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Impact of Preoperative Anemia on Outcome in Patients Undergoing Coronary Artery Bypass Graft Surgery

Alexander Kulier, MD; Jack Levin, MD; Rita Moser, MD; Gudrun Rumpold-Seitlinger, MD; Iulia Cristina Tudor, PhD; Stephanie A. Snyder-Ramos, MD; Patrick Moehnle, MD; Dennis T. Mangano, PhD, MD; for the Investigators of the Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation

Background—The risk of preoperative anemia in patients undergoing heart surgery has not been described precisely. Specifically, the impact of low hemoglobin per se or combined with other risk factors on postoperative outcome is unknown. Thus, we determined the effects of low preoperative hemoglobin and comorbidities on postoperative adverse outcomes in patients with coronary artery bypass graft in a large comprehensive multicenter study.

Methods and Results—The Multicenter Study of Perioperative Ischemia investigated 5065 patients with coronary artery bypass graft at 70 institutions worldwide, collecting ≈ 7500 data points per patient. In 4804 patients who received no preoperative transfusions, we determined the association between lowest preoperative hemoglobin levels and in-hospital cardiac and noncardiac morbidity and mortality and the impact of concomitant risk factors, assessed by EuroSCORE, on this effect. In patients with EuroSCORE < 4 ($n = 2054$), only noncardiac outcomes were increased, whereas patients with EuroSCORE ≥ 4 ($n = 2750$) showed an increased incidence of all postoperative events, starting at hemoglobin < 11 g/dL. Low preoperative hemoglobin was an independent predictor for noncardiac (renal $>$ cerebral; $P < 0.001$) outcomes, whereas the increase in cardiac events was due to other factors associated with preoperative anemia.

Conclusions—Anemic patients undergoing cardiac surgery have an increased risk of postoperative adverse events. Importantly, the extent of preexisting comorbidities substantially affects perioperative anemia tolerance. Therefore, preoperative risk assessment and subsequent therapeutic strategies, such as blood transfusion, should take into account both the individual level of preoperative hemoglobin and the extent of concomitant risk factors. (*Circulation*. 2007;116:&NA;-.)

Key Words: anemia ■ coronary disease ■ epidemiology ■ ischemia ■ revascularization

Anemia is a clinically important and increasingly frequent finding in patients presenting for surgery. In many of these patients, the perioperative risk is inherently high because of multiple concomitant diseases and is particularly aggravated when severe coronary artery disease is present.^{1–4} A significant association of anemia with increased perioperative morbidity and mortality has been established in a multitude of settings and in both cardiac and noncardiac surgery.^{1–13} Because of their extremely limited coronary reserve, patients undergoing coronary artery bypass grafting (CABG) surgery represent a population potentially most sensitive to the impact of low hemoglobin levels.^{2,3,9,11} However, available data do not describe in detail the exact relationship between the individual degree of preoperative anemia and specific adverse outcomes of CABG patients and

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do not quantify the impact of preexisting comorbidities on this association. In addition, it is unknown whether the effects of anemia on outcome are caused by low hemoglobin levels per se or by association with other risk factors frequently prevalent in anemic patients.⁴ Finally, only limited information is available about the incidence, degree, and major causes of preoperative anemia, especially in patients presenting for cardiac surgery.^{4,13} These questions have not been addressed in detail by a comprehensive worldwide multicenter study in a carefully controlled large patient population. Because of this lack of precise data, it is unknown which patient subgroups are at highest risk on the basis of the individual hemoglobin level and degree of comorbidities.

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Detailed risk stratification could provide physicians with valuable information to optimize the perioperative management of anemic CABG patients.

Therefore, the main goal of the present study was to examine the impact of preoperative anemia on postoperative adverse outcome in patients undergoing elective CABG surgery in a large prospective, multicenter setting with the use of the Multicenter Study of Perioperative Ischemia Epidemiology II (EPI II) database.¹⁴ (See Appendix for a complete list of the Investigators and Centers.) Specifically, we determined whether subnormal preoperative hemoglobin before CABG surgery was an independent predictor of postoperative cardiac and noncardiac in-hospital morbidity and mortality and evaluated the potential dose-response relationship of such effects. Second, we examined the impact of comorbidities and other risk factors, as assessed by the EuroSCORE,¹⁵ on the relationship between low preoperative hemoglobin levels and postoperative adverse outcomes. Finally, we determined which demographic factors and aspects of medical history were significant predictors for low preoperative hemoglobin levels in patients presenting for CABG surgery.

