
Child–Pugh class C	10/26 (38)	12/29 (41)	1.04 (0.45–2.37)	0.91
Bleeding from varices	10/93 (11)	17/97 (18)	0.58 (0.27–1.27)	0.18
Bleeding from peptic ulcer	7/228 (3)	11/209 (5)	0.70 (0.26–1.25)	0.26

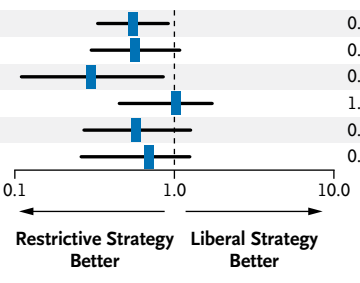


Figure 2. Rate of Survival, According to Subgroup.

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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The Commission does not shy away from speaking out against how in some places people with HIV are unable to access the services they need because "some countries have chosen to let sex workers, MSM [men who have sex with men], transgender people, and injecting drug users die of AIDS rather than change the laws and policies affecting them". The Commission calls for concrete solutions to expedite changes in laws, policies, and practices that violate the human rights of marginalised populations, while reinforcing and renewing the leadership and engagement of people living with HIV. The Commission identifies activism as a global public good, urging investment commensurate with the part it plays in improving health outcomes.

The Commission recognises the AIDS response as a forerunner to what needs to become standard practice to meet the challenges of global health and sustainable development: a whole-of-society approach with much more interconnected and inclusive governance and actions across sectors, driven by science, innovation, and human rights. As such, the UNAIDS–*Lancet* Commission identifies concrete actions that the global health community must take to reach beyond the "convergence" described by the *Lancet* Commission on Investing in Health[7] to a "grand convergence" which addresses the structural determinants of health justice and equity. Among these actions, the Commission makes a case for a global multistakeholder, multisector platform to guide action and hold stakeholders accountable to people; this platform would build on lessons from the AIDS response, the UN human rights system, and the experience of the independent Expert Review Group for the UN's Every Women Every Child global strategy.

We must heed the central messages of the UNAIDS–*Lancet* Commission—that we have the science and technical solutions to defeat the AIDS epidemic, that doing so will usher in substantial health, economic, and development gains, and that the final determining factor is that of global collective will. 2015 must be the year that we take a resolute leap towards ending AIDS.

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I am Executive Director of UNAIDS. I declare no competing interests.

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Transfusion after acute upper gastrointestinal haemorrhage

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In *The Lancet*, Vipul Jairath and colleagues[1] report on a feasibility trial of restrictive versus liberal blood transfusion in acute upper gastrointestinal haemorrhage. Six UK hospitals were randomly assigned to either a restrictive (transfusion when haemoglobin concentration fell below 80 g/L; 403 patients enrolled) or liberal (transfusion when haemoglobin concentration fell below 100 g/L; 533 patients enrolled) red blood cell transfusion policy for patients with acute upper gastrointestinal bleeding. Several feasibility outcomes were investigated, and the number of units of red blood cells that were transfused in patients according to the restrictive policy as compared with the liberal policy was non-significantly reduced (mean number of units 1·2 [SD 2·1] *vs* 1·9 [2·8]; difference –0·7 [95% CI –1·6 to 0·3]). The question of which policy to use is important, and the answer could have an effect on outcomes and economics of treatment, although the results of this trial should not be used to inform changes in present guidance, but should be viewed as an important precursor to a large randomised controlled trial.

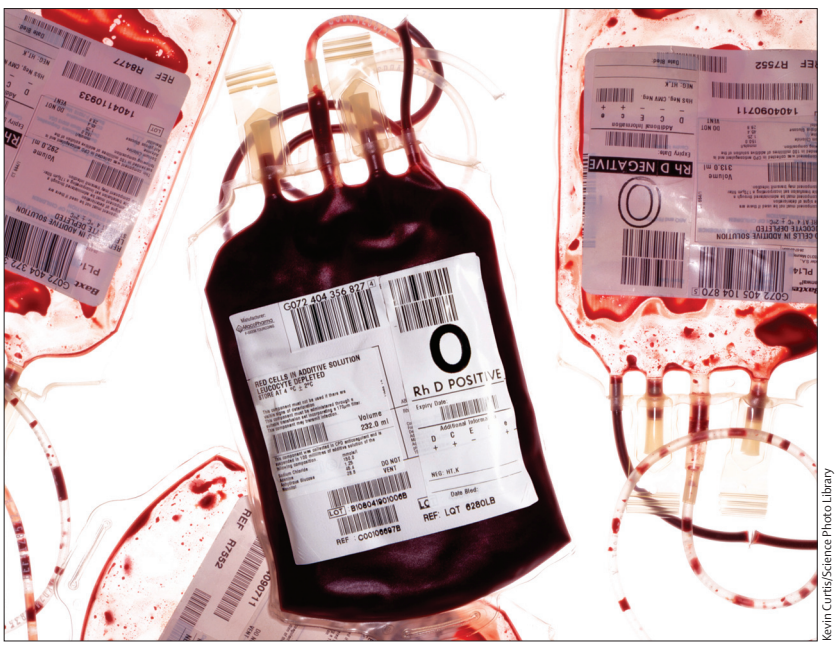
The role of blood transfusion in non-exsanguinating haemorrhage from the gastrointestinal tract is controversial, and evidence exists of substantial variation in practice.[2,3] Large observational studies[4] that have been used to create and validate risk assessment methods have shown that haemoglobin concentration is not an independent prognostic factor in multivariate

analysis, and does not feature in the resulting scoring system. Investigators of a few studies with varying levels of evidence have concluded that a restrictive policy and low trigger threshold for transfusion is beneficial, and that even if no absolute clinical advantage of a restrictive practice exists, then, as long as this is not detrimental, avoidance of blood transfusion in an increased proportion of patients both reduces transfusion risk and is economically beneficial.

