

The silent risks of blood transfusion

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Purpose of review

Clinical research has identified blood transfusion as an independent risk factor for immediate and long-term adverse outcomes, including an increased risk of death, myocardial infarction, stroke, renal failure, infection and malignancy. New findings have called into question the traditional assumptions clinicians utilize in evaluating the risks and benefits of blood transfusion. Appreciation of newly recognized risks is important for conserving scarce resources and optimizing patient outcomes.

Recent findings

Recent clinical outcomes research has examined the impact of blood transfusion on critically ill patients, trauma patients, patients undergoing cardiac surgery, patients experiencing acute coronary syndromes, oncology patients and others. These studies provide additional evidence of adverse outcomes associated with blood transfusion in a wide variety of clinical contexts.

Summary

The benefits of blood transfusion have never been conclusively demonstrated, but evidence of transfusion-related harm continues to accumulate. Given the transfusion triggers that currently predominate in clinical practice it appears that clinical outcomes could improve significantly with more widespread adoption of restrictive transfusion strategies.

Keywords

blood transfusion, cardiac surgery, clinical outcomes, interventional cardiology

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Introduction

Following dramatic decreases in the incidence of infectious disease transmission and ABO mismatch-related reactions, red blood cell (RBC) transfusion was generally considered to carry minimal risks while providing the unquestioned benefit of improving outcomes by increasing tissue oxygen delivery. Over the past two decades, these assumptions have been challenged by clinical research linking transfusion to previously unappreciated adverse outcomes. Blood transfusion has been linked to organ dysfunction, immunosuppression (increasing vulnerability to infection and malignancy) and decreased survival in a variety of clinical contexts. Recent studies have strengthened the link between transfusion and these unintended consequences, and basic research has also suggested potential mechanisms for these effects. Practice guidelines are beginning to reflect this new evidence.

Commonly emphasized risks of blood transfusion

Historically, the most significant risks of blood transfusion were felt to be infectious disease transmission and ABO mismatch hemolytic reactions. More recently, transfusion-related acute lung injury (TRALI) has been identified

as a significant risk. Infectious complications of blood transfusion have decreased but not disappeared. Although risks vary by region, the risk of transmitting HIV or hepatitis C is roughly 1 in 2 million units transfused; hepatitis B is estimated to be transmitted between 1 and 200 times for every million units of blood transfused. In the USA, West Nile virus (WNV) contaminates 1 in 350 000 units transfused. The risk of death from sepsis related to blood contaminated by bacteria is roughly 1 per million units transfused. Although of less concern in North America and Europe, parasitic diseases including malaria and Chagas disease can pose a significant risk in endemic areas [1,2]. If our experience with HIV and WNV repeats itself, it is possible that newly discovered blood-borne pathogens could pose significant risks before effective screening methods are developed. Fatal ABO mismatch reactions occur with roughly the same frequency as viral transmission and TRALI may occur in 1 in 5000 transmissions.

Impact of blood transfusion on clinical outcomes: the Transfusion Requirements in Critical Care trial

Despite 100 years of experience with blood transfusion, studies attempting to understand its impact on clinical

outcomes are comparatively recent. The landmark Transfusion Requirements in Critical Care (TRICC) trial, published in 1999, is the only large (838 patients) prospective randomized trial that supports a causal link between blood transfusion and adverse outcomes in critically ill adults. When patients were randomized to liberal (transfusion threshold of hemoglobin <10 g/dl) or restrictive (transfusion threshold <7 g/dl) groups there was a significant increase in cardiac and pulmonary complications and a trend towards increased mortality in the liberal transfusion group. When younger (<55) or less critically ill [acute physiology and chronic health enquiry (APACHE) score <20] patients were considered, there was a statistically significant increase in mortality in patients who were more liberally transfused [3]. A recent randomized trial in critically ill children using a design similar to the TRICC trial found that patients randomized to liberal and restrictive transfusion strategies experienced similar outcomes [4*].