Methods

The Multicenter Study of Perioperative Ischemia EPI II Study

The prospective and longitudinal EPI II Study enrolled patients scheduled for CABG surgery with cardiopulmonary bypass at 72 institutions in 17 countries worldwide (see Appendix), according to a systematic sampling scheme among all patients undergoing surgery at each respective institution. Further details of the EPI II Study have been described earlier.¹⁴ Of the 5436 patients enrolled, 371 were excluded because of patient withdrawal (n=32), death before surgery (n=2), cancellation or rescheduling of surgery (n=97), change in procedure (n=132), inadvertent enrollment in another study (n=11), incomplete data (n=86), or incomplete blood sampling, shipping, or storage (n=11). Furthermore, patients were excluded for receiving autologous or homologous red blood cell (RBC) transfusion before surgery (n=44) or for missing data on preoperative hemoglobin (n=217), leaving 4804 patients included in this analysis.

Study Data

For each enrolled patient, ≈7500 variables were collected throughout the patient's index hospitalization, from admission until discharge, by independent investigators; treating physicians were blinded to all research data. Data included demographic, historical, clinical, laboratory, electrocardiographic, specialized testing, resource utilization, and adverse outcome information. After the last patient enrollment, all data fields for each patient were queried centrally for completeness and accuracy, with all changes documented before database closure.

The preoperative hemoglobin level was prospectively defined as the lowest documented hemoglobin value among those measured at admission, during the preoperative period, or immediately before induction of anesthesia.

Clinical Care

Clinical decisions were not controlled by study protocol, and all patients qualifying for enrollment within the prespecified 44-month enrollment period were entered. Independent investigators coded all medications received, including anti-ischemic medications and blood products, by day throughout hospitalization, as well as at admission and at discharge, or until death during hospitalization.

Measurement of Outcomes

All outcomes were prespecified, defined by protocol, and discerned by investigators blinded to treatment group. Fatal and nonfatal outcomes occurring after surgery and during the index hospitalization were classified as cardiac events (myocardial infarction, congestive heart failure, or death from cardiac causes) or noncardiac events, as follows: (1) cerebral events (encephalopathy, stroke, or death from cerebral causes); (2) renal events (renal dysfunction or failure, death from renal causes); (3) gastrointestinal events (ischemia or infarction, death from gastrointestinal causes); or (4) other (such as infectious, pulmonary). Composite outcome was defined as any of all adverse outcomes, cardiac and noncardiac, including in-hospital mortality. The diagnosis of myocardial infarction required either the development of new Q waves; or new persistent ST-segment or T-wave changes associated with an elevation of CK-MB isoenzyme values; or autopsy evidence of acute myocardial infarction. The diagnosis of heart failure required either the use of a ventricular assist device; the use of continuous inotropic support for at least 24 hours; or autopsy evidence of heart failure. Cerebral outcomes were classified as clinically diagnosed stroke or encephalopathy; or computed tomographic, magnetic resonance imaging, or autopsy evidence of a focal or global defect. Renal dysfunction was defined as a serum creatinine ≥ 2.0 mg/dL accompanied by a ≥ 0.7 -mg/dL rise over baseline; renal failure was defined as dysfunction requiring dialysis or autopsy evidence of renal failure. Gastrointestinal ischemia was defined as abdominal pain diagnosed as intestinal ischemia or detected at exploration; gastrointestinal infarction required bowel resection or autopsy evidence of intestinal infarction.

Statistical Analysis

Descriptive statistics (mean, SD, median) were calculated for all continuous study variables. Because of nonnormality of the distribution, median hemoglobin levels in different subpopulations were compared with nonparametric tests. A nonparametric median test was also applied for the comparison of length of hospital stay in preoperatively anemic patients versus patients who were not anemic.

Two separate analyses were performed to (1) evaluate the effect of preoperative hemoglobin on major in-hospital outcomes and (2) identify predictors for preoperative hemoglobin levels. The following risk factors were initially screened for univariate association with outcomes (by χ^2 test or Fisher exact test as appropriate): EuroSCORE, body mass index, gender, insulin-dependent diabetes mellitus, non-insulin-dependent diabetes mellitus, current smoking, history of anemia, myocardial infarction, congestive heart failure, ventricular tachyarrhythmias, stroke, transient ischemic attack, chronic pulmonary disease, renal failure, percutaneous transluminal coronary angioplasty, hypertension, hypercholesterolemia, unstable angina, CABG, coronary atherectomy, intracoronary stent, surgery performed as emergency, intraoperative RBC/fresh frozen plasma/platelet transfusion, lowest intraoperative hemoglobin level, cross-clamp time, and cardiopulmonary bypass time. Those found to be significant at a nominal 2-tailed $P \leq 0.2$ were entered into stepwise (backward and forward) multiple logistic models. In the final model, significance was set at $P < 0.05$. To evaluate the influence of comorbid conditions on postoperative adverse outcome, the preoperative risk was assessed for each patient with the use of the EuroSCORE system (www.euroscore.org).¹⁵ The median of the study population was used as the threshold value for EuroSCORE to define 2 subpopulations of interest for risk stratification. Point estimates for individual outcomes and risk associated with decreased hemoglobin levels were calculated in 2 separate subanalyses for low-risk (EuroSCORE < 4) and high-risk (EuroSCORE ≥ 4) patients (data not shown).

