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Impact of Blood Transfusion on Short- and Long-Term Mortality in Patients With ST-Segment Elevation Myocardial Infarction

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Objectives We sought to examine the short- and long-term outcomes of blood transfusion in patients presenting with ST-segment elevation myocardial infarction (STEMI).

Background The short- and long-term consequences of blood transfusion in anemic patients with recent STEMI remain controversial.

Methods We evaluated 30-day, 6-month, and 1-year all-cause mortality among 4,131 STEMI patients enrolled in the GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) IIb trial. Patients were categorized according to whether they received a blood transfusion during hospitalization. Cox proportional hazards survival models with transfusion as a time-dependent covariate were conducted for the whole and for the propensity-matched groups. Additionally, a series of sensitivity analyses assessed the magnitude of hidden bias that would need to be present to explain the associations actually observed.

Results Death at 30 days (13.7% vs. 5.5%), 6 months (19.7% vs. 6.9%), and 1 year (21.8% vs. 8.7%) was significantly higher for transfused patients than for nontransfused patients, respectively. After adjusting for over 25 baseline characteristics, nadir hemoglobin, and propensity score for transfusion, and using transfusion as a time-dependent covariate, transfusion remained significantly associated with increased risk of mortality at 30 days (hazard ratio [HR]: 3.89, 95% confidence interval [CI]: 2.66 to 5.68, $p < 0.001$), 6 months (HR: 3.63, 95% CI: 2.67 to 4.95, $p < 0.001$), and 1 year (HR: 3.03, 95% CI: 2.25 to 4.08, $p < 0.001$). Similar results were observed in the propensity-matched patients.

Conclusions Blood transfusion is associated with increased short- and long-term mortality in the setting of STEMI. (J Am Coll Cardiol Intv 2009;2:46–53) © 2009 by the American College of Cardiology Foundation

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Up to one-fifth of the patients with acute coronary syndromes (ACS) may have anemia at presentation (1–5). Even though the cardiovascular adverse consequences of anemia in the setting of ACS have been well reported in the literature (1–3,5,6), opinion about blood transfusion to correct anemia is divided (7–11). Some studies have suggested potential harm where others have suggested benefit (7–10). The decision to transfuse becomes important in patients with ST-segment elevation myocardial infarction (STEMI) given the high mortality and the need for urgent

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thrombolysis or angioplasty that may further increase the risk of bleeding (12,13). Additionally, the abrupt and complete coronary occlusion seen in STEMI may make the adverse consequences of anemia more pronounced (14). On the other hand, STEMI is associated with increased viscosity and thrombogenicity that may be worsened by transfusion of stored blood (15–18), leading to further decrease in microcirculatory flow and poor oxygen delivery (19). Therefore, we sought to examine the impact of blood transfusion on short- and long-term all-cause mortality in the setting of STEMI.

Methods

The GUSTO IIb trial. The GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) IIb trial has been described in detail elsewhere (20). Briefly, GUSTO IIb was a multicenter trial conducted in 373 hospitals in 13 countries between May 1994 and October 1995 to compare the clinical efficacy of the direct thrombin inhibitor, recombinant hirudin, with that of heparin (an indirect antithrombin agent) in patients with unstable angina or acute myocardial infarction. Acute coronary syndrome patients were stratified according to the presence of STEMI on the baseline electrocardiogram (4,131 patients) or its absence (unstable angina or non–Q-wave myocardial infarction). The primary composite end point for the trial was death or nonfatal myocardial infarction in the first 30 days of follow-up.

Study population. Our study population was restricted to patients enrolled in the GUSTO IIb trial who had transient or persistent ST-segment elevation of more than 0.5 mm on the baseline electrocardiogram. From a total of 4,131 patients with STEMI enrolled in the GUSTO IIb trial, we further excluded 53 patients who did not have information about blood transfusion and 503 patients who were part of a substudy of direct coronary angioplasty, leaving 3,575 patients in our study cohort.