Transfusion in critical care and trauma patients

In addition to the TRICC trial, there have been many retrospective analyses in a variety of clinical contexts that link blood transfusion to adverse outcomes. The Anemia and Blood Transfusion in the Critically Ill – Current Clinical Practice in the United States (CRIT) study evaluated 4892 ICU patients and found that the number of blood transfusions was independently associated with length of stay and mortality [5]. A recent cohort analysis within the CRIT trial found an independent association of blood transfusion and the development of acute respiratory distress syndrome (ARDS) (adjusted odds ratios 2.74, $P < 0.0001$) [6*]. Yilmaz *et al.* [7] found that a lung protective ventilatory strategy coupled with a restrictive transfusion strategy reduced the incidence of acute lung injury from 28 to 10%. In the critically ill, recent studies have confirmed that blood transfusion is associated with an increased incidence of infection, decreased survival and increased length of stay in adults [8,9*] and in children [10,11].

Data prospectively collected on 15 534 trauma patients at Maryland Shock Trauma Center revealed that blood transfusion was independently associated with a three-fold increase in mortality [12]. A recent study of 8215 blunt trauma patients adds support to a dose–response relationship between transfusion and mortality [13].

Transfusion and malignancy

Recent studies have strengthened the association between blood transfusion and vulnerability to malignancy. Transfusions given within 5–29 years prior to initial cancer diagnosis were found to be associated with

a 26% increase in the risk of developing nonHodgkin's lymphoma [14]. Patients who received blood during hepatocellular carcinoma resection were found to have a 5-year cancer-related survival rate of 38% versus 67% in patients who avoided transfusion [15].

Transfusion in cardiac surgery

High blood product utilization, significant morbidity and mortality, and large existing clinical outcomes databases have made cardiac surgery patients a natural target of studies attempting to determine the impact of transfusion on outcomes. Studies in these patients have identified RBC transfusion as an independent variable associated with an increase in infectious complications, myocardial infarction (MI), stroke, renal failure, prolonged ventilation, atrial fibrillation, hospital length of stay and mortality [16,17,18*]. Although the immediate impact on survival is significantly greater, transfusion with as little as one unit of RBCs has been associated with decreased 10-year survival following coronary artery bypass grafting [19]. Recent studies have added to the weight of this evidence. Murphy *et al.* [20**], in reviewing outcomes in 8724 patients in the UK, found no benefit from transfusion for hematocrits as low as 21% (hemoglobin of 7 g/dl), and the risk of death within 30 days of surgery was almost six times greater for patients who received blood. In addition, transfused patients were more likely to experience increased infections and adverse outcomes characterized as ischemic complications (MI, renal compromise and stroke) [20**].

Recent studies attempting to explain adverse outcomes for women in cardiac surgery have shown that the decreased survival experienced by women can be explained by their propensity to receive blood transfusions; women have a smaller body surface area (and increased vulnerability to hemodilution when undergoing cardiopulmonary bypass) and a lower baseline hematocrit [21,22]. A recent report of 6000 coronary artery bypass patients demonstrated that inclusion of preoperative anemia and blood transfusion data into the Society of Thoracic Surgeons (STS) risk model eliminated female gender as a risk factor [23].

Transfusion for patients with acute coronary syndromes and myocardial infarction

The historic rationale for blood transfusion includes the purported benefit of improved oxygen delivery. The TRICC trial investigators raised concern about the applicability of restrictive transfusion triggers in patients with acute coronary syndromes. A subsequent subgroup analysis of patients with cardiovascular disease showed a trend towards increased survival in the liberal transfusion group, but transfusion also resulted in a statistically

significant increase in pulmonary edema and multiorgan system dysfunction [24]. Wu *et al.* [25] published an analysis based on Medicare administrative data that showed an improvement in survival for patients over 65 years treated for acute MI if they received blood transfusions when their admission hematocrit was less than 30. Subsequent studies based on prospectively collected data and more sophisticated statistical analysis suggested blood transfusion was a risk factor for death and MI in patients with acute coronary syndromes [26]. Rao *et al.* [27] found this association to be significant for patients who received blood for hematocrits more than 25%. Singla *et al.* [28] reported on 370 patients in the VA system who presented with anemia (hemoglobin <11.5 g/dl) and a suspected acute coronary syndrome. After risk adjustment, the risk of MI or death was increased by a factor of 2.5 in patients who received blood [28]. Jani *et al.* [29] reported on 4623 anemic patients undergoing a percutaneous coronary intervention 1 week following a MI. Men with a preprocedure hemoglobin less than 13 g/dl and women with a preprocedure hemoglobin less than 12 g/dl were classified as anemic. After propensity matching and multiple regression analysis, transfused patients were roughly two times more likely to die in hospital [29].