For the primary analysis, preoperative hemoglobin values along with the comprehensive group of other risk factors listed in the previous paragraph were evaluated for association with postoperative mortality and morbidity (including EuroSCORE and other demographic characteristics, previous medical conditions, and intraoperative transfusion practices). Multiple logistic regression was used to determine admission predictor variables for low preoperative hemo-

TABLE 1. Baseline Demographics and Clinical Characteristics (n=4804)

Characteristics	All Patients, n (%)	Hemoglobin Level in Patients With Characteristic, Mean (SD)	Hemoglobin Level in Patients Without Characteristic, Mean (SD)	P*
Age, mean±SD; median, y	64.0 ± 9.8; 64.8
Age group	<0.001
<65	2426 (50.5)	13.7 (1.6)
65–69	930 (19.4)	13.4 (1.7)
70–74	817 (17.0)	13.2 (1.7)
≥75	631 (13.1)	12.7 (1.7)
Body mass index >30 kg/m ² †	1166 (24.4)	13.6 (1.6)	13.4 (1.7)	<0.001
Current smoking	541 (11.3)	13.8 (1.6)	13.4 (1.7)	<0.001
Hypercholesterolemia	3398 (72.6)	13.5 (1.6)	13.3 (1.8)	0.004
Preoperative autologous blood donation	326 (6.8)	13.4 (1.6)	13.4 (1.7)	0.19
History of DM	1447 (30.2)	13.1 (1.8)	13.6 (1.6)	<0.001
NIDDM	1085 (22.6)	13.2 (1.7)	13.6 (1.6) (no DM)	<0.001
IDDM	352 (7.3)	12.8 (2.0)	13.6 (1.6) (no DM)	<0.001
Gender (female)	989 (20.6)	12.4 (1.6)	13.7 (1.6) (male)	<0.001
EuroSCORE ≥4	2750 (57.2)	13.0 (1.8)	13.9 (1.4)	<0.001
Medical history				
Transient ischemic attack	292 (6.1)	13.3 (1.6)	13.4 (1.7)	0.02
Renal disease	777 (16.2)	12.8 (1.9)	13.5 (1.6)	<0.001
Renal failure	401 (8.4)	12.3 (2.0)	13.5 (1.6)	<0.001
Hematological disorders	280 (5.8)	11.9 (2.0)	13.5 (1.6)	<0.001
Hypertension	3228 (67.4)	13.3 (1.7)	13.6 (1.6)	<0.001
Unstable angina	2920 (60.8)	13.3 (1.7)	13.6 (1.6)	<0.001
CHF (NYHA class ≥3)	687 (14.3)	13.0 (1.9)	13.5 (1.6)	<0.001
Myocardial infarction	2469 (51.9)	13.4 (1.7)	13.4 (1.7)	0.12
Coronary atherectomy	28 (0.6)	13.0 (1.5)	13.4 (1.7)	0.13
CABG	282 (5.9)	13.2 (1.7)	13.4 (1.7)	0.11
PTCA	729 (15.2)	13.4 (1.7)	13.4 (1.7)	0.19
Stroke	318 (6.6)	13.2 (1.8)	13.4 (1.7)	0.004
Chronic pulmonary disease	656 (13.7)	13.2 (1.8)	13.4 (1.7)	0.20

DM indicates diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; CHF, congestive heart failure; PTCA, percutaneous transluminal coronary angioplasty; and NYHA, New York Heart Association.

*P associated with the median (nonparametric) test, comparing hemoglobin levels in patients with listed characteristic vs those without.

†Body mass index at admission was 27.6±4.54 kg/m² (mean±SD; all patients).

globin, which was defined for this analysis by the hemoglobin level associated with a significant increase in composite outcome in the primary analysis. Receiver operating characteristic analysis was then used to determine sensitivity and specificity of the hemoglobin cutoff point.¹⁶ The final model had good fit (Hosmer-Lemeshow goodness of fit test=2.42; *P*=0.96) and good discriminating power (area under the receiver operating characteristic=0.79). Statistical significance level was set at *P*<0.05. Multiple comparisons adjustment was specified when appropriate. Missing values for concomitant risk factors were not imputed. All statistical analyses were performed with SAS version 8.12 software (SAS Institute, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Study Population

Of the 4804 patients, 28.1% of the male patients (1072 of 3815) presented with preoperative anemia according to the World

Health Organization definition (hemoglobin <13 g/dL) versus 35.9% (355 of 989) of the female patients (hemoglobin <12 g/dL). Demographic characteristics and medical history are summarized in Table 1, along with a comparison of the median hemoglobin values in patients with each analyzed characteristic versus those without. Current smoking, body mass index >30 kg/m², or hypercholesterolemia was associated with slightly higher preoperative hemoglobin levels, whereas patients with older age, female gender, diabetes, history of renal dysfunction, and EuroSCORE ≥4 were found to have lower hemoglobin values (Table 1). High-risk patients (EuroSCORE ≥4) were more likely to have decreased levels of hemoglobin compared with those with EuroSCORE <4 (*P*<0.001; data not shown).

