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Anemia Is an Independent Predictor of Mortality After Percutaneous Coronary Intervention

Paul C. Lee, MD, FRCPC, Annapoorna S. Kini, MD, MRCP, Chowdhury Ahsan, MD, Edward Fisher, MD, Samin K. Sharma, MD, FACC

New York, New York

OBJECTIVES The aim of the present study was to assess whether anemia is a marker of increased risk during interventional procedure and poor midterm survival after percutaneous coronary intervention (PCI).

BACKGROUND Anemia is associated with increased risk of mortality in patients with heart failure and myocardial infarction (MI).

METHODS We examined the outcomes of 6,116 consecutive PCI patients based on the hemoglobin (Hb) value before the interventional procedure. Patients were divided into three groups based on the baseline Hb level (g/l): Hb <10 = severe anemia; Hb 10 to 12 = mild anemia; Hb >12 = no anemia.

RESULTS The presence of anemia is associated with higher 30-day major adverse cardiac events, post-PCI peak troponin and creatine kinase-MB fraction, and a longer length of stay. After controlling for multiple covariates, significant difference in one-year survival was noted in the anemic groups compared with no anemia group (adjusted hazard ratio for Hb 10 to 12: 1.5 [95% confidence interval 1.3 to 1.8]; for Hb <10: 1.8 [95% confidence interval 1.3 to 2.3]; p = 0.004.) This adverse effect of anemia on survival was noted in all three presenting clinical syndromes (stable angina, unstable angina, and MI).

CONCLUSIONS Anemia is an independent predictor of mortality after PCI and is associated with higher short-term adverse procedural events. (J Am Coll Cardiol 2004;44:541–6) © 2004 by the American College of Cardiology Foundation

In myocardial infarction (MI) (1) and heart failure (2,3), anemia is known to result in higher mortality. Furthermore, preoperative anemia is associated with increased perioperative mortality in coronary artery bypass surgery (4). Coronary artery disease patients undergoing percutaneous coronary interventions (PCI) are prone to oxygen demand and supply mismatch during the procedure, which will be exaggerated in the presence of anemia. We examined our interventional database of PCI patients to determine whether anemia has a similar impact on PCI patients.

METHODS

Study population. We retrospectively analyzed all patients undergoing PCI at Mount Sinai Hospital, New York, from July 1999 to December 2001 with complete survival data. Survival data and hemoglobin (Hb)/cardiac enzymes were available in 95% and 100% the patients in the database, respectively.

Data collection and definitions. One-year follow-up were prospectively captured and maintained in an institutional review board-approved interventional database. All baseline clinical characteristics, procedural details, postprocedural events, in-hospital events, 30-day major adverse cardiac events (MACE) (death, urgent repeat revascularization, Q-wave MI, and/or creatine kinase-MB fraction [CK-MB] ≥3 × normal if baseline CK-MB normal and non-MI presentation) were prospectively recorded. Hemoglobin value was based on blood draws immediately before the procedure. Clinical syndromes (stable angina, unstable angina, MI) were defined as follows: stable angina = anginal symptoms with no change in frequency, duration, or intensity of symptoms within four weeks or silent ischemia; unstable angina = new-onset of angina, accelerated angina, or rest angina; MI = MI occurring within four weeks as per American College of Cardiology/European Society of Cardiology 2000 definition (5). Troponin and CK-MB were measured serially twice (every 6 to 8 h for the first 24 h) after the interventional procedures, and the peak values were recorded. Mortality data were obtained by telephone follow call to the private physician and cross-checked by social security database.

Statistical method. The World Health Organization definition of anemia has different Hb cutoff for anemia (13 mg/dl for men and 12 mg/dl for women) (6). We examined the strength and shape of the relationships of Hb and the log odds of MACE or death with cubic spline analysis (using SAS macro-based on Molinari et al. [7] and Heinzl et al. [8]), which demonstrated that the relationship of Hb and survival or MACE is not linear. Therefore, we converted Hb from a continuous variable into a categorical variable with the threshold values of 10 mg/dl and 12 mg/dl, based on the location of the knots in the cubic spline fit. For simplicity of analysis and presentation, we did not perform a separate cubic spine analysis for men and women. Multi-

From the Cardiac Catheterization Laboratory of the Cardiovascular Institute, Mount Sinai Hospital, New York, New York. Dr. Lee was supported by the Canadian Heart and Stroke Foundation/Canadian Institute of Health Research Postdoctoral Fellowship Award. Presented at the 52nd Annual Scientific Session of the American College of Cardiology in March 2003.

