

Effect of patient age on blood product transfusion after cardiac surgery

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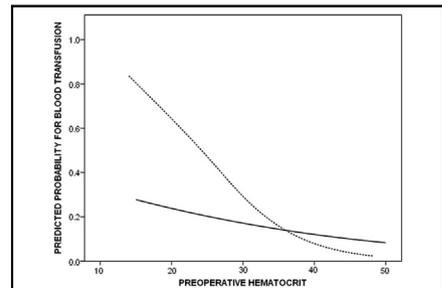
ABSTRACT

Objective: Blood product transfusion after cardiac surgery is associated with increased morbidity and mortality. Transfusion thresholds are often lower for the elderly, despite the lack of clinical evidence for this practice. This study examined the role of age as a predictor for blood transfusion.

Methods: A total of 1898 patients were identified who had nonemergent cardiac surgery, between January 2007 and August 2013, without intra-aortic balloon pumps or reoperations, and with short (<24 hours) intensive care unit stays (age ≥ 75 years; $n = 239$). Patients age ≥ 75 years were propensity-score matched to those age <75 years to balance covariates, resulting in 222 patients per group. Analyses of the matched sample examined age as a continuous variable, scaled in 5-year increments.

Results: After matching, covariates were balanced between older and younger patients. Older age significantly predicted postoperative (odds ratio = 1.39, $P = .028$), but not intraoperative (odds ratio = 0.96, $P = .559$), blood transfusion. Older age predicted longer length of stay ($B = 0.21$, $P < .001$), even after adjustment for blood product transfusion ($B = 0.20$, $P < .001$). As expected, older age was a significant predictor for poorer survival, even with multivariate adjustment (hazard ratio = 1.34, $P = .042$).

Conclusions: In patients with a routine postoperative course, older age was associated with more postoperative blood transfusion. Older age was also predictive of longer length of stay and poorer survival, even after accounting for clinical factors. Continued study into effects of transfusion, particularly in the elderly, should be directed toward hospital transfusion protocols to optimize perioperative care. (*J Thorac Cardiovasc Surg* 2015;150:209-14)



The figure shows spline curves demonstrating the relationship of preoperative hematocrit with odds for blood transfusion, for ages ≥ 75 years (dashed line) and ages <75 years (solid line) in the matched sample.

Central Message

For routine cardiac surgery, older patient age was a robust predictor for postoperative blood product transfusion and was predictive of longer length of stay and poorer survival.

Perspective

This study demonstrates that patient age is associated with a significant surgeon bias regarding blood transfusion thresholds without proven clinical merit. Future studies should focus on specific blood transfusion protocols for older patients to maximize the appropriateness of blood transfusion after cardiac surgery.

See Editorial Commentary page 214.

Cardiac surgery accounts for a substantial proportion of surgical procedures in which blood and blood products are transfused.^{1,2} The risks associated with blood transfusion are difficult to ascribe to clearly delineated risk factors.³ However, cardiac surgery that involves transfusion is associated with a higher risk of infection and ischemic

outcomes,^{2,4} longer length of stay,⁵ and increased perioperative and long-term morbidity and mortality^{6,7} compared with cardiac procedures without transfusion. Recent studies have found that cardiac surgery programs that develop and adhere to a blood conservation protocol succeed in reducing the incidence of blood transfusion, improving outcomes, and minimizing health care costs.⁸⁻¹⁰

In general, when postoperative hemoglobin levels are ≤ 10 g/dL, elderly patients are more likely than younger patients to receive transfusion.^{9,11} Transfusion thresholds are often lower (ie, transfusion occurs at higher hemoglobin levels) in the elderly, despite the scarcity of clinical evidence to support this practice.⁹ Few published studies have examined blood transfusion in elderly (age >75 years) patients undergoing cardiac surgery, and the effects of transfusion after cardiac surgery in a specific subset

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Abbreviations and Acronyms

CI	= confidence interval
EuroSCORE	= European System for Cardiac Operative Risk Evaluation
HR	= hazard ratio
OR	= odds ratio

of elderly patients have not been previously described. In this study, we examined the role of age as a predictor for blood transfusion and the effects of age on postoperative outcomes in elderly patients undergoing cardiac surgery.

