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Transfusion White Paper and Referenced Manuscripts

December 2013

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1. Colleen G. Koch, Liang Li, Daniel I. Sessler, Priscilla Figueroa, Gerald A. Hoeltge, Tomislav Mihaljevic, Eugene H. Blackstone. **Duration of Red-Cell Storage and Complications after Cardiac Surgery**. *N Engl J Med* 2008; 358:1229-39.

2. Dean A. Fergusson, Paul Hebert, Debora L. Hogan, et al. **Effect of Fresh Red Blood Cell Transfusions on Clinical Outcomes in Premature, Very Low-Birth-Weight Infants: The ARIPI Randomized Trial**. *JAMA* 2012; 308:1443–51.

- **Effects of Anemia on Mortality and Morbidity** **(Tabs 3 and 4)**

3. Jeffrey L. Carson, Amy Duff, Roy M. Poses, Jesse A. Berlin, Richard K. Spence, Richard Trout, Helaine Noveck, Brian L. Strom. Effect of Anemia and Cardiovascular Disease on Surgical Mortality and Morbidity. *Lancet* 1996; 348: 1055–60.

4. Jeffery L. Carson, Helaine Noveck, Jesse A. Berlin, Steven A. Gould. Mortality and Morbidity in Patients with Very Low Postoperative Hb Levels Who Decline Blood Transfusion. *Transfusion* 2002; 42: 812-818.

- **The Efficacy of Blood Transfusion on Mortality and Morbidity** **(Tabs 5 – 14)**

5. Paul C. Hebert, George Wells, Morris A. Blajchman, John Marshall, Claudio Martin, Giuseppe Pagliarello, Martin Tweeddale, Irwin Schweitzer, Elizabeth Yetisir. A Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care. *N Engl J Med* 1999; 340: 409-17.

6. Ludhmila A. Hajjar, Jean-Louis Vincent, Filomena R. B. G. Galas, et al. Transfusion Requirements after Cardiac Surgery. *JAMA* 2010; 304(14):1559-1567.

7. Jeffrey L. Carson, Michael L. Terrin, Helaine Noveck, David W. Sanders, Bernard R. Chaitman, George G. Rhoads, George Nemo, Karen Dragert, Lauren Beaupre, Kevin Hildebrand, William Macaulay, Courtland Lewis, Donald Richard Cook, Gwendolyn Dobbin, Khwaja J. Zakriya, Fred S. Apple, Rebecca A. Horney, Jay Magaziner. Liberal or Restrictive Transfusion in High-Risk Patients after Hip Surgery. *N Engl J Med* 2011; 365:2453-62.

8. Càndid Villanueva, Alan Colomo, Alba Bosch, Mar Concepción, Virginia Hernandez-Gea, Carles Aracil, Isabel Graupera, María Poca, Cristina Alvarez-Urturi, Jordi Gordillo, Carlos Guarner-Argente, Miquel Santaló, Eduardo Muñiz, Carlos Guarner. Transfusion Strategies for Acute Upper Gastrointestinal Bleeding. *N Engl J Med* 2013; 368:11-21.

9. Jeffrey L. Carson, Maria Mori Brooks, J. Dawn Abbott, Bernard Chaitman, Sheryl F. Kelsey, Darrell J. Triulzi, Vankeepuram Srinivas, Mark A. Menegus, Oscar C. Marroquin, Sunil V. Rao, Helaine Noveck, Elizabeth Passano, Regina M. Hardison, Thomas Smitherman, Tudor Vagaonescu, Neil J. Wimmer, David O. Williams. Liberal versus Restrictive Transfusion Thresholds for Patients with Symptomatic Coronary Artery Disease. *Am Heart J* 2013; 165:964-971.

10. Jeffrey L. Carson, Paul A. Carless, Paul C. Hebert. Outcomes Using Lower vs Higher Hemoglobin Thresholds for Red Blood Cell Transfusion. *JAMA* 2013; 309: 1.

11. Paul E. Marik, Howard L. Corwin. Efficacy of Red Blood Cell Transfusion in the Critically Ill: A Systematic Review of the Literature. *Crit Care Med* 2008; 36: 9.

12. Saurav Chatterjee, Jørn Wetterslev, Abhishek Sharma, Edgar Lichstein, Debabrata Mukherjee. Association of Blood Transfusion with Increased Mortality in Myocardial Infarction: A Meta-analysis and Diversity-Adjusted Study Sequential Analysis. *JAMA Intern Med*. 2013; 173(2):132-139.

13. Sunil V. Rao, James G.Jollis, Robert A. Harrington, Christopher B. Granger, et al. Relationship of Blood Transfusion and Clinical Outcomes in Patients With Acute Coronary Syndromes. *JAMA* 2004; 292:1555-1562.

14. Jeffrey L. Carson, Paul C. Hebert. Here We Go Again—Blood Transfusion Kills Patients? *JAMA Intern Med.* 2013; 173: 139-140.

- **Summary of a Clinical Practice Guideline (Tab 15)**

15. Jeffrey L. Carson, Brenda J. Grossman, Steven Kleinman, Alan T. Tinmouth, Marisa B. Marques, Mark K. Fung, John B. Holcomb, Orieji Illoh, Lewis J. Kaplan, Louis M. Katz, Sunil V. Rao, John D. Roback, Aryeh Shander, Aaron A.R. Tobian, Robert Weinstein, Lisa Grace Swinton McLaughlin, Benjamin Djulbegovic. Red Blood Cell Transfusion: A Clinical Practice Guideline from the AABB. *Ann Intern Med*. 2012; 157:49-58.