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Abbreviations and Acronyms

CK-MB = creatine kinase-MB fraction
Hb = hemoglobin
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
MACE = major adverse cardiac event
MI = myocardial infarction
PCI = percutaneous coronary intervention

ple group comparisons for categorical variables were performed using Pearson's chi-square test. Comparisons for continuous variables were performed using analysis of variance or the Kruskal-Wallis test as appropriate. Kaplan-Meier analysis of mortality data was performed using the log-rank test both with and without stratification for clinical syndromes. The proportional hazard assumption for categorical variables was verified using a simplified Kaplan-Meier survival estimate procedure (9); the continuous variable terms were tested by Cox proportional model incorporating interaction of survival time and each individual covariate (10). Because the clinical syndrome variable exhibits non-proportionality, stratified Cox analysis over clinical syndrome was performed. Hazard ratios for mortality (adjusted and unadjusted) were obtained using the Cox proportional hazard model (stratified for clinical syndrome). Adjusted odd ratio for 30-day MACE was obtained by multiple logistic regressions. Simple two-way analysis of baseline variables was performed with SAS/JMP 5.01 (SAS Institute Inc., Cary, North Carolina). Logistic and Cox survival analysis were performed with SPSS 11.1 (SPSS Inc., Chicago, Illinois). Survival function cubic spline was performed with SAS 8.0 (SAS Institute Inc.) utilizing macro written by Molinari et al. (7). The relationship between Hb and MACE was analyzed with SAS/JMP spline analysis platform. Receiver operating curve analysis was performed with STATA 8.0 (Stata Corp., College Station, Texas).

RESULTS

Baseline characteristics are summarized in Table 1. The anemic groups (Hb <10 and Hb = 10 to 12) have more cardiac comorbidities including lower left ventricular (LV) ejection fraction (LVEF) and more multivessel disease. Other significant differences include higher age, higher incidence of diabetes, and hypertension.

There are no differences in angiographic success ($p = 0.63$) or procedural complications ($p = 0.22$) (Table 2). However, the anemic groups have higher CK-MB ($p = 0.04$) and troponin I ($p = 0.0003$) after PCI, after excluding MI patients and patients with elevated baseline troponin or CK-MB (Table 2). The total length of stay for the anemic groups is higher ($p < 0.001$) (Table 2). The 30-day MACE is higher in the anemic groups ($p = 0.0002$). Because there are significant differences in baseline characteristics between

Table 1. Baseline Characteristics

	Hb >12 (n = 4,712)	Hb = 10–12 (n = 1,163)	Hb <10 (n = 241)	p Value
Male gender (%)	3,567 (76)	509 (44)	107 (44)	<0.0001
Age (yrs)	64.1 ± 11.6	69.7 ± 12.0	70.0 ± 12.1	<0.0001
Angina class III–IV (%)	1,602 (34)	430 (37)	75 (31)	0.55
Clinical syndromes (%)				<0.0001
Stable angina	1,508 (32)	337 (29)	55 (23)	
Unstable angina	2,356 (50)	582 (50)	135 (56)	
Acute MI	848 (18)	244 (21)	51 (21)	
Diabetes (%)	1,366 (29)	535 (46)	125 (52)	<0.0001
Prior bypass surgery (%)	754 (16)	221 (19)	65 (27)	0.0001
History of hypertension (%)	3,958 (84)	1,058 (91)	219 (91)	<0.0001
LVEF (%)	53 ± 11	51 ± 12	47 ± 13	<0.0001
Prior MI (%)	1,272 (27)	337 (29)	77 (32)	0.08
LDL (mmol/l)	2.64 ± 0.85	2.46 ± 0.80	2.36 ± 0.88	<0.0001
Multivessel disease (%)	2,686 (57)	675 (58)	164 (68)	0.0002
GP IIb/IIIa inhibitor use (%)	3,958 (84)	907 (78)	171 (71)	<0.0001
ACC/AHA B2/C lesion (%)	3,910 (83)	965 (83)	202 (84)	0.71
Contrast volume (ml)	175 ± 72	168 ± 70	159 ± 78	<0.0001
Chronic renal failure (%)	211 (4)	136 (11)	48 (20)	<0.0001
NYHA functional class III to IV	147 (6)	82 (12)	14 (10)	
Pre-PCI medications (%)				
Aspirin	4,382 (93)	1,097 (92)	212 (88)	<0.01
ACE inhibitor	2,049 (43)	609 (51)	129 (53)	<0.0001
Beta-blocker	3,307 (69)	798 (67)	154 (63)	0.084
Digoxin	276 (6)	105 (9)	40 (16)	<0.0001
Diuretic	956 (20)	451 (38)	105 (43)	<0.0001
Statin	2,977 (62)	712 (60)	145 (59)	0.28

