Anesthesiology 2009; 111:327–33

Moderate Exposure to Allogeneic Blood Products Is Not Associated with Reduced Long-term Survival after Surgery for Coronary Artery Disease

William M. Weightman, F.A.N.Z.C.A., Neville M. Gibbs, M.D.,† Matthew R. Sheminant, R.N.,‡ Mark A. J. Newman, M.D.,§ Dianne E. Grey, B.Sc., F.A.I.M.S.‖*

Background: **It has been suggested that blood transfusion has an adverse effect on long-term health, mainly through immune modulation and tumor promotion. To further assess this concern, the authors have performed a prospective observational study with the hypothesis that after taking perioperative risk factors relevant to long-term survival into account, patients undergoing coronary artery surgery who receive a perioperative allogeneic blood transfusion have worse long-term survival than those who do not.**

Methods: **The health outcomes of 1,841 consecutive subjects who had isolated nonemergency first-time coronary artery surgery and who survived more than 60 days after surgery were determined by record linkage. The association between length of survival, blood products transfused, and risk factors for long-term survival at entry to the study were determined by Cox proportional hazards regression.**

Results: **A total of 1,062 subjects were transfused. Of these, 266 subjects died during a mean follow-up of 8.1 yr. Of subjects who were transfused, 27% had a new malignant condition recorded on the death certificate, compared with 43% who were not transfused. Older age, cerebrovascular disease, use of a mammary graft, chronic pulmonary disease, renal dysfunction, reduced left ventricular function, and preoperative anemia were predictive of reduced long-term survival. There was no association between transfusion of blood products and long-term survival.**

Conclusions: **Patients who have undergone coronary artery surgery and who have received moderate amounts of blood as part of responsible and conservative management should be reassured that they are unlikely to experience a reduction in long-term survival.**

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

* Consultant Anaesthetist, Department of Anaesthesia, Sir Charles Gairdner Hospital, and Clinical Lecturer, University of Western Australia, Perth, Western Australia. † Head of Department, Department of Anaesthesia, ‡ Senior Clinical Perfusionist, Department of Cardiac Surgery, Sir Charles Gairdner Hospital. § Head of Department, Department of Cardiac Surgery, Sir Charles Gairdner Hospital, and Senior Clinical Lecturer, University of Western Australia. ‖ Principal Scientist, Department of Haematology, PathWest, Perth, Western Australia.

Received from Sir Charles Gairdner Hospital, Perth, Western Australia. Submitted for publication October 24, 2008. Accepted for publication April 17, 2009. Support was provided solely from institutional and/or departmental sources.

Address correspondence to Dr. Weightman: Department of Anaesthesia, Sir Charles Gairdner Hospital, Nedlands, Western Australia, 6009. wweightman@meddent.uwa.edu.au.

IT has been suggested that blood transfusion has an adverse effect on health. Under ideal circumstances, this hypothesis would be tested with a randomized controlled trial, but blood transfusion has such an established place in medical treatment that this is unlikely to be performed. Some light has been shed on this concern by alternative research strategies; for example, investigators have randomized the administration of leukocyte-filtered blood[1–5] or have randomized patients to high and low transfusion triggers.[6–8] However, no definitive conclusion has been reached,[9] and further information is required. In this setting, epidemiological information may be useful.

Coronary artery bypass grafting is a surgical procedure that causes sufficient hemoglobin loss to require blood-product transfusion in around 50% of patients. Once recovery from surgery has taken place, there is rarely any requirement for further blood transfusion. This is a convenient setting to test the hypothesis of long-term adverse effects resulting from blood transfusion.

The test hypothesis of the current study is as follows: after taking perioperative risk factors relevant to long-term survival into account, patients undergoing coronary artery surgery who receive a perioperative allogeneic blood transfusion have worse long-term survival than those who do not receive an allogeneic blood transfusion, and the magnitude of this effect is related to the number of donor units transfused.

Materials and Methods

The study was approved by the ethics committee of the Sir Charles Gairdner Hospital, and the Confidentiality of Health Information Committee at the Health Department of Western Australia. Individual written consent was not considered necessary because no interventions were performed. Subjects were prospectively included if they underwent first-time isolated coronary artery graft surgery between March 1993 and June 2000 and survived longer than 60 days. Subjects undergoing emergency surgery (defined as surgery required within 24 h) were excluded.