The impact of anemia on clinical outcomes

Anemia has been associated with increased morbidity and mortality in a wide variety of clinical contexts including MI [30], heart failure [31], and cardiac [32] as well as noncardiac surgery [33]. The CRIT study, in contrast, found that anemia predicted the risk that a patient would be transfused but did not predict any other significant outcomes. A study by the Northern New England Cardiovascular Disease Study Group initially stimulated an increase in blood transfusion throughout the region when it was reported that the lowest hematocrit on bypass was correlated with increased mortality and postoperative heart failure [34]. Subsequent analysis suggested that though anemia is a marker for poor outcomes, the tendency for anemic patients to be transfused explains much of the association; moreover, blood transfusions were associated with postoperative requirements for mechanical and inotropic support independent of the degree of anemia [35]. Aronson *et al.* [36•] found that nadir hemoglobin in hospitalized patients following MI predicted increased mortality. After risk adjustment, anemic patients who received blood were 50% more likely to die within the follow-up period (6–48 months) than anemic patients who avoided transfusion [36•]. Kulier *et al.* [37••] collected 7500 data points on 5065 patients undergoing coronary artery bypass grafting in an attempt to determine the impact of preoperative anemia on postoperative adverse events. Investigators found that low preoperative hemoglobin was a signifi-

cant marker for severe underlying comorbidities [e.g. diabetes, renal failure, hypertension, current smoking, unstable angina and congestive heart failure (CHF)]. Adverse cardiac events were attributed to these concomitant risk factors, and adverse postoperative neurologic and renal outcomes were attributed directly to anemia. Multiple regression analysis showed that preoperative anemia and intraoperative blood transfusion were both independent risk factors for adverse outcomes. At the same hemoglobin level, the incidence of adverse outcomes increased significantly as a function of numbers of units of RBCs transfused [37••].

Efficacy of blood transfusion as therapy for anemia

Available evidence not only suggests that anemia predicts adverse outcomes but also suggests that correction of anemia by transfusion using current transfusion practices either provides no benefit or is harmful. Attempts to determine the significance of anemia therefore demands inclusion of transfusion as a risk factor. Murphy *et al.* [20••] found that ischemic complications (MI, neurologic and renal injury) were not decreased with blood transfusion irrespective of the patient's nadir hematocrit or comorbidities. The lack of benefit from blood transfusions in decreasing these complications might be explained because hemoglobin levels rarely limit oxygen delivery given the transfusion triggers that predominate in current clinical practice [38]. Possible mechanisms for the contribution of transfusion to ischemic complications include pro-inflammatory effects and storage defects. Stored RBCs are 2,3-diphosphoglycerate (DPG) deficient and consequently less adept at unloading oxygen. It has also been proposed that loss of nitric oxide activity in banked blood impairs the vasodilatory response to hypoxia [39], though the clinical significance of these findings is controversial [40]. Stored RBCs are also less deformable, possibly leading to sludging and capillary occlusion. If stored RBCs have greater affinity for oxygen and capillary flow is impaired, blood transfusion could increase mixed venous oxygen saturation while decreasing tissue oxygen delivery [41•].

Clinical data supporting a role for storage defects as a contributor to adverse outcomes appeared recently. Having previously contributed significantly to the evidence implicating blood transfusion as a risk factor for adverse outcomes following cardiac surgery, Koch *et al.* [42•] at the Cleveland Clinic retrospectively evaluated the impact of differences in RBC storage duration. Patients who received blood that was stored for more than 2 weeks prior to transfusion had a statistically significant increase in in-hospital mortality, prolonged intubation, renal failure and sepsis or septicemia [42•].

