Red Blood Cell Transfusion Trigger in Cardiac Surgery

5

Gavin J. Murphy, Nishith N. Patel, and Jonathan A.C. Sterne

Abstract

In cardiac surgery, the principal aim of red blood cell transfusion is to maintain oxygen delivery and prevent tissue hypoxia in the setting of acute anaemia and severe bleeding. Both these clinical indications are common, and over 50 % of all cardiac surgery patients receive red blood cell transfusion, utilising a significant proportion of blood service resources in developed countries. Severe anaemia accounts for the vast majority of all red blood cells used; however, there is uncertainty as to what constitutes a safe level of anaemia or a trigger for transfusion. There is also uncertainty as to the risks and benefits of transfusion; experimental and early clinical studies suggest that transfusion may promote organ injury. Existing blood management guidelines recommend restrictive transfusion practice, and this is supported by observational analyses in cardiac surgery patients showing strong associations between transfusion and adverse outcome. However, these studies fail to address the important clinical question as to what constitutes the anaemia threshold where transfusion is indicated. They are also beset my multiple sources of bias that confound analysis and contribute to

G.J. Murphy (✉)
Department of Cardiovascular Sciences, University of Leicester, Clinical Sciences Wing, Glenfield General Hospital, Leicester LE3 9QP, UK
e-mail: gjm19@le.ac.uk

N.N. Patel
Academic Cardiac Surgery Group, National Heart and Lung Institute, Imperial College London, Hammersmith Hospital, DuCane Road, London W12 0NN, UK
e-mail: nishith.patel@imperial.ac.uk

J.A.C. Sterne
School of Social and Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol BS8 2PS, UK
e-mail: jonathan.sterne@bristol.ac.uk

N.P. Juffermans, T.S. Walsh (eds.), *Transfusion in the Intensive Care Unit*,
DOI 10.1007/978-3-319-08735-1_5

inflated estimates of risk. RCTs in non-cardiac surgery patients do not demonstrate harm from more restrictive thresholds (lower haematocrits) and suggest that this is the best practice. These studies do not reflect the lack of cardiovascular reserve in cardiac surgery patients, however, that is often compounded by the abnormal oxygen utilisation that follows cardiopulmonary bypass. Meta-analyses of RCTs in cardiac surgery appear to support a benefit for more liberal thresholds. These analyses are dominated however by a single large study, the Transfusion Indication Threshold Reduction (TITRe 2) trial, that demonstrated a benefit from a more liberal transfusion threshold of 9 g/dL. We conclude therefore that in the absence of high-quality evidence to the contrary, cardiac surgery patients may be considered a specific high-risk group where restrictive transfusion practice will promote harm.

5.1 Introduction

The aim of perioperative red blood cell (RBC) transfusion in cardiac surgery is to improve or preserve oxygen delivery in the setting of blood loss and anaemia, with the intention of preventing oxygen supply dependency and organ injury. Cardiac surgery is characterised by a high prevalence of anaemia. Perioperative anaemia, defined arbitrarily as a haemoglobin concentration <12 g/dL, is common, affecting over 75 % of patients [1, 2]. It occurs as a consequence of low preoperative red blood cell mass; haemodilution during surgery, including the use of crystalloid prime; perioperative blood loss; and decreased haematopoiesis as a consequence of chronic disease or as a result of a perioperative inflammatory state [1, 2]. Red blood cell transfusion is the preferred and most rapid treatment for acute anaemia in this setting. Cardiac surgery is also characterised by a high prevalence of coagulopathy and severe bleeding [3, 4]. Red blood cell transfusion in the setting of severe blood loss and incipient haemorrhagic shock is clearly lifesaving. Studies in trauma indicate that massive red blood cell transfusion in isolation may not adequately treat bleeding patients however and suggest that these should be accompanied by high ratios of non-red blood cell to red blood cell components if best outcomes are to be achieved. This has not been demonstrated thus far in cardiac surgery. Red blood cell transfusion rates in clinical studies, typically in the range of 45–95 % [5, 6], far outstrip estimates of coagulopathic or severe bleeding, estimated in up to 15 % of patients, depending on the definition used [3, 7]. Although it has not been clearly demonstrated, this suggests that the greater proportion of all red blood cells transfused are for the treatment of anaemia.