Subjects presenting for elective surgery were advised to stop aspirin at least 7 days before surgery; subjects presenting for urgent surgery had aspirin continued until closer to the time of surgery at the discretion of the patient's surgeon and cardiologist. Other medications with antiplatelet effects, such as nonsteroidal antiinflam-

matory drugs and dipyridamole, were stopped at least 24 h before surgery and recommenced within 24 h of surgery. All subjects had 5,000 units of unfractionated heparin twice a day by subcutaneous injection starting the evening before surgery. These practices did not vary during the study.

Where possible, the left internal thoracic artery was used to graft the left anterior descending artery and leg vein grafts to other vessels. Low-dose aprotinin therapy was used if patients had recently ingested aspirin. Red blood cell transfusions were administered where the hemoglobin concentration was 6 g/dl or less during cardiopulmonary bypass and between 8 and 10 g/dl after cardiopulmonary bypass. In the setting of nonsurgical bleeding, fresh frozen plasma was given when the International Normalized Ratio was above 1.5, platelet concentrates were administered when the platelet count was below 100×10^9/l or recent antiplatelet drugs had been given, and cryoprecipitate was given when the fibrinogen concentration was less than 100 mg/dl.

The following data were collected prospectively; history of cerebrovascular disease, defined as a history of stroke, transient ischemic attack, or the presence of a hemodynamically significant carotid stenosis; impaired left ventricular function, defined as a cardiologist's assessment of the left ventriculogram showing moderate or severe impairment of left ventricular systolic function; history of diabetes requiring treatment with insulin or oral hypoglycemic agents; history of hypertension requiring drug treatment; history of chronic pulmonary disease requiring treatment with steroids or bronchodilators; preoperative creatinine clearance was estimated for each patient using the Cockroft formula. Preoperative anemia was considered to be present if the hemoglobin concentration was less than 13 g/dl in men or 12 g/dl in women.

The number and type of allogeneic blood product exposures was determined from transfusion records. The total allogeneic exposure for each subject was estimated by counting all units of blood and blood products given between 5 days before surgery and 30 days after surgery. Units of packed cells, fresh frozen plasma, and cryoprecipitate were each counted as separate units. Small single donor bags of platelets were counted as individual unit exposures, large bags of pooled multidonor platelets were counted as four units of platelets, large single-donor plateletpheresis-derived bags were counted as one unit. Leukocyte-depleted blood or blood products were not used during the study. Fractionated blood products were used in all cases. No predonated autologous blood was used during this study. Intraoperative scavenging of blood was only used where a religious objection to blood transfusion existed. This blood was not included in the perioperative transfusion total.

Subject death and cause of death recorded on the death certificate were determined from the Western Australia Death Register by using probabalistic record linkage by the Data Linkage Unit at the Western Australia Department of Health as described by Holman and coworkers.[10] This involves linking hospital and community records on the basis of personal identifying information by using a match strategy to minimize mismatches and missed matches, with extensive clerical review to minimize error. The estimated error rate is less than 0.3%. The death was considered as cancer-linked if a malignancy was mentioned either as the cause of death or as an associated condition.

A power estimate was made with the assumptions that 14% of subjects would experience an event, 27% of subjects would be exposed to between 1 and 2 donor units, and 50% of subjects exposed overall. With an alpha of 5%, 1,665 subjects would be required to give a power of 80% to detect a 7% absolute difference in mortality between the transfused and nontransfused subjects and a power of 80% to detect a 9% absolute difference in mortality between nontransfused subjects and those exposed to 1–2 donor units.

Statistical Analysis

Subjects were divided into the following groups: group 1 subjects received no blood or blood products, group 2 subjects received blood or blood products resulting in 1 or 2 donor exposures, group 3 subjects were exposed to 3–6 units, and group 4 subjects were exposed to 7 or more units. The boundaries between groups was determined *post hoc* to allow approximately equal numbers in each of the transfused groups.

Summary statistics were calculated by using the mean and SD for normally distributed variables and the median and 90th centiles for skewed variables (days since aspirin and blood products transfused). Demographic data were compared between the groups using ANOVA for continuous variables, contingency tables for categorical variables, and a Kruskall-Wallis test to compare days since aspirin. Two-tailed comparisons were made throughout, with alpha at the 5% level. A Bonferroni correction was used where multiple groups were compared.