Summary of Key Points in the White Paper:

In a presentation made by Dr. Jeffrey Carson* to the BMC2 Vascular Interventions Collaborative on October 19, 2013, based on results from clinical trials to date, Dr. Carson made these recommendations to the interventional cardiologists and vascular surgeons (and teams) in attendance:

1. **In hospitalized hemo-dynamically stable patients, at what Hgb should a decision to transfuse RBC be considered?**
   - We recommend adhering to a restrictive transfusion strategy.
   - In adult and pediatric ICU patients, transfusion should be considered at Hgb < 7 g/dL.
   - In surgical patients, transfusion should be considered at Hgb < 8 g/dL or for symptoms.
   - Quality of evidence: High
   - Strength of recommendation: Strong

2. **In hospitalized hemo-dynamically stable patients, with pre-existing cardiovascular disease, at what Hgb should a decision to transfuse RBC be considered?**
   - We suggest adhering to a restrictive transfusion strategy.
   - Transfusion should be considered at Hgb < 8g/dL or for symptoms.
   - Quality of evidence: Moderate
   - Strength of recommendation: Weak

3. **In hospitalized hemo-dynamically stable patients, should transfusion be guided by symptoms rather than hemoglobin concentration?**
   - We suggest that transfusion decisions should be influenced by symptoms as well as hemoglobin concentration
   - Quality of evidence: Low
   - Strength of recommendation: Weak

4. **In hospitalized hemo-dynamically stable patients, with acute coronary syndrome, at what Hgb should a decision to transfuse RBC be considered?**
   - We cannot recommend for or against liberal or restrictive transfusion threshold. Further research is needed to determine optimal RBC transfusion threshold.
   - Quality of evidence: Very low
   - Strength of recommendation: Uncertain

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Whitepaper on Transfusion – Based on the 10/19/2013 Presentation by Jeffrey Carson, MD* at the BMC2 VIC Collaborative Meeting at the Amway Grand in Grand Rapids, Michigan

This white paper is intended to be a summary compendium of the major recent studies and manuscripts published on the subject of transfusion of red blood. The topics to be covered in this whitepaper will include:

1. **Potential side effects of blood transfusion**
2. **Quality of blood product**
3. **The effect of anemia on mortality and morbidity**
4. **The effects of blood transfusion on mortality and morbidity**
    - **A review of clinical trials**
    - **The FOCUS Trial results**
    - **A review of results from observational data reviews**
5. **Summary of a clinical practice guideline**

1. Potential side effects of transfusion

Potential adverse events from blood transfusion are numerous and include HIV, HCV, HBV, fatal hemolysis, life threatening reaction, fever, transfusion related acute lung injury (TRALI), and transfusion associated circulatory overload (TACO). Some of these outcomes are rare events. These include HIV, HCV, HBV and fatal hemolysis and life threatening reaction all of which occur in the range of 1:500,000 and 1: 1.2 million cases.

TRALI and TACO are both more common outcomes at rates of 1:100. TRALI involves acute lung injury with bilateral infiltrates with an absence of circulatory overload, chills fever, dyspnea, cyanosis, hypotension or hypertension and occurs

within 6 hours (usually 2 hours) of receipt of plasma containing blood or blood components. TACO involves volume overload from transfusion. It is common, clinically important but treatable in most cases.

In summary, the risks of blood transfusion from known problems, is very low. TRALI is an important and serious side effect but TACO is more common. Human error, the administration of the wrong unit of blood to the wrong patient, is a preventable cause of serious adverse effect from blood transfusion.

2. Quality of blood product

Colleen Gorman Koch, MD, et al. sought to evaluate the clinical implications of duration of red-cell storage and published the resulting manuscript entitled, "Duration of red-cell storage and complications after cardiac surgery" in NEJM 2008; 358:1229-39.

The authors stated that stored red cells undergo progressive structural and functional changes over time. Researchers tested the hypothesis that serious complications and mortality after cardiac surgery are increased when transfused red cells are stored for more than 2 weeks.

They examined data from patients given red-cell transfusions during coronary-artery bypass grafting, heart-valve surgery, or both between June 30, 1998, and January 30, 2006. A total of 2872 patients received 8802 units of blood that had been stored for 14 days or less ("newer blood"), and 3130 patients received 10,782 units of blood that had been stored for more than 14 days ("older blood").

Multivariable logistic regression with propensity-score methods was used to examine the effect of the duration of storage on outcomes. Survival was estimated by the Kaplan–Meier method and Blackstone's decomposition method.

The median duration of storage was 11 days for newer blood and 20 days for older blood. Patients who were given older units had higher rates of in-hospital mortality (2.8% vs. 1.7%, P = 0.004), intubation beyond 72 hours (9.7% vs. 5.6%, P<0.001), renal failure (2.7% vs. 1.6%, P = 0.003), and sepsis or septicemia (4.0% vs. 2.8%, P = 0.01). A composite of complications was more common in patients

given older blood (25.9% vs. 22.4%, P = 0.001). Similarly, older blood was associated with an increase in the risk-adjusted rate of the composite outcome (P = 0.03). At 1 year, mortality was significantly less in patients given newer blood (7.4% vs. 11.0%, P<0.001).

The authors concluded that in patients undergoing cardiac surgery, transfusion of red cells that had been stored for more than 2 weeks was associated with a significantly increased risk of postoperative complications as well as reduced short-term and long-term survival.

Table 2. Postoperative Complications, According to the Duration of Blood Storage.

Complication	Patients Receiving Newer Blood (N=2872)*	Patients Receiving Older Blood (N=3130)†	P Value‡
	no. (%)		
In-hospital death	49 (1.7)	88 (2.8)	0.004
Cardiac			
Myocardial infarction	15 (0.5)	16 (0.5)	0.95
Ventricular tachycardia	155 (5.4)	175 (5.6)	0.74
Ventricular fibrillation	35 (1.2)	31 (1.0)	0.40
Cardiac arrest or asystole	47 (1.6)	54 (1.7)	0.79
Cardiac tamponade	48 (1.7)	67 (2.1)	0.19
Aortic dissection	1 (<1)	2 (0.1)	0.99
Neurologic			
Stroke	49 (1.7)	61 (1.9)	0.48
Coma >24 hr	9 (0.3)	12 (0.4)	0.65
Pulmonary			
Ventilation >72 hr	160 (5.6)	304 (9.7)	<0.001
Pneumonia	81 (2.8)	111 (3.5)	0.11
Pulmonary embolism	5 (0.2)	7 (0.2)	0.67
Respiratory insufficiency	177 (6.2)	278 (8.9)	<0.001
Renal			
Renal failure	45 (1.6)	84 (2.7)	0.003
Infectious			
Septicemia or sepsis	80 (2.8)	125 (4.0)	0.01
Deep sternal wound	25 (0.9)	25 (0.8)	0.76
Superficial sternal wound	44 (1.5)	62 (2.0)	0.19
Multiorgan failure	7 (0.2)	23 (0.7)	0.007
Peripheral vascular			
Iliac or femoral dissection	0	0	
Acute limb ischemia	7 (0.2)	18 (0.6)	0.05
Composite outcome§	642 (22.4)	810 (25.9)	0.001

Age of red blood cells in premature infants – a double blinded multi center randomized clinical trial (ARIPI).

