

# Relationship of Blood Transfusion and Clinical Outcomes in Patients With Acute Coronary Syndromes

Sunil V. Rao, MD

James G. Jollis, MD

Robert A. Harrington, MD

Christopher B. Granger, MD

L. Kristin Newby, MD

Paul W. Armstrong, MD

David J. Moliterno, MD

Lauren Lindblad, MS

Karen Pieper, MS

Eric J. Topol, MD

Jonathan S. Stamler, MD

Robert M. Califf, MD

**T**HE USE OF INVASIVE PROCEDURES for treatment of ischemic heart disease has more than tripled in the past 2 decades and is likely to increase in high-risk patients.<sup>1</sup> This, coupled with the widespread use of potent fibrinolytic and antithrombotic drugs,<sup>2,3</sup> has increased the potential for bleeding and blood transfusion among patients with cardiovascular disease. Approximately 12 million units of blood are transfused to 3.5 million patients each year in the United States,<sup>4</sup> and although transfusing blood to anemic patients with ischemic heart disease may theoretically increase oxygen delivery and improve outcomes, there is no definitive evidence to support such a practice. Some studies actually indicate no increase in tissue oxygenation with blood transfusion.<sup>5-7</sup>

**See also p 0 and Patient Page.**

**Context** It is unclear if blood transfusion in anemic patients with acute coronary syndromes is associated with improved survival.

**Objective** To determine the association between blood transfusion and mortality among patients with acute coronary syndromes who develop bleeding, anemia, or both during their hospital course.

**Design, Setting, and Patients** We analyzed 24 112 enrollees in 3 large international trials of patients with acute coronary syndromes (the GUSTO IIb, PURSUIT, and PARAGON B trials). Patients were grouped according to whether they received a blood transfusion during the hospitalization. The association between transfusion and outcome was assessed using Cox proportional hazards modeling that incorporated transfusion as a time-dependent covariate and the propensity to receive blood, and a landmark analysis.

**Main Outcome Measure** Thirty-day mortality.

**Results** Of the patients included, 2401 (10.0%) underwent at least 1 blood transfusion during their hospitalization. Patients who underwent transfusion were older and had more comorbid illness at presentation and also had a significantly higher unadjusted rate of 30-day death (8.00% vs 3.08%;  $P < .001$ ), myocardial infarction (MI) (25.16% vs 8.16%;  $P < .001$ ), and death/MI (29.24% vs 10.02%;  $P < .001$ ) compared with patients who did not undergo transfusion. Using Cox proportional hazards modeling that incorporated transfusion as a time-dependent covariate, transfusion was associated with an increased hazard for 30-day death (adjusted hazard ratio [HR], 3.94; 95% confidence interval [CI], 3.26-4.75) and 30-day death/MI (HR, 2.92; 95% CI, 2.55-3.35). In the landmark analysis that included procedures and bleeding events, transfusion was associated with a trend toward increased mortality. The predicted probability of 30-day death was higher with transfusion at nadir hematocrit values above 25%.

**Conclusions** Blood transfusion in the setting of acute coronary syndromes is associated with higher mortality, and this relationship persists after adjustment for other predictive factors and timing of events. Given the limitations of post hoc analysis of clinical trials data, a randomized trial of transfusion strategies is warranted to resolve the disparity in results between our study and other observational studies. We suggest caution regarding the routine use of blood transfusion to maintain arbitrary hematocrit levels in stable patients with ischemic heart disease.

JAMA. 2004;292:1555-1562

www.jama.com

Studies of clinical outcomes have shown disparate findings. A randomized trial found no benefit of liberally transfusing blood in critically ill patients to maintain a hemoglobin level of 10.0 mg/dL compared with restricting transfusion to patients in whom the

hemoglobin was 7.0 mg/dL or lower.<sup>8</sup> A post hoc analysis of this trial, limited to patients with cardiovascular dis-

**Author Affiliations** are listed at the end of this article.  
**Corresponding Author:** Sunil V. Rao, MD, Duke Clinical Research Institute, PO Box 17969, 2400 Pratt St, Durham, NC 27715 (sunil.rao@duke.edu).

ease, supported the overall results.<sup>9</sup> In contrast, an observational study of elderly patients with acute myocardial infarction (MI) found an association between transfusion and improved short-term survival when hematocrit at admission was 30% to 33% or less.<sup>10</sup> This study did not examine the association between transfusion and outcome in patients who developed anemia during their hospital course.

Patients hospitalized for an acute coronary syndrome (ACS) are at risk of developing anemia acutely as a consequence of bleeding. For clinical practice, a crucial issue is whether blood transfusion is beneficial or harmful for patients with ischemic heart disease who have developed anemia acutely during their hospitalization.

We used detailed clinical data from 3 large international trials of patients with ACS to determine the association between blood transfusion and outcomes among patients who developed moderate to severe bleeding, anemia, or both during their hospitalization.

## METHODS

### Patient Population and Treatments

The institutional review boards of all participating institutions reviewed and approved the protocols of the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), and Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON) B trials. All patients enrolled gave written informed consent.