The hypothesis was tested using Cox proportional hazards regression analysis. Risk factors included as covariates in the analysis were age, gender, estimated creatinine clearance, history of cerebrovascular disease, hypertension, diabetes, impaired left ventricular function, chronic pulmonary disease, the use of a mammary artery graft, preoperative anemia, and transfusion group. The covariates entered into the model were selected because we believed on the basis of clinical experience and literature that they had potential clinical relevance to the longer-term mortality outcome. After peer review, cardiopulmonary bypass time greater than 80 min and off-pump surgery were included as covariates in the model. The covariates were entered without stepwise selection. The assumptions of proportional hazards were checked

Table 1. Distribution of Subjects among Groups

	Group 1	Group 2	Group 3	Group 4
Transfusion	No transfusion	1–2 units	3–6 units	> 6 units
n	779	402	333	327
Died during study (%)	80 (11)	56 (14)	58 (19)	72 (23)

by dividing each predictor variable in turn into equal strata and performing proportional hazards regression analysis using the remaining variables. The log of the cumulative hazard was plotted against time and approximately parallel equidistant curves were taken as evidence that the assumption of proportional hazards was met for that variable. All of the variables satisfied the requirements of Cox proportional hazards. Cox proportional hazard regression analysis was performed using Epi Info 3.4.3 (Centers for Disease Control and Prevention, Atlanta, GA). The effect of transfusion group on outcome was displayed graphically by performing Cox proportional hazard analysis with the above covariates, with the analysis stratified by transfusion group.

Results

A total of 1,841 subjects with a mean age of 62.7 yr were included in the study. The mean length of follow-up was 8.1 yr (range 4.6–11.9 yr). The distribution of subjects between groups is displayed in table 1. Data were missing for 5% of subjects regarding last date of aspirin use, 4% of subjects regarding left ventricular function, 2% of subjects regarding creatinine concentration, 0.9% of subjects regarding height and weight, 0.4% of subjects regarding hemoglobin concentration, and 0.2% of subjects regarding airways disease. Noninformative imputation was used to replace this missing data in the regression model – mean values were substituted for missing continuous data, and median values were substituted for other data. Data were missing for eight subjects regarding blood transfusion, and these subjects were excluded from the multivariate analysis.

Table 2 describes the demographic and surgical characteristics for each of these groups. Subjects who did not receive a blood transfusion were younger, larger, less likely to be female, less likely to be anemic, more likely to have off-pump surgery, had greater creatinine clearance, less prolonged surgery, and a lesser number of distal grafts. There were no significant differences between the groups in the proportion of subjects who received at least one arterial conduit, nor in the proportion of subjects who had chronic pulmonary disease, hypertension, diabetes, reduced left ventricular function, or cerebrovascular disease.

Hematologic data are described in table 3. Subjects were transfused to a similar end-point, transfused groups had hemoglobin concentrations within 0.3 g/dL of each other, and platelet counts within 20×10^9/L, both on arrival in the intensive care unit and on the morning of the 3rd postoperative day. In all transfused groups the International Normalized Ratio on arrival in the intensive care unit was similar. Group 2 subjects were exposed to 647 units of red cells, 43 units of fresh frozen plasma, and 15 units of platelets. Group 3 subjects were exposed

Table 2. Demographic and Surgical Characteristics

	Group 1 No transfusion	Group 2 1–2 units	Group 3 3–6 units	Group 4 > 6 units
n	779	402	333	327
Age, yr	59.9 (9)	64.3 (9)*	64.7 (9)*	65.4 (10)*
Female	7%	35%*	28%*	24%*‖
Weight, kg	85.4 (14)	77.4 (14)*	76.2 (13)*	74.8 (13)*
BMI	28.4 (4)	27.5 (5)†	26.8 (4)*	26.1 (4)*§
Base eCC, ml · min^{-1} · m^{-2}	43.7 (12)	39.5 (12)*	37.7 (11)*	35.8 (14)*§
Distal anastomoses	3.0 (1)	3.3 (1)*	3.3 (1)*	3.7 (1)*§#
Duration of cross clamp	50.2 (25)	57.2 (26)	58.4 (31)*	68.8 (32)*§**
Duration of CPB	79.0 (28)	88.2 (29)*	89.9 (34)*	103 (39)*§#
Anemia	3%	18%*	23%*	22%*
Off-pump	17%	12%*	8%*	1%*§**
Mammary conduit	90%	88%	87%	88%
Poor LV function	15%	18%	21%	17%
COPD	10%	8%	9%	7%
Hypertension	44%	44%	48%	45%
Diabetes	17%	20%	21%	17%
CVD	4%	5%	6%	6%

Data are mean with SD except where indicated.