ACC = American College of Cardiology; ACE = angiotensin-converting enzyme; AHA = American Heart Association; GP = glycoprotein; Hb = hemoglobin; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

Table 2. Procedural Outcome and Follow-Up

	Hb >12 (n = 4,712)	Hb = 10–12 (n = 1,163)	Hb <10 (n = 241)	p Value
Angiographic success (%)	4,571 (97)	1,116 (96)	231 (96)	0.63
Minor procedural events (%)	565 (12)	151 (13)	24 (10)	0.22
Elevated CK-MB peak* (%)	333 (14)	93 (17)	22 (21)	0.041
Elevated troponin peak* (%)	773 (33)	188 (35)	46 (43)	0.0003
30-day MACE (%)	57 (1.2)	40 (3.4)	10 (4.3)	0.0002
Total length of stay (days)	2.1 ± 3.7	3.4 ± 5.3	5.7 ± 9.5	<0.001
Death within 1 year (%)	80 (1.7)	48 (4.1)	31 (12.8)	<0.0001

*Exclude patients presenting with mycardial infarction, elevated baseline creatine kinase-MB (CK-MB), or troponin or without baseline cardiac enzyme measurements (n = 2,379, 545, and 104 for the hemoglobin (Hb) >12, Hb = 10–12, and Hb <10 groups, respectively).
MACE = major adverse cardiac events.

the anemic and nonanemic groups, we used multivariate logistic regression to control for these variables (Table 3). The difference in 30-day MACE for the anemia group remained significant after adjustment.

Post-PCI patients with preprocedure Hb >12 g/l have a higher one-year survival compared with 10 to 12 g/l group ($p < 0.0001$); while patients in the 10 to 12 g/l group have higher survival than patients with <10 g/l Hb ($p < 0.0001$) (Table 2, Fig. 1A). The c-statistic for Hb as a predictor for one-year mortality is 0.71. To determine whether this difference is dependent on the presenting clinical syndromes (stable angina, unstable angina, and MI), we performed a stratified survival analysis. In all strata, similar survival difference is seen among the three Hb subgroups ($p < 0.005$), although, in the stable angina patient group, only the Hb >12 and Hb <10 groups have statistically different survival ($p = 0.0017$) (Figs. 1B to 1D).

Because renal failure is commonly associated with anemia (10), we performed a stratified analysis of the risk of anemia separately in patients with or without history of chronic renal insufficiency. As shown in Figure 2, anemia is associated with increased mortality in both groups of patients. The risk of anemia is particularly pronounced in the group with Hb <10 in combination with a history of renal insufficiency, with one-year mortality approaching 20%. Furthermore, the mortality and MACE risk of anemia is independent of the presence of renal impairment (Table 3) in our multivariate models. Because of the higher incidence of diabetes and multivessel disease in the anemia group, we also confirmed the risk associated with anemia in the nondiabetic PCI patients without triple-vessel disease (Table 3).

To test whether other potential confounding factors completely explain the role of anemia in resulting higher PCI mortality, Cox proportional hazard model (stratified for clinical syndromes) was used after we had validated that anemia as a mortality risk factor fulfills the proportional hazard assumption. After controlling for multiple covariates including LVEF, age, diabetes, number of vessels diseased, diuretics, digoxin, contrast used, renal failure, and prior MI, anemia (Hb >12 vs. Hb ≤12) was still a significant predictor of mortality (Table 3).