5.1.1 Consequences of Anaemia During Cardiac Surgery

Anaemia is associated with an increased risk of developing low cardiac output, acute kidney injury, and death in cardiac surgery [1, 2, 8, 9]. However, there is uncertainty as to the anaemia threshold below which tissues develop hypoxia and injury. Observational studies have demonstrated increased neurological and renal injury once haematocrits fall below 24 % [8, 9]. Oxygen supply and utilisation are

different in cardiac surgery as compared to other patient groups. This is because these patients often demonstrate impaired autoregulation and tissue hypoxia during cardiopulmonary bypass (CPB) that is attributed to non-pulsatile blood flow in the setting of microvascular dysfunction, as commonly observed in patients with diabetes, hypertension and those with severe peripheral vascular disease. Cardiac surgery patients also commonly demonstrate oxygen supply dependency postoperatively despite apparently adequate oxygen delivery [10], probably due in part to systemic inflammation and mitochondrial dysfunction that occurs as a consequence of CPB. It should also be remembered that cardiac surgery patients at the outset are at the limits of their cardiovascular reserve; the principal indication for cardiac surgery is *symptomatic* cardiac disease [11, 12]. Safe levels of anaemia may therefore change with time and be patient specific, and higher levels of haemoglobin may be required to prevent oxygen supply dependency in this population. This raises the question as to whether it is possible to define a universal anaemia threshold below which tissue hypoxia is likely or, as is reflected in contemporary transfusion guidelines, a patient-specific threshold is required [13, 14].

5.1.2 Consequences of Red Blood Cell Transfusion in Cardiac Surgery

There is also uncertainty as to the potential harms from red blood cell transfusion. Experimental studies have demonstrated that red blood cell transfusion promotes lung, myocardial, and renal inflammation by the activation of platelet and leucocytes [15, 16]. This has been attributed to the 'storage lesion' whereby the accumulation of harmful and pro-inflammatory substances in the storage supernatant and deterioration in erythrocyte structure and function are thought to result in posttransfusion inflammation and organ injury in recipients [16]. Clinical studies support these observations; Koch and colleagues in a study of 6,001 patients at the Cleveland Clinic demonstrated that transfusion of older blood, stored for >14 days, was associated with an increase in pulmonary, renal, and cardiac complications compared to transfusion of blood stored for <14 days [17]. In a randomised crossover trial, Weiskopf and colleagues demonstrated that transfusion of older red blood cells to healthy recipients resulted in altered lung function, although in these subjects, there was only a very modest effect of transfusion on conventional inflammatory markers [18].

5.1.3 Practice of Red Blood Cell Transfusion in Cardiac Surgery

Uncertainty as to the risks and benefits of anaemia and red blood cell transfusion is reflected by wide variations in red blood cell transfusion rates, ranging from 25 to 75 % between cardiac centres in the UK [5] and 8–93 % in the USA [6]. This variation represents a potentially modifiable source of morbidity and perhaps mortality. Variation in practice also has significant resource issues; cardiac surgery utilises 5 % of all red blood cells in the UK [19] and up to 25 % in the USA [20]. Incipient

blood shortages, due to the effects of demographic shifts on the supply and demand of blood, mandate more appropriate use of this precious resource [21]. Variation in clinical practice arises due to the lack of high-quality evidence. Systematic reviews of the available evidence have increasingly advocated more restrictive practice; i.e. the toleration of lower levels of anaemia and less frequent transfusion [22]. Restrictive practice is also increasingly reflected in contemporary blood management guidelines [13, 14] as well as in health policy [23, 24]. Here we consider the strengths and limitations of the available evidence that is used to guide transfusion decisions in cardiac surgery.