* $P < 0.0001$ compared to group 1. † $P = 0.0002$ compared to group 1. ‡ $P = 0.002$ compared to group 1. § $P < 0.0001$ compared to group 2. ‖ $P = 0.002$ compared to group 2. # $P < 0.0001$ compared to group 3. ** $P = 0.0007$ compared to group 3.

Anemia = hemoglobin concentration less than 12 g/dl for females, 13 g/dl for males; BMI = body mass index, kg/m^2; COPD = history of chronic pulmonary disease requiring treatment; CPB = cardiopulmonary bypass in minutes; CVD = cerebrovascular disease; eCC = estimated creatinine clearance; LV function = left ventricular systolic function.

Table 3. Perioperative Hematological Data

	Group 1 No transfusion	Group 2 1–2 units	Group 3 3–6 units	Group 4 > 6 units
n	779	402	333	327
Days since aspirin	5 (4)	5 (5)	4 (4)	4 (4)
Prior warfarin therapy	4%	5%	6%	3%
Aprotinin MKIU	0.4 (0.8)	0.4 (0.9)	0.5 (1.0)	0.5 (1.0)‖
Hb, g/dl	14.7 (1.1)	13.7 (1.2)*	13.6 (1.5)*	13.7 (1.6)*
Hb CPB, g/dl	8.0 (0.04)	7.2 (0.06)*	7.3 (0.07)*	7.1 (0.06)*
Hb ICU, g/dl	10.7 (1.2)	9.8 (1.3)*	9.7 (1.4)*	9.5 (1.4)*‖
Hb day 3, g/dl	11.0 (1.4)	10.9 (1.3)	11.0 (1.5)	11.1 (1.5)
Platelet count	236 (59)	236 (58)	238 (73)	227 (68)
Platelet count ICU	158 (48)	148 (48)*	143 (47)*	131 (46)*§
Platelet count day 3	185 (56)	160 (49)*	156 (84)*	137 (52)*§#
INR ICU	1.3 (0.2)	1.4 (0.2)	1.4 (0.3)‡	1.4 (0.3)†
RBC transfused	0	2 (1)	3 (2)	5 (4)
FFP transfused	0	0 (0)	0 (2)	3 (2)
Platelets transfused	0	0 (0)	0 (2)	3 (2)

Days since aspirin and products transfused are described using median with interquartile range; other data are mean with SD, except proportion of patients receiving prior warfarin therapy.

* $P < 0.0001$ compared to group 1. † $P = 0.0004$ compared to group 1. ‡ $P = 0.003$ compared to group 1. § $P < 0.0001$ compared to group 2. ‖ $P = 0.001$ compared to group 2. # $P = 0.0001$ compared to group 3.

CPB = at end of pump run; Day 3 = 06:00 AM of post op day 3; FFP = fresh frozen plasma units; Hb = hemoglobin concentration; ICU = on arrival to intensive care unit; INR = international normalized ratio; MKIU = million kallekrein inhibitor units; platelet counts are 10^9/L; RBC = red blood cell units.

to 855 units of red cells, 264 units of fresh frozen plasma, and 289 units of platelets. Group 4 subjects were exposed to 1,959 units of red cells, 1,229 units of fresh frozen plasma, 54 units of cryoprecipitate, and 1,799 units of platelets. 533 patients (30%) received a median dose of 1×10^6 units of aprotinin.