Blood transfusion and outcomes. The information about transfusion was prospectively collected in the trial. Patient's hemoglobin and hematocrit values on admission (the first measurement within 24 h of admission) were recorded as the baseline value. The lowest hemoglobin during the hospital stay was recorded as the nadir hemoglobin. Patients were divided into 2 groups, those who received transfusion (any transfusion of whole blood or packed red blood cells) at any point during the hospital stay, and those who did not. Bleeding was categorized in accordance with the GUSTO IIb trial into severe or life-threatening (either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention), moderate bleeding (no evidence of hemodynamic compromise but requiring blood transfusion), and mild bleeding (all others). The principal outcome was all-cause mortality at 30 days, 6 months, and 1 year.

Statistical analysis. Baseline clinical, hematological, and demographic characteristics of those who received transfusion and those who did not were compared by the chi-square test or Fisher exact test for categorical variables and by the *t* test or Kruskal-Wallis test for continuous variables. Rates of freedom from events at 30 days, 6 months, and 1 year were calculated via the Kaplan-Meier approach.

To determine the independent effect of transfusion on mortality, we used Cox proportional hazards survival models that adjusted for over 25 baseline characteristics including age; gender; race; height; weight; country of origin; comorbidities including diabetes, hypertension, hypercholesterolemia; smoking; chronic obstructive pulmonary disease; chronic renal insufficiency; peripheral arterial disease; heart failure; stroke; cancer diagnosed in the past 5 years; and history of coronary artery bypass grafting and percutaneous coronary artery interventions. Adjustments were also made for Killip class at presentation, family history of cardiac diseases and risk factors, and medical therapy and interventions (both ambulatory and in-hospital). Transfusion was adjusted for as a time-dependent covariate to account for the effect of timing of transfusion and to eliminate the potential bias of not receiving a blood transfusion because of death (survival bias).

Abbreviations and Acronyms

ACS = acute coronary syndromes

STEMI = ST-segment elevation myocardial infarction

Because transfusion was not randomly assigned in the GUSTO IIb trial, multivariable analysis alone may not adequately control for confounding and bias. Hence, we further analyzed the data using propensity score and matching (21). A propensity score for transfusion was generated for 30 days, 6 months, and 1 year separately using logistic regression analysis that included all variables shown in Table 1. To be more conservative and to try to underestimate the hazard of transfusion, the propensity analysis was conducted for those that received blood transfusion or for those that had moderate or severe bleeding (n = 316). Subsequently, each patient who had a blood transfusion or had moderate to severe bleeding without

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Table 1. Baseline Characteristics

Characteristic	Received Transfusion (n = 307)	Did Not Receive Transfusion (n = 3,268)	p Value
Age, yrs	67 ± 11	62 ± 12	<0.001
Female gender, n (%)	126 (41)	726 (22)	<0.001
Black race, n (%)	17 (6)	79 (2)	<0.001
Height, cm, mean ± SD	167 ± 10	171 ± 9	<0.001
Weight, kg, mean ± SD	73 ± 14	79 ± 15	<0.001
Medical history, n (%)			
Cancer diagnosed in last 5 yrs	14 (5)	101 (3)	0.16
History of congestive heart failure	12 (4)	91 (3)	0.26
Peripheral vascular disease	31 (10)	234 (7)	0.06
History of cigarette smoking	195 (64)	2,297 (70)	0.01
History of cerebrovascular disease	1 (0.3)	18 (0.5)	1.00
Family history of coronary heart disease	126 (42)	1,215 (38)	0.17
History of angina	185 (60)	1,569 (48)	<0.001
History of coronary bypass surgery	22 (7)	165 (5)	0.11
History of percutaneous coronary intervention	20 (6)	183 (6)	0.51
Clinical presentation			
Heart rate, beats/min, mean ± SD	78 ± 19	76 ± 17	0.10
Systolic blood pressure, mm Hg, mean ± SD	130 ± 19	130 ± 23	0.55
Diastolic blood pressure, mm Hg, mean ± SD	77 ± 15	78 ± 14	0.06
Baseline Killip class, n (%)			<0.001
I	251 (83)	2,868 (88)	
II	49 (16)	331 (10)	
III	3 (0.9)	38 (1.1)	
IV	1 (0.3)	16 (0.5)	
Coexisting conditions, n (%)			
Renal insufficiency	6 (2)	14 (0.43)	0.01
Diabetes	59 (19)	507 (15)	0.09
Hypercholesterolemia	115 (37)	1,180 (36)	0.71
Hypertension	139 (45)	1,303 (40)	0.07
Severe chronic obstructive lung disease	12 (4)	82 (2)	0.10
Procedures performed within 168 h after randomization, n (%)			
Percutaneous coronary intervention	596 (18)	67 (21)	0.11
Coronary artery bypass graft surgery	68 (2)	86 (27)	<0.001
Hematological parameters			
Baseline hemoglobin, g/dl, median ± IQR	13.9 ± 2.0	14.7 ± 4.1	<0.001
Baseline hematocrit, g/dl, median ± IQR	41.4 ± 5.6	43.2 ± 4.2	<0.001
Nadir hemoglobin, g/dl, median ± IQR	8.6 ± 1.4	12.6 ± 3.8	<0.001
Nadir hematocrit, g/dl, median ± IQR	25.1 ± 4.3	37.2 ± 5.1	<0.001
Moderate or severe bleeding, n (%)	297 (97)	19 (0.6)	<0.001