Clinical data from the multicenter international GUSTO IIb, PURSUIT, and PARAGON B trials were pooled and included 24 112 patients with ACS. The details of the trials have been published elsewhere.<sup>3,11,12</sup> Briefly, GUSTO IIb randomly assigned 12 142 patients with ACS to receive either intravenous heparin or hirudin. For this analysis, we included 8011 patients from

GUSTO IIb without persistent ST-segment elevation on initial electrocardiogram. PURSUIT randomly assigned 10 948 ACS patients without persistent ST-segment elevation to receive either eptifibatid or placebo; PARAGON B randomly assigned 5225 ACS patients without ST-segment elevation to either intravenous lamifiban or placebo. For the current study, the analysis was limited to patients from the 3 trials who had complete data on transfusion and bleeding occurrence.

Concomitant treatment with aspirin in dose ranges of 80 to 325 mg/d was recommended by protocol in all 3 trials. Use of antithrombin agents was also recommended in the PURSUIT and PARAGON B trials and was mandated by protocol in the GUSTO IIb trial. Use of other medications and procedures was at the discretion of the treating physicians in all 3 trials.

### Definitions and End Points

**Bleeding.** The GUSTO IIb investigators used the GUSTO definition of bleeding<sup>2</sup> that classifies bleeding as mild, moderate, severe, or life-threatening. Severe or life-threatening bleeding was defined as either intracranial hemorrhage or bleeding that caused hemodynamic compromise and required intervention. Moderate bleeding was defined as bleeding that required blood transfusion but did not result in hemodynamic compromise. The PURSUIT investigators used the GUSTO and TIMI (Thrombolysis in Myocardial Infarction)<sup>13</sup> bleeding classifications. The TIMI classification defines bleeding events as major or minor, where major bleeding is either intracranial hemorrhage or bleeding associated with a hemoglobin decrease of 5 g/dL or more (or a hematocrit decrease of  $\geq 15\%$ ). Minor bleeding is defined as observed blood loss resulting in a hemoglobin decrease of 3 g/dL or more (hematocrit decrease of  $\geq 10\%$ ) or a decrease in hemoglobin of 4 g/dL (hematocrit decrease of  $\geq 12\%$ ) if no bleeding site was identifiable.

The PARAGON B investigators defined bleeding complications as major or life-threatening and intermediate.

Major or life-threatening bleeding was defined as any intracranial hemorrhage or bleeding leading to hemodynamic compromise requiring intervention. Intermediate bleeding was defined as bleeding requiring transfusion or a decrease in hemoglobin of 5 g/dL or more, or a decrease in hematocrit  $\geq 15\%$  when hemoglobin measurement was unavailable.

Data on the date, time, severity, and location (including unidentifiable) of each bleeding event were collected prospectively. To be consistent across trials, the GUSTO definition of bleeding was used for the GUSTO IIb and PURSUIT trials; for PARAGON B, major or life-threatening bleeding episodes and intermediate bleeding episodes were considered to be GUSTO severe and moderate bleeding, respectively. For the purpose of this analysis, only the first moderate or severe bleeding episode was considered, and the nadir hemoglobin or hematocrit was defined as the lowest value occurring during the hospitalization if no transfusion or bleeding occurred. When studying bleeding or transfusion events, only the nadir level before the event was considered. Nadir hematocrit was considered a continuous variable.

**Transfusion.** Data on the number of units of packed red blood cells and whole blood transfused as well as the date of transfusion were collected prospectively in each trial.

**End Points.** The primary end point was 30-day all-cause mortality. Secondary end points were occurrence of the composite of 30-day death or MI. Myocardial infarction was defined according to the protocol of each trial. The GUSTO IIb investigators defined MI as an increase in creatine kinase-MB (CK-MB) fraction (or total CK, if CK-MB measurement was unavailable) to greater than the upper limit of normal or at least 2 times the previous value if it was elevated at enrollment and/or new significant Q waves in 2 contiguous electrocardiographic (ECG) leads, along with the appropriate signs and symptoms.

The PURSUIT and PARAGON B investigators defined MI as new chest pain and ST-segment elevation within 18

hours of enrollment, new or repeat CK-MB fraction elevation greater than the upper limit of normal after 18 hours, new Q waves in 2 contiguous ECG leads, or both. Creatine kinase-MB elevations greater than 3 times the upper limit of normal after percutaneous coronary intervention and greater than 5 times the upper limit of normal after coronary artery bypass graft surgery (CABG) were also classified as MI. All end points were adjudicated by an independent, blinded events committee.

### Statistical Analysis

**Patient Comparisons.** Patients were categorized according to the occurrence of transfusion. Baseline characteristics were compared using  $\chi^2$  tests for categorical variables and the nonparametric Kruskal-Wallis test for continuous variables. Baseline differences with *P* values <.01 were considered statistically significant. Kaplan-Meier analysis was used to illustrate 30-day event-free survival for patients who did and did not undergo transfusion. Analyses were computed using SAS software, version 8.2 (SAS Institute Inc, Cary, NC).