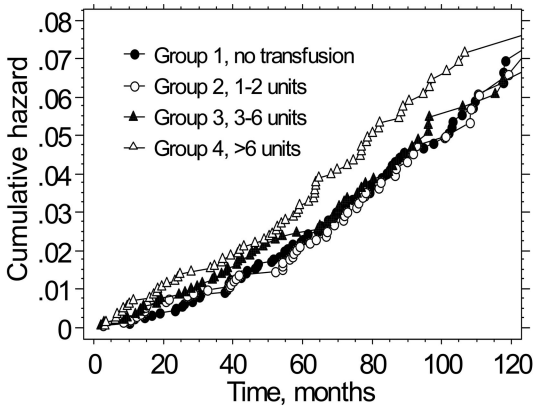
Details of the Cox proportional hazards survival model are described in table 4. The association between each variable and survival is expressed as a hazard ratio with 95% confidence intervals of the hazard ratio. The variables that explain the greatest variation in the model were age, cerebrovascular disease, use of a mammary graft, chronic pulmonary disease, renal dysfunction, reduced left ventricular function, and preoperative anemia. Gender, hypertension, and transfused product group explained little of the variation in the model. Subjects in group 4, who received the greatest exposure to blood products, had an estimated hazard ratio of 1.25 with confidence intervals between 0.9 and 1.8. As a result of these wide confidence intervals, we can neither prove nor exclude a clinically significant association between being in this group and reduced survival. Subjects in groups 2 and 3 were not observed to have increased risk, with estimated hazard ratios close to 1 and confidence intervals between 0.7 and 1.4.

Table 4. Results of Cox Proportional Hazards Regression Analysis

	HR	95% CI of HR	Z-statistic	Chi Square	*P* Value
Age, yr	1.06	1.04–1.08	5.68	32.2	< 0.0001
CVD	2.08	1.42–3.04	3.76	14.0	0.0002
Mammary conduit	0.59	0.44–0.79	–3.52	12.4	0.0004
Poor LV function	1.58	1.19–2.09	3.2	10.2	0.0014
Anemia	1.65	1.21–2.25	3.2	10.2	0.001
COPD	1.70	1.20–2.4	3.01	9.1	0.003
Base eCC, $ml \cdot min^{-1} \cdot m^{-2}$	0.98	0.97–1.00	–2.2	4.6	0.03
Diabetes	1.35	1.02–1.79	2.07	4.3	0.04
Offpump	0.63	0.33–1.22	–1.36	1.9	0.17
Male gender	1.18	0.87–1.61	1.09	1.2	0.17
Prolonged bypass	0.88	0.67–1.14	–0.97	1.0	0.33
Hypertension	1.03	0.81–1.32	0.26	0.1	0.80
Transfusion status, compared to group 1					
Group 2, 1–2 units	1.00	0.70–1.44	0.19	0.01	0.98
Group 3, 3–6 units	0.98	0.67–1.41	–0.13	0.1	0.89
Group 4, > 6 units	1.25	0.87–1.79	1.2	1.5	0.23

Note that a Bonferroni correction is not required in this table.

Anemia = hemoglobin concentration less than 12 g/dl for females, 13 g/dl for males; COPD = history of chronic pulmonary disease requiring treatment; CVD = history of stroke, transient ischemic attack, or the presence of a hemodynamically significant carotid stenosis; eCC = estimated creatinine clearance; HR = hazard ratio; LV = left ventricular; Offpump = surgery performed without cardiopulmonary bypass; prolonged bypass = bypass time greater than 80 min.



Subjects at risk, indicating all cause attrition

	0 months	40 months	80 months	120 months
Group 1	773	751	574	235
Group 2	402	385	288	102
Group 3	326	306	228	91
Group 4	332	308	242	97

Fig. 1. Cumulative hazard by blood transfusion group. The *graph* shows the cumulative hazard for mortality estimated by the model described in table 4 but stratified by blood transfusion group. *Symbols* indicate individual events.

The Cox model is displayed graphically in figure 1. The figure shows cumulative hazard, using mean values for the coefficients of each covariate stratified by transfusion group. The curves for groups 1, 2, and 3 are almost superimposed, indicating that there is little difference in risk between these groups. The curve for group 4 would appear to be more distinct, with an excess cumulative hazard of 1% at 10 yr.

So that we could more clearly distinguish the risk of preoperative anemia *versus* blood transfusion, we reanalyzed the Cox model after excluding the 238 subjects with preoperative anemia. The model coefficients were mostly unchanged. The hazard ratio (with 95% CI) for blood transfusion groups, compared to group 1 were group 2, 0.92 (0.61–1.38), group 3, 0.92 (0.61–1.38), group 4, 1.04 (0.69–1.56). See Supplemental Digital Content 1, which tables this model in more detail, http://links.lww.com/A1456, and Supplemental Digital Content 2, which demonstrates this graphically, http://links.lww.com/A1457. The Cox model was also reanalyzed with two blood transfusion groups rather than three, which did not produce major changes to the results (see table, Supplemental Digital Content 3, http://links.lww.com/A1458).