Other variables not shown in the table but included in the analysis were height, weight, country of study, history of myocardial infarction, previous angina, prior exposure to hirudin, and prior medication use.
IQR = interquartile range; SD = standard deviation.

transfusion was matched with 2 patients without transfusion using the propensity score. Nadir hemoglobin was not included in building the propensity score but was adjusted for in the final model. To confirm the validity of our propensity analysis, a time-dependent Cox regression analysis stratified by quintiles of propensity score was conducted.

Even though propensity score and matching were adjusted to control for overt biases, hidden bias is more difficult to address because potential confounding variables may not have been measured. Therefore, sensitivity analysis was performed to examine the magnitude of the hidden bias that would have to be present to explain the associations observed (22). Proportional hazard assumption was tested for all time points by examining the interaction between blood transfusion and time. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

Results

Baseline characteristics. From a total of 3,575 STEMI patients, 1,605 (44.9%) patients were from the U.S. and Canada, 1,749 (49.0%) from Europe, and 221 (6.1%) from Australia and New Zealand. Of 3,575 study patients, 307 (8.6%) received a transfusion during their hospitalization. In general, patients who underwent blood transfusion were older, more likely to be female, had Killip class ≥2 on presentation and were more likely to have a prior history of chronic renal insufficiency, angina, and smoking (Table 1). Out of 307 patients in the transfusion group, 297 (96.7%) patients had moderate to severe bleeding. Patients in the transfusion group had lower nadir hemoglobin and required an average of 3.5 ± 2.9 U of blood transfusion per patient.

Unadjusted analysis. Patients receiving transfusions had a significantly higher rates of mortality when compared with nontranfusion patients at 30 days (13.7% vs. 5.5%, $p < 0.01$), 6 months (19.7% vs. 6.9%, $p < 0.01$), and 1 year (21.8% vs. 8.7%, $p < 0.01$). Kaplan-Meier curves for death at 30 days (Fig. 1A), 6 months (Fig. 1B), and 1 year (Fig. 1C) show a nonproportional increase in mortality with blood transfusion. Similarly, unadjusted Cox proportional hazards survival models with transfusion as a time-dependent covariate showed a strong association between blood transfusion and all-cause mortality (Table 2).

Multivariable and propensity score adjusted analysis. Transfusion was strongly associated with all-cause mortality in multivariable Cox proportional-hazard analysis for 30 days, 6 months, and 1 year with transfusion as a time-dependent covariate (Table 2). Additionally, transfusion was associated with increased 30-day, 6-month, and 1-year mortality when all patients were included in the model that adjusted for propensity to receive transfusion. Transfusion was also associated with incident myocardial infarction at 30-day (chi-square: 32.53, adjusted hazard ratio [HR]: 3.44, $p < 0.001$) and 6-month (chi-square: 26.30, adjusted HR: 2.69, $p < 0.001$).