Adverse Outcome

Univariate analysis established a primary association between decreased preoperative hemoglobin levels and increased post-

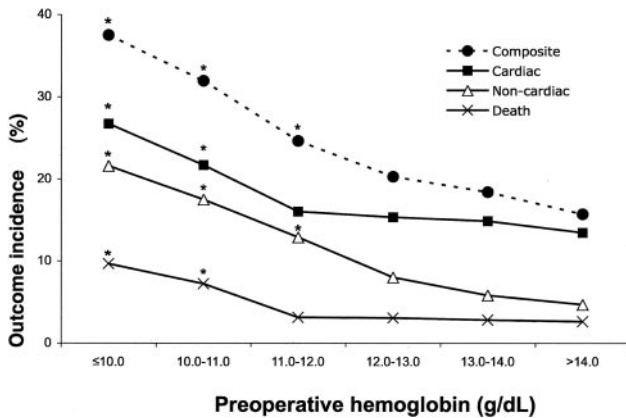


Figure 1. Incidence of postoperative adverse events for all patients vs preoperative hemoglobin level. The incidence of in-hospital death, cardiac and noncardiac outcome (=total of morbidity+mortality), and composite outcome (cardiac+noncardiac outcome) vs decreasing preoperative hemoglobin levels is shown. There was a dose-dependent significant increase in all outcome classes with decreasing hemoglobin levels. * $P<0.05$ vs hemoglobin >14 g/dL (pairwise significance without adjustment for multiple comparisons). In 163 patients, both cardiac and noncardiac events were observed.

operative cardiac and noncardiac adverse events. Figure 1 illustrates the dose-dependent nature of this effect. When patients were divided into high and low EuroSCORE groups (EuroSCORE <4 , $n=2054$ versus EuroSCORE ≥ 4 , $n=2750$), the association between decreased preoperative hemoglobin levels and the incidence of postoperative adverse events was better defined: In patients with EuroSCORE <4 , only the incidence of noncardiac outcome increased with decreasing hemoglobin levels (Figure 2), whereas in patients with EuroSCORE ≥ 4 , the incidence was increased for both cardiac and noncardiac outcome. Table 2 shows the incidence of adverse outcomes for all patients and divided by EuroSCORE risk group.

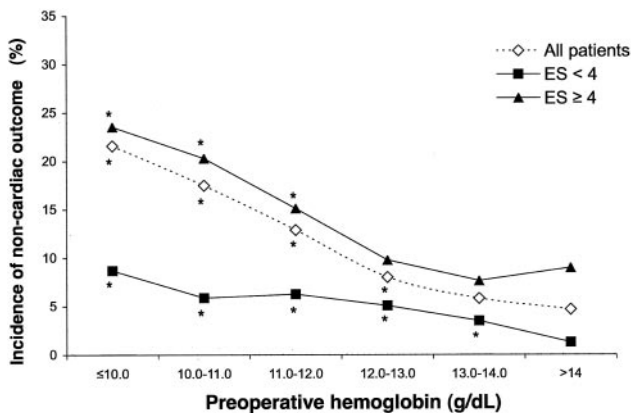


Figure 2. Incidence of noncardiac postoperative adverse events for high and low EuroSCORE (ES) risk groups vs preoperative hemoglobin level. The incidence of noncardiac postoperative outcome relative to both the low (ES <4) and the high (ES ≥ 4) ES risk groups and for all patients vs decreasing preoperative hemoglobin levels is shown. There was a significant dose-dependent relationship between decreasing hemoglobin levels and increased outcome. * $P<0.05$ vs hemoglobin >14 g/dL (pairwise significance without adjustment for multiple comparisons).

The final multivariable model, which identified and adjusted for confounding variables for adverse outcome (footnote Tables 3 and 4), showed that low preoperative hemoglobin was a significant independent predictor only for noncardiac ($P<0.001$) but not for cardiac outcome ($P=0.398$; Tables 3 and 4). The increased incidence of cardiac adverse events found in patients with low hemoglobin and EuroSCORE ≥ 4 was therefore attributable to other risk factors concomitantly present in these patients (Table 3). The effect of low preoperative hemoglobin on noncardiac outcomes was greatest for postoperative renal events (Figure 3).

There was also a significant association between low preoperative hemoglobin and the length of postoperative hospital stay. The mean length of postoperative hospital stay was 12.2 ± 9.7 days (median 9) for patients with hemoglobin ≤ 11 g/dL versus 10.1 ± 7.9 days (median 8) for patients with hemoglobin >11 g/dL ($P<0.001$).