Subjects who reported a preoperative history of malignant disease (excluding nonmelanoma skin cancer) were more likely to be transfused: 46 (71%) of the 65 subjects who reported a history of malignant disease before surgery were transfused compared to 1,016 (57%) of 1,776 without a history of malignant disease ($P = 0.03$). Only 16 of the 65 subjects who reported a history of malignant disease at the time of surgery died during follow-up. There were 250 subjects who died during follow-up who did not have a history of malignant disease at the time of surgery, comprising 77 subjects in group 1 and 183 in the transfused groups. In this subset, the proportion of subjects who died with a cancer-related diagnosis was greater in group 1 (32 of 77) than in the transfused groups (49 out of 183) ($P = 0.03$).

Discussion

We did not observe an association between transfusion of moderate amounts of blood products (up to six units) and reduced long-term survival. The 95% confidence intervals surrounding our point estimates for groups 2 and 3 suggest that the study is powered to exclude an increase in hazard rates greater than 40%. After exposure to more than six donor units, we observed an increased hazard. Although this did not reach statistical significance, our study does not have the power to draw any conclusions in this group. The lack of power in this group is confirmed both by the 95% confidence intervals and by *post hoc* power estimates, which suggest that we cannot exclude the possibility that the true hazard ratio in this group could be as high as 1.8.

The study has some strengths. Data were collected prospectively to test this hypothesis. The data were collected by clinicians, and we did not rely on nonclinician assessment of risk factors. We had consistent protocols during the study period. All blood was donated by volunteer donors. We can estimate an accurate death rate because Western Australia is an isolated state with little emigration of patients in this age group. Bradshaw *et al.*[11] compared the Western Australia death register with the Australian National Death Index in a large cohort of subjects at nearby hospitals undergoing coronary artery surgery during a similar period of time; they found that less than 2% of deaths had been registered outside of Western Australia. If this proportion applied in the current study, then we would estimate that we missed six deaths because they were registered outside of Western Australia.

Our study has several limitations. The observational nature of the study prevents determination of whether the observed associations are casual or causal. The study population was limited to subjects undergoing low-risk cardiac surgery, and our findings may not apply to surgical procedures where greater blood loss may be expected, in subjects with known malignant or immune-related disease, or where immune suppressants may be used as part of the postoperative treatment. We recognize that it is possible that our follow-up was incomplete; for example, subjects could have died but not have been registered; we allowed an extended time (7 months) between the study end date and checking the Death Register. It is possible that important confounders may exist that we have not taken into account. We accept that our study design is unable to adjust for

diseases, such as generalized atherosclerosis, that are difficult to quantify but that may confound the result by causing both increased operative blood loss and poor long-term outcome. Our sample size is small. We have insufficient power to state that all blood transfusion is safe; in particular, we do not have sufficient power to exclude a clinically significant effect in those subjects exposed to more than six units. Nevertheless, the majority of transfused cardiac surgical patients have fewer than six donor exposures, and our main findings apply to a large proportion of patients undergoing coronary artery surgery.

There have been previous studies with similar hypotheses and methodology. Engoren *et al.*[12] studied 1,915 subjects undergoing first-time isolated coronary artery bypass at St. Vincent Mercy Medical Center, Toledo, Ohio. In a Cox regression model, they demonstrated that age, New York Heart Association functional class IV, chronic obstructive pulmonary disease, peripheral vascular disease, and perioperative blood transfusion were predictors of mortality occurring between 1 and 5 yr after surgery. Detailed information about the number of units transfused was not available; therefore, quantification of transfusion was done in a limited manner, subjects were grouped according to transfusions given during the intraoperative period, postoperative period, or both. Koch *et al.*[13] studied 10,289 subjects undergoing isolated coronary artery surgery at the Cleveland Clinic, follow-up was 10 yr, and transfusion was quantified by the number of units of red cells transfused to subjects in the perioperative period. Risk was adjusted by using a proportional hazards model. A battery of predictors for late mortality were identified, including age, history of heart failure, lower ejection fraction, chronic pulmonary disease, diabetes, raised creatinine, and others. The late hazard for death was estimated as 0.074 per unit transfused. An association between the number of units of blood transfused and long-term outcome was shown, but the evidence for an incremental dose-dependant risk-adjusted association was not made clear. Kuduvalli *et al.*[14] studied 3,024 subjects undergoing isolated coronary artery surgery, with a 12-month follow-up. Subjects who received perioperative transfusions had a lower risk-adjusted survival rate between 1 and 12 months. The relation between the number of donor exposures and outcome was not directly explored.