Important publications in 2013 seemed to favour a restrictive policy,[5,6] but, as pointed out by Jairath and colleagues,[1] both the case-mix and exclusions in the only existing sufficiently powered randomised controlled trial, done in Barcelona, Spain,[6] make generalisation of the conclusions difficult. The very rapid access to interventional endoscopy in this Barcelona trial is not replicated in most hospitals in the UK, and this access in itself could affect transfusion. The proportion of patients with liver disease was much higher in the Barcelona study than the UK generally, and patients with major cardiovascular comorbidity were excluded. One of the recruitment discrepancies in Jairath and colleagues' feasibility trial was the proportion of patients with liver disease at each site, and this discrepancy is likely to be due to the specialist services provided within the clusters. Patients with liver disease who bleed could be argued to form a very different subgroup to those without liver disease and might reasonably be excluded from a future trial, and, in any case, only represent about 10% of all bleeds in the UK.

To obtain systematic evidence of an appropriate transfusion trigger after acute upper gastrointestinal haemorrhage is therefore a worthy aim. Jairath and colleagues' trial[1] has achieved good case ascertainment and protocol adherence, and identified areas of the protocol that could be adjusted to improve a future trial. A problem such as reduced protocol adherence in the liberal group is likely to be at least partly corrected by exclusion of the lowest-risk patients.

The benefit of blood transfusion in stable patients is difficult to assess. Many studies outside the context of gastrointestinal haemorrhage have been done, such as in trauma,[7] critical care,[8] cardiac surgery,[9] and hip surgery,[10] that describe either worse outcomes in transfused patients or no advantage in the liberally transfused group compared with the restrictive group.[11] Transfused blood has some well known risks, and is not entirely effective at



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replacing all normal blood functions. Sound physiological reasons also exist for why reduction of a transfusion trigger should be considered.[12] Replacement of blood in the anaemic patient aims to increase oxygen delivery, but oxygen delivery to tissues is not dependent on a normal haemoglobin concentration once normovolaemia has been restored. Oxygen delivery is dependent on cardiac output and oxygen extraction, both of which are increased by a reduction in blood viscosity (a consequence of anaemia) that leads directly to redistribution of blood flow, allowing increased oxygen extraction and ventricular performance. In fact, oxygen delivery only starts to fall when haematocrit is less than 25%, which equates to a haemoglobin concentration of about 80 g/L.[12] Even then, oxygen delivery is substantially greater than demand, so this demand can still be met well below this haemoglobin concentration. Therefore, in the non-exsanguinating case of most gastrointestinal bleeds, blood transfusion might not affect the main aim of increased oxygen delivery.

Guidelines on transfusion after acute upper gastrointestinal haemorrhage vary in their recommendations. A criticism of guidelines generally is that, by necessity, they are often based more on opinion than fact. If guidelines on this subject are to be updated in the future, then the proposed trial will hopefully provide the data on which to formulate solid guidance. A large, well run, pragmatic trial is to be welcomed.

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I declare no competing interests.

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Public health: real-world network targeting of interventions


Alex Slobodkin/Getty Images

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Public health interventions rarely introduce health innovations to every individual in a population all at once. Rather, practitioners target some people for early adoption, hoping that the innovation will spread by word of mouth through social networks. Selection of optimum targets for health interventions in social networks is difficult, because little is known about the spread of health innovations in real-world social networks.[1] In *The Lancet*, David Kim and colleagues[2] deliver the first randomised comparison of multiple network-targeting strategies to promote the spread of health innovations in real-world face-to-face social networks.

The authors establish two practically important results. First, on the encouraging side, they show that a new and cheap targeting strategy can substantially improve the spread of health innovations in social networks compared with a conventional and expensive targeting strategy. In 32 villages in rural Honduras, with a total population of 5773, villages were randomly assigned to receive one, both, or neither of two interventions (chlorine for water purification or multivitamins, each accompanied by vouchers which could be used by others to obtain further quantities of the same intervention). In each village, interventions were introduced to target groups composed either of randomly selected villagers, the best-connected villagers, or the friends of randomly selected villagers. As judged by redemption of vouchers, asking the friends of a random sample of villagers to distribute vouchers for multivitamins to other villagers led to a greater diffusion of multivitamins throughout the villages than asking the best-connected people in the villages to distribute the vouchers ($p<0·01$), and to an increase of 12·2% (95% CI 6·9–17·9) compared with a randomly targeted intervention. Targeting friends of a random sample of villagers is fairly cheap because it does not require a mapping of the entire social network, as would finding the most connected villagers. Getting more for less is always good news.

Second, on the cautionary side, Kim and colleagues[2] establish that the efficacy of different targeting strategies is highly context dependent: the targeting strategy that most improved the spread of multivitamins made no difference to the spread of chlorine for water purification. For any specific innovation, it will be difficult to predict which targeting strategy will produce the best results in practice. Yet Kim and colleagues' study marks real progress. Empirical confirmation that targeting the most-connected people in a network does not guarantee that a health innovation will ultimately reach the greatest number of people in the network challenges the conventional practice of focusing innovations on so-called opinion leaders or hubs.[3]

This study[2] should motivate further empirical research on how best to exploit face-to-face social networks for the seeding of health innovations. Among other things, future research should probe whether other network targeting strategies might reach even more people while maintaining cost savings. The difficulty of this

Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial

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Summary

Background Transfusion thresholds for acute upper gastrointestinal bleeding are controversial. So far, only three small, underpowered studies and one single-centre trial have been done. Findings from the single-centre trial showed reduced mortality with restrictive red blood cell (RBC) transfusion. We aimed to assess whether a multicentre, cluster randomised trial is a feasible method to substantiate or refute this finding.

Methods In this pragmatic, open-label, cluster randomised feasibility trial, done in six university hospitals in the UK, we enrolled all patients aged 18 years or older with new presentations of acute upper gastrointestinal bleeding, irrespective of comorbidity, except for exsanguinating haemorrhage. We randomly assigned hospitals (1:1) with a computer-generated randomisation sequence (random permuted block size of 6, without stratification or matching) to either a restrictive (transfusion when haemoglobin concentration fell below 80 g/L) or liberal (transfusion when haemoglobin concentration fell below 100 g/L) RBC transfusion policy. Neither patients nor investigators were masked to treatment allocation. Feasibility outcomes were recruitment rate, protocol adherence, haemoglobin concentration, RBC exposure, selection bias, and information to guide design and economic evaluation of the phase 3 trial. Main exploratory clinical outcomes were further bleeding and mortality at day 28. We did analyses on all enrolled patients for whom an outcome was available. This trial is registered, ISRCTN85757829 and NCT02105532.