Transfused patients received intraoperatively 2.6 U (mean; SD 1.9, median 2) of RBCs ($n=1838$), 3.1 U (mean; SD 2.4, median 2) of fresh frozen plasma ($n=502$), and 6.3 U (mean; SD 6.1, median 5) of platelets ($n=428$). Multivariable logistic regression demonstrated that the number of units of intraoperative RBC transfusion was independently associated with an increased risk for both cardiac and noncardiac outcome, whereas fresh frozen plasma and platelets were not predictors of either (Tables 3 and 4). Furthermore, multivariable logistic regression indicated that the lowest intraoperative hemoglobin level (mean 7.7 g/dL; SD 1.3; median 7.7 g/dL) was not independently associated with cardiac or noncardiac adverse outcomes (data not shown). Cardiopulmonary bypass time was 103.8 minutes (mean; SD 43.4, median 97.0), and cross-clamp time was 65.6 minutes (mean; SD 32.3, median 60.0). Multivariable logistic regression indicated that the cardiopulmonary bypass time was a highly significant independent predictor for increased cardiac or noncardiac adverse outcomes (Tables 3 and 4).

Anemia

Multiple logistic regression identified independent, significant demographic characteristics and medical conditions that were predictive of low preoperative hemoglobin levels in patients scheduled for CABG (Table 5). In this analysis, a history of anemia or renal failure and female gender showed the highest predictive value (odds ratio) for preoperative anemia. All other significant risk factors for low preoperative hemoglobin are also listed in Table 5, along with the prevalence of anemia in each respective risk group.

Discussion

This large epidemiological study is the first to investigate the nature and extent of the combined effects of preoperative anemia and comorbidities on postoperative outcome in patients undergoing CABG surgery, using a comprehensive worldwide multicenter, prospective design. Our results showed that preoperative anemia was associated with an increase of all postoperative adverse events, starting at hemoglobin levels <11 g/dL in a dose-dependent fashion. Specifically, low preoperative hemoglobin was an independent predictor for postoperative renal and central nervous

TABLE 2. Incidence of Adverse Outcomes

Events	Incidence, n (%)			P
	All Patients (n=4804)	EuroSCORE <4 (n=2054)	EuroSCORE ≥4 (n=2750)	
Composite outcome	951 (19.8)	252 (12.3)	699 (25.4)	<0.001
In-hospital death	159 (3.3)	13 (0.6)	146 (5.3)	<0.001
Cardiac outcome	737 (15.3)	205 (10.0)	532 (19.4)	<0.001
Noncardiac outcome	372 (7.7)	60 (2.9)	312 (11.4)	<0.001
Central nervous system	171 (3.6)	35 (1.7)	136 (5.0)	<0.001
Renal	238 (5.0)	28 (1.4)	210 (7.6)	<0.001
Gastrointestinal	29 (0.6)	2 (0.1)	27 (1.0)	<0.001

Composite outcome: total incidence of cardiac and noncardiac morbidity and mortality. There were 163 patients with both cardiac and noncardiac outcome.

system outcome, and the association with increased cardiac adverse events was caused by concomitant risk factors prevalent in anemic patients. The extent of comorbidities substantially amplified the adverse effects of low preoperative hemoglobin, which in turn was a significant marker for severe underlying diseases and comorbidities.

On the basis of demographic developments, especially in developed countries, more elderly patients are being admitted to hospitals to undergo surgery. In addition to the primary

diagnosis warranting surgery, these patients also suffer from many cardiac and noncardiac comorbidities that increase the perioperative risk. Moreover, the average hemoglobin level decreases with old age, so that many of these patients present with substantial preoperative anemia.^{5-7,12,17} A significant association of anemia with increased morbidity and mortality has been found both in large epidemiological studies^{5,6,12} and in a variety of perioperative settings,^{2-11,17-21} including both cardiac^{8,9,11,21} and noncardiac^{2,17-20} surgery. However, avail-