5.2 Observational Studies on Red Blood Cell Transfusion in Cardiac Surgery

Observational studies uniformly demonstrate strong associations between red blood cell transfusion and low cardiac output, acute kidney injury, pulmonary injury, sepsis, increased use of healthcare resources, and death (Fig. 5.1 and associated references). The principal limitation of these studies is that they do not attempt to establish a safe level of anaemia below which transfusion may be beneficial, i.e. the

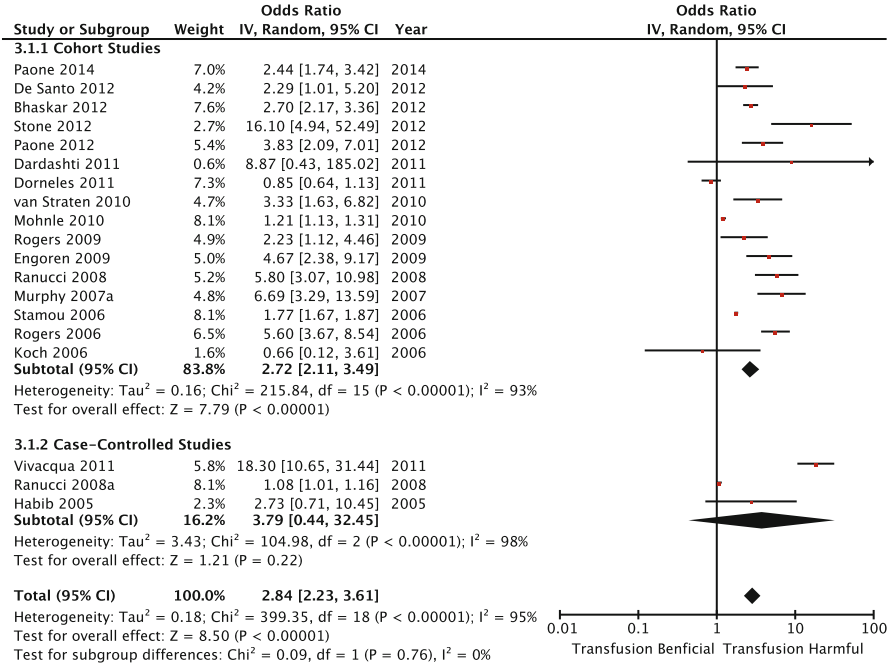

Fig. 5.1 Forest plot of the odds of mortality for transfusion versus no transfusion from observational studies. Individual references are available on request

principal clinical question they seek to address. Rather these trials compare transfusion with no transfusion. It follows that the estimated effects of transfusion from these studies are likely to have been subject to unmeasured confounding, because they included in the transfusion group patients who became so severely ill during surgery that they could never have remained transfusion-free. For example, almost none of these studies attempted to adjust for bleeding and the severity of perioperative anaemia, the two principal indications for red blood cell transfusion, which are also risk factors for adverse outcome. This also leads to lead time bias; these studies do not attempt to adjust for adverse events that are likely to have preceded transfusion. This is compounded when transfusion is considered as a categorical variable, as is the case in many of these studies. This assumes homogeneity in the transfused population. It is reasonable to suggest however that patients who receive massive transfusions will have a poor outcome due in part to other possibly unmeasured variables that precede transfusion, but by grouping these patients with those receiving single-unit transfusions, the estimates of the association between transfusion and adverse outcomes are both confounded and inflated. Studies that have attempted to consider the effects of anaemia, as distinct from transfusion, suffer from similar limitations. Overall, the observational studies published thus far lack the methodological rigour required to demonstrate a causal association between either anaemia or transfusion and adverse outcome. More importantly, they offer little evidence to support transfusion decisions in the setting of anaemia. This is best demonstrated by randomised controlled trials (RCTs).

5.3 Randomised Controlled Trials on Red Blood Cell Transfusion in Non-Cardiac Surgery Patients

A recent Cochrane review summarised the results of published RCTs that have attempted to determine safe levels of anaemia or appropriate transfusion threshold across a range of clinical settings [25]. These RCTs, commonly referred to as 'trigger trials', determine whether patient allocation to a more liberal transfusion threshold, based usually on a higher blood haematocrit or haemoglobin concentration, results in a different clinical outcome to a more restrictive or lower transfusion threshold. Thus, both groups are exposed to transfusion albeit at different frequencies and also to different levels of anaemia. In this respect, they differ from observational studies in that they do not attempt to define the risks of transfusion or anaemia in isolation and reflect the absolute interdependence of these two factors. This is pragmatic, there is no ethical basis upon which transfusion could be completely withheld from one group of patients, and they reflect the almost universal use of haemoglobin/haematocrit measurements to guide red blood cell transfusion decisions. These trials are limited in that they assume a universal anaemia threshold that is applicable to all patients and cannot inform individual treatment decisions, although this is commonplace in clinical practice and a criticism of all RCTs. Many of these trials also have design limitations that significantly increase the risk of bias. Firstly, most are underpowered to detect differences in important clinical endpoints such as