**Modeling of Outcomes.** Because blood transfusion was a postrandomization event that was left to the discretion of the investigator, the association between transfusion and the primary and secondary end points could be confounded by patient characteristics and influenced by in-hospital events such as bleeding and procedures. To control for these biases, we developed 4 statistical models. The first 2 models examined patients' propensity to bleed or receive a transfusion and used moderate or severe bleeding and transfusion, respectively, as the outcomes. Logistic regression using a stepwise variable selection technique was used in each model and incorporated baseline demographic characteristics, medical comorbidities, age (as a continuous variable), sex, body weight (as a continuous variable), presenting characteristics, baseline hematocrit, site (US vs non-US), and in-hospital medical therapy received within the 2 weeks prior to randomization as independent variables.

Because the likelihood of receiving a transfusion may vary over time, 2 further models were developed. One used Cox proportional hazards regression to determine the association between transfusion and 30-day death and incorporated transfusion as a time-dependent covariate. The use of transfusion as a time-dependent covariate enables accounting for survivor bias (ie, not living long enough to undergo blood transfusion) and for the possibility that the timing of the transfusion relative to the outcome may be influential (eg, if the transfusion occurred after MI). The model was then adjusted for baseline variables found to be predictive of 30-day death among patients with non-ST-segment elevation ACS,<sup>14</sup> propensity for bleeding and transfusion from the models described herein, and nadir hematocrit. Because of the influence of CABG on transfusion practice and mortality, we repeated the analysis by censoring patients at the time of CABG.

The final model of 30-day death incorporated transfusion as a "time-fixed" covariate in a landmark analysis.<sup>15,16</sup> With this approach, the follow-up time is divided into periods of interest. Patient survival is then described with standard techniques conditional on the patient being alive and not yet having received a transfusion at the start of the period. All procedures and bleeding events that occurred prior to the end of each interval are included in the analysis. This approach provides a general trend of the adjusted association between the independent variable (transfusion) and dependent variable (30-day mortality) over time.

For the purposes of this study, the analysis was performed on the first seven 24-hour periods after trial enrollment because the majority of events (transfusions, bleeding events, and procedures) occurred during this time interval. The analysis for each time period compares outcomes between patients who did and did not undergo transfusion within the discrete 24-hour period and then adjusts for differences between these 2 populations.

The analysis adjusted for baseline characteristics, nadir hematocrit occurring prior to the end of each interval, and bleeding and invasive procedures that occurred prior to the end of each interval.

This approach has several advantages. First, it deals with nonproportionality because the analysis is fitted to a restricted time period. Second, it minimizes survivor bias because the analysis is performed on data captured within relatively short time intervals (24 hours in the case of our study) among patients who are alive at the start of each period. Third, it incorporates other covariates that may be time-dependent, such as invasive procedures and bleeding. In light of prior work showing an association between transfusion and lower mortality at certain hematocrit levels in elderly persons,<sup>10</sup> we also explored the interactions between age and transfusion and baseline and nadir hematocrit and transfusion in the landmark analyses.

We also examined the predicted probability of 30-day death among patients undergoing and not undergoing transfusion using a multivariable logistic regression model that incorporated nadir hematocrit as a continuous variable and adjusted for baseline characteristics. The association of nadir hematocrit with 30-day mortality was evaluated using restricted cubic splines. It appeared that this association followed 2 lines, 1 below a nadir hematocrit value of 25% and 1 above a nadir hematocrit value of 25%. Therefore, a linear spline transformation with a nadir hematocrit value of 25% as the knot point was used. The 2 continuous components of this transformation were added to the model along with transfusion use and the interaction of transfusion with nadir hematocrit. Owing to the influence of coronary artery bypass surgery on transfusion practice and mortality, we repeated the analysis censoring at the time of CABG. To account for survival bias, we also repeated the analysis excluding patients who died within the first 5 days.

**RESULTS**

**Baseline Characteristics**

From the 3 trials, 24 112 patients had complete data on bleeding, transfusion, and outcomes. Of these, 2401

(10.0%) underwent transfusion of at least 1 unit of whole blood or packed red blood cells. TABLE 1 displays the baseline characteristics of patients who did and did not receive a transfusion.

Compared with those who did not receive blood, patients who received a blood transfusion were older, more often female, more often black, and had lower median body weight. They also had more medical comorbidities at presentation, with a higher proportion having ST-segment depression on the initial ECG and Killip class greater than II. The median baseline and nadir hematocrit measurements for patients who received a transfusion were 39.9% and 29.0%, respectively. For patients who did not receive blood, the values were 41.7% and 37.6%, respectively.