Paul Hebert, MD, et al. (JAMA 2012) sought to determine the "Effect of Fresh Red Blood Cell Transfusions on Clinical Outcomes in Premature, Very Low-Birth-Weight Infants" (The ARIPI Trial).

Authors argued that even though red blood cells (RBCs) are lifesaving in neonatal intensive care, transfusing older RBCs may result in higher rates of organ dysfunction**,** nosocomial infection, and length of hospital stay.

Their objective was to determine if RBCs stored for 7 days or less compared with usual standards decreased rates of major nosocomial infection and organ dysfunction in neonatal intensive care unit patients requiring at least 1 RBC transfusion.

Researchers conducted a double-blind, randomized controlled trial in 377 premature infants with birth weights less than 1250 g admitted to 6 Canadian tertiary neonatal intensive care units between May 2006 and June 2011. Intervention Patients were randomly assigned to receive transfusion of RBCs stored 7 days or less (n=188) vs. standard-issue RBCs in accordance with standard blood bank practice (n=189). The primary outcome was a composite measure of major neonatal morbidities, including necrotizing entero-colitis, retinopathy of prematurity**,** broncho-pulmonary dysplasia, and intra-ventricular hemorrhage, as well as death. The primary outcome was measured within the entire period of neonatal intensive care unit stay up to 90 days after randomization. The rate of nosocomial infection was a secondary outcome.

The mean age of transfused blood was 5.1 (SD, 2.0) days in the fresh RBC group and 14.6 (SD, 8.3) days in the standard group. Among neonates in the fresh RBC group, 99 (52.7%) had the primary outcome compared with 100 (52.9%) in the standard RBC group (relative risk, 1.00; 95% CI, 0.82-1.21). The rate of clinically suspected infection in the fresh RBC group was 77.7% (n=146) compared

with 77.2% (n=146) in the standard RBC group (relative risk, 1.01; 95% CI, 0.90-1.12), and the rate of positive cultures was 67.5% (n=127) in the fresh RBC group compared with 64.0% (n=121) in the standard RBC group (relative risk, 1.06; 95% CI, 0.91-1.22).

Authors concluded that the use of fresh RBCs compared with standard blood bank practice did not improve outcomes in premature, very low-birth-weight infants requiring a transfusion. (A potentially mitigating factor in the analysis was the fact that the age of the standard blood bank blood was only two weeks so there may not have been much difference in the age of blood between the two study groups.)

ARIPI Trial, JAMA 2012

Table 4. Primary Outcomes

Primary Outcomes	No. (%) Standard Red Blood Cell Group (n = 189)	No. (%) Fresh Red Blood Cell Group (n = 188)	Relative Risk (95% CI)
Necrotizing enterocolitis (Bell criteria stage ≥2)	15 (7.9)	15 (8.0)	1.00 (0.48-2.12)
Intraventricular hemorrhage (Papile criteria grade ≥3)	11 (5.8)	18 (9.6)	1.65 (0.80-3.39)
Retinopathy of prematurity (stage ≥3)	26 (13.8)	23 (12.2)	0.89 (0.53-1.50)
Bronchopulmonary dysplasia	63 (33.3)	60 (31.9)	0.96 (0.72-1.28)
Death	31 (16.4)	30 (16.0)	0.97 (0.61-1.54)
Composite primary outcome: any of above	100 (52.9)	99 (52.7)	1.00 (0.82-1.21)

Authors concluded that it remains unclear whether or not the age of blood is important. They suggested that this requires further testing in clinical trials.

3. Effect of anemia on morbidity and mortality

Jeffrey Carson, MD, et al. published results of a study in Lancet (1996; 348:1055-60) on the effects of anemia and cardiovascular disease on surgical mortality and morbidity.

A retrospective cohort study was performed in1958 patients, 18 years and older, who underwent surgery and declined blood transfusion for religious reasons. The primary outcome was 30-day mortality and the secondary outcome was 30-day mortality or in-hospital 30-day morbidity. Cardiovascular disease was defined as a history of angina, myocardial infarction, congestive heart failure, or peripheral vascular disease.

The study found that low preoperative hemoglobin or a substantial operative blood loss increases the risk of death or serious morbidity more in patients with cardiovascular disease than in those without. The authors concluded that decisions about transfusion should consider cardiovascular status and operative blood loss as well as the hemoglobin concentration.

Preop Hgb and Mortality – Carson J, et al. Lancet 1996			
Preop Hgb	**N**	**% Dead**	**95% CI**
< = 5.9	**36**	**33.3**	**18.6-51.0**
6.0-6.9	**27**	**18.5**	**6.3-38.1**
7.0-7.9	**49**	**12.2**	**4.6-24.7**
8.0-8.9	**39**	**12.8**	**4.3-27.4**
9.0-9.9	**75**	**8.0**	**3.0-16.6**
10.0-10.9	**109**	**4.6**	**1.5-10.4**
11.0-11.9	**212**	**2.4**	**0.8-5.4**
12+	**1411**	**1.3**	**0.8-2.0**

Jeffrey Carson, MD, et al. sought to understand the risks associated from withholding transfusion. Their study was published in Transfusion, Volume 42, and July 2002.

The study was performed on a retrospective cohort study of patients who declined RBC transfusions for religious reasons. This analysis was restricted to consecutive patients ≥ 18 years old, who underwent surgery in the operating room from 1981 to 1994 and had a postoperative Hgb count of 8 g per dL or less. The primary outcome was defined as any in-hospital death occurring within 30 days of the surgery. The secondary outcome was 30-day morbidity. Morbidity was defined as myocardial infarction, arrhythmia, congestive heart failure, or infection.

The authors found that of 2083 eligible patients, 300 had postoperative Hgb counts of 8 g per dL or less. The study population was predominantly female (70.3%) with a mean age of 57 years (SD, ± 17.7). In patients with a postoperative Hgb level of 7.1 to 8.0, 0 died (upper 95% CI, 3.7%), and 9.4 percent (95% CI, 4.4-17.0%) had a morbid event. In patients with a postoperative Hgb level of 4.1 to 5.0, 34.4 percent (95% CI, 18.6-53.2%) died and 57.7 percent (95% CI, 36.9-76.6%) had a morbid event or died. After adjusting for age, cardiovascular disease and Acute Physiology and Chronic Health Evaluation II score, the odds of death in patients with a postoperative Hgb level of ≤ 8 g per dL increased 2.5 times (95% CI, 1.9-3.2) for each gram decrease in Hgb level.