Propensity-matched analysis. To account for the differences in baseline characteristics between the 2 groups, propensity analyses for 30 days, 6 months, and 1 year were performed separately. In these analyses, each patient that had blood transfusion or had moderate to severe bleeding was matched with 2 individuals in the no blood transfusion group using a propensity score. Of the 316 subjects that underwent blood transfusion or had moderate to severe bleeding, all 316 (100%) were matched with 2 patients that did not receive transfusion, indicating an excellent number of matched patients with good statistical discrimination (C statistic: 0.81, 0.84, and 0.82 for the 30 days, 6 months, and 1 year models, respectively).

Despite the propensity-matched analysis, transfusion remained an independent and strong predictor of all-cause mortality at 30 days (Fig. 2A), 6 months (Fig. 2B), and 1 year (Fig. 2C) in unadjusted models. Similarly, in Cox proportional hazards survival models that used transfusion as a time-dependent covariate and adjusted for over 25 variables in addition to propensity score, transfusion was associated with a higher risk of 30-day, 6-month, and 1-year mortality (Table 2). Proportional hazard assumption was met because the interaction between transfusion as a time-

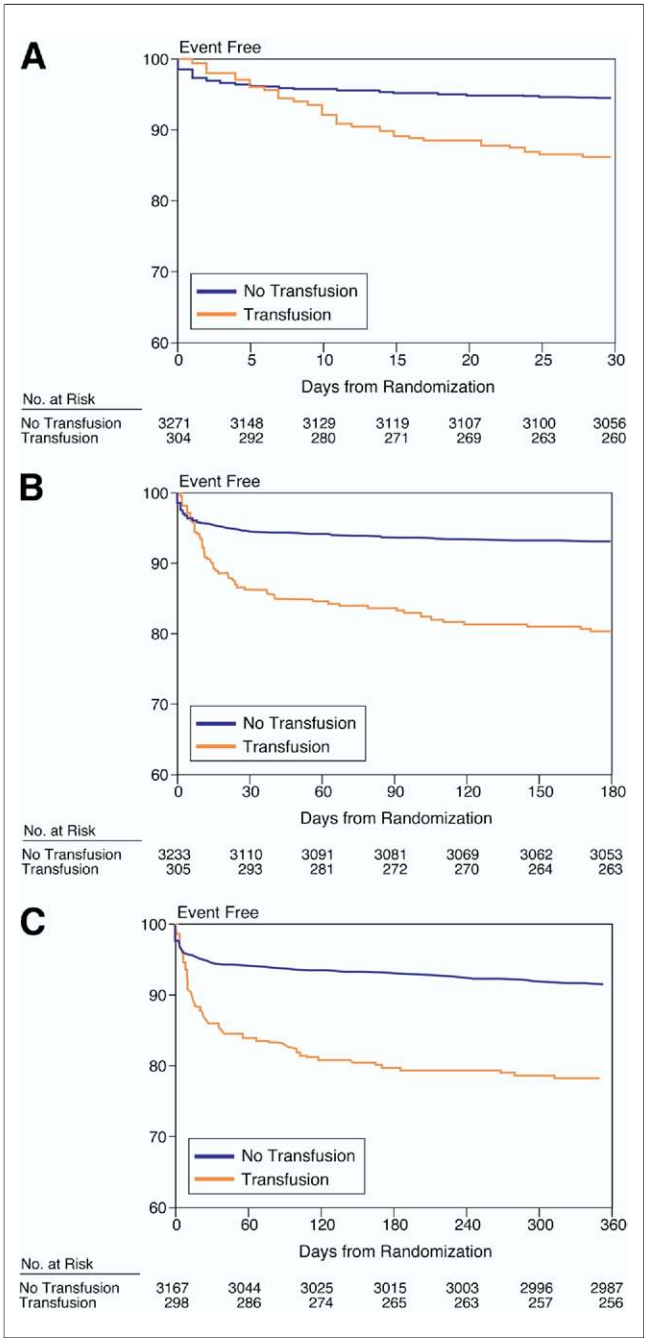

Figure 1. Kaplan-Meier Curves for Mortality in the Overall Population

Kaplan-Meier curves **(A)** for 30-day mortality in the overall population (n = 3,575), **(B)** for 6-month mortality in the overall population (n = 3,538), and **(C)** for 1-year mortality in the overall population (n = 3,465).

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Table 2. Univariate and Multivariable Cox Proportional Hazards Survival Models for Blood Transfusion According to 30-Day, 6-Month, and 1-Year Mortality for the Whole Population and the Propensity-Matched Patients

Variables	Number of Deaths (%)	Hazard Ratio (95% Confidence Interval)	p Value
All patients			
30-day (n = 3,575)	221 (6)	—	—
Unadjusted	—	6.12 (4.31–8.69)	<0.001
Multivariable adjusted	—	3.89 (2.66–5.68)	<0.001
6-month (n = 3,575)*	285 (8)	—	—
Unadjusted	—	5.63 (5.31–5.97)	<0.001
Multivariable adjusted	—	3.63 (2.67–4.95)	<0.001
1-year (n = 3,575)†	340 (10)	—	—
Unadjusted	—	4.52 (4.27–4.77)	<0.001
Multivariable adjusted	—	3.03 (2.25–4.08)	<0.001
Propensity-matched patients			
30-day (n = 948)	96 (10)	—	—
Unadjusted	—	3.84 (2.45–6.02)	<0.001
Multivariable adjusted	—	5.44 (3.21–9.22)	<0.001
6-month (n = 958)	128 (13)	—	—
Unadjusted	—	3.75 (2.57–5.48)	<0.001
Multivariable adjusted	—	4.81 (3.00–7.71)	<0.001