METHODS

A total of 1898 consecutive patients who had undergone nonemergent cardiac surgery between January 2007 and August 2013 were identified. These patients did not have placement of an intra-aortic balloon pump or reoperation for bleeding or any other indication, and all had short (<24 hours) stays in the intensive care unit. Most patients (64%) who met these criteria underwent coronary artery bypass graft surgery, either alone or in combination with another cardiac surgical procedure. Of this sample, 239 patients (13%) were age ≥ 75 years.

This study was approved by our local institutional review board (nos. 06.022 and 12.055) and was granted a waiver of consent. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Data were obtained from our local Society of Thoracic Surgeons database and were merged with survival and clinical information collected at our institution. Data on long-term survival were obtained from the National Death Index (closing date: December 31, 2010), the Social Security Death Index (closing date: January 31, 2013), and our institutional follow-up program (ongoing).

Blood Transfusion Protocol

In 2007, we implemented a rigorous, multidisciplinary, criteria-driven algorithm for blood transfusion in cardiac surgery patients at our center. Cardiopulmonary bypass techniques, anesthesia, management of perioperative bleeding, and strict indications for blood transfusion were modified as part of this protocol. Transfusion was approved only by an attending cardiac surgeon in symptomatic patients, and specific criteria were developed for intraoperative and postoperative transfusion (Figure 1). Regardless of this protocol, transfusion can be ordered by the attending surgeon if it is deemed clinically justified.

Statistical Analyses

All analyses were conducted with SPSS, Version 17.0 (SPSS Inc, Chicago, Ill) and R 2.10.1 (R Foundation for Statistical Computing, Vienna, Austria). A 2-sided *P* was computed. Data are presented as mean \pm SD, median (interquartile range), or frequency (percentage). Comparisons involving dichotomous dependent variables were evaluated with χ^2 analysis, Fisher's exact test, or logistic regression; comparisons involving continuous dependent variables were evaluated with Student's *t* test, the Mann-Whitney *U* test, or linear regression.

To improve balance between the 2 groups, patients age <75 years were matched by propensity score to patients age ≥ 75 years, using the MatchIt package for R (R Foundation for Statistical Computing, Vienna, Austria). The propensity for age ≥ 75 years was estimated with a logistic model, using the following covariates: gender; body mass index; ejection fraction;

EuroSCORE II (European System for Cardiac Operative Risk Evaluation); preoperative hematocrit; status (urgent or elective); hypertension; surgery (isolated coronary artery bypass graft or other); chronic pulmonary disease; diabetes; peripheral vascular disease; and cerebrovascular disease. Patients were matched based on propensity score, using a caliper of 0.25 propensity-score SD. After matching, 222 patients remained in each age group, and good covariate balance was achieved between the 2 age groups (Figure 2).

Outcome analyses were conducted exclusively on the matched sample, and age was examined as a continuous variable (scaled by 5 years), unless otherwise noted. Logistic regressions were performed to evaluate the effect of age on the risk for intraoperative and postoperative blood transfusion, as well as on perioperative outcomes. Univariate logistic regressions were run separately within each matched age group to evaluate the effect of preoperative hematocrit on the probability of perioperative blood transfusion and to visualize these relationships using spline curves. In addition, multivariate logistic regression analysis was used to formally test for interaction of age and preoperative hematocrit before the analysis of separate age groups. Cox proportional hazards modeling was conducted to examine the effects of age as a continuous variable (scaled by 5 years) and blood transfusion on long-term survival.

RESULTS

Mean age for the unmatched sample was 61.4 ± 11.6 years, and most patients (79%) were men. Before propensity-score matching, the prevalence of preoperative comorbid conditions, including hypertension, congestive heart failure, history of stroke, and peripheral vascular disease, was higher for patients age ≥ 75 years (Table 1). No difference by age group was found for type of cardiac surgery procedure. After propensity-score matching, all preoperative characteristics of patients age ≥ 75 years ($n = 222$) were similar to those of patients age <75 years ($n = 222$), except age (Table 2). All results that follow were found within the propensity score-matched sample ($N = 444$).

Blood products were transfused in 55 patients (12%). Intraoperative transfusion only was used in 35 patients, postoperative transfusion only in 15 patients, and intraoperative and postoperative transfusion in 5 patients. The incidence of Society of Thoracic Surgeons-defined complications was low in this matched sample. Such complications included: 2 patients with pneumonia (0.5%); 2 with a stroke and/or transient ischemic attack (0.5%); 2 who died within 30 days (0.5%); 4 with major morbidity or mortality (0.9%); and 33 with readmissions within 30 days (7%).