The authors concluded that the risk of death was low in patients with postoperative Hgb levels of 7.1 to 8.0 g per dL, although morbidity occurred in 9.4 percent. As postoperative blood counts fall, the risk of mortality and/or morbidity rises and becomes extremely high below 5 to 6 g per dL.

Postop Hgb Level and Mortality in Patients with Hgb < 8 g/dl			
Postop Hgb	**N(300)**	**% 30 day Mortality**	**% 30 day Mortality Morbidity**
1.1-2	7	100	100
2.1-3	24	54.2	91.7
3.1-4	28	25	52.6
4.1-5	32	34.4	57.7
5.1-6	54	9.3	28.6
6.1-7	56	8.9	22
7.1-8	99	0	9.4

Carson JL, et al. Transfusion 2002

4. Effects of blood transfusion on mortality and morbidity

In a study published in NEJM 1999, Paul Hebert, MD, et al. sought to determine whether a restrictive strategy of red-cell transfusion and a liberal strategy produced equivalent results in critically ill patients. They compared the rates of death from all causes at 30 days and the severity of organ dysfunction.

Researchers enrolled 838 critically ill patients with euvolemia after initial treatment, which had hemoglobin concentrations of less than 9.0 g per deciliter within 72 hours after admission to the intensive care unit. 418 Patients were randomly assigned to a restrictive strategy of transfusion, in which red cells were transfused if the hemoglobin concentration dropped below7.0 g per deciliter and hemoglobin concentrations were maintained at 7.0 to 9.0 g per deciliter. 420 patients were randomly assigned to a liberal strategy, in which transfusions were given when the hemoglobin concentration fell below 10.0 g per deciliter and hemoglobin concentrations were maintained at 10.0 to 12.0 g per deciliter.

Researchers found that overall, 30-day mortality was similar in the two groups (18.7 percent vs. 23.3 percent, P= 0.11). However, the rates were significantly lower with the restrictive transfusion strategy among patients who were less acutely ill — those with an Acute Physiology and Chronic Health Evaluation II

score of 20 (8.7 percent in the restrictive-strategy group and 16.1 percent in the liberal-strategy group=0.03) — and among patients who were less than 55 years of age (5.7 percent and 13.0 percent, respectively; P=0.02), but not among patients with clinically significant cardiac disease (20.5 percent and 22.9 percent, respectively; P=0.69). The mortality rate during hospitalization was significantly lower in the restrictive-strategy group (22.2 percent vs. 28.1 percent, P=0.05).

Researchers concluded that a restrictive strategy of red-cell transfusion is at least as effective as and possibly superior to a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina. (N Engl J Med 1999; 340:409-17.)

In the Transfusion Requirements after Cardiac Surgery (TRACS) Randomized Control Trial, Ludhmila Hajjr, MD, PhD, et al. sought to define whether a restrictive perioperative red blood cell transfusion strategy is as safe as a liberal strategy in patients undergoing elective cardiac surgery.

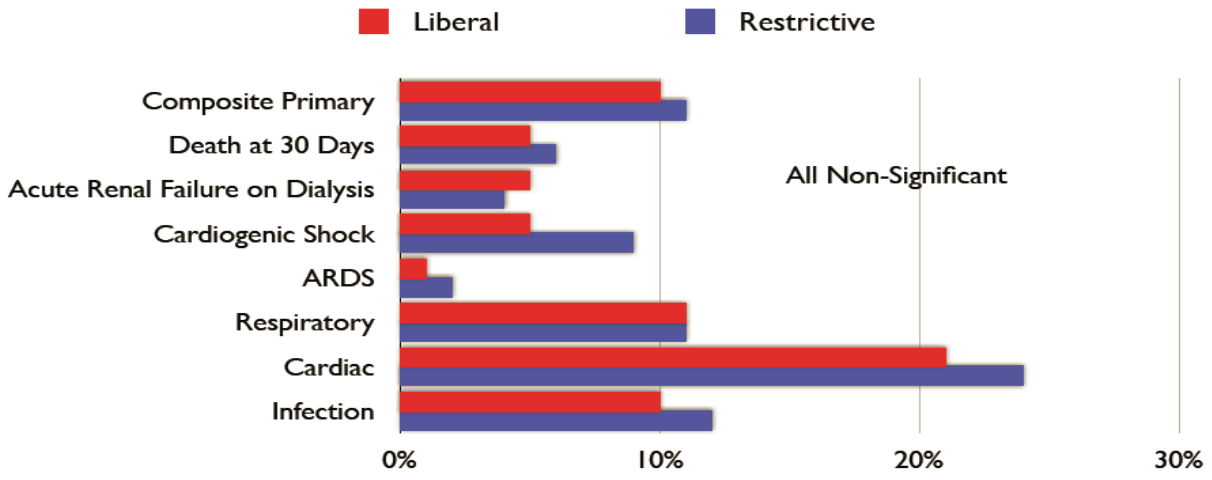
The TRACS study was a prospective, randomized, controlled clinical non-inferiority trial conducted between February 2009 and February 2010 in an intensive care unit at a university hospital cardiac surgery referral center in Brazil. Consecutive adult patients (n=502) who underwent cardiac surgery with cardiopulmonary bypass were eligible; analysis was by intention-to-treat. Intervention patients were randomly assigned to a liberal strategy of blood transfusion (to maintain a hematocrit of 30%) or to a restrictive strategy (to maintain a hematocrit of 24%). The main outcome measure was a composite end point of 30-day all-cause mortality and severe morbidity (defined as cardiogenic shock, acute respiratory distress syndrome, or acute renal injury requiring dialysis or hemofiltration) occurring during the hospital stay. The non-inferiority margin was predefined at −8% (i.e., 8% minimal clinically important increase in occurrence of the composite end point).

Hemoglobin concentrations were maintained at a mean of 10.5 g/dL (95% confidence interval [CI], 10.4-10.6) in the liberal-strategy group and 9.1 g/dL (95%

CI, 9.0- 9.2) in the restrictive-strategy group (P=.001). A total of 198 of 253 patients (78%) in the liberal-strategy group and 118 of 249 (47%) in the restrictive-strategy group received a blood transfusion (P=.001). Occurrence of the primary end point was similar between groups (10% liberal vs. 11% restrictive; between-group difference, 1% [95% CI, −6%to 4%]; P=.85). Independent of the transfusion strategy, the number of transfused red blood cell units was an independent risk factor for clinical complications or death at 30 days (the hazard ratio for each additional unit transfused was, 1.2 [95% CI, 1.1-1.4]; P=.002).