The above studies demonstrate a clear association between blood transfusion and reduced long-term outcome. How could our findings be discordant with such careful and detailed studies? We speculate that this is because our multivariate analysis has included anemia as a risk factor.

In the setting of cardiac surgery, preoperative anemia is a predisposing factor for blood transfusion, and it could be argued that any association between anemia and adverse outcome is actually the result of blood transfusion. However, there is now considerable evidence to show that, even in the absence of blood transfusion, a single measurement of reduced hemoglobin concentration is associated with reduced long-term survival. This has been observed in community studies of elderly persons,[15–18] in middle aged persons (between 45 and 65 yr of age) in the general community without cardiovascular disease,[19] in patients with acute cardiovascular disease undergoing nonsurgical treatment,[20–22] and in patients undergoing surgery for vascular disease with minimal exposure to blood transfusion.[23]

The cause of death was not part of our original hypothesis; however, it has not escaped our notice that subjects who received blood were less likely to die with a cancer diagnosis. Although this is a *post hoc* observation, we may infer that any hypothesized association between blood transfusion and long-term survival is unlikely to be related to cancer promotion.

We do not anticipate that our study should encourage clinicians to transfuse allogeneic blood without careful consideration of the balance of risks and benefits. There are many reasons to use blood responsibly and conservatively in relation to potential short-term adverse effects and also in relation to reducing the use of a scarce and costly resource. However, we should reassure patients who have undergone coronary artery surgery and who have received blood as part of responsible and conservative management that they are unlikely to experience a reduction in long-term survival.

In summary, after adjusting for major preoperative risk factors, we did not observe a strong association between the transfusion of up to 6 units of blood or blood products during coronary artery surgery and long-term survival. Also, in the subjects who died during the study, we did not observe an association between blood transfusion and a cancer diagnosis at the time of death. Our study does not have the power to draw any valid conclusions in subjects exposed to more than 6 units of blood and blood products.

Diana Rosman, B.Sc., Grad. Dip. Comp., M.Med.Sc., Program Manager, Western Australia Data Linkage Unit, Department of Health, Perth, Western Australia, gave invaluable help linking our data with the Western Australia Death Register. David J. Joske, M.B.B.S., Consultant Hematologist, Department of Hematology, Queen Elizabeth Medical Centre, Perth, Western Australia, suggested the research hypothesis. Neil Gordon, B.App.Sci., Information Manager, PathWest, Royal Perth Hospital, Perth, Western Australia, assisted with data linkage.

References

1. van de Watering LMC, Brand A, Houbiers JGA, Kranenbarg WMK, Hermans J, van der Velde CJH: Perioperative blood transfusions, with or without allogeneic leucocytes, relate to survival, not to cancer recurrence. Br J Surg 2001; 88:267–72

2. Collier AC, Kalish LA, Busch MP, Gernsheimer T, Assmann SF, Lane TA, Asmuth DM, Lederman MM, Murphy EL, Kumar P, Kelley M, Flanigan TP, McMahon DK, Sacks HS, Kennedy MS, Holland PV: Leukocyte-reduced red blood cell transfusions in patients with anemia and human immunodeficiency virus infection: The viral activation transfusion study: A randomized controlled trial. JAMA 2001; 285:1592–601

3. Fergusson D, Khanna MP, Tinmouth A, Hébert PC: Transfusion of leukore-

duced red blood cells may decrease postoperative infections: Two meta-analyses of randomized controlled trials. Can J Anaesth 2004; 51:417–25

4. Blumberg N: Deleterious effects of transfusion immunomodulation: Proven beyond a reasonable doubt. Transfusion 2005; 45:33S–40S

