Revisiting blood transfusion and predictors of outcome in cardiac surgery patients: a concise perspective [version 1; peer review: 2 approved]

Carlos E Arias-Morales¹, Nicoleta Stoica¹, Alicia A Gonzalez-Zacarias¹, Diana Slawski², Sujatha P. Bhandary², Theodosios Saranteas³, Eva Kaminiotis³, Thomas J Papadimos²

¹Department of Anesthesiology, The Ohio State University Wexner Medical Center, Columbus, OH, USA
²College of Medicine and Life Sciences, The University of Toledo, Toledo, OH, USA
³Second Department of Anesthesiology, School of Medicine, University of Athens, Athens, Greece

Abstract
In the United States, cardiac surgery-related blood transfusion rates reached new highs in 2010, with 34% of patients receiving blood products. Patients undergoing both complex (coronary artery bypass grafting [CABG] plus valve repair or replacement) and non-complex (isolated CABG) cardiac surgeries are likely to have comorbidities such as anemia. Furthermore, the majority of patients undergoing isolated CABG have a history of myocardial infarction. These characteristics may increase the risk of complications and blood transfusion requirement. It becomes difficult to demonstrate the association between transfusions and mortality because of the fact that most patients undergoing cardiac surgery are also critically ill. Transfusion rates remain high despite the advances in perioperative blood conservation, such as the intraoperative use of cell saver in cardiac surgery. Some recent prospective studies have suggested that the use of blood products, even in low-risk patients, may adversely affect clinical outcomes. In light of this information, we reviewed the literature to assess the clinical outcomes in terms of 30-day and 1-year morbidity and mortality in transfused patients who underwent uncomplicated CABG surgery.

Keywords
blood transfusion, cardiopulmonary bypass, cardiac surgery, length of stay, mortality
Corresponding author: Nicoleta Stoica (nicoleta.stoicea@osumc.edu)

Competing interests: The authors declare that they have no competing interests.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2017 Arias-Morales CE et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Arias-Morales CE, Stoica N, Gonzalez-Zacarias AA et al. Revisiting blood transfusion and predictors of outcome in cardiac surgery patients: a concise perspective [version 1; peer review: 2 approved] F1000Research 2017, 6(F1000 Faculty Rev):168 https://doi.org/10.12688/f1000research.10085.1

First published: 20 Feb 2017, 6(F1000 Faculty Rev):168 https://doi.org/10.12688/f1000research.10085.1
Introduction
According to the National Blood Collection & Utilization Survey (NBCUS), blood transfusion rates, with the exception of platelet transfusions, decreased between 2008 and 2011. Specifically, there was an 8.2% decrease in red blood cell (RBC) transfusions as well as a 13.4% decrease in plasma transfusions. In the United States, however, cardiac surgery-related blood transfusion reached new highs in 2010, with 34% of patients receiving blood products. Cardiac surgeries generate the greatest need for blood transfusion, followed by orthopedic surgeries. Transfusion is often necessary in cardiac procedures to correct coagulopathy, blood loss, and hemodilution from pump priming. Furthermore, patients undergoing cardiac surgeries are likely to have comorbidities such as anemia and history of myocardial infarction (MI), thereby increasing the risk of complications and blood transfusion requirements. It is important to note that the majority of cardiac surgery patients who are transfused and show a high morbidity and mortality receive approximately two units of blood. These patients are likely being treated for anemia and are otherwise hemodynamically stable. However, patients in the high-risk subset, based on the European System for Cardiac Operative Risk Evaluation (EuroSCORE) >8, consumed blood products owing to hemorrhagic complications. In light of this information, we reviewed the literature to assess the 30-day and 1-year morbidity and mortality outcomes in transfused patients who underwent complicated and uncomplicated coronary artery bypass grafting (CABG) surgery as the absence of postoperative complications by the Society of Thoracic Surgeons (STS).

Blood transfusion in critically ill patients
Anemia is a common complication in critically ill patients. According to the World Health Organization (WHO), anemia is defined as a hemoglobin level of less than 13 g/dL in men and 12 g/dL in women. There is a complex relationship between RBC transfusions and clinical outcome in critically ill patients. The increased mortality seen in transfused patients might be attributed to a complex illness and might not be related to blood transfusion per se. Statistical measures controlling for mortality risk factors such as preoperative hematocrit, age, or comorbidities allow for presumably unbiased comparison between transfused and non-transfused groups.