1-year (n = 958)	152 (16)	—	—
Unadjusted	—	3.13 (2.92–3.35)	<0.001
Multivariable adjusted	—	3.10 (2.18–4.40)	<0.001

*A total of 37 patients were lost to follow-up at 6 months. †A total of 110 patients were lost to follow-up at 1 year.
— = not applicable.

dependent variable and time was not significant in any of the models.

Validity and sensitivity analysis. Among all quintiles of propensity score, baseline characteristics were well matched and transfusion remained significantly associated with all-cause mortality for each quintile confirming the validity of our propensity analysis (22). A simple sensitivity analysis that introduced a single sensitivity parameter gamma that measured the degree of departure from random assignment of treatment, which in our case was transfusion, was performed (22). In all 3 matched models (30 days, 6 months, and 1 year), we tested gamma from 1 to 6. For all models, at gamma = 6, the p value was < 0.01, indicating our results are highly insensitive to bias and that hidden bias has to be enormous to alter our conclusions (22).

Discussion

We observed a higher death rate at 30 days, 6 months, and 1 year in patients with STEMI receiving blood transfusions. Patients in the blood transfusion group had lower hemoglobin levels, were older, and had a higher prevalence of cardiovascular risk factors, but the increased mortality in the transfusion group persisted even after adjustment for baseline characteristics, nadir hemoglobin, comorbidities, in-hospital medical therapy, and procedures. Additionally, the association persisted across all statistical models and was even stronger when patients were matched based on propensity to receive transfusion.

The historic clinical standard of transfusing when the hemoglobin levels dropped below 10 g/dl was challenged in earlier studies in patients admitted to the intensive care units or undergoing coronary artery bypass graft surgery (21,23). These studies established that routine transfusion can lead to increased mortality, prolonged hospital length of stay, and adverse outcomes (21,23). Although, the association between anemia and clinical outcomes is well established in patients presenting with ACS, the literature on the role of transfusion is more limited and has yielded conflicting results (9,10,24). Few studies have shown improved outcomes with blood transfusion (9), and others have suggested harm (7,8,10). Overall, few studies have examined the association between blood transfusion and long-term mortality. Additionally, potential biases and confounding may have led to the contradictory results observed in these studies (7–10,25).