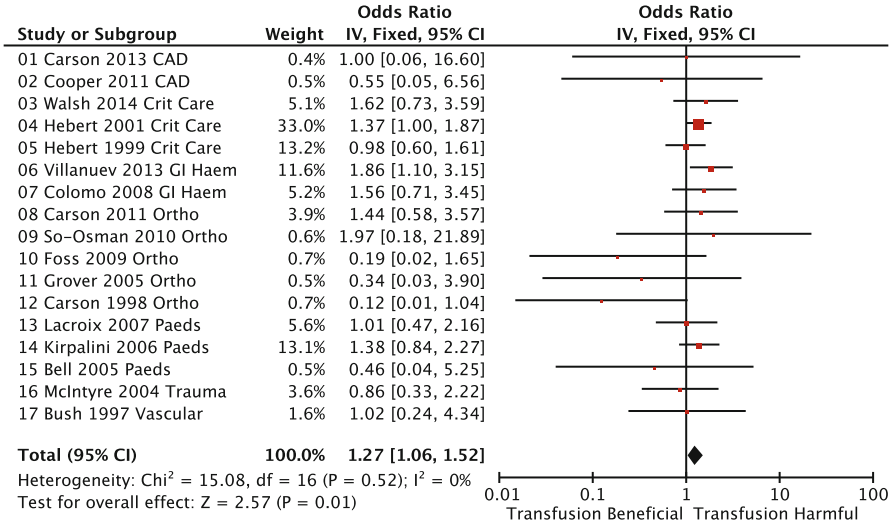

Fig. 5.2 Forest plot of the odds of mortality for restrictive transfusion versus liberal transfusion from non-cardiac surgery RCTs. Individual studies are as labelled in reference [25]

death. Secondly, randomised trials commonly recruit selected groups of relatively low-risk patients who have low frequencies of the adverse outcomes the intervention is intended to influence. Thirdly, by randomising all consented patients, many of whom never develop severe anaemia, they result in large proportions of patients in either group who never require transfusion. Finally, few of these studies report compliance to allocated transfusion thresholds, a potential source of procedural bias. These sources of bias tend to move the effect estimate of the intervention towards the null. Quantitative meta-analyses of the outcomes from these trials do not overcome all of these limitations. They are also limited in that they assume that the patient groups will be homogeneous, with a similar balance of risks and benefits over a wide range of restrictive and liberal transfusion thresholds in different clinical settings. Perhaps unsurprisingly, these meta-analyses show no apparent difference between restrictive and liberal transfusion strategies (Fig. 5.2). That is not to say that these findings must be discounted. They are supported by the findings of a recent large high-quality RCT in high-risk patients. The Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) trial compared liberal and restrictive transfusion thresholds in 2016 hip fracture patients, of whom 63 % had a history of cardiovascular disease. This trial only randomised patients with haemoglobin levels <10 g/dL and carefully documented non-adherence to the study protocol (8 %). The FOCUS trial reported no difference in a range of clinical outcomes, including death or major morbidity. Thus, best evidence suggests that restrictive transfusion is not harmful in non-cardiac surgery patients. Moreover, in the absence of harm, restrictive practice should be adopted; there is no clinical indication to provide a therapy that has no benefit but a considerable cost, as concluded by the Cochrane review [22, 25]. Importantly however, the patients in the

FOCUS and other trials did not have symptomatic cardiac disease and did not undergo surgery with cardiopulmonary bypass. Transfusion decisions in cardiac surgery are best informed by trials conducted in cardiac surgery patients.