5. Vamvakas EC: White-blood-cell containing allogeneic blood transfusion and postoperative infection or mortality: An updated meta-analysis. Vox Sanguinis 2007; 92:224–32

6. Vichinsky EP, Haberkern CM, Neumayr L, Earles AN, Black D, Koshy M, Pegelow C, Abboud M, Ohene-Frempong K, Ivyer RV: A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. NEJM 1995; 333:206–13

7. Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E: A multicentre, randomized, controlled clinical trial of transfusion requirements in critical care. NEJM 1999; 340:409–17

8. Bracey AW, Radovancevic R, Riggs SA, Houston S, Cozart H, Vaughn WK, Radovanevic B, McAllister HA Jr, Colley DA: Lowering the hemoglobin threshold for transfusion in coronary artery bypass procedures: Effect on patient outcome. Transfusion 1999; 39:1070–7

9. Strumper-Groves D: Perioperative blood transfusion and outcome. Curr Opin Anaesthesiol 2006; 19:198–206

10. Holman CDJ, Bass AJ, Rouse IL, Hobbs MST: Population-based linkage of health records in Western Australia: Development of a health services research linked database. Aust N Z J Public Health 1999; 23:453–9

11. Bradshaw PJ, Jamrozik K, Le M, Gilfillan I, Thompson PL: Mortality and recurrent cardiac events after coronary artery graft: Long term outcomes in a population study. Heart 2002; 88:488–94

12. Engoren MC, Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ: Effect of blood transfusion on long-term survival after cardiac operation. Ann Thorac Surg 2002; 74:1180–6

13. Koch CG, Li L, Duncan AI, Mihaljevic T, Loop FD, Starr NJ, Blackstone EH: Transfusion in coronary artery bypass grafting is associated with reduced long-term survival. Ann Thorac Surg 2006; 81:1650–7

14. Kuduvalli M, Oo AY, Newall N, Grayson AD, Jackson M, Desmond MJ, Fabri BM, Rashid A: Effect of peri-operative red blood cell transfusion on 30-day and 1-year mortality following coronary artery bypass surgery. Eur J Cardiothorac Surg 2005; 27:592–8

15. Pennix BW, Pahor M, Woodman RC, Guralnik JM: Anemia in old age is associated with increased mortality and hospitalization. J Gerontol A Biol Sci Med Sci 2006; 61:474–9

16. Zakai NA, Katz R, Hirsch C, Shlipak MG, Chaves PH, Newman AB, Cushman M: A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort. Arch Intern Med 2005; 165:2214–20

17. Chaves PHM, Xue QL, Guralnik JM, Ferrucci L, Volpato S, Fried LP: What constitutes normal hemoglobin concentration in community-dwelling disabled older women? J Am Geriatr Soc 2004; 52:1811–6

18. Landi F, Russo A, Danese P, Liperoti R, Barrillaro C, Bernabei R, Onder G: Anemia status, hemoglobin concentration, and mortality in nursing home residents. J Am Med Dir Assoc 2007; 8:322–7

19. Sarnak MJ, Tighiouart H, Manjunath G, MacLeod B, Griffith J, Salem D, Levey AS: Anemia as a risk factor for cardiovascular disease in the atherosclerosis risk in communities (ARIC) study. J Am Coll Cardiol 2002; 40:27–33

20. Vaglio J, Safley DM, Rahman M, Kosiborod M, Jones P, Thompson R, Krumholz HM, Spertus JA: Relation of anemia at discharge to survival after acute coronary syndromes. Am J Cardiol 2005; 96:496–9

21. Valeur N, Nielsen OW, McMurray JJV, Torp-Pedersen C, Køber L: Anaemia is an independent predictor of mortality in patients with left ventricular systolic dysfunction following acute myocardial infarction. Eur J Heart Fail 2006; 8:577–84

22. Lupón J, Urrutia A, González B, Herreros J, Altimir S, Coll R, Prats M, Rey-Joly C, Valle V: Prognostic significance of hemoglobin levels in patients with heart failure. Rev Esp Cardiol 2005; 58:48–53

23. Diehm N, Benenati JF, Becker GJ, Quesada R, Tsoukas AI, Katzen BT, Kovacs M: Anemia is associated with abdominal aortic aneurysm (AAA) size and decreased long-term survival after endovascular AAA repair. J Vasc Surg 2007; 46:676–81