DISCUSSION

The main finding of the present study is that anemia is associated with higher post-PCI mortality. Both moderate-severe (Hb <10) and mild anemia (Hb = 10 to 12) are associated with increased one-year mortality, while moderate-severe anemia is associated with higher risk than mild anemia. Hospital length of stay, post-PCI cardiac enzymes, and 30-day MACE are higher in patients with

Table 3. Adjusted 30-Day MACE Odds Ratio and 1-Year Mortality Hazard Ratio for Anemia

	Odds Ratio for 30-Day MACE			Hazard Ratio for 1-Year Mortality		
Covariates Adjusted	Odds Ratio	95% CI	p Value	Hazard Ratio	95% CI	p Value
Nonadjusted						
Hb 10–12*	1.9	1.3–2.8		1.7	1.5–2.0	
Hb <10*	2.3	1.5–3.1	0.0001	2.5	2.0–3.0	<0.0001
Excluded renal failure						
Hb 10–12	1.6	1.2–2.8		1.8	1.5–2.1	
Hb <10	2.2	1.1–5.4	0.003	2.3	1.7–2.9	<0.0001
Excluded diabetes and triple-vessel disease						
Hb 10–12	1.7	1.0–2.8		2.1	1.6–2.7	
Hb <10	1.8	1.2–4.1	0.04	2.7	1.7–4.1	0.0005
Adjusted for first order covariates (multivariate model)†						
Hb 10–12	1.8	1.3–3.2		1.5	1.3–1.8	
Hb <10	1.9	1.2–6.0	0.003	1.8	1.3–2.3	0.004

*Compared with hemoglobin (Hb) >12 group; †Age, diabetes, chronic renal failure, prior bypass surgery, clinical syndrome, prior myocardial infarction, peripheral vascular disease, American College of Cardiology/American Heart Association class, multivessel disease, left ventricular ejection fraction, percutaneous coronary intervention index artery, sex, contrast amount, diuretic use, digoxin use and smoking, glycoprotein IIb/IIIa use, congestive heart failure New York Heart Association III or IV, statin use, beta-blocker use.
CI = confidence interval; MACE = major adverse cardiac events.