**Table 1.** Baseline Characteristics of Patients Who Did and Did Not Receive Blood Transfusion\*

Characteristics	Transfusion (n = 2401)	No Transfusion (n = 21 711)	P Value
<b>Demographics</b>			
Age, median (IQR), y	68.9 (61.0-74.1)	64.0 (54.9-71.6)	<.001
Female	41.5	33.6	<.001
Black race	5.1	3.9	.002
Body weight, median (IQR), kg	74.0 (65.0-85.0)	77.3 (68.0-88.0)	<.001
<b>Medical history</b>			
Diabetes mellitus	27.9	20.6	<.001
Hypertension	58.8	52.4	<.001
Hyperlipidemia	46.6	43.0	<.001
Prior stroke	7.8	4.6	<.001
Prior CABG	11.3	12.2	.18
Prior congestive heart failure	11.4	9.5	.003
<b>Presenting characteristics</b>			
ST-segment elevation	10.1	11.2	.12
ST-segment depression	51.4	40.9	<.001
Killip class ≥II	15.8	10.7	<.001
Systolic blood pressure, median (IQR), mm Hg	134 (120-150)	135 (120-150)	.91
Randomization at a US site	47.8	30.7	<.001
<b>Hematocrit, median (IQR), %</b>			
Baseline	39.9 (36.3-43.1)	41.7 (38.8-44.5)	<.001
Nadir	29.0 (24.6-35.2)	37.6 (34.4-40.5)	<.001
Units of blood transfused, median (IQR)	3.6 (2.0-6.0)	NA	NA

Abbreviations: CABG, coronary artery bypass graft surgery; NA, data not applicable; IQR, interquartile range. \*Data are presented as percentages unless otherwise noted.

**Table 2.** Baseline Predictors of Moderate or Severe Bleeding and Transfusion From Linear Regression Models

Variables	Odds Ratio (95% Confidence Interval)*	
	Moderate or Severe Bleeding	Transfusion
Randomization at a US site	2.44 (2.22-2.68)	2.56 (2.32-2.82)
Age >75 y	0.96 (0.94-0.98)	0.96 (0.94-0.98)
Baseline hematocrit per 1% decrease	0.97 (0.97-0.98)	0.97 (0.96-0.97)
Prior bypass surgery	0.58 (0.51-0.67)	0.59 (0.51-0.68)
Body weight <80 kg	0.99 (0.98-0.99)	...
ST-segment depression on initial electrocardiogram	1.33 (1.22-1.45)	1.35 (1.24-1.49)
Diastolic blood pressure >95 mm Hg	1.04 (1.02-1.05)	...
Chronic renal insufficiency	2.01 (1.46-2.76)	1.95 (1.39-2.73)
Prior use of nitrates	0.82 (0.74-0.90)	...
Hyperlipidemia	1.18 (1.08-1.30)	...
Body weight <75 kg	...	0.98 (0.98-0.99)
Diabetes mellitus	...	1.28 (1.15-1.42)
Prior β-blocker use	...	1.22 (1.11-1.34)
Heart rate per 1/min increase	...	1.01 (1.00-1.01)

Ellipses indicate variable was not a significant predictor of the outcome in question. \*All P values <.001.

**Predictors of Bleeding and Transfusion**

The first 2 regression models examined significant baseline predictors of moderate or severe bleeding and blood transfusion. TABLE 2 shows the baseline characteristics that were most associated with bleeding and blood transfusion during hospitalization. Similar baseline characteristics were associated with both bleeding and blood transfusion.

**Outcomes**

**Kaplan-Meier and Cox Regression Analyses.** FIGURE 1 shows the Kaplan-Meier curves for 30-day mortality among patients who did and did not receive blood transfusion. TABLE 3 shows the unadjusted rates of 30-day death, MI, and composite death/MI among patients who did and did not receive a transfusion. For all 3 outcomes, the rates were significantly higher among patients who received a transfusion (30-day death, 8.00% for patients who received a transfusion vs 3.08% for patients who did not;  $P < .001$ ; 30-day MI, 25.16% vs 8.16%;  $P < .001$ ; 30-day composite death/MI, 29.24% vs 10.02%;  $P < .001$ ).

Table 3 also shows the results of the Cox model that examined the association between blood transfusion as a time-dependent covariate and 30-day death and 30-day composite death/MI. After adjustment for baseline characteristics, blood transfusion was associated with a hazard ratio for death

of 3.54 (95% confidence interval, 2.96-4.23) for 30-day death. After adjustment for baseline characteristics, bleeding and transfusion propensity, and nadir hematocrit, blood transfusion was associated with a hazard ratio for death of 3.94 (95% confidence interval, 3.26-4.75).

**Landmark Analysis.** FIGURE 2 shows the results of the landmark analysis that adjusted for baseline characteristics, nadir hematocrit occurring prior to the end of each time period, bleeding events that occurred prior to the end of each time period, and invasive procedures (cardiac catheterization, percutaneous coronary intervention, and/or CABG) that occurred before the end of each time period. During the first 7 days after randomization, there was a trend association between blood transfusion and increased 30-day mortality. In the landmark analysis, there were no significant interactions between transfusion and age or transfusion and baseline or nadir hematocrit.

**Predicted Probabilities of 30-Day Death.** TABLE 4 shows the adjusted predicted probability of 30-day death with and without transfusion by nadir hematocrit. The interaction between nadir hematocrit and transfusion was significant ( $P=.003$ ) such that there was no significant association between transfusion and 30-day mortality at a nadir hematocrit of 25% or less. However, at a nadir hematocrit higher than 25%, transfusion was associated with a significantly higher odds of 30-day

death. The results were unchanged after excluding patients who underwent CABG or those who died within the first 5 days of follow-up.