TABLE 3. Multiple Logistic Regression Analysis of Cardiac Outcome (n=4641)*

Risk Factor	Incidence of Outcome in Risk Group, % (n/N)	Adjusted Odds Ratio (95% CI)	P
Hemoglobin preoperative, g/dL			
>14 (n=1835)	13.5% (247/1835)	1	0.398
13 to 14 vs >14 (n=1170)	14.9% (174/1170)	0.97 (0.91 to 1.04)	...
12 to 13 vs >14 (n=848)	15.3% (130/848)	0.95 (0.84 to 1.07)	...
11 to 12 vs >14 (n=512)	16.0% (82/512)	0.92 (0.77 to 1.11)	...
10 to 11 vs >14 (n=263)	21.7% (57/263)	0.90 (0.70 to 1.15)	...
≤10 vs >14 (n=176)	26.7% (47/176)	0.87 (0.64 to 1.19)	...
EuroSCORE ≥4	19.4% (532/2750)	1.49 (1.23 to 1.80)	<0.001
History of myocardial infarction	17.2% (425/2469)	1.29 (1.09 to 1.52)	0.004
History of congestive heart failure	21.4% (358/1676)	1.59 (1.34 to 1.88)	<0.001
History of ventricular tachyarrhythmias	25.4% (73/288)	1.65 (1.23 to 2.22)	<0.001
History of coronary atherectomy	25.0% (7/28)	2.74 (1.13 to 6.68)	0.026
CPB time ≥97 min	19.2% (465/2419)	1.40 (1.17 to 1.66)	<0.001
Intraoperative homologous RBC transfusion per 1-unit increase	NA†	1.21 (1.15 to 1.27)	<0.001

To establish the dose-dependent effect of decreased vs normal preoperative hemoglobin values on adverse outcome, odds ratio values of decreased hemoglobin levels are shown in steps of 1 g/dL, and each was compared with patients with hemoglobin >14 g/dL. Odds ratio was adjusted for outcome in the presence of all significant, independent covariates. Higher odds ratio (>1) indicates worse outcome. P value for preoperative hemoglobin is associated with the test for trend. Variables analyzed for adverse postoperative outcomes (as covariates of preoperative hemoglobin): EuroSCORE, body mass index, gender, age, insulin-dependent diabetes mellitus, non-insulin-dependent diabetes mellitus, current smoking, history of anemia, myocardial infarction, congestive heart failure, ventricular tachyarrhythmias, stroke, transient ischemic attack, chronic pulmonary disease, renal failure, percutaneous transluminal coronary angioplasty, hypertension, hypercholesterolemia, unstable angina, CABG, coronary atherectomy, intracoronary stent, surgery performed as emergency, intraoperative RBC transfusion per 1-unit increase, intraoperative fresh frozen plasma transfusion per 1-unit increase, intraoperative platelet transfusion per 1-unit increase, lowest intraoperative hemoglobin level, cross-clamp time, and CPB time.

*163 patients were excluded because of missing values for at least 1 risk factor in the model.

†A single incidence of outcome cannot be provided for a continuous variable. However, if analyzed as a binary variable, intraoperative RBC transfusion resulted in a 19.6% (361/1838) incidence of outcome.

TABLE 4. Multiple Logistic Regression Analysis of Noncardiac Outcome (n=4756)*

Risk Factor	Incidence of Outcome in Risk Group, % (n/N)	Adjusted Odds Ratio (95% CI)	P
Hemoglobin preoperative, g/dL	4.7% (86/1835)	1	<0.001
>14 (n=1835)
13 to 14 vs >14 (n=1170)	5.8% (68/1170)	1.14 (1.06 to 1.24)	...
12 to 13 vs >14 (n=848)	8.0% (68/848)	1.31 (1.12 to 1.53)	...
11 to 12 vs >14 (n=512)	12.9% (66/512)	1.49 (1.18 to 1.89)	...
10 to 11 vs >14 (n=263)	17.5% (46/263)	1.71 (1.25 to 2.34)	...
≤10 vs >14 (n=176)	21.6% (38/176)	1.95 (1.32 to 2.90)	...
EuroSCORE ≥4	11.4% (312/2750)	2.47 (1.83 to 3.34)	<0.001
History of stroke	15.4% (49/318)	1.53 (1.08 to 2.19)	0.018
History of chronic pulmonary disease	12.0% (79/656)	1.51 (1.14 to 2.01)	0.004
History of renal failure	27.4% (110/401)	3.69 (2.80 to 4.86)	<0.001
CPB time ≥97 min	10.5% (253/2419)	1.58 (1.24 to 2.02)	<0.001
Intraoperative homologous RBC transfusion per 1- unit increase	NA†	1.16 (1.09 to 1.22)	<0.001

To establish the dose-dependent effect of decreased vs normal preoperative hemoglobin values on adverse outcome, odds ratio values of decreased hemoglobin levels are shown in steps of 1 g/dL, and each was compared with patients with hemoglobin >14 g/dL. Odds ratio was adjusted for outcome in the presence of all significant, independent covariates. Higher odds ratio (>1) indicates worse outcome. *P* value for preoperative hemoglobin is associated with the test for trend. Variables analyzed for adverse postoperative outcomes (as covariates of preoperative hemoglobin): EuroSCORE, body mass index, gender, age, insulin-dependent diabetes mellitus, non-insulin-dependent diabetes mellitus, current smoking, history of anemia, myocardial infarction, congestive heart failure, ventricular tachyarrhythmias, stroke, transient ischemic attack, chronic pulmonary disease, renal failure, percutaneous transluminal coronary angioplasty, hypertension, hypercholesterolemia, unstable angina, CABG, coronary atherectomy, intracoronary stent, surgery performed as emergency, intraoperative RBC transfusion per 1-unit increase, intraoperative fresh frozen plasma transfusion per 1-unit increase, intraoperative platelet transfusion per 1-unit increase, lowest intraoperative hemoglobin level, cross-clamp time, and CPB time.