Age and Outcomes

Age as a continuous variable did not predict intraoperative transfusion (odds ratio [OR] = 0.96, 95% confidence interval [CI], 0.85-1.10, $P = .559$), but age was a significant predictor for postoperative transfusion (OR = 1.39, 95% CI, 1.04-1.87, $P = .028$). For every 5-year increase in patient age, the odds of postoperative transfusion were 39% greater. Age remained a significant predictor for postoperative transfusion (OR = 1.40, 95% CI, 1.04-1.88, $P = .027$) after adjustment for preoperative hematocrit.

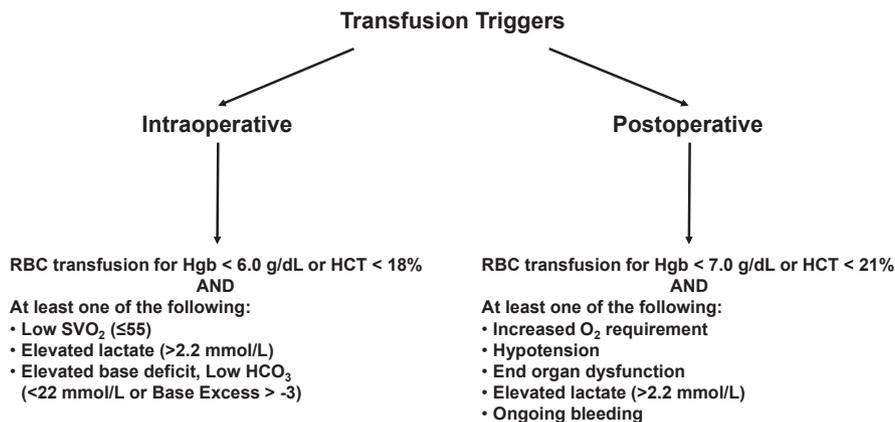


FIGURE 1. The figure shows a diagram of the transfusion protocol implemented at our cardiac surgery center. *RBC*, Red blood cell; *Hgb*, hemoglobin; *HCT*, hematocrit; *SVO₂*, venous oxygen saturation; *HCO₃*, blood bicarbonate; *O₂*, oxygen.

For double robustness, adjustment was made for all clinical covariates included in the propensity model, but it did not eliminate the predictive effect of age as a continuous variable on postoperative transfusion (OR = 1.40, 95% CI, 1.04-1.89, *P* = .029). Older age as a continuous variable was significantly correlated with more units of postoperative blood products (*r_s* = 0.10, *P* = .039).

Finally, an examination of the interaction of preoperative hematocrit and age on transfusion found hematocrit (OR = 1.39, *P* = .03), age (OR = 1.27, *P* = .006), and the interaction term (OR = 0.99, *P* = .005) to be significantly predictive of perioperative blood product transfusion.

Specifically, the relationship between preoperative hematocrit and the odds for receiving any perioperative blood product transfusion was significant among patients age ≥75 years (OR = 0.86, 95% CI, 0.78-0.94, *P* = .001) but not for those age <75 years (OR = 0.96, 95% CI, 0.89-1.03, *P* = .277; **Figure 3**). For patients age ≥75 years, a 1% increase in preoperative hematocrit was associated with a 14% reduction in odds for blood product transfusion.

The incidence of stroke and/or transient ischemic attack, pneumonia, major morbidity or mortality, and readmission within 30 days was not significantly predicted by age as a continuous variable (**Table 3**). However, older age was predictive of longer total length of stay in days (*B* = 0.21, *P* < .001). This finding remained significant after multivariate analysis (*B* = 0.20, *P* < .001). Furthermore, addition of blood product transfusion did not remove the effect of age on length of stay (*B* = 0.20, *P* < .001), but transfusion was also significantly associated with longer length of stay (*B* = 1.30, *P* < .001).

Survival

Long-term follow-up for survival was captured over a mean follow-up period of 35.1 ± 20.4 months. As expected, Cox proportional hazards regression revealed that age as a continuous variable was a significant predictor of poorer survival (hazard ratio [HR] = 1.43, 95% CI = 1.07-1.92, *P* = .016). After adjustment for the covariates from the propensity-score model, age remained a significant predictor of poorer survival (HR = 1.34, 95% CI = 1.01-1.77, *P* = .042).