5.4 Randomised Trials on Red Blood Cell Transfusion in Cardiac Surgery Patients

Six RCTs [26–31] have thus far compared liberal with restrictive transfusion practices in patients undergoing cardiac surgery in a total of 3,356 patients (Fig. 5.3). These trials demonstrate many of the limitations observed in non-cardiac surgery RCTs. In particular, all but 1 of these trials, the Transfusion Indication Threshold Reduction (TITRe 2) trial, did not select only those who required transfusion, i.e. those that developed predefined level of anaemia prior to randomisation. TITRe 2 was also the only trial adequately powered to demonstrate differences in important clinical outcomes. Meta-analysis of these trials is dominated by this and another trial, the single-centre Transfusion Requirements After Cardiac Surgery (TRACS) trial [20]. The TRACS trial randomised 502 patients to restrictive and liberal transfusion thresholds. However, all consented patients were randomised in this study, reducing the ability of the trial to detect a treatment effect; 22 % in the liberal group did not receive any transfusion despite a liberal trigger which was higher than in most other trials (haematocrit 30 %). In the TRACS trial, there was no difference between the groups with respect to death or major morbidity. The TITRe 2 trial was a multicentre trial in 16 UK cardiac centres that recruited 3,565 patients of whom 2007 breached the threshold of 9 g/dL and were randomised to either a restrictive threshold of 7.5 g/dL or a liberal threshold of 9 g/dL. Fifty-three percent of patients were transfused in the restrictive group, and 92 % were transfused in the liberal group. Non-adherence was closely monitored and was similar to that observed in the FOCUS trial (8 %). There was no difference between the two groups in terms of the primary outcome, a composite of any infectious or ischaemic complication. However, sensitivity analyses that included acute kidney

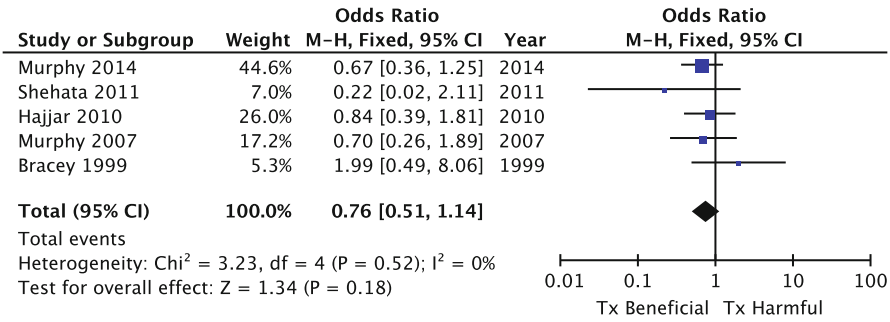

Fig. 5.3 Forest plot of the odds of mortality for restrictive transfusion versus liberal transfusion from cardiac surgery RCTs (Data extracted from references [26–31])

injury as objectively determined by serial creatinine measurements in the primary outcome did demonstrate increased risk of harm in the restrictive group (odds ratio for infectious or ischaemic morbidity = 1.20, 95 % confidence intervals (CI) 1.00–1.44, $p = 0.045$). This finding was supported by an analysis of secondary outcomes including death, which was increased in the restrictive group (4.2 % versus 2.6 %; hazard ratio = 1.64, 95 % CI 1.00–2.67, $p = 0.045$). Quantitative meta-analysis of all the trials that have compared liberal with restrictive transfusions in cardiac surgery also indicates a benefit from more liberal transfusion thresholds (Fig. 5.3), with, importantly, a reduced risk of death from liberal transfusion (OR = 0.76, 95 % CI 0.51–1.14). The cardiac surgery trials used different thresholds, and there is insufficient evidence from these trials to recommend a specific anaemia threshold. The TITRe 2 trial suggested that a threshold of 9 g/dL may be appropriate. Interestingly, subgroup analysis did not detect any interaction between the effect estimate and a range of risk factors including poor left ventricular function, diabetes, and age greater than 75 years, factors commonly used to influence transfusion decisions.