Findings Between Sept 3, 2012, and March 1, 2013, we enrolled 936 patients across six hospitals (403 patients in three hospitals with a restrictive policy and 533 patients in three hospitals with a liberal policy). Recruitment rate was significantly higher for the liberal than for the restrictive policy (62% *vs* 55%; p=0·04). Despite some baseline imbalances, Rockall and Blatchford risk scores were identical between policies. Protocol adherence was 96% (SD 10) in the restrictive policy *vs* 83% (25) in the liberal policy (difference 14%; 95% CI 7–21; p=0·005). Mean last recorded haemoglobin concentration was 116 (SD 24) g/L for patients on the restrictive policy and 118 (20) g/L for those on the liberal policy (difference –2·0 [95% CI –12·0 to 7·0]; p=0·50). Fewer patients received RBCs on the restrictive policy than on the liberal policy (restrictive policy 133 [33%] *vs* liberal policy 247 [46%]; difference –12% [95% CI –35 to 11]; p=0·23), with fewer RBC units transfused (mean 1·2 [SD 2·1] *vs* 1·9 [2·8]; difference –0·7 [–1·6 to 0·3]; p=0·12), although these differences were not significant. We noted no significant difference in clinical outcomes.

Interpretation A cluster randomised design led to rapid recruitment, high protocol adherence, separation in degree of anaemia between groups, and non-significant reduction in RBC transfusion in the restrictive policy. A large cluster randomised trial to assess the effectiveness of transfusion strategies for acute upper gastrointestinal bleeding is both feasible and essential before clinical practice guidelines change to recommend restrictive transfusion for all patients with acute upper gastrointestinal bleeding.

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Introduction

Acute upper gastrointestinal bleeding accounts for 70 000 admissions every year to UK hospitals[1] and for 11% of all red blood cells (RBCs) transfused in England.[2] Despite being the most common single indication for RBC transfusion, the optimum threshold for transfusion is uncertain.[3] Findings from randomised trials in other cohorts such as those who have had cardiac surgery,[4] are in critical care,[5] or have had hip surgery[6] have shown that thresholds for transfusion can be safely lowered without adversely affecting outcomes. Whether a restrictive approach to transfusion can safely be extrapolated to elderly patients with acute bleeding or cardiovascular disease is unclear,[7–10] which is particularly relevant to patients with acute upper gastrointestinal bleeding, in whom the burden of comorbidity is often high.[3,11]

Findings from cohort studies suggest associations between RBC transfusion after acute upper gastrointestinal bleeding and adverse clinical outcomes.[12,13] Investigators of a single-centre, randomised controlled trial[14] that took place for 6 years in a specialist

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gastrointestinal bleeding unit in Barcelona, Spain, reported reduced mortality and rebleeding with implementation of restrictive transfusion for acute upper gastrointestinal bleeding. However, these results are unlikely to be generalisable to routine clinical practice because of exclusion of patients with major cardiovascular comorbidity, stringent processes of care, and differing case mix.[3] A large, pragmatic, multicentre trial is essential to either substantiate or refute these findings before clinical practice guidelines are changed worldwide to recommend restrictive transfusion for all patients with acute upper gastrointestinal bleeding. Because acute upper gastrointestinal bleeding is a medical emergency that can need early transfusion and many care providers, a trial that needs adherence to transfusion strategies across many centres would be challenging to do.

In the Transfusion in Gastrointestinal Bleeding Trial (TRIGGER), we aimed to assess whether a restrictive or liberal RBC transfusion policy for acute upper gastrointestinal bleeding in routine clinical practice is feasible and safe to implement through cluster randomisation, and did an exploratory analysis of the major clinical effects, enrolling all new adult admissions, irrespective of their comorbidity (except for exsanguinating haemorrhage) or age.