DISCUSSION

This study focused specifically on age as a discriminator for perioperative transfusion of blood and blood products in patients who underwent cardiac surgery and had a routine and relatively smooth course afterward. We found age to be a robust predictor for blood product transfusion after surgery. Older age as a continuous variable was associated with

Distribution of Propensity Scores

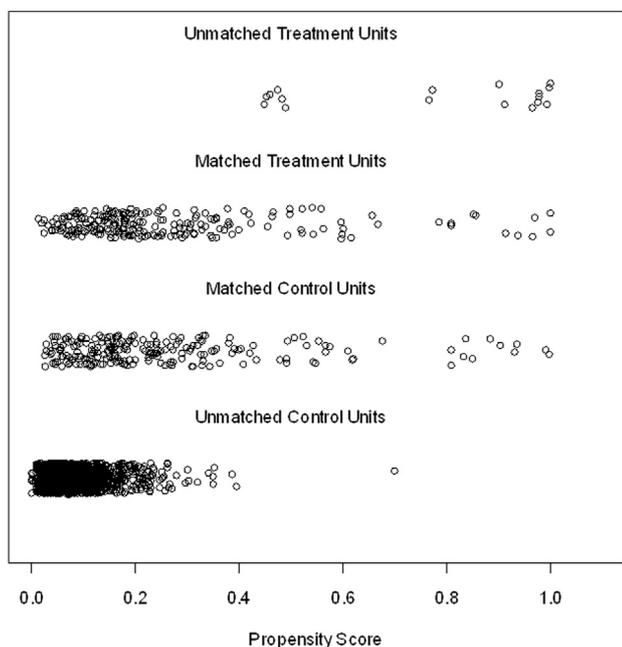


FIGURE 2. The figure shows the distribution of propensity scores for control (age <75 years) and treatment (age ≥75 years) units.



TABLE 1. Preoperative and operative characteristics by age group before matching

Characteristic	Age <75 y (n = 1659)	Age ≥75 y (n = 239)	P value
Age (y)	58.8 ± 10.0	78.8 ± 3.2	<.001
Gender, female	329 (20)	64 (27)	.013
Diabetes mellitus	447 (27)	62 (26)	.744
Body mass index (kg/m ²)	29.0 ± 8.3	26.7 ± 4.2	<.001
Hypertension	1122 (68)	204 (85)	<.001
Congestive heart failure	130 (8)	40 (17)	<.001
Ejection fraction (%)	57.9 ± 7.7	58.5 ± 7.1	.284
Previous CVA	68 (4)	20 (8)	.003
Cerebrovascular disease	152 (9)	41 (17)	<.001
Chronic pulmonary disease	229 (14)	49 (21)	.006
Creatinine >2 mg/dL	15 (1)	4 (2)	.286
Peripheral vascular disease	106 (6)	27 (11)	.005
Urgent status	561 (34)	63 (26)	.022
Preoperative hematocrit	40.1 ± 4.5	38.3 ± 4.5	<.001
EuroSCORE II	1.3 ± 1.3	3.3 ± 3.2	<.001
Type of surgery			
CABG	1064 (64)	148 (62)	.506
Valve surgery	516 (31)	84 (35)	.209
Surgical ablation	107 (6)	18 (8)	.528
CPB time (min)	102.6 ± 37.2	95.8 ± 30.2	.003

Data are presented as mean ± SD or frequency (%), unless otherwise indicated. The categories for type of surgery are not mutually exclusive. CVA, Cerebrovascular accident; EuroSCORE, European System for Cardiac Operative Risk Evaluation; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass.

greater odds of receiving a blood product transfusion after surgery, which in previous studies was associated with a greater likelihood of complications, regardless of age.^{2,4-7} In our sample, older age was significantly associated with longer length of stay and poorer survival after discharge. Older age was associated with greater odds for transfusion; the relationship between hematocrit before surgery and