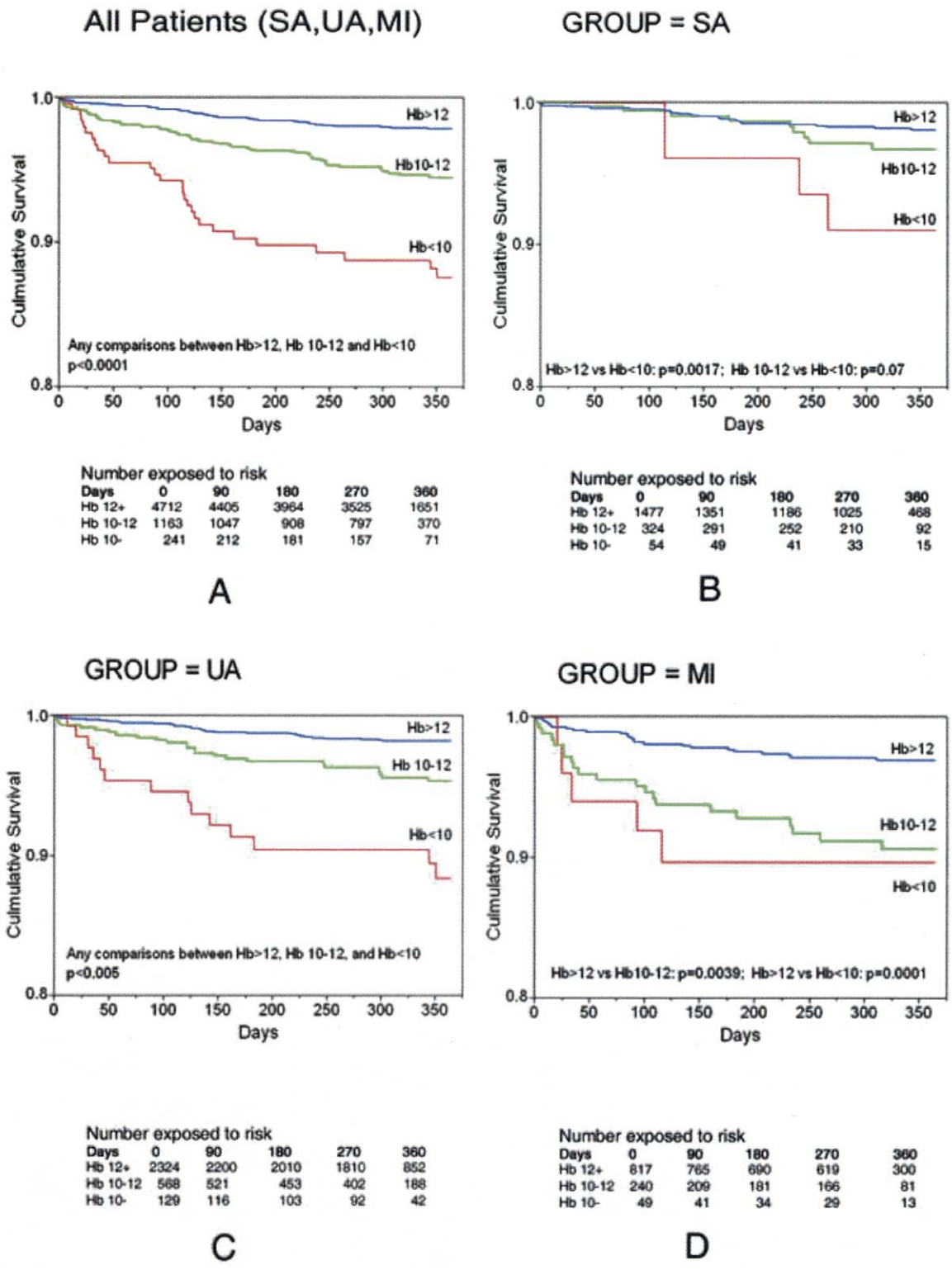

Figure 1. Kaplan-Meier curves for one-year survival of percutaneous coronary intervention patients by hemoglobin (Hb) groups stratified by clinical syndromes. **(A)** All patients. **(B)** Stable angina patients (SA). **(C)** Unstable angina patients (UA). **(D)** Myocardial infarction patients (MI).

anemia. The increased PCI mortality risk associated with anemia is independent of many baseline risk factors including LVEF, diabetes, history of renal failure, multivessel disease, and history of bypass surgery.

Anemia has been associated with increased mortality in the presence of significant medical or surgical conditions such as MI (1), heart failure (2,3), hematologic malignancy (12), renal failure (11,13), vascular surgery (14), and radical