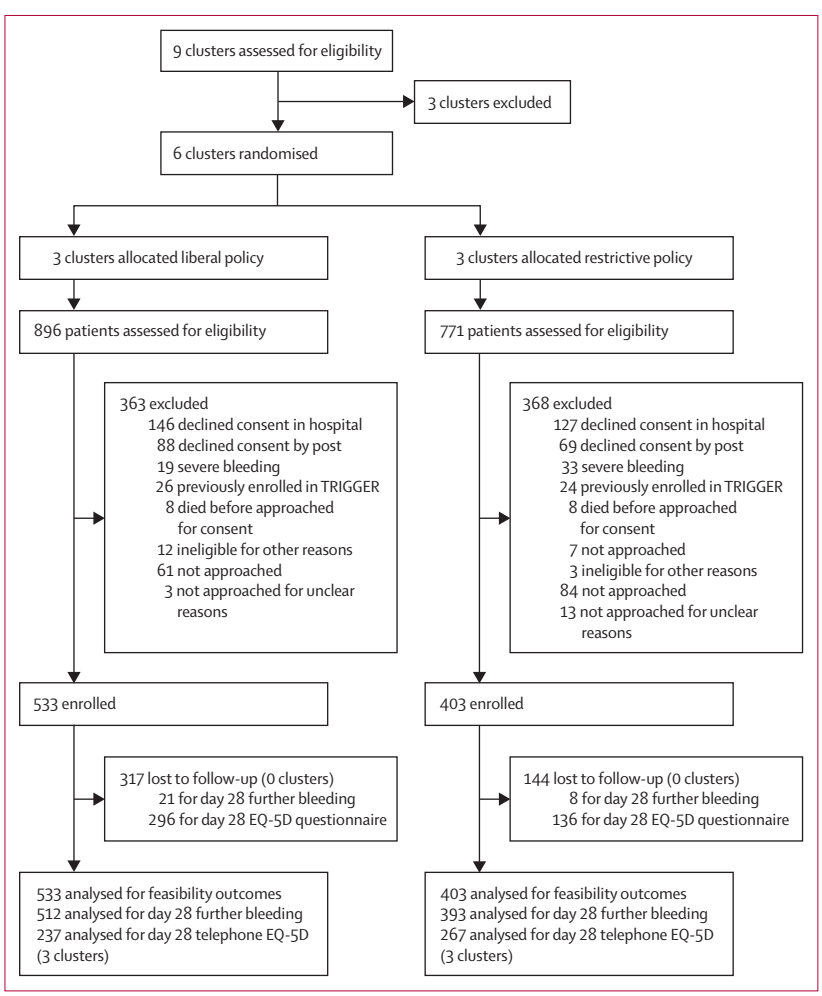

Figure 1: **Trial profile**

Methods

Study design and patients

We did this pragmatic, multicentre, open-label, cluster randomised feasibility trial of a restrictive versus liberal RBC transfusion policy in adults with acute upper gastrointestinal bleeding in the UK to inform the feasibility and design of a phase 3 trial. Because of the need for immediate implementation of an RBC transfusion policy from first presentation until discharge, across several specialty groups in different clinical areas of a hospital, we chose a cluster design to simplify intervention delivery and reduce contamination between policies. We deemed a feasibility trial essential to establish whether clinician behaviour could be changed on a hospital-wide scale and to assess potential for selection bias or outcome-reporting bias because of the open-label nature of the study. A rationale and methodology study has been published,[15] and the full protocol is available online.

Hospitals were eligible if they had more than 20 acute upper gastrointestinal bleeding admissions monthly, more than 400 adult beds, endoscopy available 24 h a day, onsite access to intensive care and surgery, and staff willing to be randomly allocated to and implement a transfusion policy for all new acute upper gastrointestinal bleeding admissions. Patients were eligible if they presented with new acute upper gastrointestinal bleeding (defined by haematemesis or melaena) and were aged 18 years or older; the only exclusion criterion was exsanguinating haemorrhage, for which we provided objective guidance criteria (appendix p 1). We sought written informed consent from individual patients or their representatives for use of routine hospital records and telephone follow-up at day 28. Ethics approval was granted in England (National Research Ethics Service Committee South Central—Oxford C; reference 12/SC/0062) and Scotland (Scotland A Research Ethics Committee; reference 12/SS/0023).

Randomisation and masking

We randomly allocated (using a computer-generated randomisation sequence) centres to a transfusion policy using a random permuted block of six (three hospitals per policy), without stratification or matching (randomisation done by BCK). We identified patients from emergency departments and acute admissions units. All clinicians, patients, and outcome assessors were unmasked to treatment allocation.

Procedures

For the restrictive policy, patients were eligible for RBC transfusion when their haemoglobin concentration fell below 80 g/L, with a post-transfusion target of 81–100 g/L.

For the liberal policy, patients were eligible when their haemoglobin concentration fell below 100 g/L, with a post-transfusion target of 101–120 g/L. These thresholds were informed by present UK transfusion practice.[15] The number of RBC units transfused and the timing of repeat haemoglobin concentration measurements was per clinician discretion. All clinicians could deviate from the policy, but were asked to document the reason. In keeping with the pragmatic design no other aspects of care were protocol driven, although clinicians were encouraged to follow evidence-based guidelines.[16,17]

A lead clinician championed the study at each site, supported by a coinvestigator from an allied acute specialty. We used a multifaceted approach to implement the policy, including the daily presence of a research nurse in acute areas, regular attendance by a member of the trial team at medical and nursing handovers in acute areas to reinforce the policy, departmental and grand round presentations, posters, regular email reminders, and a flagging system in transfusion laboratories to remind doctors and transfusion laboratory scientific staff of the policy whenever a transfusion request for acute upper gastrointestinal bleeding occurred.

Outcomes

We collected both feasibility outcome measures and exploratory clinical outcome measures, listed in the study protocol. Feasibility outcomes were recruitment rate, adherence to transfusion policy (overall, per patient, and per haemoglobin count), difference in haemoglobin concentration between groups, RBC exposure, evidence of selection bias, and information to guide the design and economic evaluation of the phase 3 trial. We measured haemoglobin concentrations (during the first 7 days, the entire follow-up, and before discharge), the proportion of patients receiving at least one RBC transfusion, and the number of units transfused. Clinical outcomes included further bleeding, thromboembolic and ischaemic events, and number of infections (inhospital and day 28, with day 28 being the main analysis timepoint). We also assessed mortality, serious adverse events, and health-related quality of life (with Euroqol EQ-5D questionnaire) at day 28, and need for therapeutic intervention at index endoscopy, need for surgery or radiological intervention to control bleeding, and transfusion reactions.

Statistical analysis

On the basis of our predicted sample size of 849 patients, we estimated the precision with which we would be able to detect a difference in the mean Rockall[18] score between treatment policies, which might show selection bias. With a two-sided significance level of 5%, an intracluster correlation coefficient of 0·033, and an SD of 1·84, 849 patients would provide 92% power to detect a mean difference of one point.[15]

	Liberal policy (n=533)	Restrictive policy (n=403)
Baseline characteristics		
Male	322 (60%)	244 (61%)
Age (years)	60·4 (20·0)	58·0 (20·3)
Rockall score*	2 (1–4)	2 (1–4)
Blatchford score†	6 (2–10)	6 (1–9)
Signs and symptoms		
Melaena‡	266 (50%)	209 (52%)
Haematemesis	302 (57%)	209 (52%)
Heart rate (beats per min)§	95·6 (20·1)	94·8 (21·8)
Systolic blood pressure (mm Hg)¶	125·9 (22·7)	126·9 (22·8)
Pre-existing comorbidities		
Ischaemic heart disease	76 (14%)	61 (15%)
Cardiac failure‖	21 (4%)	18 (4%)
Hypertension‖	109 (20%)	123 (31%)
Respiratory disease‖	74 (14%)	84 (21%)
Renal disease	36 (7%)	18 (4%)
Liver disease	91 (17%)	45 (11%)
Malignancy‖	58 (11%)	41 (10%)
Stroke‖	34 (6%)	25 (6%)
First recorded laboratory data		
Haemoglobin (g/L)	114 (34)	119 (32)
Urea (mmol/L)**	10·2 (7·2)	10·0 (7·6)
Albumin (g/L)††	36 (8)	38 (7)
Lowest haemoglobin during follow-up		
≤79 g/L	146 (27%)	118 (29%)
80–99 g/L	146 (27%)	69 (17%)
100–120 g/L	91 (17%)	70 (17%)
≥121 g/L	149 (28%)	146 (36%)
Medications and fluids		
Proton pump inhibitor (pre-endoscopy)	270 (53%)	225 (56%)
Iron (oral or intravenous)‡‡	47 (9%)	43 (11%)
Any intravenous fluids§§	412 (81%)	297 (75%)
Colloid volume in 24 h	0·2 (0·6)	0·1 (0·4)
Crystalloid volume in 24 h	1·6 (1·4)	1·9 (1·7)
Platelets¶¶	13 (2%)	13 (3%)
Fresh frozen plasma¶¶	22 (4%)	24 (6%)
Cryoprecipitate¶¶	1 (<1%)	2 (<1%)
Source of bleeding‖‖		
Peptic ulcer	94 (24%)	59 (20%)
Gastro-oesophageal varix	56 (15%)	25 (8%)
Oesophagitis/gastritis/duodenitis	89 (23%)	82 (28%)
Mallory-Weiss tear	8 (2%)	22 (8%)
Malignancy	13 (3%)	9 (3%)
Non-identified	60 (16%)	49 (17%)
Other	67 (17%)	40 (16%)