In a retrospective analysis of non-STEMI patients enrolled in 3 clinical trials, Rao et al. (8) showed that transfusion was associated with increased hazard for 30-day mortality (adjusted HR: 3.94, 95% CI: 3.26 to 4.75). However, the investigators (8) did not conduct propensity-matched analysis, and long-term effects of transfusion on mortality could not be ascertained from the study. Sabatine et al. (26) in a post hoc analysis of pooled ACS clinical trials

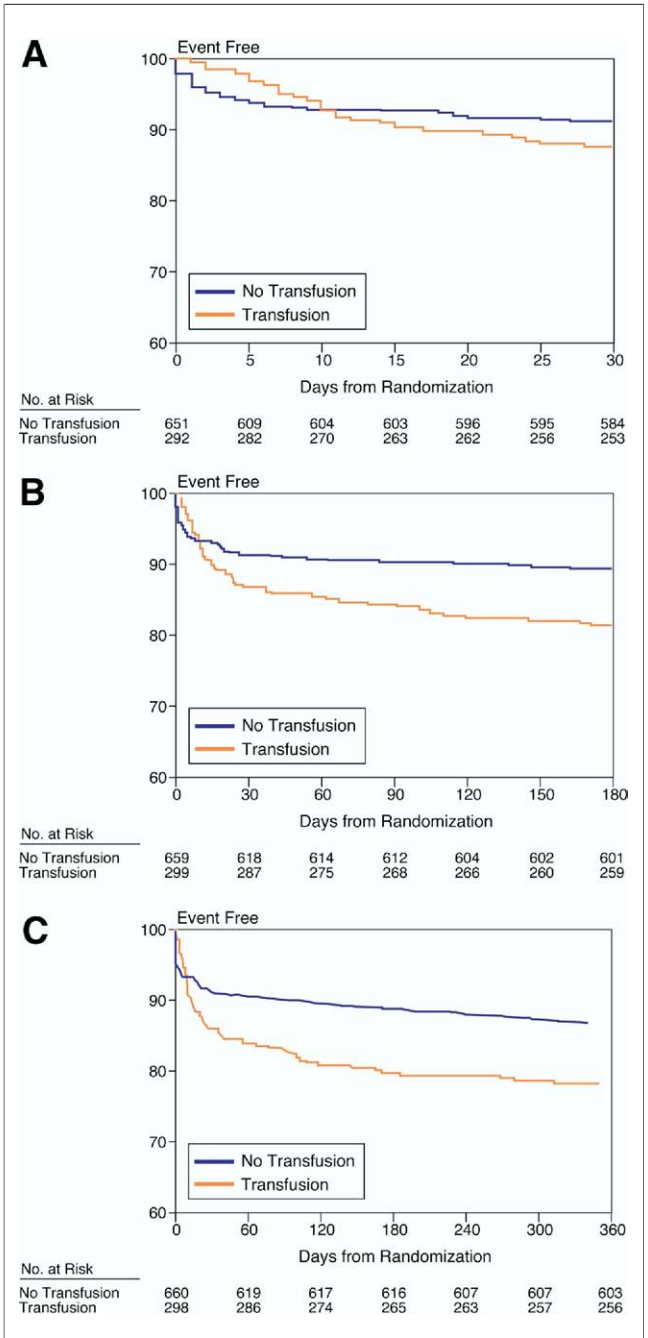

Figure 2. Kaplan-Meier Curves for 30-Day Mortality in Propensity-Matched Population

Kaplan-Meier curves **(A)** for 30-day mortality in propensity-matched population (n = 943), **(B)** for 6-month mortality in propensity-matched population (n = 958), and **(C)** for 1-year mortality in propensity-matched population (n = 958).