Researchers concluded that among patients undergoing cardiac surgery, the use of a restrictive perioperative transfusion strategy compared with a more liberal strategy resulted in non-significant differences in the rates of the combined outcome of 30-day all-cause mortality and severe morbidity. JAMA, 2010; 304(14):1559-1567.

Transfusion in Cardiac Surgery
Hajjar, L.A. et al. JAMA 2010; 304: 1559-1567.



Jeffrey Carson, MD, et al. evaluated liberal versus restrictive transfusion in high risk patients after hip surgery and results of the study were published in NEJM December 2011. (This is the FOCUS transfusion trigger trial)

The study enrolled 2016 patients who were 50 years of age or older, who had either a history of cardiovascular disease or risk factors for cardiovascular disease, and whose hemoglobin level was below 10 g per deciliter after hip-fracture surgery. Patients were randomly assigned to a liberal transfusion strategy (a hemoglobin threshold of 10 g per deciliter) or a restrictive transfusion strategy (symptoms of anemia or at physician discretion for a hemoglobin level of <8 g per deciliter). The primary outcome was death or an inability to walk across a room without human assistance on 60-day follow-up.

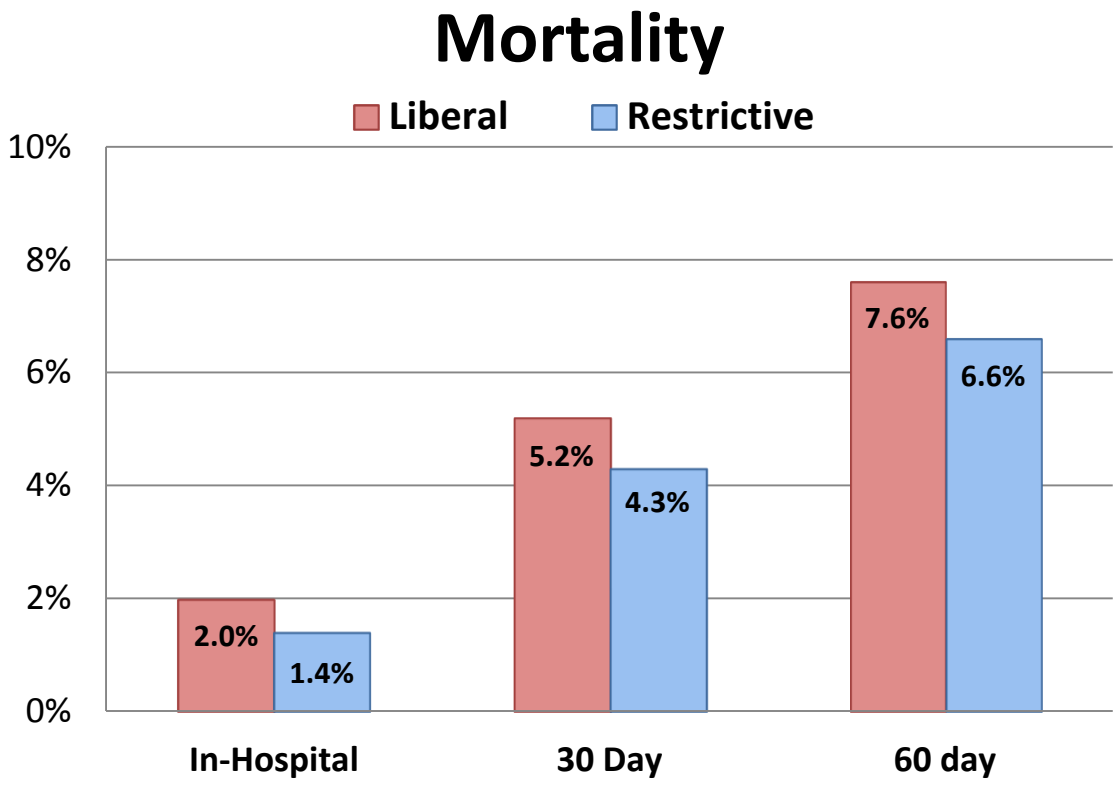
A median of 2 units of red cells were transfused in the liberal-strategy group and none in the restrictive-strategy group. The rates of the primary outcome were 35.2% in the liberal-strategy group and 34.7% in the restrictive-strategy group (odds ratio in the liberal-strategy group, 1.01; 95% confidence interval [CI], 0.84 to 1.22), for an absolute risk difference of 0.5 percentage points (95% CI, −3.7 to 4.7). The rates of in-hospital acute coronary syndrome or death were 4.3% and 5.2%, respectively (absolute risk difference, −0.9%; 99% CI, −3.3 to 1.6), and rates of death on 60-day follow-up were 7.6% and 6.6%, respectively (absolute risk difference, 1.0%; 99% CI, −1.9 to 4.0). The rates of other complications were similar in the two groups.

The authors concluded that a liberal transfusion strategy, as compared with a restrictive strategy, did not reduce rates of death or inability to walk independently on 60-day follow-up or reduce in-hospital morbidity in elderly patients at high cardiovascular risk.

Hgb and Transfusions		
Key Indicators	**Liberal N=1007**	**Restrictive N=1009**
Hgb Prior to Transfusion	9.2 (SD±0.5)	7.9 (SD±0.6)
Transfused Patients	974 (96.7%)	415 (41.0%)
Median Units Transfused	2.0 (Interquartile range, 1, 2)	0 (Interquartile range, 0, 1)
Total Units Transfused	1866 units	652 units

Primary Outcome: Not Walking or Dead at 60 Days				
Postop Timeframe	**Liberal N=1007**	**Restrictive N=1009**	**Risk Difference (95% CI)**	**Odd Ratio (95% CI)**
30 days	459 (46.1%)	481 (48.1%)	-2.0% (-7.7 to 3.8)*	0.92 (0.73 to 1.16)*
60 days	351 (35.2%)	347 (34.7%)	0.5% (-3.7% to 4.7%)	1.01 (0.84 to 1.22)