Data are n (%), mean (SD), or median (IQR). *Data missing for one patient in the liberal policy. †Data missing for one patient in the liberal policy and six in the restrictive policy. ‡Data missing for two patients in the liberal policy. §Data missing for two patients in the liberal policy and one in the restrictive policy. ¶Data missing for one patient in the restrictive policy. ‖Data missing for one patient in the liberal policy. **Data missing for two patients in the liberal policy and nine in the restrictive policy. ††Data missing for 53 patients in the liberal policy and 37 in the restrictive policy. ‡‡Data missing for 24 patients in the liberal policy and 11 in the restrictive policy. §§Data missing for 24 patients in the liberal policy and eight in the restrictive policy. ¶¶Data missing for nine patients in the liberal policy and one in the restrictive policy. ‖‖Endoscopy not performed for 146 patients in the liberal policy and 117 in the restrictive policy.

Table 1: **Baseline characteristics, laboratory variables, and cointerventions**

For the **study protocol** see http://www.nhsbt.nhs.uk/trigger/documents/study-protocol/TRIGGER_%20Protocol.pdf

See Online for appendix

	Liberal policy			Restrictive policy			p value for difference between treatment policies
	Enrolled (n=533)	Not enrolled (n=363)	Difference	Enrolled (n=403)	Not enrolled (n=368)	Difference	
Age (years)	59·9 (20·0)	53·9 (23·4)	5·2	57·4 (20·3)	59·8 (23·6)	−2·6	0·05
Haemoglobin concentration (g/L)	115 (34)	128 (31)	−10	119 (32)	126 (27)	−4·0	0·08
Rockall score	2·3 (1·8)	1·7 (1·9)	0·6	2·4 (2·1)	2·5 (1·9)	−0·1	0·07
Blatchford score	6·1 (4·6)	3·8 (4·1)	2·4	5·8 (4·6)	4·7 (4·5)	1·3	0·07

Data are mean (SD).

Table 2: **Differences between eligible patients who were enrolled versus those not enrolled**

	Liberal policy	Restrictive policy	Treatment effect*	p value
All enrolled patients†				
Overall adherence‡	83% (25)	96% (10)	14% (7 to 21)	0·005
Patients receiving at least one transfusion	247 (46%)	133 (33%)	−12% (−35 to 11)	0·23
Number of units transfused	1·9 (2·8)	1·2 (2·1)	−0·7 (−1·6 to 0·3)	0·12
Mean haemoglobin over entire follow-up (g/L)	115 (23)	115 (26)	−1·0 (−12·0 to 11·0)	0·90
Last recorded haemoglobin (g/L)	118 (20)	116 (24)	−2·0 (−12·0 to 7·0)	0·50
Patients with haemoglobin concentration <120 g/L§				
Overall adherence	76% (27)	94% (12)	19% (11 to 26)	0·003
Patients receiving at least one transfusion	246 (64%)	132 (51%)	−12% (−36 to 12)	0·24
Number of units transfused	2·6 (3·0)	1·8 (2·5)	−0·8 (−1·9 to 0·3)	0·12
Mean haemoglobin over entire follow-up (g/L)	103 (13)	98 (15)	−5 (−13 to 3)	0·18
Last recorded haemoglobin before discharge (g/L)	107 (12)	101 (13)	−7 (−14 to 0)	0·05
Patients with haemoglobin concentration <100 g/L¶				
Overall adherence	69% (28)	93% (14)	24% (16 to 32)	0·001
Patients receiving at least one transfusion	242 (83%)	130 (68%)	−14% (−32 to 4)	0·09
Number of units transfused	3·4 (3·0)	2·4 (2·6)	−1·0 (−2·0 to 0·01)	0·05
Mean haemoglobin over entire follow-up (g/L)‖	98 (10)	92 (10)	−6 (−11 to −1)	0·02
Last recorded haemoglobin before discharge (g/L)**	105 (12)	96 (11)	−9 (−14 to −4)	0·007

Data are mean (SD) or n (%). *Treatment effects are differences in means for continuous outcomes, and differences in percentages for binary outcomes. †Liberal policy: n=533; restrictive policy: n=403. ‡Overall adherence refers to the proportion of haemoglobin counts for which no deviation from the transfusion policy occurred for each patient. §Liberal policy: n=383; restrictive policy: n=257. ¶Liberal policy: n=293; restrictive policy: n=190. ‖18 patients had missing data and were excluded from this analysis (16 liberal and two restrictive). **50 patients had missing data and were excluded from this analysis (37 liberal and 13 restrictive).

Table 3: **Protocol adherence, red blood cell transfusion, and haemoglobin results**

The statistical analysis plan was published before database lock.[19] All analyses were predefined unless otherwise stated. We did analyses on all enrolled patients for whom an outcome was available. We also did analyses on all enrolled patients with a haemoglobin concentration of less than 120 g/L during follow-up because this group was expected to be most likely to receive a transfusion and be affected by the treatment policy.

We analysed feasibility and clinical outcomes using cluster-level summaries, giving equal weight to each cluster.[20,21] We presented results as a difference in means for continuous outcomes, and a difference in proportions for binary outcomes. Prespecified subgroup analyses and post-hoc analyses are listed in the appendix p 3.