Current guidelines

In an effort to conserve a limited and expensive resource and minimize the injury caused by transfusion therapy, the STS and the Society of Cardiovascular Anesthesiologists have joined forces and recently produced a clinical practice guideline. Their guidelines emphasize that the benefits of transfusion have not been adequately demonstrated and that existing evidence is an imperfect guide to transfusion decisions. They suggest a transfusion trigger of hemoglobin less than 7 g/dl in postoperative cardiac surgery patients (class IIa recommendation). In addition, they suggest (class IIb recommendation) that it is 'not unreasonable to transfuse red cells in certain patients with critical noncardiac end-organ ischemia (e.g. central nervous system and gut) whose hemoglobin levels are as high as 10 g/dl, but more evidence to support this recommendation is required' [43^{••}]. Given the growing evidence of an association between transfusion and ischemic outcomes, this last recommendation appears to be poorly supported by current data.

Citing Rao *et al.* [27] the Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology issued guidelines recommending transfusing all patients with non-ST-segment elevation acute coronary syndromes (NSTEMI/ACS) with hematocrits less than 25% [44]. Rao *et al.* [27] were able to show an association with adverse outcomes when patients were transfused for a hematocrit more than 25%, but there was no indication that transfusion for a hematocrit less than 25% was beneficial.

Conclusion

The historic assumptions that blood transfusion consistently provides effective therapy for anemia and poses minimal risks to patients has been called into question by two decades of accumulating clinical evidence. The primarily retrospective studies summarized here will always be vulnerable to the criticism that these associations between blood transfusion and adverse outcomes reflect the tendency of clinicians to transfuse patients who are sicker than estimated by current risk adjustment measures or that important confounders have been missed. In addition, mechanisms by which transfused blood appears to cause harm are still unclear. In the aggregate, however, these studies increase the probability that blood transfusion is an important contributor to morbidity and mortality. If the links between blood transfusion and previously underappreciated adverse outcomes are causal, the true risks of blood transfusion increase by orders of magnitude. The benefits of blood transfusion have never been conclusively demonstrated, but evidence of transfusion-related harm continues to accumulate. Given the transfusion triggers that currently

predominate in clinical practice, it appears that clinical outcomes could improve significantly with more widespread adoption of restrictive transfusion strategies. Current transfusion guidelines are changing in an effort to incorporate new data emphasizing the previously silent risks of blood transfusion.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 691–692).