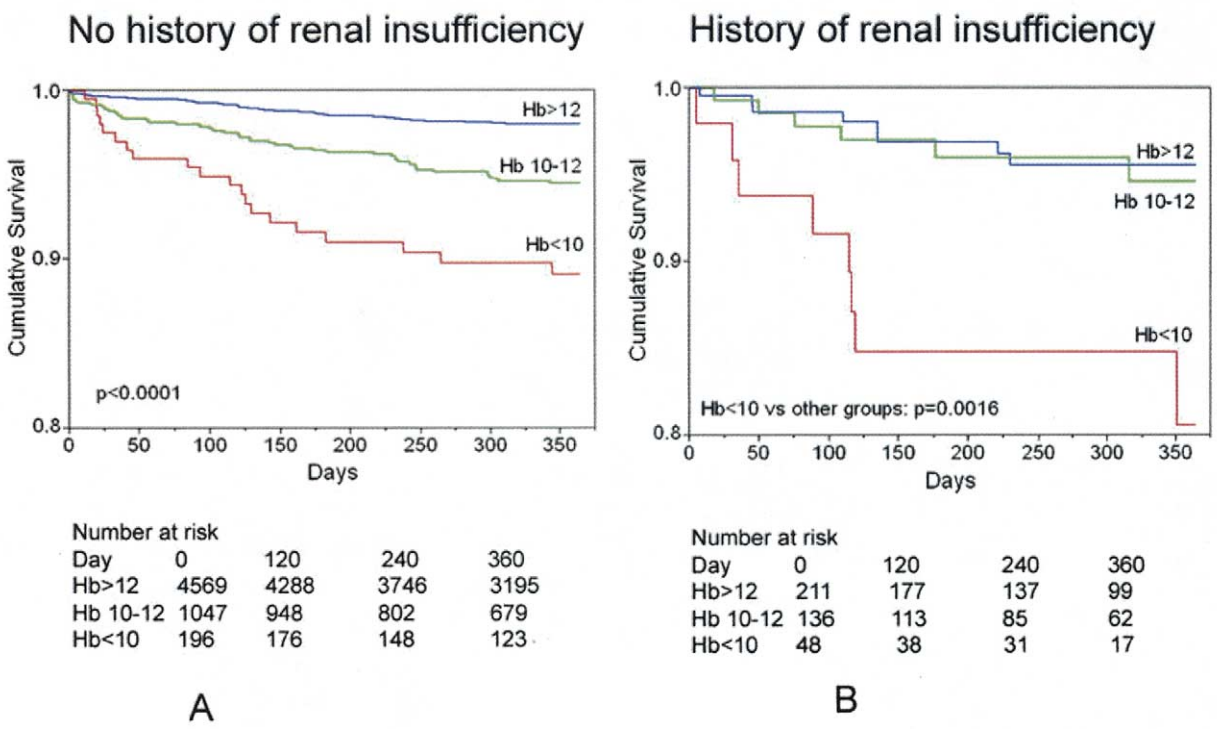

Figure 2. Kaplan-Meier curves for one-year survival of percutaneous coronary intervention patients by hemoglobin (Hb) groups stratified by history of renal insufficiency.

prostatectomy (15). We found that anemia is associated with a similar risk in PCI patients: both the short-term and long-term outcomes are worse in the anemic patients.

Very recently, Reinecke et al. (16) also noted that anemia increases the mortality after PCI in a smaller study. However, their study is limited by the small sample size, which limits the author's ability to perform statistical adjustment for confounders and addresses the difference in mortality between mild and more severe anemia. Because of our large sample size, we are able to detect actual progressive increase in mortality with decreasing Hb. Furthermore, we are able to enter a large number of covariates in multivariate models and to perform stratified analysis to control for various confounding factors.

Increased cardiac enzymes after PCI and 30-day MACE with anemia is consistent with the hypothesis that ischemia induced by balloon inflation during PCI may be less well-tolerated because lower Hb results in decreased blood-oxygen carrying capacity and inadequate tissue-oxygen delivery (17). Higher periprocedural myonecrosis might have translated into higher one-year morality in the anemic patients (18). Measures to decrease oxygen demand in this setting, such as the use of pre-PCI beta-blockers, may be particularly beneficial (19).

Anemia contributes to the development of LV hypertrophy, mainly via increased cardiac output. Anemia results in an increase in LV mass, while in others it also results in LV end-diastolic volume dilation. These changes increase the risk of arrhythmias, MI, and myocardial fibrosis (20).

Given the recent finding that bone marrow may be a source of cardiac stem cells and that they are mobilized during cardiac injury, endothelial and cardiac stem cell recruitment after cardiac injury may be impaired in the anemic state where the marrow may be dysfunctional (21,22). This is obviously controversial in view of the recent report of the failure of hematopoetic stem cell transdifferentiation into cardiac myocyte in a transgenic mouse model (23).

Incorporation of Hb in risk-stratification scheme will improve the performance of risk adjustment algorithms. None of the major risk prediction instruments (e.g., New York State Percutaneous Transluminal Coronary Angioplasty Mortality model, American College of Cardiology-National Cardiovascular Data Registry) currently incorporate anemia in their multivariate models (24,25).

Study limitations. The major limitations of this study are the retrospective nature of the analysis and the possibility that potentially important risk factors may not be included in our statistical adjustment, even though we have adjusted 19 risk factors and analyzed the data according to clinical syndromes. In addition, we do not have the etiology of anemia of the vast majority of the anemic patients, and we cannot absolutely rule out the contribution of the underlying medical disorders to the increased mortality risk.

Conclusions. Our study uncovers an important risk factor for stratifying PCI patients. Our finding does not prove that transfusion for significant anemia pre-PCI will decrease mortality, though it is prudent to incorporate the patient's

Hb into the overall PCI strategy, especially if the degree of anemia is severe.

Reprint requests and correspondence: Dr. Samin K. Sharma, Mount Sinai Hospital, Box 1030, One Gustave Levy Place, New York, New York 10029-6574. E-mail: samin.sharma@msnyuhealth.org.

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