*48 patients were excluded from this analysis because of missing values for at least 1 of the risk factors in the model.

†A single incidence of outcome cannot be provided for a continuous variable. However, if analyzed as a binary variable, intraoperative RBC transfusion resulted in a 12.6 % (231/1838) incidence of outcome.

able studies do not discriminate between the influence of morbid conditions typically present in anemic patients and the effects of low hemoglobin levels per se and do not identify high-risk subgroups on the basis of concomitant risk factors. We found that a high number of comorbidities and other risk factors, as reflected by high EuroSCORE values, substantially altered both the extent and the nature of the impact of anemia.

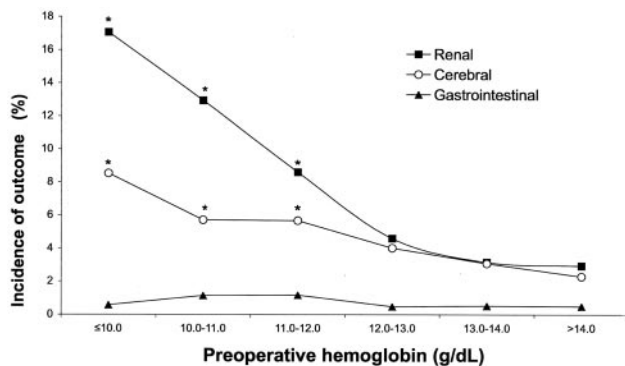


Figure 3. Incidence of different noncardiac outcomes for all patients vs preoperative hemoglobin level. Within the class of noncardiac adverse outcomes, the effect of decreased preoperative hemoglobin levels was greatest for postoperative renal events, moderate for cerebral events, and absent for gastrointestinal complications. **P*<0.05 vs hemoglobin >14 g/dL (pairwise significance without adjustment for multiple comparisons).

In cardiac surgery, anemia has been found to be a major predictor for adverse outcome both preoperatively and postoperatively and even during extracorporeal circulation,^{3,8,9,11,17-19,21,22} but data about the specific tolerance of CABG patients for anemia are conflicting and may in part be confounded by the effects of bypass surgery. In theory, patients with coronary artery disease may tolerate anemia well as long as the compensating mechanisms of the cardiovascular system are largely uncompromised and no extensive comorbidity exists.^{4,23,24} Our results indicate that adverse effects of anemia occurred at individually different hemoglobin thresholds on the basis of the coexistence of risk-enhancing factors.^{2,9} Furthermore, we did not detect a direct and independent effect of low preoperative hemoglobin on postoperative cardiac events. Conversely, we found that renal dysfunction was an important perioperative pathophysiological factor for adverse outcome, being both a cause for and a result of preoperative anemia. It appears that the renal system, especially with a history of dysfunction, was more sensitive than other organs to a temporary relative hemoglobin deficiency,^{25,26} thereby acting as a particularly sensitive and early indicator of pending ischemic injury to other vital organs.

Because the association between low hemoglobin levels and increased adverse outcome has been described for a variety of surgical patient populations, preoperative anemia was assigned a major role in several perioperative risk assessments.^{9,11,17} However, these models do not provide

TABLE 5. Significant Predictors of Low Preoperative Hemoglobin in 4648 Patients*

Risk Factor	Incidence of Low Preoperative Hemoglobin in Patients With Risk Factor Present, % (n/N)	Odds Ratio (95% CI)	P
History of anemia	76.8 (149/194)	7.15 (5.09 to 10.10)	<0.001
History of renal failure	56.4 (226/401)	4.29 (3.23 to 5.71)	<0.001
Gender, female	55.2 (546/989)	3.23 (2.55 to 4.08)	<0.001
Age†	NA	1.18 (1.04 to 1.33)	0.008
IDDM vs no DM	44.9 (158/352)	2.02 (1.42 to 2.88)	<0.001
NIDDM vs no DM	35.6 (386/1085)	1.76 (1.37 to 2.27)	<0.001
Unstable angina	31.6 (924/2920)	1.43 (1.12 to 1.81)	0.004
History of CABG	34.0 (96/282)	1.72 (1.14 to 2.61)	0.001
Body mass index ≥ 30 kg/m ² at admission	25.4 (296/1166)	0.68 (0.51 to 0.90)	0.007
History of hypercholesterolemia	27.4 (932/3398)	0.62 (0.49 to 0.79)	<0.001

Multiple logistic regression analysis. The threshold value to define low preoperative hemoglobin for this analysis was the hemoglobin level associated with a significant increase in the adjusted risk of composite outcome and the noncardiac composite outcome in the primary analysis (hemoglobin = 11 g/dL). Among the above risk factors, only body mass index ≥ 30 kg/m² and a history of hypercholesterolemia were associated with a reduced frequency of preoperative anemia. IDDM indicates insulin-dependent diabetes mellitus; DM, diabetes mellitus; and NIDDM, non-insulin-dependent diabetes mellitus.