Kulier et al. describe the problematic paradox faced by clinicians treating anemic patients undergoing CABG surgery. While the authors did not dispute that transfusion may be associated with a variety of complications previously reported in the literature, the authors’ own investigation found a significant correlation between preoperative anemia and renal and central nervous system outcomes as well as in-hospital mortality. Increased cardiac adverse events were attributed to an interaction between preoperative anemia and other comorbidities. Thus, there is a paradox: should anemic patients, especially those with compromised compensatory cardiovascular mechanisms, be preoperatively transfused with RBCs, thus incurring one set of possible complications, or should these patients be transfused only during or after surgery as needed, risking the occurrence of another set of adverse events? Effort should always be made to correct anemia without transfusion prior to cardiac surgery, even in patients able to compensate for their anemia with increased stroke volumes; however, a consensus on when hemoglobin levels indicate preoperative transfusion has yet to be firmly established.

Generally, 95% of patients admitted to the intensive care unit (ICU) for more than 3 days develop anemia, resulting in multiple blood product transfusions. It is estimated that 50% of these admitted ICU patients receive RBC transfusions during their stay. Furthermore, the proportion of patients transfused increases by 30% when the ICU length of stay (LOS) exceeds 7 days. These patients receive a mean of 9.5 units of blood products, and it is estimated that two-thirds of these transfusions are not related to acute blood loss.

Postoperative anemia is common after CABG surgery and is associated with a compromised cardiovascular outcome. The STS recommended a strict transfusion protocol for cardiac surgery patients with hemoglobin levels below 7 g/dL, with RBC transfusions being reasonable and lifesaving if the patient exhibits hemodynamic instability.

Transfusion of RBCs has been recognized as a risk factor for adverse outcomes in cardiac surgery and related to patient characteristics such as left ventricular ejection fraction (LVEF) <35%, age >70, preoperative hemoglobin <11 g/dL, insulin-dependent diabetes, emergency surgeries, female gender, impaired renal function (creatinine >1.6 mg/dL), and re-operation. Pattakos et al. studied the outcome of patients undergoing cardiac surgery who refused transfusions owing to religious beliefs. The authors included 322 Jehovah’s Witness patients and 87,453 non-Jehovah’s Witness patients. They concluded that patients who refused transfusion had fewer acute complications and shorter length of stay, better 1-year survival, and similar 20-year survival when compared to transfused patients.

A retrospective study published by Dejam et al. demonstrated that RBC transfusion improved outcomes in some patients and worsened the clinical course in patients with particular comorbidities, such as cirrhosis, congestive heart failure, diabetes, sepsis, respiratory disease, solid cancer, and hematologic cancer. However, considering that patients undergoing cardiac surgery are often critically ill, it may be difficult to establish the causation between transfusions and mortality.

Blood transfusion in uncomplicated cardiac patients
Few studies have recorded the effects of blood transfusions in anemic and non-anemic patients who are otherwise stable. A retrospective study carried out by the Cleveland Clinic found that non-anemic patients (hematocrit >25% during bypass) who received intraoperative blood transfusion for CPB surgery experienced longer ventilator support times, LOS, and decreased long-term survival when compared to non-anemic patients or untreated anemia patients. Blood transfusion in CABG patients with low- to moderate-risk profiles (EuroSCORE <8), postoperative hemoglobin >10 g/dL, minimal postoperative blood loss, and no preoperative morbidities within 24 hours of surgery posed a greater risk for postoperative cardiac events and infections when compared to those who did not receive any blood transfusion.
Shaw et al.24 retrospectively compared the effects of blood transfusion in a cohort stratified according to hematocrit values. The researchers recovered preoperative hematocrit data from transfused and non-transfused cardiac surgery patients. The authors reported a significantly higher 30-day mortality rate for the transfused group when compared with the non-transfused group. These results aligned with the existing evidence of increased mortality in transfused patients8,24-26. Studies of blood transfusion in uncomplicated cardiac surgery allow a more objective evaluation of postoperative outcomes8,9,23,24,27 and indicate that stable transfused patients do not receive a benefit from this practice in terms of LOS, 30-day morbidity, and 1-year mortality24,27,28.