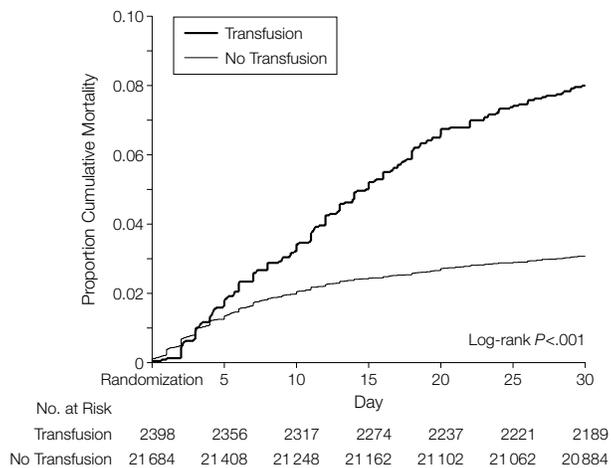
**COMMENT**

The results of our study show that blood transfusion in the setting of anemia during hospitalization for ACS is associated with increased 30-day mortality. This association persisted across the 3 different analytical methods we used. The increased risk of death associated with transfusion was present after adjustment for demographic characteristics and in-hospital events such as bleeding and invasive procedures. When included as a time-dependent co-

variate in the Cox model, blood transfusion was associated with a higher risk of death. In the landmark analysis, the odds ratios showed a trend toward increased mortality with transfusion after adjustment for both baseline and nadir hematocrit. When hematocrit level was included as a continuous variable in the logistic regression model, we found an association between transfusion and increased 30-day mortality at a nadir hematocrit above 25%. This suggests that a hematocrit as low as 25% may be tolerated without blood transfusion in otherwise stable patients with ischemic heart disease.

Our findings differ from those of Wu et al,<sup>10</sup> who analyzed data from an ad-

**Figure 1.** Kaplan-Meier Estimates of 30-Day Mortality Among Patients Who Did and Did Not Receive Blood Transfusion



Survival data were missing for 3 patients who received transfusion and for 27 patients who did not receive transfusion.

**Table 3.** Unadjusted Rates of Outcomes and Adjusted Results of Cox Regression Predicting 30-Day Death and Death or Recurrent Myocardial Infarction Using Transfusion as a Time-Dependent Covariate

Outcomes	Underwent Transfusion, No. (%)			Hazard Ratio (95% CI)*		
	Yes (n = 2401)	No (n = 21711)	P Value	Adjusted for Transfusion Propensity	Adjusted for Baseline Characteristics†	Adjusted for Baseline Characteristics, Bleeding and Transfusion Propensity, and Nadir Hematocrit†
Death	192 (8.00)	669 (3.08)	<.001	3.77 (3.14-4.52)	3.54 (2.96-4.23)	3.94 (3.26-4.75)
MI	604 (25.16)	1771 (8.16)	<.001	...	...	...
Composite (death/MI)	702 (29.24)	2176 (10.02)	<.001	2.79 (2.45-3.18)	2.80 (2.45-3.19)	2.92 (2.55-3.35)

Abbreviations: CI, confidence interval; MI, myocardial infarction. Ellipses indicate data not computed.

\* $P<.001$  for all comparisons.

†Baseline characteristics adjusted to include US vs non-US site, age, race, weight in kilograms, diabetes mellitus, systolic blood pressure, diastolic blood pressure, heart rate at baseline, time from symptom onset to hospitalization, prior stroke, prior MI, sex, history of angina prior to qualifying episode, hypertension, hyperlipidemia, family history of coronary artery disease, history of congestive heart failure, peripheral vascular disease, prior percutaneous coronary intervention, prior coronary artery bypass graft surgery, Killip class, baseline hematocrit, maximum creatine kinase ratio at baseline, chronic renal insufficiency, ST-segment elevation or depression on initial electrocardiogram,  $\beta$ -blocker use at baseline, calcium channel blocker use at baseline, nitrate use at baseline, and current smoking.

ministrative database and found that blood transfusion was associated with lower 30-day mortality among elderly patients with MI if the admission hematocrit was 30% or lower. There are many likely reasons for the disparity between our study and that of Wu et al. First, Wu et al used hematocrit measurement at admission in their analysis, whereas we examined the association among anemia developing during the hospitalization (ie, nadir hematocrit), transfusion, and mortality. The latter is a critical issue for clinical practice. Given that many current therapies

for ACS rely on mechanisms that increase the risk of bleeding (antithrombotic medications and invasive procedures), a fundamental problem facing clinicians is whether to use transfusion in patients who are otherwise stable but have developed anemia as a consequence of medications, procedures, or both. We included in-hospital procedures and bleeding events, which are important drivers of transfusion, in our landmark analysis, while Wu et al did not.