We did all analyses with Stata/IC 12.1. This trial is registered, ISRCTN85757829 and NCT02105532.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data analysis, data interpretation, or writing of the report. The writing committee had full access to all the data in the study and had final responsibility for the decision to submit to publication. BCK and CJD are statistical guarantors.

Results

Between Sept 3, 2012, and March 1, 2013, 1667 patients were admitted to the six university hospitals in the UK participating in the trial with acute upper gastrointestinal bleeding, of whom 1600 (96%) were eligible and 936 (59%) of whom we enrolled: 533 (57%) into the liberal RBC transfusion policy and 403 (43%) into the restrictive policy (figure 1). Recruitment rate was significantly higher in the liberal policy than the restrictive policy (62% *vs* 55%; p=0·04). 3% were ineligible because of exsanguinating bleeding (liberal group 19 [2%] of 896; restrictive group 33 [4%] of 771; p=0·08). The commonest reason for non-enrolment was consent refusal for data collection and telephone follow-up, which occurred in 430 (27%) of the 1600 eligible patients. Data for further bleeding at day 28 were missing in 29 (3%) of 936 patients randomly allocated, who we excluded from analysis. Telephone contact at day 28 to administer an EQ-5D questionnaire was not possible in 136 (34%) of 403 participants in the restrictive policy and 296 (56%) of 533 in the liberal policy.

Baseline characteristics were similar in terms of Rockall and Blatchford risk scores, blood pressure, heart rate, and symptoms of bleeding (table 1, appendix p 2). Some baseline imbalances in comorbidities existed, with a greater proportion of patients in the liberal policy than the restrictive policy with liver disease, whereas more patients in the restrictive policy had respiratory disease or hypertension. Ischaemic heart disease was

similar between treatment groups. In the liberal policy, patients enrolled were older than those not enrolled compared with the restrictive policy, in which patients enrolled were younger than those not enrolled (table 2).

Overall adherence to the transfusion protocol (mean number of haemoglobin counts with no deviations, per patient) was significantly higher in the restrictive policy (96%; SD 10) than the liberal policy (83%; SD 25; difference 14% [95% CI 7–21]; p=0·005), with a similar pattern noted in patients with a haemoglobin concentration of less than 120 g/L (restrictive policy 94% [SD 12] *vs* liberal policy 76% [27]; difference 19% [95% CI 11–26]; p=0·003) (table 3). Adherence each month was consistent in the restrictive policy, but decreased over time in the liberal policy (figure 2). In the liberal policy, 675 (24%) of 2769 of all haemoglobin measurements led to a protocol deviation (672 no transfusion when haemoglobin concentration was less than 100 g/L; three transfusions when haemoglobin concentration was 100 g/L or higher), compared with 93 (5%) of 1754 in the restrictive group (67 no transfusion when haemoglobin concentration was less than 80 g/L; 26 transfusions when haemoglobin concentration was 80 g/L or higher).

247 (46%) of 533 patients allocated to the liberal policy were transfused compared with 133 (33%) of 403 patients allocated to the restrictive policy (difference –12%; 95% CI –35 to 11; p=0·23; table 3). The mean number of units transfused was lower in the restrictive policy than the liberal policy, although this difference was not significant (restrictive policy 1·2 [SD 2·1]; liberal policy 1·9 [2·8]; difference –0·7 [95% CI –1·6 to 0·3]; p=0·12). In patients with a haemoglobin concentration of less than 120 g/L, concentration at hospital discharge was significantly lower in the restrictive policy than in the liberal policy (restrictive policy 101 g/L [SD 13]; liberal policy 107 g/L [12]; difference –7 g/L, 95% CI –14 to 0; p=0·05) (figure 3). In patients with a haemoglobin concentration of less than 100 g/L, mean concentration during the entire follow-up and at discharge was significantly lower in the restrictive policy than the liberal policy (table 3). We noted no significant differences in clinical outcomes or mean EQ-5D scores between treatment groups (table 4).

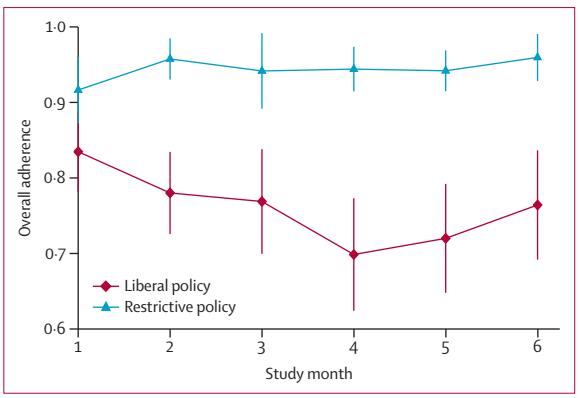

Figure 2: **Overall adherence to transfusion policy by study month (patients with a haemoglobin concentration of less than 120 g/L)**

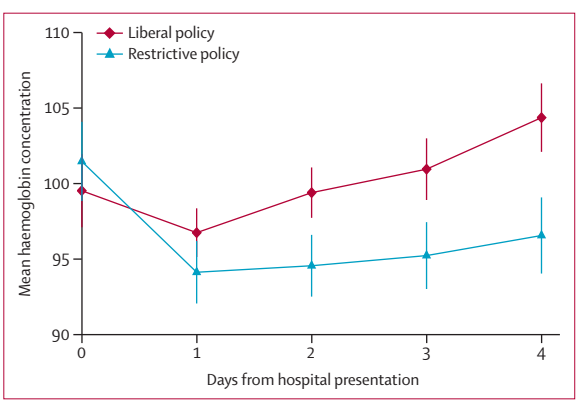

Figure 3: **Mean haemoglobin concentration over time (patients with haemoglobin concentration of less than 120 g/L)**

Discussion

We report the first multicentre randomised trial comparing transfusion strategies for acute upper gastrointestinal bleeding, gathering evidence for the feasibility of a phase 3 trial (panel). The pragmatic eligibility criteria meant that 96% of patients admitted to the six hospitals during the recruitment period were eligible, of whom almost 60% were enrolled. The cluster design was acceptable to clinicians, resulted in an efficient recruitment rate, and enabled implementation of the transfusion policy hospital-wide, alongside routine clinical care. High adherence to both transfusion policies was achieved, resulting in a 13% absolute reduction in the proportion of patients transfused in the restrictive policy, reduction in the amount of blood transfused between treatment policies, and separation in haemoglobin concentration, although none of these between-group differences were significant. The small, non-significant reduction in mean number of RBC units transfused was in keeping with that reported in a meta-analysis of transfusion trigger trials.[26]