* 99% Confidence Intervals for secondary outcomes



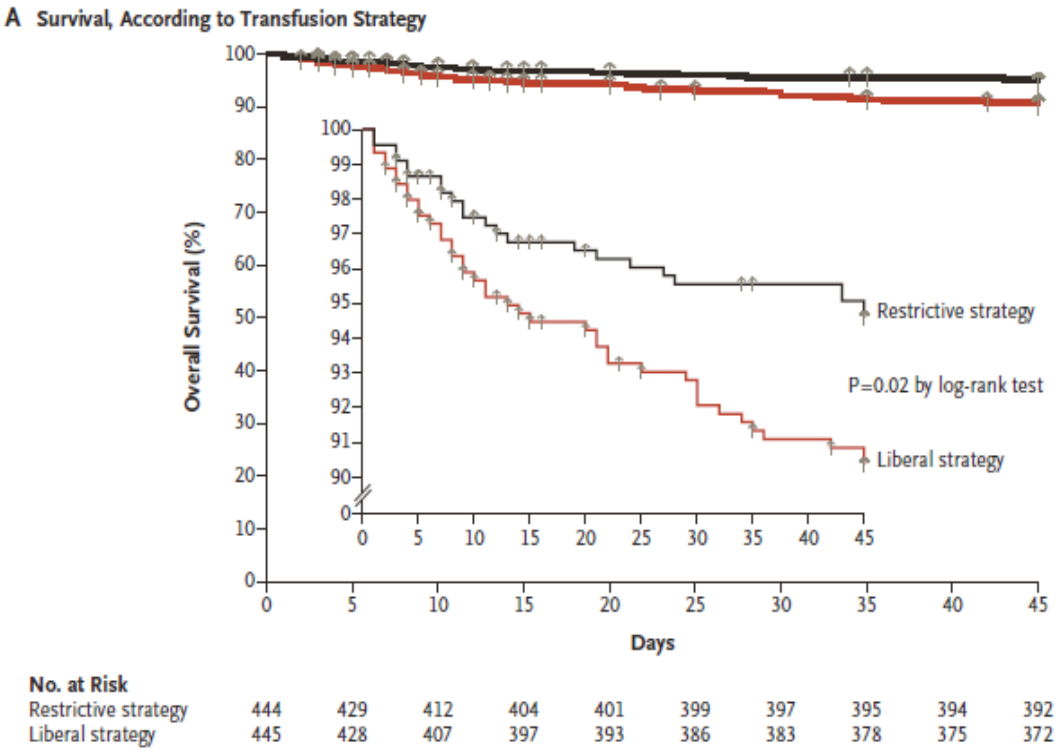
Transfusion strategies for acute upper gastrointestinal bleeding were evaluated in a study by Candid Villanueva, MD, et al. and results were published in NEJM January 3, 2013.

The hemoglobin threshold for transfusion of red cells in patients with acute gastrointestinal bleeding is controversial. Authors compared the efficacy and safety of a restrictive transfusion strategy with those of a liberal transfusion strategy.

Investigators enrolled 921 patients with severe acute upper gastrointestinal bleeding and randomly assigned 461 of them to a restrictive strategy (transfusion when the hemoglobin level fell below 7 g per deciliter) and 460 to a liberal strategy (transfusion when the hemoglobin fell below 9 g per deciliter). Randomization was stratified according to the presence or absence of liver cirrhosis.

A total of 225 patients assigned to the restrictive strategy (51%), as compared with 61 assigned to the liberal strategy (14%), did not receive transfusions (P<0.001). The probability of survival at 6 weeks was higher in the restrictive-strategy group than in the liberal-strategy group (95% vs. 91%; hazard ratio for death with restrictive strategy, 0.55; 95% confidence interval [CI], 0.33 to 0.92; P = 0.02). Further bleeding occurred in 10% of the patients in the restrictive-strategy group as compared with 16% of the patients in the liberal-strategy group (P = 0.01), and adverse events occurred in 40% as compared with 48% (P = 0.02). The probability of survival was slightly higher with the restrictive strategy than with the liberal strategy in the subgroup of patients who had bleeding associated with a peptic ulcer (hazard ratio, 0.70; 95% CI, 0.26 to 1.25) and was significantly higher in the subgroup of patients with cirrhosis and Child–Pugh class A or B disease (hazard ratio, 0.30; 95% CI, 0.11 to 0.85), but not in those with cirrhosis and Child–Pugh class C disease (hazard ratio, 1.04; 95% CI, 0.45 to 2.37). Within the first 5 days, the portal-pressure gradient increased significantly in patients assigned to the liberal strategy (P = 0.03) but not in those assigned to the restrictive strategy.

Authors concluded that a restrictive strategy significantly improved outcomes in patients with acute upper gastrointestinal bleeding.
Villanueva – New England Journal of Medicine 2013



Jeffrey Carson, MD, et al. conducted a study of liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. Results (Myocardial Ischemia and Transfusion – MINT) were published in the American Heart Journal in 2013.

Prior trials suggest it is safe to defer transfusion at hemoglobin levels above 7 to 8 g/dL in most patients. The investigators theorized that patients with acute coronary syndrome may benefit from higher hemoglobin levels.

Investigators performed a pilot trial in 110 patients with acute coronary syndrome or stable angina undergoing cardiac catheterization and a hemoglobin b10 g/dL. Patients in the liberal transfusion strategy received one or more units of blood to raise the hemoglobin level ≥10 g/dL. Patients in the restrictive transfusion strategy were permitted to receive blood for symptoms from anemia or for a hemoglobin b8 g/dL. The predefined primary outcome was the composite of death, myocardial infarction, or unscheduled revascularization 30 days post randomization.

The authors found that baseline characteristics were similar between groups except age (liberal, 67.3; restrictive, 74.3). The mean number of units transfused was 1.6 in the liberal group and 0.6 in the restrictive group. The primary outcome occurred in 6 patients (10.9%) in the liberal group and 14 (25.5%) in the restrictive group (risk difference = 15.0%; 95% confidence interval of difference 0.7% to 29.3%; P = .054 and adjusted for age P = .076). Death at 30 days was less frequent in liberal group (n = 1, 1.8%) compared to restrictive group (n = 7, 13.0%; P = .032).

Authors concluded that the liberal transfusion strategy was associated with a trend for fewer major cardiac events and deaths than a more restrictive strategy. These results support the feasibility of and the need for a definitive trial. (Am Heart J 2013; 165:964-971.e1.)