A retrospective study published by Schwann et al. examined the association between transfusions and mortality among 6,947 patients who underwent CABG. The overall RBC transfusion rate was 33.9%. Postoperative complications were reported in 35.2% of the patients, specifically in patients who received RBC transfusion when compared with the uncomplicated group. The group reporting complications included older females with previous comorbidities. At 30-day and 5-year follow-up survival, the incidence of death was higher in transfused versus non-transfused patients. RBC transfusion increased the risk of long-term cardiac and non-cardiac mortality after CABG30.

**Blood transfusion in complicated cardiac patients**

Blood transfusion is a common practice in complicated patients undergoing CABG surgery. Cardiac patients require higher rates of transfusions than do non-cardiac patients30. Complicated patients generally present with advanced heart disease, co-existing diabetes mellitus, end-stage renal disease, or liver dysfunction, postoperative complications yielding a greater LOS and higher mortality rates31.

Cardiogenic shock (CS) is the primary cause of hospital death after acute MI (AMI). Operative mortality of patients who undergo CABG in the setting of AMI-CS ranges from 20% in isolated CABG to 33% in CABG plus valve surgery, reaching 58% in CABG plus ventricular septal repair32. Similarly, Acharya et al.33 evaluated outcomes of 5,496 patients with AMI-CS undergoing non-elective CABG from 2005 to 2013. The authors found an intraoperative mortality of 18.1% for patients who received intraoperative blood products (65.2%) in 2013 when compared to 19.3% in 2005 (p<0.001)33.

Gundling et al. conducted an 8-year retrospective study and concluded that the necessity of blood product administration was increased in patients with liver cirrhosis undergoing cardiac surgery; the 30-day mortality rate was higher and long-term survival rate lower when compared to patients without liver cirrhosis34.

Furthermore, recent reports have indicated worse outcomes when transfusion is due to preoperative anemia or blood dyscrasias35,36. In 2014, Engoren et al. evaluated late mortality in 922 patients who underwent isolated CABG during a 3.5-year period. They found that patients with preoperative anemia who received intraoperative transfusion had an increased rate of death compared with those without anemia and transfusion35. Similarly, Paone et al. concluded that most of the patients who died postoperatively received blood transfusions and presented a prolonged and complicated postoperative evolution. Additionally, patients diagnosed with immune thrombocytopenia (ITP) undergoing CABG surgery may require corticosteroid treatment before surgery in order to decrease intraoperative and postoperative bleeding. Jubelirer et al. reviewed cases of patients with ITP who underwent CABG. From 51 patients, 21 received platelet transfusion and 27 received RBCs intraoperatively. CABG was successfully performed in these patients without the need of preoperative splenectomy or prolongation of hospital stay36.

Perioperative risk factors might affect the length of ICU stay. Generally, older cardiac surgery patients have longer ICU stays because of their existing comorbidities. Azafarin et al. determined in a cross-sectional study that cigarette smoking, opioid addiction, preoperative ejection fraction of ≤40%, and intraoperative blood transfusion are predictors for prolonged ICU stay and a higher rate of complications37.

Paone et al. used the predicted risk of mortality measures to confirm the hypothesis that preoperative profile played a more dominant role when considering mortality and transfusion rates in patients undergoing cardiac surgery3. Likewise, other studies have reported weak or no associations between transfusion and mortality38,39. Koster et al.30 in a single-center retrospective study demonstrated no association between the transfusion of one to two units of leucocyte-depleted RBCs and 30-day mortality in CABG patients. Haanschoten et al. found that patients with a baseline hemoglobin of ≥11.3 g/dL who underwent isolated CABG surgery without the availability of RBCs in the operating room presented a decrease in complications and LOS40.

Shander also commented on the lack of temporality as a major weakness in this area of research and stated that cause and effect cannot be confirmed based on retrospective studies with unknown blood transfusion time and onset of complications3. Though certain complications may arise quickly following transfusion, other adverse events may develop in the hours, days, and weeks after blood-product administration, making definitive causation more difficult. While in the former case close temporality provides evidence that transfusion was the impetus for the complication, adverse events which occur days or more after transfusion has concluded may be caused by the transfusion, surgical insult or drug administration, patient comorbidity, or antagonism of several factors. Moreover, transfusion threshold recommendations, despite the evidence-based guidelines, remain an indefinite parameter for blood transfusion; therefore, physicians must carefully deliberate the benefits and potential adverse effects when deciding to transfuse3.