Second, Wu et al used an observational data set based on Medicare claims

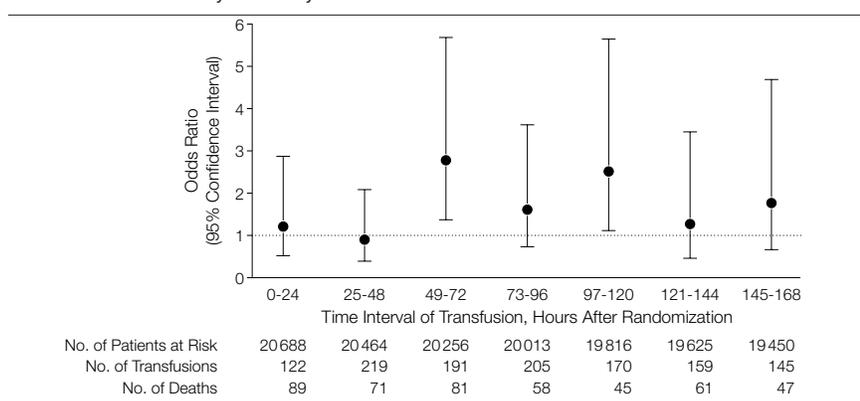
data. Although the clinical information was abstracted from hospital records, data on transfusion were likely derived from claims that may have been incomplete. Our analysis was performed on information from clinical trials databases in which data collection, especially bleeding and transfusion data, was meticulous.

Third, Wu et al excluded patients younger than 65 years, those with bleeding within 48 hours of admission, and those who underwent open-heart surgery. In our analysis, we included all patients, regardless of age, bleeding events, or procedures, for whom all clinical information was complete.

Finally, Wu et al attempted to control for survival bias (ie, living long enough to receive a transfusion) in a secondary analysis by excluding patients who died within 48 hours of admission. This eliminated the association between transfusion and improved mortality in patients with a hematocrit of 30% to 33%. We believe that our statistical methods were robust because we performed our analysis first by including transfusion as a time-dependent covariate and second by using a landmark analysis. Both methods not only minimized survivor bias but the landmark analysis also included other time-dependent events such as bleeding and procedures.

Our results also run counter to conventional clinical thinking about cardiac function and anemia. Mild to moderate anemia (hemoglobin level of 7.0-10.0 g/dL) increases cardiac output, primarily through reduced blood viscosity leading to reduced afterload. Under these conditions, myocardial oxygen demand does not change.<sup>17</sup> The myocardium has a high oxygen-extraction ratio, however, and can augment oxygen delivery only by increasing coronary blood flow. Such an increase might not be possible in patients with fixed coronary stenoses. Considerable experimental model data suggest that a hemoglobin level of 7 g/dL is tolerated without myocardial is-

**Figure 2.** Results of the Landmark Analysis Examining the Association Between Blood Transfusion and 30-Day Mortality



Odds ratios were adjusted for baseline characteristics (site, age, race, weight in kilograms, diabetes mellitus, systolic and diastolic blood pressure, heart rate at baseline, time from symptom onset to hospitalization, prior stroke, prior myocardial infarction, sex, history of angina prior to qualifying episode, hypertension, hyperlipidemia, family history of coronary artery disease, history of congestive heart failure, peripheral vascular disease, prior percutaneous coronary intervention [PCI], prior coronary artery bypass graft surgery [CABG], Killip class, baseline hematocrit, maximum creatine kinase ratio at baseline, chronic renal insufficiency, ST-segment elevation or depression on initial electrocardiogram,  $\beta$ -blocker use at baseline, calcium channel blocker use at baseline, nitrate use at baseline, and current smoking), bleeding events occurring before the end of each time period, and procedures (PCI and CABG) occurring before the end of each time period.

**Table 4.** Adjusted Predicted Probabilities of 30-Day Death With and Without Transfusion by Nadir Hematocrit Value

	Nadir Hematocrit, %*			
	20	25	30	35
Adjusted odds ratio (95% CI)†	1.59 (0.95-2.66)	1.13 (0.70-1.82)	168.64 (7.49-3797.69)	291.64 (10.28-8273.85)

Abbreviation: CI, confidence interval.

\*Nadir hematocrit value was incorporated into the multivariable logistic regression model as a continuous variable. The association between nadir hematocrit value and 30-day mortality was evaluated using restricted cubic splines. Because the association followed 2 lines, 1 below and 1 above a nadir hematocrit value of 25%, a linear spline transformation with a nadir hematocrit value of 25% as the knot point was used. Nadir hematocrit values in the table are sample values above and below 25%.

†Adjusted for US vs non-US site, age, race, weight in kilograms, diabetes mellitus, systolic and diastolic blood pressure, heart rate at baseline, time from symptom onset to hospitalization, prior stroke, prior myocardial infarction, sex, history of angina prior to qualifying episode, hypertension, hyperlipidemia, family history of coronary artery disease, history of congestive heart failure, peripheral vascular disease, prior percutaneous coronary intervention, prior coronary artery bypass graft surgery, Killip class, baseline hematocrit, maximum creatine kinase ratio at baseline, chronic renal insufficiency, ST-segment elevation or depression on initial electrocardiogram,  $\beta$ -blocker use at baseline, calcium channel blocker use at baseline, nitrate use at baseline, and current smoking.

chemia if there is no obstructive coronary artery disease. With coronary artery obstruction, however, ischemia can occur with even mild anemia in experimental circumstances.<sup>18</sup> Furthermore, prior observational studies have shown an association between anemia and increased mortality in patients with cardiovascular disease.<sup>10,19</sup> In this circumstance, there are no definitive data that show that treating anemia with blood transfusion either mitigates myocardial ischemia or improves survival.