Clinical Endpoints at 30 Days			
Clinical Endpoints	**A N= 55**	**B N=54**	**Absolute Risk Difference (95% CI)**
Death/MI/ Revascularization	6 (10.9%)	14 (25.9%)	15.0% (0.7 to 29.3%)*
Death	1 (1.8%)	7 (13.0%)	11.2% ** (1.5 to 20.8)
MI	5 (9.1%)	7 (13.0%)	13.0% (-7.9 to 15.6)
Revascularization	0 (0.0%)	2 (3.7%)	3.7% (-1.3 to 8.7)

* P=0.054, adjusted for age p=0.076 **p=0.032

Clinical Endpoints at 30 Days			
Clinical Endpoints	**Liberal N= 55**	**Restrictive N=54**	**Absolute Risk Difference (95% CI)**
Death/MI/ Revascularization	6 (10.9%)	14 (25.9%)	15.0% (0.7 to 29.3%)*
Death	1 (1.8%)	7 (13.0%)	11.2% ** (1.5 to 20.8)
MI	5 (9.1%)	7 (13.0%)	13.0% (-7.9 to 15.6)
Revascularization	0 (0.0%)	2 (3.7%)	3.7% (-1.3 to 8.7)

* P=0.054, adjusted for age p=0.076 **p=0.032

Jeffrey Carson, MD, et al. published a clinical evidence synopsis in JAMA January 2013 which addressed the clinical question: "Is a lower vs. higher hemoglobin threshold best for minimizing both red blood cell use and adverse clinical outcomes when used to trigger red blood cell transfusions in anemic patients in critical care and acute care settings?

Bottom Line: Compared with higher hemoglobin thresholds, a hemoglobin threshold of 7 or 8 g/dL is associated with fewer red blood cell units transfused without adverse associations with mortality, cardiac morbidity, functional recovery, or length of hospital stay.

- **Summary of Clinical Trial Data**

There have been 7,167 patients enrolled in clinical trials evaluating transfusion thresholds. Most trials are small and only one (FOCUS) is larger than 1,000 patients. Results consistently suggest that the more restrictive transfusion is safe. To date, there has not been an adequately powered randomized clinical trial in acute coronary syndrome (ACS) so the "jury is still out" on whether or not a restrictive transfusion strategy is optimal in ACS cases.

- **<u>Efficacy of Transfusion – Observational Studies</u>**

There have been 45 observational studies to date involving 272,596 patients. In 42 of the 45 studies, the risks associated with transfusion out-weighed the benefits.

Paul Marik, MD, et al. evaluated the literature to determine the association between red blood cell transfusion, and morbidity and mortality in high-risk hospitalized patients. They published results of their evaluation in a 2008 article entitled: "Efficacy of red blood cell transfusion in the critically ill: A systematic review of the literature". Crit Care Med 2008 Vol. 36, No. 9.

In their manuscript, the authors argued that although blood cell (RBC) transfusions are common in intensive care unit, trauma, and surgical patients the hematocrit that should be maintained in any particular patient because it remains unclear whether or not the risks of further transfusion of RBC outweigh the benefits.

The authors undertook a systematic review of the literature to determine the association between red blood cell transfusion, and morbidity and mortality in high-risk hospitalized patients. Their data sources were MEDLINE, Embase, Cochrane Register of Controlled Trials, and citation review of relevant primary and review articles. They looked at cohort studies that assessed the independent effect of RBC transfusion on patient outcomes. From 571 articles screened, 45 met inclusion criteria and were included for data extraction. Forty-five studies including 272,596 were identified (the outcomes from one study were reported in four separate publications). The outcome measures were mortality, infections, multi-organ dysfunction syndrome, and acute respiratory distress syndrome. The overall risks vs. benefits of RBC transfusion on patient outcome in each study was classified as (i) risks outweigh benefits, (ii) neutral risk, and (iii) benefits outweigh risks. The odds ratio and 95% confidence interval for each outcome measure was recorded if available. The pooled odds ratios were determined using meta-analytic techniques.

Data Synthesis: Forty-five observational studies with a median number of 687 included patients (range, 63–78,974) were analyzed. In 42 of the 45 studies the risks of RBC transfusion outweighed the benefits; the risk was neutral in two studies with the benefits outweighing the risks in a subgroup of a single study (elderly patients with an acute myocardial infarction and a hematocrit <30%). Seventeen of 18 studies, demonstrated that RBC transfusions were an independent predictor of death; the pooled odds ratio (12 studies) was 1.7 (95% confidence interval, 1.41.9). Twenty-two studies examined the association between RBC transfusion and nosocomial infection; in all these studies blood transfusion was an independent risk factor for infection. The pooled odds ratio (nine studies) for developing an infectious complication was 1.8 (95% confidence interval, 1.5–2.2). RBC transfusions similarly increased the risk of developing multi-organ dysfunction syndrome (three studies) and acute respiratory distress syndrome (six studies). The pooled odds ratio for developing acute respiratory distress syndrome was 2.5 (95% confidence interval, 1.6 –3.3).

Conclusions: Despite the inherent limitations in the analysis of cohort studies, analysis suggested that in adult, intensive care unit, trauma, and surgical patients, RBC transfusions are associated with increased morbidity and mortality and therefore, current transfusion practices may require reevaluation. The risks and benefits of RBC transfusion should be assessed in every patient before transfusion.

Saurav Chatterjee, MD, et al. conducted another meta-analysis and published results in Archives of Internal Medicine in 2012 in a manuscript entitled: "Association of Blood Transfusion with Increased Mortality in Myocardial Infarction: A Meta-analysis and Diversity-Adjusted Study Sequential Analysis."

Authors conducted a systematic search of studies published between January 1, 1966, and March 31, 2012 using MEDLINE, EMBASE, CINAHL, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials databases. English-language studies comparing blood transfusion with no blood transfusion or a liberal vs. restricted blood transfusion strategy were identified. Two study

authors independently reviewed 729 originally identified titles and abstracts and selected 10 for analysis. Study title, follow-up period, blood transfusion strategy, and mortality outcomes were extracted manually from all selected studies, and the quality of each study was assessed.

Authors found that studies of blood transfusion strategy in anemia associated with myocardial infarction were abstracted, as well as all-cause mortality rates at the longest available follow-up periods for the individual studies. Pooled effect estimates were calculated with random effects models. Analyses of blood transfusion in myocardial infarction revealed increased all-cause mortality associated with a strategy of blood transfusion vs. no blood transfusion during myocardial infarction (18.2% vs. 10.2%) (risk ratio, 2.91; 95% CI, 2.46-3.44; P=.001), with a weighted absolute risk increase of 12% and a number needed to harm of 8 (95% CI, 6-17). Multivariate meta-regression revealed that blood transfusion was associated with a higher risk for mortality independent of baseline hemoglobin level, nadir hemoglobin level, and change in hemoglobin level during the hospital stay. Blood transfusion was also significantly associated with a higher risk for subsequent myocardial infarction (risk ratio, 2.04; 95% CI, 1.06-3.93; P=.03).