Protocol adherence was better in the restrictive policy than the liberal policy—restrictive policy protocol adherence was consistent throughout the trial. In the liberal policy, most violations were due to RBCs not being administered below the threshold of 100 g/L. This greater adherence to the restrictive policy than the liberal policy could be due to clinician bias towards low transfusion thresholds for acute upper gastrointestinal bleeding, particularly for low-risk patients, extrapolated from evidence of the safety of restrictive transfusion in trials of critical care,[5] cardiac surgery,[4] and hip surgery.[10] Our liberal threshold of 100 g/L was informed by actual UK transfusion practice at the time the study was designed in 2009. Guidelines advocating restrictive transfusion for acute upper gastrointestinal bleeding are based on one trial done in an intensive care population[5] in which patients with acute bleeding were specifically excluded; transfusion requirements might

	Liberal policy (n=383)	Restrictive policy (n=257)	Treatment effect*
Further bleeding†			
Day 28	31 (9%)	13 (5%)	−4 (−12 to 5)
Hospital discharge	24 (6%)	9 (4%)	−3 (−13 to 7)
All-cause mortality‡			
Day 28	25 (7%)	14 (5%)	−1 (−8 to 6)
Thromboembolic or ischaemic events§			
Day 28	23 (7%)	9 (4%)	−4 (−10 to 3)
Hospital discharge	21 (5%)	7 (3%)	−3 (−9 to 2)
Surgical or radiological intervention			
Hospital discharge	11 (3%)	10 (4%)	1 (−4 to 6)
Acute transfusion reactions¶			
Hospital discharge	9 (2%)	2 (1%)	−2 (−4 to 1)
Therapeutic intervention			
Hospital discharge	144 (38%)	81 (32%)	−7 (−25 to 11)
Infections‖			
Hospital discharge	92 (24%)	67 (26%)	1 (−25 to 27)
Length of hospital stay (days)**			
Hospital discharge	5 (3–9)	4 (3–7)	−1 (−2 to 0)
EQ-5D††			
Day 28	0·69 (0·32)	0·76 (0·27)	0·07 (−0·10 to 0·23)
Serious adverse events‡‡			
Day 28	83 (22%)	45 (18%)	−5 (−23 to 13)

Data are n (%), median (IQR), mean (SD), or effect (95% CI). *Treatment effects are differences in means for continuous outcomes and differences in percentages for binary outcomes. †27 patients had missing data and were excluded from this analysis (19 liberal and eight restrictive). ‡One patient had missing data in the liberal group and was excluded from this analysis. §48 patients had missing data and were excluded from this analysis (33 liberal and 15 restrictive). ¶Five patients had missing data and were excluded from this analysis (three liberal and two restrictive). ‖One patient had missing data in the liberal group and was excluded from this analysis. **31 patients had missing data and were excluded from this analysis (21 liberal and ten restrictive). ††295 patients had missing data and were excluded from this analysis (214 liberal and 81 restrictive). ‡‡One patient in the liberal group was missing data and was excluded from this analysis.

Table 4: **Clinical outcomes (patients with haemoglobin concentration of less than 120 g/L)**

reasonably be expected to differ after acute bleeding because of rapid development of anaemia and haemodynamic compromise. For the phase 3 trial, we plan to lower the threshold for transfusion in the liberal group to take account of this changing practice and we would also exclude low-risk patients (with a Rockall score of 0) who are unlikely to be transfused.

The greater protocol adherence in the restrictive than the liberal policy might also have been influenced by the Barcelona trial of transfusion strategies for gastrointestinal bleeding,[14] published during recruitment to TRIGGER. In this single-centre trial, improved survival and rebleeding rates were noted in patients transfused below a haemoglobin concentration of 70 g/L compared with those transfused below 90 g/L. Whether these results could be collected in other hospitals, particularly in the UK, is questionable on several grounds. First, a high proportion of the trial population had liver cirrhosis and variceal bleeding, and a treatment effect was only seen in patients for whom mechanisms of bleeding differ and who account for only 10% of UK presentations with acute upper gastrointestinal bleeding. Second, the trial excluded patients with major comorbidities, including ischaemic heart disease, vascular disease, or stroke, which excludes almost 40% of all UK presentations with acute upper gastrointestinal bleeding,[27] representing the group at greatest potential of complications from acute anaemia. Third, processes of care are unlikely to be reproducible at other institutions, specifically delivery of therapeutic endoscopy to all patients within 6 h, which might affect transfusion use. Furthermore, single-centre trials tend to find larger treatment effects than multicentre trials,[28] highlighting the risk of strong recommendations on the basis of a single-centre trial.[28,29]

Despite some baseline imbalances, participants in each policy had similar risk scores and haemodynamic status. Patients enrolled in the liberal policy were older than those not enrolled, whereas in the restrictive group, patients enrolled were younger than those not enrolled. These differences are probably chance imbalances due to the small number of clusters. For the main trial, about 30 clusters would need to be randomly allocated, which should achieve acceptable balance between treatment arms. Prespecified covariate adjustment would account for any unexpected baseline imbalances in important prognostic factors.[30] Baseline imbalances could have been due to selection bias because of the open-label nature of the study. Prevention of selection bias will be important in the phase 3 trial. A potential solution would be to seek a consent waiver for anonymous data collection to allow routinely collected data to be summarised for all eligible participants.

TRIGGER was not a phase 3 trial, so its clinical outcomes should not be used to inform clinical practice directly. A key area of uncertainty in transfusion practice concerns safe transfusion thresholds in patients with ischaemic heart disease,[8,10,31] particularly relevant to acute upper gastrointestinal bleeding; 14% of patients with acute upper gastrointestinal bleeds have ischaemic heart disease.[11,12] Findings from a pilot trial of transfusion strategies in patients with ischaemic heart disease[10] showed a 15% absolute increase in mortality in patients receiving transfusion at a threshold of haemoglobin concentration of 80 g/L compared with 100 g/L, a similar magnitude of excess mortality as that observed in TRIGGER (appendix, p 4), showing the need for further evidence before universal restrictive transfusion for acute upper gastrointestinal bleeding can be advocated.