showed an interaction between STEMI and blood transfusion, whereby transfusing STEMI patients with hemoglobin below 12 g/dl was associated with lower mortality but an increased risk of adverse events and death among non-STEMI patients who were transfused. In a retrospective study of Medicare data, Wu et al. (9) showed improved survival in elderly patients with STEMI if hematocrit was below 30%. However, the investigators (9) excluded all patients younger than 65 years and those having bleeding within 48 h of admission, which limits the generalizability of the study. Additionally, their study was limited to 30-day outcomes and did not consider propensity analysis. Our study supports the findings of Rao et al. (8) and demonstrates that transfusion is associated with both short- and long-term mortality in patients with STEMI.

The exact reasons for the harmful effect of blood transfusion in the setting of STEMI are not yet completely understood. Animal models have shown that STEMI is a state of increased viscosity, and transfusion may lead to decreased microcirculatory flow and poor oxygen delivery (27–29). Some of the harm may also be due to blood being stored for prolonged periods (30–32). In vitro studies show that stored red blood cells undergo various morphologic and functional changes from discoid to spherical that decreases their ability to deform and pass through microcirculation. Additionally, there is depletion of 2,3-diphosphoglycerate, thereby reducing red blood cells' capacity to carry oxygen as well as increasing free radical production (19,33–37). Whether these changes account for the majority of in vivo adverse outcomes associated with transfusion is uncertain at this time (23,38,39). It has been suggested that, with increased hemoglobin, the platelets are exposed to increased shear forces, which increases platelet aggregation toward the vessel wall and may worsen ischemia (40,41).

Recently Bennett-Guerrero et al. (42) and Reynolds et al. (43) suggested that stored blood results in loss of nitric oxide bioactivity, leading to decreased levels of S-nitrosothiol hemoglobin in stored blood. However, repletion of stored blood with nitric oxide led to increased levels of S-nitrosothiol hemoglobin and improved vasodilatory response to hypoxia (42,43).

Our study also showed long-term increase in mortality with blood transfusion. Because the life of a red blood cell is around 120 days it is not clear why patients receiving blood transfusion would have long-term adverse events. One potential explanation for this is the immunomodulatory and pro-inflammatory properties of transfused blood. A number of pro-inflammatory mediators are released from white blood cells during storage. These include myeloperoxidase, plasminogen activator inhibitor-1, eosinophil protein X, and histamine (44). Collectively, these factors may enhance atherosclerosis or lead to diffuse inflammation within the coronary tree. Furthermore, in the setting of STEMI, they may have adverse effects on the infarcted myocardium.

Study limitations. Our study has several limitations in that our results are based on a post hoc analysis of prospectively collected, randomized, controlled trial data. Hence, there is a possibility of unmeasured biases. However, a series of statistical modeling and adjustments including propensity

analysis only strengthened the relationship between blood transfusion and mortality. Sensitivity analysis also showed that hidden bias had to be extraordinary to alter our results. Also, GUSTO IIb included a broad representation of population with a wide spectrum of coexisting conditions, but it may still not reflect the real world population. In addition, data regarding age of stored blood or ABO blood groups compatibility were noted as available. Lastly, this cohort is outdated and the current therapies (pharmacological and interventional) have drastically changed during this period. However, bleeding remains an important complication associated with pharmacologic therapy in patients presenting with ACS and its treatment with stored blood product has not changed since the GUSTO IIb era.

Conclusions

In patients with STEMI, blood transfusion was an independent predictor of both short- and long-term mortality. The relationship between transfusion and clinical outcomes persisted after adjustment for a wide array of baseline characteristics including nadir hemoglobin and in-hospital treatments. Our study results warrant a prospective, randomized clinical trial to determine whether blood transfusion to target specific hemoglobin levels improves outcomes in patients with STEMI. There certainly appears to be a foundation for evaluating newer methods that may avoid the potential adverse impact of stored blood.

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Key Words: blood transfusion ■ ST-segment elevation myocardial infarction ■ long-term outcome ■ propensity analysis.