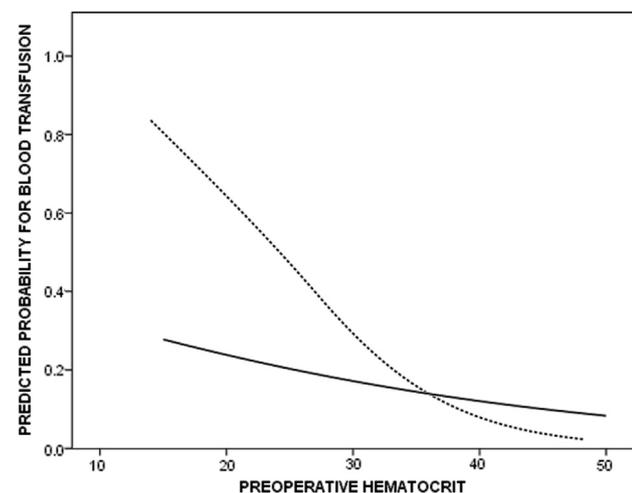


FIGURE 3. The figure shows spline curves demonstrating the relationship of preoperative hematocrit with odds for blood transfusion, for ages ≥75 years (dashed line) and ages <75 years (solid line) in the matched sample.

TABLE 2. Preoperative and operative characteristics by age group after matching

Characteristic	Age <75 y (n = 222)	Age ≥75 y (n = 222)	P value
Age (y)	61.0 ± 11.0	78.6 ± 3.1	<.001
Gender, female	60 (27)	54 (24)	.515
Diabetes mellitus	57 (26)	56 (25)	.913
Body mass index (kg/m ²)	26.3 ± 3.8	26.7 ± 4.1	.325
Hypertension	184 (83)	187 (84)	.701
Congestive heart failure	24 (11)	31 (14)	.313
Ejection fraction (%)	58.9 ± 9.1	58.7 ± 6.9	.772
Previous CVA	15 (7)	14 (6)	.848
Cerebrovascular disease	37 (17)	31 (14)	.429
Chronic pulmonary disease	38 (17)	46 (21)	.332
Creatinine >2 mg/dL	10 (5)	4 (2)	.103
Peripheral vascular disease	22 (10)	24 (11)	.755
Urgent status	61 (28)	61 (28)	>.999
Preoperative hematocrit	38.1 ± 4.9	38.4 ± 4.5	.534
EuroSCORE II	2.6 ± 2.6	2.8 ± 2.5	.393
Type of surgery			
CABG	135 (61)	139 (63)	.696
Valve surgery	84 (38)	77 (35)	.490
Surgical ablation	13 (6)	13 (6)	>.999
CPB time (min)	109.5 ± 43.3	94.6 ± 28.9	<.001

Data are presented as mean ± SD, or frequency (%), unless otherwise indicated. The categories for type of surgery are not mutually exclusive. CVA, Cerebrovascular accident; EuroSCORE, European System for Cardiac Operative Risk Evaluation; CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting.

the odds for receiving any perioperative blood product transfusion was significant among only patients age ≥75 years, and not for those age <75 years.

Intraoperative transfusion of blood and blood products is primarily intended to maintain or restore tissue oxygenation. Cardiac surgical patients are at risk of severe bleeding, and some patients are at risk of hemorrhagic shock. Consensus is lacking, however, on the hematocrit level at which the benefit of transfusion in cardiac surgery patients outweighs the risks. The World Health Organization defines anemia as a hemoglobin level of <13 g/dL for adult men and <12 g/dL for nonpregnant adult women.¹² Several other organizations have issued guidelines for perioperative blood transfusion.¹³⁻²⁰

TABLE 3. Perioperative outcomes by age as a continuous variable, scaled in 5-year increments

Outcome	OR	95% CI	P value
Length of stay (d)	0.21	0.11-0.30	<.001
Permanent stroke or TIA	0.94	0.55-1.61	.828
Pneumonia	1.22	0.56-2.66	.623
Blood transfusion			
Intraoperative	0.96	0.85-1.10	.559
Postoperative	1.39	1.04-1.87	.028
Mortality and major morbidity	1.68	0.76-3.72	.200
Readmission within <30 d	0.99	0.85-1.15	.578

Data are presented as B coefficient from linear regression for length of stay only. The blood transfusion categories are not mutually exclusive. OR, Odds ratio; CI, confidence interval; TIA, transient ischemic attack.