*156 patients were excluded because of missing values for risk factors in the model.

†Odds ratios calculated per 10-year increase in age.

detailed and unconfounded evaluations that clearly discriminate between the effects of low preoperative hemoglobin and subsequent transfusions. Retrospective cohort studies of patients refusing RBC transfusions established an association between very low perioperative hemoglobin and increased postoperative morbidity and mortality without the confounding influence of transfusions.^{2,18,20} Accordingly, it was our specific intention to exclude any potential preoperative transfusion effects in order to accurately describe the risk associated with preoperative anemia only.

However, multiple logistic regression clearly showed that preoperative anemia and intraoperative RBC transfusion were both independent but additive risk factors for adverse outcome (Tables 3 and 4). Patients with low preoperative hemoglobin had a higher rate of postoperative adverse events, but at the same hemoglobin level, the risk of suffering a postoperative complication increased significantly with transfusion of RBCs. Furthermore, there was a direct relationship between the number of units of RBCs transfused intraoperatively and the incidence of adverse outcomes (Tables 3 and 4). The independent association of RBC transfusion with adverse outcome has been described repeatedly,²⁷⁻³² but beneficial effects of RBC transfusions have not yet been described precisely in defined subsets of anemic patients undergoing heart surgery.

The present study has some limitations. For the purpose of a realistic clinical risk assessment, the main goal of this investigation was to define the risk for patients with mild to moderate preoperative anemia (hemoglobin 10 to 13 g/dL), the true prevalence of which tends to be underestimated.⁴ Relatively few patients presented with more severe preoperative anemia who were not transfused before CABG surgery. Thus, we cannot exclude that lower preoperative hemoglobin levels may indeed lead to an increased incidence of postoperative cardiac events independent of other risk factors or comorbidities.

Our findings raise several important questions that are not immediately resolvable but nevertheless may have an impact on the care of cardiac surgery patients. First, we have shown that preexistent anemia carries inherent risk, therefore indicating the need for informed consent and risk stratification. However, it is unknown whether this risk can be reduced by correction of preoperative anemia (by transfusion or improvement of an underlying condition). Clinical trials to assess this issue are critically needed. Second, we believe that our findings may be pertinent for the development of care paradigms. Clearly, the cardiac surgery population is aging, and thus comorbid renal and central nervous system complications warrant increased attention because they play an important role in the decision to proceed with surgery. Our observations therefore delineate critical characterizations that enable more exacting risk stratification for adverse events, particularly for older patients. Third, over the past decade, care paradigm constructs have been subjected to critical review and amendment because of widespread concerns regarding avoidance of transfusion of RBCs and other blood products. Although we generally share such concerns, we believe that our studies are pertinent here as well and that recognition of our findings regarding low hemoglobin risk should serve as a caution to indiscriminate application of transfusion-sparing strategies. Specialty-developed guidelines should account for patient-specific characteristics (here, preexisting hemoglobin level), as well as collateral risk factors and diseases, especially for the older patient.

Appendix

Multicenter Study of Perioperative Ischemia Epidemiology II Coordinators

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Disclosures

None.

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CLINICAL PERSPECTIVE

Anemia is an increasingly frequent clinical finding and is well known to be associated with increased morbidity and mortality, especially in patients with coronary artery disease and in the perioperative setting. The present observational study documented the clinical course of >5000 patients undergoing coronary artery bypass surgery, comprehensively describing the impact of low preoperative hemoglobin levels on postoperative outcomes and delineating the marked influence of comorbidities and other risk factors on the individual tolerance of anemia. Anemic patients with few additional risk factors have increased postoperative renal and cerebral complications only, whereas high-risk patients show an additional propensity for cardiac adverse events. However, although the increase in noncardiac postoperative complications was independently associated with low preoperative hemoglobin levels, cardiac adverse events were caused by other factors frequently present in anemic patients. Thus, a patient's perioperative risk must be assessed individually, considering both the hemoglobin level and other comorbid conditions. The present study demonstrates that preexistent anemia carries inherent risk. The best therapeutic strategies to reduce the perioperative risk of anemic patients are still unknown, specifically whether this risk can be reduced by correction of preoperative anemia (by transfusion or improvement of an underlying condition). The findings should serve as a caution against indiscriminate application of transfusion-sparing strategies, especially in the older patient.