- 1 Bihl F, Castelli D, Marincola F, *et al.* Transfusion-transmitted infections. *J Translational Med* 2007; 5:25.
- 2 Despotis G, Eby C, Lublin DM. A review of transfusion risks and optimal management of perioperative bleeding with cardiac surgery. *Transfusion* 2008; 48:2S–30S.
- 3 Hebert PC, Wells G, Blajchman MA, *et al.* A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; 340:409–417.
- 4 Lacroix J, Hébert PC, Hutchison JS, *et al.* Transfusion strategies for patients in
 - pediatric intensive care units. *N Engl J Med* 2007; 365:1609–1619.
 The present randomized controlled trial in critically ill children demonstrated no difference in outcomes between restrictive and liberal transfusion strategies.
- 5 Corwin HL, Gettinger A, Pearl RG, *et al.* The CRIT Study: anemia and blood transfusion in the critically ill – current clinical practice in the United States. *Crit Care Med* 2004; 32:290–291.
- 6 Zilberberg MD, Carter C, Lefebvre P, *et al.* Red blood cell transfusions and the
 - risk of acute respiratory distress syndrome among the critically ill: a cohort study. *Crit Care* 2007; 11:R63.
 A cohort study of the CRIT trial.
- 7 Yilmaz M, Keegan MT, Iscimen R, *et al.* Toward the prevention of acute lung injury: protocol-guided limitation of large tidal volume ventilation and inappropriate transfusion. *Crit Care Med* 2007; 35:1660–1666.
- 8 Taylor RW, O'Brien J, Trotter SJ, *et al.* Red blood cell transfusions and nosocomial infections in critically ill patients. *Crit Care Med* 2006; 34:2302–2308.
- 9 Zilberberg MD, Stern LS, Wiederkehr DP, *et al.* Anemia, transfusions and
 - hospital outcomes among critically ill patients on prolonged acute mechanical ventilation: a retrospective cohort study. *Crit Care* 2008; 12:R60.
 The study included 4344 critically ill patients. Transfusion was independently associated with a 21% increase in the risk for in-hospital death.
- 10 Kneyber MC, Hersi MI, Twisk JW, *et al.* Red blood cell transfusion in critically ill children is independently associated with increased mortality. *Intensive Care Med* 2007; 33:1414–1422.
- 11 Jeschke MG, Chinkes DL, Finnerty CC, *et al.* Blood transfusions are associated with increased risk for development of sepsis in severely burned pediatric patients. *Crit Care Med* 2007; 35:579–583.
- 12 Malone DL, Dunne J, Tracy JK, *et al.* Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. *J Trauma* 2003; 54:898–905.
- 13 Charles A, Shaikh AA, Walters M, *et al.* Blood transfusion is an independent predictor of mortality after blunt trauma. *Am Surg* 2007; 73:1–5.
- 14 Cerhan JR, Engels EA, Cozen W, *et al.* Blood transfusion, anesthesia, surgery and risk of non-Hodgkin lymphoma in a population-based case-control study. *Int J Cancer* 2008; 123:888–894.
- 15 Sugita S, Sasaki A, Iwaki K, *et al.* Prognosis and postoperative lymphocyte count in patients with hepatocellular carcinoma who received intraoperative allogenic blood transfusion: a retrospective study. *Eur J Surg Oncol* 2008; 34:339–345.
- 16 Engoren MC, Habib RH, Zacharias A, *et al.* Effect of blood transfusion on long-term survival after cardiac operation. *Ann Thorac Surg* 2002; 74:1180–1186.
- 17 Koch CG, Liang L, Duncan AI, *et al.* Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. *Crit Care Med* 2006; 34:1608–1616.