Despite these guidelines, the rate at which transfusion is used for cardiac surgery varies widely among hospitals, clinical trials, and cardiac intensive care units.²¹⁻²³ Recommendations are based primarily on expert opinion rather than established evidence.^{7,16-18} Several reports support the use of a more restrictive transfusion strategy (ie, at lower hemoglobin levels). The Transfusion Requirements After Cardiac Surgery (TRACS) study²⁴ compared a liberal blood transfusion strategy (hematocrit $\geq 30\%$) with a restrictive strategy (hematocrit $\geq 24\%$). The restrictive strategy was not inferior to the liberal strategy in terms of postoperative (≤ 30 -day) morbidity and mortality. In another study evaluating transfusion thresholds, patients undergoing coronary artery bypass grafting were randomly assigned to receive transfusion at hemoglobin thresholds of < 8 g/dL and < 9 g/dL. No differences were found in morbidity, mortality, or self-assessed fatigue or anemia.²⁵

The lack of clarity on transfusion thresholds complicates the decision regarding when to transfuse elderly patients who have had cardiac surgery and may put these patients at greater risk, compared with younger patients, for complications associated with transfusion. In general, given similar hemoglobin levels of ≤ 10 g/dL, the tendency among surgeons to give postoperative blood transfusion is greater with elderly versus younger patients,^{9,11} despite the lack of evidence supporting this practice. Possibly, surgeons perceive older patients as being frailer simply because of their age, and not because of other, more objective determinants of vulnerability.

Given the lack of consensus on the hematocrit level at which transfusion should be employed, elderly patients remain particularly at risk of the complications that attend blood transfusion, especially given that they are more likely than younger patients to receive transfusion at a given hemoglobin level. The results of our study add to the body of evidence showing an increased risk associated with transfusion in elderly patients undergoing cardiac surgery. They also lend further support to a more restrictive approach to transfusion during and after cardiac surgery, particularly in elderly patients.

Limitations

The results of this study provide evidence that patient age is a factor in the transfusion decision-making process. Owing to the complex nature of the clinical elements involved in blood product transfusion, these results do not provide confirmation of causality, but they can provide directions for future research. In addition, the rigorous nature of our institutional blood protocol may affect the generalizability of these findings to other centers. However, without a rigorous protocol for transfusion, the independent impact of patient age on transfusion may be stronger.

CONCLUSIONS

In patients who experience a routine course immediately after cardiac surgery, older age was found to be associated with a greater likelihood of blood and blood product transfusion after surgery. In addition, older age was found to be predictive of longer length of stay and poorer survival, even after adjustment for clinical factors. Continued study of transfusion effects, particularly in the elderly, should be directed toward more-sophisticated transfusion protocols to optimize perioperative care.

Conflict of Interest Statement

Dr Niv Ad is a consultant and a member of the speaker's bureau for Medtronic, Inc and AtriCure, Inc. All other authors have nothing to disclose with regard to commercial support.

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Key Words: Transfusion, elderly, cardiac surgery

EDITORIAL COMMENTARY

Does the “retrospectroscope” help define best practices in transfusion?

John W. Hammon, MD

See related article on pages 209-14.

In the past several years, there has been an almost irresistible push by cardiac surgeons, anesthesiologists, critical care physicians, and blood bank personnel to lower the number of transfusions of whole blood and blood products for patients undergoing cardiac surgery. A mechanism for achieving this goal has been to adjust one indication for transfusion from a serum hemoglobin of less than 10 g/dL to less than 7 g/dL.¹ Because of the lack of hard evidence to support this recommendation, the variation in hospital practice in the United States has been extraordinary, ranging from 5% adoption to more than 90% among patients undergoing coronary artery bypass grafting surgery.² There have

been many attempts to test the effects of this change, including the study by Ad and colleagues³ in this issue of the *Journal*.

With a retrospective analysis of 1898 consecutive patients undergoing nonemergency cardiac surgery between 2007 and 2013, Ad and colleagues³ sought to ascertain the transfusion status of these patients and to find out the effect of transfusion on 222 patients aged 75 or older. This project was driven by evidence that older patients require more transfusions. Their hospital had instituted a rigorous blood conservation protocol, as recommended by the Society of Thoracic Surgeons guideline; how would this change effect outcomes? Because the groups were unequal in size, and the older patients were at significantly greater risk, Ad and colleagues³ were obliged to use propensity-matching analysis to balance the groups and studied patients older and younger than 75 years.

They found that older age predicted postoperative blood transfusion, longer hospital stay, and poorer survival, even with the new more restrictive blood conservation protocol. It would seem logical that the new protocol failed to reduce blood use in the older group, and this may have led to poorer survival. We must, however, take a closer look at



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