5.5 Summary and Conclusions

Contemporary blood management guidelines, and increasingly health policy, advocate restrictive transfusion practice, with the caveat that thresholds should be increased in high-risk patients. The use of restrictive thresholds is supported by the findings of observational studies and RCTs in non-cardiac surgery patients. These studies are not adequate to inform transfusion decisions in cardiac surgery however. Existing observational studies in cardiac surgery patients lack the methodological rigour to determine safe levels of anaemia, and the findings of RCTs in non-cardiac surgery patients fail to address the specific nature of the patients presenting for cardiac surgery, principally the existence of symptomatic disease, and the altered oxygen utilisation characteristic of CPB. RCTs in cardiac surgery have until recently suffered from significant limitations making interpretation difficult. However, the recent TITRe 2 trial, which has randomised significantly more patients than all the previous cardiac surgery RCTs combined, indicates that restrictive transfusion practice may not be safe in this highly specific clinical setting, and this is supported by quantitative meta-analysis of this and other cardiac surgery 'trigger' trials. Moreover, other risk factors that are often considered to influence transfusion requirements such as age and co-morbidity did not influence this result, further supporting a hypothesis that these patients exist at the limits of the oxygen supply/utilisation balance. Here we suggest that cardiac surgery therefore represents a specific high-risk group where restrictive practice is not safe. This hypothesis will be tested by the Transfusion Requirements in Cardiac Surgery III (TRACS III) trial (NCT02042898). TRACS III is an international multicentre RCT comparing liberal with restrictive thresholds that started recruiting in January 2014. This trial will enrol 3,592 patients, more than all previous trials combined that is powered to detect differences in death and major morbidity. However, until the results of this trial are presented, expected in 2018, the available evidence suggests that more liberal transfusion thresholds of a haemoglobin of 9 g/dL be adopted in cardiac surgery.

References

1. Karkouti K, Wijeysundera DN, Beattie WS. Risk associated with preoperative anemia in cardiac surgery: a multicenter cohort study. Circulation. 2008;117:478–84.
2. Kulier A, Levin J, Moser R, Rumpold-Seitlinger G, Tudor IC, Snyder-Ramos SA, Moehnle P, Mangano DT, Investigators of the Multicenter Study of Perioperative Ischemia Research Group; Ischemia Research and Education Foundation. Impact of preoperative anemia on outcome in patients undergoing coronary artery bypass graft surgery. Circulation. 2007; 116:471–9.
3. Unsworth-White MJ, Herriot A, Valencia O, Poloniecki J, Smith EE, Murday AJ, Parker DJ, Treasure T. Resternotomy for bleeding after cardiac operation: a marker for increased morbidity and mortality. Ann Thorac Surg. 1995;59:664–7.
4. Moulton MJ, Creswell LL, Mackey ME, Cox JL, Rosenbloom M. Reexploration for bleeding is a risk factor for adverse outcomes after cardiac operations. J Thorac Cardiovasc Surg. 1996;111:1037–46.
5. Bennett-Guerrero E, Zhao Y, O'Brien SM, Ferguson Jr TB, Peterson ED, Gammie JS, Song HK. Variation in use of blood transfusion in coronary artery bypass graft surgery. JAMA. 2010;304(14):1568–75.
6. Murphy MF, Murphy GJ, Gill R, Herbertson M, Allard S, Grant-Casey J. 2011 audit of blood transfusion in adult cardiac surgery. NHS Blood & Transplant. Available from: http://hospital.blood.co.uk/library/pdf/2011_Use_of_Blood_in_Adult_Cardiac_Surgery_report.pdf. Accessed 25 Aug 2014.
7. Karkouti K, Wijeysundera DN, Yau TM, Beattie WS, Abdelnaem E, McCluskey SA, Ghannam M, Yeo E, Djaiani G, Karski J. The independent association of massive blood loss with mortality in cardiac surgery. Transfusion. 2004;44:1453–62.
8. Ranucci M, Conti D, Castelvecchio S, Menicanti L, Frigiola A, Ballotta A, Pelissero G. Hematocrit on cardiopulmonary bypass and outcome after coronary surgery in nontransfused patients. Ann Thorac Surg. 2010;89:11–7.
9. Habib RH, Zacharias A, Schwann TA, Riordan CJ, Engoren M, Durham SJ, et al. Role of hemodilutional anemia and transfusion during cardiopulmonary bypass in renal injury after coronary revascularization: implications on operative outcome. Crit Care Med. 2005; 33:1749–56.
10. Utoh J, Moriyama S, Okamoto K, Kunitomo R, Hara M, Kitamura N. The effects of cardiopulmonary bypass on postoperative oxygen metabolism. Surg Today. 1999;29:28–33.
11. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI), Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Eur Heart J. 2010;31(20):2501–55.
12. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC), European Association for Cardio-Thoracic Surgery (EACTS), Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J. 2012;33(19):2451–96.
13. Ferraris VA, Brown JR, Despotis GJ, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg. 2011;91(3):944–82.
14. Carson JL, Grossman BJ, Kleinman S, Tinmouth AT, Marques MB, Fung MK, Holcomb JB, Illoh O, Kaplan LJ, Katz LM, Rao SV, Roback JD, Shander A, Tobian AA, Weinstein R, Swinton McLaughlin LG, Djulbegovic B, Clinical Transfusion Medicine Committee of the AABB. Red blood cell transfusion: a clinical practice guideline from the AABB*. Ann Intern Med. 2012;157(1):49–58.
15. Patel NN, Lin H, Jones C, Walkden G, Ray P, Sleeman PA, Angelini GD, Murphy GJ. Interactions of cardiopulmonary bypass and erythrocyte transfusion in the pathogenesis of pulmonary dysfunction in swine. Anesthesiology. 2013;119:365–78.
16. Tinmouth A, et al. Clinical consequences of red cell storage in the critically ill. Transfusion. 2006;46(11):2014–27.

17. Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, Blackstone EH. Duration of red-cell storage and complications after cardiac surgery. N Engl J Med. 2008; 358:1229–39.
18. Weiskopf RB, Feiner J, Toy P, Twiford J, Shimabukuro D, Lieberman J, Looney MR, Lowell CA, Gropper MA. Fresh and stored red blood cell transfusion equivalently induce subclinical pulmonary gas exchange deficit in normal humans. Anesth Analg. 2012;114(3):511–9.
19. Wells AW, Llewelyn CA, Casbard A, Johnson AJ, Amin M, Ballard S, Buck J, Malfroy M, Murphy MF, Williamson LM. The EASTER Study: indications for transfusion and estimates of transfusion recipient numbers in hospitals supplied by the National Blood Service. Transfus Med. 2009;19(6):315–28.
20. US Department of Health and Human Services. The 2007 nationwide blood collection and utilization survey report. Washington, DC: Dept of Health and Human Services; 2007.
21. Greinacher A, Fendrich K, Brzenska R, Kiefel V, Hoffmann W. Implications of demographics on future blood supply: a population-based cross-sectional study. Transfusion. 2011; 51(4):702–9.
22. Carson JL, Carless PA, Hébert PC. Outcomes using lower vs higher hemoglobin thresholds for red blood cell transfusion. JAMA. 2013;309(1):83–4.
23. Farmer SL, Towler SC, Leahy MF, Hofmann A. Drivers for change: Western Australia Patient Blood Management Program (WA PBMP), World Health Assembly (WHA) and Advisory Committee on Blood Safety and Availability (ACBSA). Best Pract Res Clin Anaesthesiol. 2013;27(1):43–58.
24. World Health Organization. Global forum for blood safety: patient blood management: priorities for action. Dubai; 2011. Available from: URL: http://www.who.int/bloodsafety/events/gfbs_01_pbm/en/index.html. Cited 20 Jul 2013.
25. Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2012;4:CD002042.
26. Shehata N, Burns LA, Nathan H, et al. A randomized controlled pilot study of adherence to transfusion strategies in cardiac surgery. Transfusion. 2012;52(1):91–9.
27. Murphy GJ, Rizvi SI, Battaglia F, et al. A pilot randomized controlled trial of the effect of transfusion- threshold reduction on transfusion rates and morbidity after cardiac surgery. Transfus Altern Transfus Med. 2007;9 Suppl 1:41–2.
28. Slight RD, Fung AK, Alonzi C, Bappu NJ, McClelland DB, Mankad PS. Rationalizing blood transfusion in cardiac surgery: preliminary findings with a red cell volume-based model. Vox Sang. 2007;92(2):154–6.
29. Bracey AW, Radovancevic R, Riggs SA, et al. Lowering the hemoglobin threshold for transfusion in coronary artery bypass procedures: effect on patient outcome. Transfusion. 1999;39(10):1070–7.
30. Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. JAMA. 2010;304(14):1559–67.
31. Brierley R, et al. A multi-centre randomised controlled trial of Transfusion Indication Threshold Reduction on transfusion rates, morbidity and healthcare resource use following cardiac surgery: Study protocol. Transfus Apher Sci. 2014;50(3):451–61.