While clinical studies suggest that increasing hemoglobin level via transfusion increases oxygen delivery,<sup>5,7,20</sup> studies also show that measures of tissue oxygenation either decrease or do not change.<sup>5-7</sup> Increasing oxygen delivery through transfusion leads to increases in oxygen utilization by tissues only at severe levels of anemia. At higher but subnormal hematocrit levels, this relation does not appear to exist—as delivery increases, tissue uptake decreases and tissue utilization of oxygen remains constant.

The reason for this paradox (greater oxygen delivery but no improvement in tissue use) is unclear. Alterations in erythrocyte nitric oxide biology in stored blood may be a partial explanation. Nitric oxide (NO) is essential for oxygen exchange,<sup>21</sup> but the half-life of NO in erythrocytes is believed to be short. Red blood cells in stored blood, once depleted of NO, may function as NO “sinks,” promoting vasoconstriction, platelet aggregation, and ineffective oxygen delivery. Moreover, red blood cells in stored blood are low in 2,3-diphosphoglyceric acid and have high oxygen affinity,<sup>17</sup> which may further impair the delivery of oxygen to hypoxic tissues. Also, administration of blood to patients with coronary artery disease may lead to increases in inflammatory mediators that are associated with exacerbation of myocardial ischemia.<sup>22</sup> All of this, in aggregate, may act to promote myocardial ischemia rather than mitigate it.

Previous randomized studies support the conclusion that blood transfusion may, at best, be neutral with

respect to survival or, at worst, be associated with either decreased survival or worsening cardiac function. Fortune et al<sup>5</sup> examined the effect of maintaining a hematocrit of 30% vs 40% on hemodynamic variables in 25 patients with trauma, acute hemorrhage, or both. They found no differences in cardiac index, heart rate, or left ventricular stroke index between the groups. Johnson et al<sup>23</sup> compared a liberal transfusion strategy (hematocrit of 32%) vs a conservative strategy (hematocrit of 25%) in 38 patients undergoing elective CABG. They found no adverse effects with the conservative strategy and reported better exercise tolerance in this group. Bush et al<sup>24</sup> preoperatively randomized 99 patients undergoing elective aortic and infringuinal arterial reconstruction procedures to receive either a liberal transfusion strategy (maintain a hemoglobin level  $\geq 10$  g/dL) or a restrictive strategy (transfusion only for hemoglobin level  $< 9.0$  g/dL). In an intention-to-treat analysis, there was no difference in myocardial ischemia, MI, or death between the strategies.

The largest trial to date comparing aggressive and conservative transfusion strategies randomized 838 critically ill patients to a restrictive transfusion strategy (transfusion for hemoglobin  $< 7.0$  g/dL) or a liberal strategy (transfusion for hemoglobin  $< 10.0$  g/dL).<sup>8</sup> In an intention-to-treat analysis, there was no difference in 30-day all-cause mortality between the 2 groups. There also were significantly more MIs and cases of pulmonary edema with the liberal transfusion strategy. When the subgroup of patients with coronary artery disease was analyzed separately, there was no difference in 30-day mortality between the study groups.<sup>9</sup> Further post hoc analysis of patients with MI and unstable angina revealed a trend toward better survival with maintenance of a higher hematocrit level, but this finding was not statistically significant. Our study, which was much larger, had the statistical power to determine the association between transfusion and out-

come in patients with ischemic heart disease and supports the results observed in the randomized trial.

There are several limitations to our study. First, our study was a post hoc analysis of prospectively collected data within the context of multiple clinical trials. As such, transfusion was a postrandomization event and any attempt to draw associations between postrandomization variables and outcome has the potential for bias. Indeed, one reason transfusion was associated with a worse outcome was that all of the bias could not be adjusted for in the analysis. Although we repeated the analysis using several rigorous statistical methods and found similar results, there may still be unmeasured confounders that might account for the finding of increased mortality with transfusion. Second, we could not explore the indications for or the appropriateness of blood transfusion in our analyses because this information was not captured in our database. Third, the patients in our study were all participants in a clinical trial and therefore may not reflect the real-world population of patients with ACS, which may include patients with different comorbidities in whom transfusion decisions may be more complicated. Finally, because our study was not randomized, it should not be considered as evidence to change practice; rather, it should be considered as evidence that caution is warranted when making transfusion decisions.

## CONCLUSION

In our study, blood transfusion in the setting of ACS was associated with an increased risk of short-term mortality. This risk persisted despite adjustment for patient characteristics, including baseline and nadir hematocrit, bleeding, and in-hospital procedures. Given the disparity in results between our study and other observational studies of transfusion and outcome, a randomized trial of transfusion strategies in anemic patients with ACS is warranted to guide clinical practice. Until then, we

caution against the routine use of blood transfusion to maintain arbitrary hematocrit levels in stable patients with ischemic heart disease.