Authors concluded that blood transfusion or a liberal blood transfusion strategy compared with no blood transfusion or a restricted blood transfusion strategy is associated with higher all-cause mortality rates. A practice of routine or liberal blood transfusion in myocardial infarction should not be encouraged but requires investigation in a large trial with low risk for bias.

Sunil Rao, MD, et al. evaluated the "Relationship of Blood Transfusion and Clinical Outcomes in Patients with Acute Coronary Syndromes" and published their manuscript in JAMA, October 6, 2004.

Authors argued that it is unclear if blood transfusion in anemic patients with acute coronary syndromes is associated with improved survival. Their objective was to determine the association between blood transfusion and mortality

in patients with acute coronary syndromes who develop bleeding, anemia, or both, during their hospital course. Authors analyzed 24112 enrollees in 3 large international trials of patients with acute coronary syndromes (the GUSTO IIb, PURSUIT, and PARAGON B trials). Patients were grouped according to whether they received a blood transfusion during the hospitalization. The association between transfusion and outcome was assessed using the Cox-proportional hazards modeling that incorporated transfusion as a time-dependent covariate and the propensity to receive blood, and a landmark analysis. The author's main outcome measure was thirty-day mortality.

2401 (10.0%) underwent at least 1 blood transfusion during their hospitalization. Patients who underwent transfusion were older and had more comorbid illness at presentation and also had a significantly higher unadjusted rate of 30-day death (8.00% vs. 3.08%; P.001), myocardial infarction (MI) (25.16% vs. 8.16%; P.001), and death/MI (29.24% vs. 10.02%; P.001) compared with patients who did not undergo transfusion. Using Cox proportional hazards modeling that incorporated transfusion as a time-dependent covariate, transfusion was associated with an increased hazard for 30-day death (adjusted hazard ratio [HR], 3.94; 95% confidence interval [CI], 3.26-4.75) and 30-day death/MI (HR, 2.92; 95% CI, 2.55-3.35). In the landmark analysis that included procedures and bleeding events, transfusion was associated with a trend toward increased mortality. The predicted probability of 30-day death was higher with transfusion at nadir hematocrit values above 25%.

Authors concluded that blood transfusion in the setting of acute coronary syndromes is associated with higher mortality, and this relationship persists after adjustment for other predictive factors and timing of events. Given the limitations of post hoc analysis of clinical trials data, a randomized trial of transfusion strategies is warranted to resolve the disparity in results between our study and other observational studies. Authors suggest caution regarding the routine use of blood transfusion to maintain arbitrary hematocrit levels in stable patients with ischemic heart disease.

On January 28, 2013, Jeffrey Carson, MD and Paul Hebert, MD published a JAMA Internal Medicine rebuttal to the Chaterjee manuscript, entitled "Here we Go Again – Blood Transfusion Kills Patients?"

In their rebuttal, Carson and Hebert argue that clinically important information is missing from the Chaterjee analysis – chiefly, Hgb concentration before transfusion. They argue that it was impossible in this analysis to examine the risk for death at lower hemoglobin levels (7, 8, or 9 g/dL) as was done in an earlier study. The article did not clearly describe the patients in the trials so that one might try to infer the level of risk from anemia or from blood transfusions. Also, the study did not examine the effects of clinically meaningful evaluations of subgroups to explore whether risks are different in different subgroups.

Authors state that in examining blood transfusions in other settings, observational studies evaluating transfusion thresholds have not correlated with the results of clinical trials. A meta-analysis8 of 45 observational studies in 272 596 patients (Merik) evaluating transfusion found that transfusion was associated with a 70% increase in the odds of death (1.7; 95% CI, 1.4-1.9) compared with no transfusion. In contrast, the odds of death associated with liberal transfusion was not significantly increased compared with that in patients randomized to restrictive transfusion in another meta-analysis (Carson 2012) of clinical trials.

In summary Drs. Carson and Hebert conclude by arguing that high quality (clinical trial) research related to red cell blood transfusion in patients with acute coronary syndrome is long overdue.

Jeffrey Carson, MD, et al. published a Red Blood Cell Transfusion: A Clinical Practice Guideline from the AABB* for the Clinical Transfusion Medicine Committee of the AABB on March 26, 2012 in the Annals of Internal Medicine.

Although approximately 85 million units of red blood cells (RBCs) are transfused annually worldwide, transfusion practices vary widely. The AABB (formerly, the American Association of Blood Banks) developed this guideline to provide clinical

recommendations about hemoglobin concentration thresholds and other clinical variables that trigger RBC transfusions in hemo-dynamically stable adults and children.

Methods: These guidelines are based on a systematic review of randomized clinical trials evaluating transfusion thresholds. We performed a literature search from 1950 to February 2011 with no language restrictions. We examined the proportion of patients who received any RBC transfusion and the number of RBC units transfused to describe the effect of restrictive transfusion strategies on RBC use. To determine the clinical consequences of restrictive transfusion strategies, we examined overall mortality, nonfatal myocardial infarction, cardiac events, pulmonary edema, stroke, thromboembolism, renal failure, infection, hemorrhage, mental confusion, functional recovery, and length of hospital stay.

Recommendation 1: The AABB recommends adhering to a restrictive transfusion strategy (7 to 8 g/dL) in hospitalized, stable patients (Grade: strong recommendation; high-quality evidence).

Recommendation 2: The AABB suggests adhering to a restrictive strategy in hospitalized patients with preexisting cardiovascular disease and considering transfusion for patients with symptoms or a hemoglobin level of 8 g/dL or less (Grade: weak recommendation; moderate-quality evidence).

Recommendation 3: The AABB cannot recommend for or against a liberal or restrictive transfusion threshold for hospitalized, hemo-dynamically stable patients with the acute coronary syndrome (Grade: uncertain recommendation; very low-quality evidence).

Recommendation 4: The AABB suggests that transfusion decisions be influenced by symptoms as well as hemoglobin concentration (Grade: weak recommendation; low-quality evidence).