- 18 Ngaage DL, Cowen ME, Griffin S, *et al*. Early neurological complications after coronary artery bypass grafting and valve surgery in octogenarians. *Eur J Cardiothorac Surg* 2008; 33:653–659.
- A review of 6791 heart surgery patients over 80 years of age showed an independent association between neurologic complications and blood transfusion (odds ratio 3.6).
- 19 Koch CG, Li L, Duncan AI, *et al*. Transfusion in coronary artery bypass grafting is associated with reduced long-term survival. *Ann Thorac Surg* 2006; 81:1650–1657.
- 20 Murphy G, Reeves BC, Rogers CA, *et al*. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation* 2007; 116:2544–2552.
- The present study analyzed outcomes in 8724 cardiac surgery patients and found decreased survival, increased infection and stroke, MI and renal function associated with blood transfusion independent of pretransfusion hematocrit.
- 21 Ranucci M, Pazzaglia A, Bianchini C, *et al*. Body size, gender, and transfusions as determinants of outcome after coronary operations. *Ann Thorac Surg* 2008; 85:481–487.
- 22 Rogers MAM, Blumberg N, Heal JM, Hicks G. Increased risk of infection and mortality in women after cardiac surgery related to allogeneic blood transfusion. *J Women's Health* 2007; 16:1412–1420.
- 23 Nwakanma LU, Alejo DA, Yuh DD, *et al*. Prevalence and impact of preoperative anemia and red blood cell transfusion in women: twelve-year experience in 6000 isolated coronary artery bypass surgeries. Abstract presented at the 2008 annual meeting of the Society of Thoracic Surgeons. Baltimore, Maryland: Johns Hopkins Medical Institutions.
- 24 Hébert PC, Yetisir E, Martin C, *et al*. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? *Crit Care Med* 2001; 29:227–234.
- 25 Wu WC, Rathore SS, Wang Y, *et al*. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001; 345:1230–1236.
- 26 Yang X, Alexander KP, Chen AY, *et al*. The implications of blood transfusions for patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE National Quality Improvement Initiative. *J Am Coll Cardiol* 2005; 46:1490–1495.
- 27 Rao SV, Jollis JG, Harrington RA, *et al*. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA* 2004; 292:1555–1562.
- 28 Singla I, Zahid M, Good CB, *et al*. Impact of blood transfusions in patients presenting with anemia and suspected acute coronary syndrome. *Am J Cardiol* 2007; 99:1119–1121.
- 29 Jani SM, Smith DE, Share D, *et al*. Blood transfusion and in-hospital outcomes in anemic patients with myocardial infarction undergoing percutaneous coronary intervention. *Clin Cardiol* 2007; 30 (Suppl II):II-49–II-56.
- 30 Lipsic E, Van der Horst IC, Voors AA, *et al*. Hemoglobin levels and 30-day mortality in patients after myocardial infarction. *Int J Cardiol* 2005; 100:289–292.
- 31 O'Meara E, Clayton T, McEntegart MB, *et al*. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) Program. *Circulation* 2006; 113:986–994.
- 32 Karkouti K, Wijeyesundera DN, Beattie WS. Risk associated with preoperative anemia in cardiac surgery a multicenter cohort study. *Circulation* 2008; 117:478–484.
- 33 Wu WC, Schifftner T, Henderson WG, *et al*. Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. *JAMA* 2007; 297:2481–2488.
- 34 Defoe GR, Ross CS, Olmstead EA, *et al*. Lowest hematocrit on bypass and adverse outcomes associated with coronary artery bypass grafting. *Ann Thorac Surg* 2001; 71:769–776.
- 35 Surgenor SD, DeFoe GR, Fillingner MP, *et al*. Intraoperative red blood cell transfusion during coronary artery bypass graft surgery increases the risk of postoperative low-output heart failure. *Circulation* 2006; 114:143–148.
- 36 Aronson D, Suleiman M, Agmon Y, *et al*. Changes in haemoglobin levels during hospital course and long-term outcome after acute myocardial infarction. *Eur Heart J* 2007; 28:1289–1296.
- Development of anemia following MI predicts increased mortality. Blood transfusion in anemic patients additionally increases mortality.
- 37 Kulier A, Levin J, Moser R, *et al*. Impact of preoperative anemia on outcome in patients undergoing coronary artery bypass graft surgery. *Circulation* 2007; 116:471–479.
- The study identifies comorbidities associated with anemia that predict poor outcomes in addition to identifying anemia and blood transfusion as independent predictors of postoperative adverse events.
- 38 Mathru M, Kleinman B, Blakeman B, *et al*. Myocardial metabolism and adaptation during extreme hemodilution in humans after coronary revascularization. *Crit Care Med* 1992; 20:1420–1425.
- 39 Reynolds JD, Ahearn GS, Angelo M, *et al*. S-nitrosohemoglobin deficiency: a mechanism for loss of physiological activity in banked blood. *Proc Natl Acad Sci U S A* 2007; 104:17058–17062.
- 40 Winslow RM, Intaglietta M. Red cell age and loss of function: advance or SNO-job? *Transfusion* 2008; 48:411–414.
- 41 Spiess BD. Red cell transfusions and guidelines: a work in progress. *Hematol/Oncol Clin North Am* 2007; 21:185–200.
- The review discusses oxygen delivery by transfused RBCs and reviews outcomes data.
- 42 Koch CG, Li L, Sessler DI, *et al*. Duration of red-cell storage and complications after cardiac surgery. *N Engl J Med* 2008; 358:1229–1239.
- The study links adverse outcomes with the age of transfused blood.
- 43 The Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Ferraris VA, Ferraris SP, Saha SP, Hessel EA 2nd, Haan CK, Royston BD, Bridges CR, Higgins RS, Despotis G, Brown JR; Society of Cardiovascular Anesthesiologists Special Task Force on Blood Transfusion, Spiess BD, Shore-Lesserson L, Stafford-Smith M, Mazer CD, Bennett-Guerrero E, Hill SE, Body S. Perioperative blood transfusion and blood conservation in cardiac surgery: The Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists Clinical Practice Guideline. *Ann Thorac Surg* 2007; 83:S27–S86.
- A thoughtful and detailed analysis.
- 44 The Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 2007; 28:1598–1660.