This feasibility trial provides key learning points for design of the phase 3 trial. We plan to enrol the same patient population as in TRIGGER, using broad and inclusive eligibility criteria to promote efficient recruitment and generalisability, although we would exclude the lowest-risk patients who are unlikely to be recipients of transfusion. For high-risk patients with ischaemic heart or cerebrovascular disease who might be particularly susceptible to adverse effects of anaemia, we would ask the Independent Data Monitoring Committee to monitor serious adverse events and provide

recommendations at a formal interim analysis for their continued enrolment, and do a prespecified subgroup analysis for ischaemic heart disease. Despite the results of the Barcelona trial,[14] we would also enrol patients with liver cirrhosis because of the limitations of external validity in that trial. For the interventions, we plan to lower thresholds for transfusion to a haemoglobin concentration of 90 g/L in the liberal arm and to 70 g/L in the restrictive arm, which accounts for the uncertainty in present practice. Although previous transfusion strategy trials have used haemoglobin concentration as an entry criterion,[5,6,8,14] we designed this trial to assess the effect of implementation of a treatment policy on a hospital-wide scale for all patients presenting with acute upper gastrointestinal bleeding, and would repeat this efficient design for a phase 3 trial, but additionally incorporate a prespecified secondary analysis of clinical outcomes using the transfusion threshold in the liberal group as a cutoff.

The primary outcome for the phase 3 trial would be mortality. Our estimate of the intracluster correlation coefficient, essential for sample size calculation, was similar to that estimated from a UK audit of acute upper gastrointestinal bleeding,[27] which probably shows that both studies were pragmatic, recording all presentations with acute upper gastrointestinal bleeding. We would still randomly allocate by cluster to assess the treatment effect of a policy in a diverse patient population in routine clinical care, while minimising contamination. These benefits far outweigh the often-cited limitation of statistical inefficiency in cluster randomised trials, particularly since sufficient recruitment would not be a barrier in this trial; we estimate that although 15% more participants would need to be recruited through cluster randomisation than through individual randomisation, recruitment time would be almost 40% less, resulting in a more efficient trial design (appendix p 5). We believe that this design offers an attractive method of comparative effectiveness research in the NHS for treatment policies that are within the boundaries of normal care and that have clinical equipoise.

Patient consent for routine clinical data collection and telephone follow-up was lower than we expected. For the phase 3 trial, we would seek a consent waiver to enable analysis of routinely recorded inhospital data for all patients. The trial design would be more efficient through linkage to routine administrative data to record mortality and readmissions, which would allow follow-up for longer periods than would be possible without this data. Telephone follow-up at day 28 for patient-reported outcomes would be replaced by assessment of functional status at discharge to reduce attrition rates due to difficulties with telephone contact.

Reduction of RBC transfusion for acute upper gastrointestinal bleeding would have substantial financial implications for health-care agencies. In 2013–14, 1·7 million units of RBCs were issued in England, with an estimated 204 000 units for acute upper gastrointestinal bleeding alone, costing UK£123·31 per unit.[32] A 13% reduction, as shown in this trial, would lead to annual savings to the NHS of about £3·3 million for the blood alone, which excludes blood transfusion laboratory and blood administration costs.

We used a pragmatic cluster randomised design to show the feasibility of implementation of hospital-wide transfusion policies for acute upper gastrointestinal bleeding, resulting in a non-significant reduction in blood use and separation in haemoglobin concentration. A large, cluster randomised phase 3 trial to assess the effectiveness of transfusion strategies for acute upper gastrointestinal bleeding is now essential before practice guidelines are changed to recommend restrictive transfusion for all patients with acute upper gastrointestinal bleeding.

Panel: Research in context

Systematic review

We did a Cochrane review of randomised controlled trials comparing red blood cell (RBC) transfusion strategies for acute upper gastrointestinal bleeding in 2008, and updated it in 2010.[22] We identified three underpowered trials of 93 participants.[23-25] The small numbers of participants, missing data, and methodological deficiencies did not allow meaningful conclusions, justifying the need for a trial of transfusion strategies for acute upper gastrointestinal bleeding. We have identified one single-centre trial from Barcelona,[14] which started in 2003 and had the report published in 2013, halfway through TRIGGER recruitment. Investigators of this trial reported a reduction in mortality and rebleeding with restrictive transfusion and thus recommended restrictive transfusion for acute upper gastrointestinal bleeding. The population in this trial differed from ours because a third of participants had liver cirrhosis for which the mechanism of bleeding differs and the investigators excluded patients with cardiovascular comorbidity and used care processes unlikely to be generalisable to most health-care institutions.[3]

Interpretation

In our trial, the randomised transfusion policies were successfully implemented on a hospital-wide scale across different specialty groups and clinical areas for 6 months, with a high level of protocol adherence, leading to a non-significant reduction in RBC exposure in the restrictive policy and separation in haemoglobin concentration between treatment groups. We did not note any significant differences in clinical outcomes, although the trial was not powered for these outcomes. If restrictive transfusion is proven to be safe and effective in a large, similarly pragmatic trial, this trial would have the potential to safely reduce use of RBCs for the largest single indication for transfusion in England, and might have broad implications for restrictive use of RBCs after acute haemorrhage. A large cluster randomised trial is feasible and essential to do before clinical practice guidelines recommend restrictive transfusion for all patients with acute upper gastrointestinal bleeding.

Contributors

VJ and MFM conceived of the study. VJ, BCK, AG, CJD, SM, CL, KRP, RFL, SPT, TSW, and MFM designed the study. AM, MWJ, AJS, SME, AAB, HD, JG, ILJ, MD, NC, IR, RH, and CD acquired data. BCK analysed data. VJ, BCK, AG, CJD, MWJ, AJS, RFL, SPT, TSW, and MFM interpreted data. VJ and BCK drafted the report. AG, CJD, AM, MWJ, AJS, SME, AAB, HD, JG, ILJ, MD, NC, IR, RH, CD, SM, CL, KRP, RFL, SPT, TSW, and MFM revised the report for important intellectual content. All authors approved the final version.

TRIGGER trial collaboration

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Participating hospitals and personnel (number of patients enrolled)

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Declaration of interests

We declare no competing interests.

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