**Author Affiliations:** Duke Clinical Research Institute (Drs Rao, Jollis, Harrington, Granger, Newby, and Califf and Mss Lindblad and Pieper) and Department of Medicine and the Howard Hughes Medical Institute, Duke University Medical Center (Dr Stamler), Durham, NC; Department of Cardiology, University of Alberta, Edmonton (Dr Armstrong); Division of Cardiology, University of Kentucky, Lexington (Dr Mo-

litzerno); and Cleveland Clinic Foundation, Cleveland, Ohio (Dr Topol).

**Author Contributions:** Dr Rao had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Rao, Harrington, Moliterno, Pieper, Stamler, Califf.

**Acquisition of data:** Harrington, Granger, Newby, Moliterno, Califf.

**Analysis and interpretation of data:** Rao, Jollis, Harrington, Newby, Armstrong, Moliterno, Lindblad, Pieper, Topol, Califf.

**Drafting of the manuscript:** Rao, Topol.

**Critical revision of the manuscript for important intellectual content:** Jollis, Harrington, Granger, Newby,

Armstrong, Moliterno, Lindblad, Pieper, Topol, Stamler, Califf.

**Statistical analysis:** Rao, Jollis, Granger, Lindblad, Pieper.

**Obtained funding:** Harrington, Armstrong, Topol, Califf.

**Administrative, technical, or material support:** Harrington, Califf.

**Study supervision:** Rao, Harrington, Granger, Moliterno, Topol, Stamler.

**Funding/Support:** This work was supported by the Duke Clinical Research Institute, Durham, NC.

**Role of the Sponsor:** The study's sponsor had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.

## REFERENCES

- American Heart Association Cardiovascular procedures. Available at: <http://www.americanheart.org/downloadable/heart/1014758374254FS18CVP2WEB.pdf>. Accessed November 18, 2003.
- GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med*. 1993;329:673-682.
- PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatid in patients with acute coronary syndromes: Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med*. 1998;339:436-443.
- Goodnough LT, Soegiarso RW, Birkmeyer JD, Welch HG. Economic impact of inappropriate blood transfusions in coronary artery bypass graft surgery. *Am J Med*. 1993;94:509-514.
- Fortune JB, Feustel PJ, Saifi J, Stratton HH, Newell JC, Shah DM. Influence of hematocrit on cardiopulmonary function after acute hemorrhage. *J Trauma*. 1987;27:243-247.
- Dietrich KA, Conrad SA, Hebert CA, Levy GL, Romero MD. Cardiovascular and metabolic response to red blood cell transfusion in critically ill volume-resuscitated nonsurgical patients. *Crit Care Med*. 1990;18:940-944.
- Casutt M, Seifert B, Pasch T, Schmid ER, Turina MI, Spahn DR. Factors influencing the individual effects of blood transfusions on oxygen delivery and oxygen consumption. *Crit Care Med*. 1999;27:2194-2200.
- Hebert PC, Wells G, Blajchman MA, et al; Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med*. 1999;340:409-417.
- Hebert PC, Yetisir E, Martin C, et al. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? *Crit Care Med*. 2001;29:227-234.
- Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med*. 2001;345:1230-1236.
- Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med*. 1996;335:775-782.
- PARAGON B Investigators. Randomized, placebo-controlled trial of titrated intravenous lamifiban for acute coronary syndromes. *Circulation*. 2002;105:316-321.
- Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase: clinical findings through hospital discharge. *Circulation*. 1987;76:142-154.
- Boersma E, Pieper KS, Steyerberg EW, et al, PURSUIT Investigators. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation: results from an international trial of 9461 patients. *Circulation*. 2000;101:2557-2567.
- Anderson J, Cain KC, Gelber RD. Analysis of survival by tumor response. *J Clin Oncol*. 1983;1:710-719.
- Anderson J, Cain KC, Gelber RD, Gelman RC. Analysis and interpretation of the comparison of survival by treatment outcome variables in cancer clinical trials. *Cancer Treat Rep*. 1985;69:1139-1146.
- Welch HG, Meehan KR, Goodnough LT. Prudent strategies for elective red blood cell transfusion. *Ann Intern Med*. 1992;116:393-402.
- Hebert PC, Hu LQ, Biro GP. Review of the physiologic mechanisms in response to anemia. *CMAJ*. 2001;156(suppl 11):S27-S40.
- Carson JL, Duff A, Poses RM, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet*. 1996;348:1055-1060.
- Greenburg AG. A physiologic basis for red blood cell transfusion decisions. *Am J Surg*. 1995;170(6A suppl):44S-48S.
- McMahon TJ, Moon RE, Lusching BP, et al. Nitric oxide in the human respiratory cycle. *Nat Med*. 2002;8:711-717.
- Fransen E, Maessen J, Dentener M, Senden N, Buurman W. Impact of blood transfusions on inflammatory mediator release in patients undergoing cardiac surgery. *Chest*. 1999;116:1233-1239.
- Johnson RG, Thurer RL, Kruskal MS, et al. Comparison of two transfusion strategies after elective operations for myocardial revascularization. *J Thorac Cardiovasc Surg*. 1992;104:307-314.
- Bush RL, Pevco WC, Holcroft JW. A prospective, randomized trial limiting perioperative red blood cell transfusions in vascular patients. *Am J Surg*. 1997;174:143-148.