**Conclusion**

The relationship between transfusion and clinical outcomes in cardiac patients undergoing complicated and uncomplicated CABG remains poorly understood, suggesting a complex interaction among various patient characteristics, demographics, type of procedure, patients’ preoperative status, and the preferences of surgeons and anesthesiologists and may not be the result of transfusions per se. The increased mortality in transfused patients may
or may not be triggered by transfusion itself but rather the out-
come of transfusion in a more complex perioperative experience.
To better elucidate if and to what degree transfusion plays a role
in patient complications following coronary procedures, prospec-
tive studies controlling for patient demographics and comorbid-
ities, surgical and anesthesia parameters, and transfusion thresh-
olds are needed. With other previously implicated factors excluded
or controlled for, a more definitive consensus on transfusion as a
causative factor for specific adverse events, which is lacking in the
currently published literature, may be possible regardless of tem-
porality. If transfusion is established as an independent factor for
complications, then interactions with other comorbidities and pa-
ient and surgical factors should be explored to identify those
transfusion patients at highest risk for complication.

Competing interests
The authors declare that they have no competing interests.

Grant information
The author(s) declared that no grants were involved in supporting
this work.

References

1. US Department of Health and Human Services: The 2011 national blood
collection and utilization survey report. Washington, DC: US Department
of Health and Human Services, Office of the Assistant Secretary for Health.
2011; 15. Reference Source

2. Robich MP, Koch CG, Johnston DR, et al.: Trends in blood utilization in United
States cardiac surgical patients. Transfusion. 2015; 55(4): 806–14.
Published Abstract | Publisher Full Text

3. Geissler RG, Rotering H, Buddendorf H, et al.: Utilisation of blood components in
cardiac surgery: a single-centre retrospective analysis with regard to
diagnosis-related procedures. Transfus Med Hemother. 2015; 42(2): 75–82.
Published Abstract | Publisher Full Text | Free Full Text

4. Stoica N, Bergese SD, Ackerman W, et al.: Current status of blood transfusion
and antifibrinolytic therapy in orthopedic surgeries. Front Surg. 2015; 2: 3.
Published Abstract | Publisher Full Text | Free Full Text

5. Koch CG: Tolerating anemia: taking aim at the right target before pulling the
transfusion trigger. Transfusion. 2014; 54(10 Pt 2): 2595–7.
Published Abstract | Publisher Full Text

6. Ad N, Massimiano PS, Burton NA, et al.: Effect of patient age on blood
product transfusion after cardiac surgery. J Thorac Cardiovasc Surg. 2015;
150(1): 209–14. Published Abstract | Publisher Full Text | F1000 Recommendation

7. Paone G, Likosky DS, Brewer R, et al.: Transfusion of 1 and 2 units of red
cells is associated with increased morbidity and mortality. Ann Thorac Surg.
2014; 97(1): 87–93; discussion 93–4. Published Abstract | Publisher Full Text | F1000 Recommendation

8. Paone G, Herbert MA, Theurer PF, et al.: Red blood cells and mortality after
Coronary artery bypass graft surgery: an analysis of 672 operative deaths. Ann
Thorac Surg. 2015; 99(5): 1583–9; discussion 1589–90. Published Abstract | Publisher Full Text | F1000 Recommendation

9. Shander A, Goodough LT: Can blood transfusion be not only ineffective, but
also injurious? Ann Thorac Surg. 2014; 97(1): 11–4. Published Abstract | Publisher Full Text

10. Vincent JL, Baron JF, Reinhart K, et al.: Anemia and blood transfusion in critically
ill patients. JAMA. 2002; 288(12): 1489–507. Published Abstract | Publisher Full Text

11. Ania BJ, Suman VJ, Fairbanks VF, et al.: Incidence of anemia in older people: an
epidemiologic study in a well defined population. J Am Geriatr Soc. 1997; 45(7):
825–31. Published Abstract | Publisher Full Text

12. Dejam A, Malley BE, Feng M, et al.: The effect of age and clinical
circumstances on the outcome of red blood cell transfusion in critically ill
patients. Crit Care. 2014; 18(4): 487. Published Abstract | Publisher Full Text | F1000 Recommendation

13. Kuler A, Levin J, Moser R, et al.: Impact of preoperative anemia on outcome in
patients undergoing coronary artery bypass graft surgery. Circulation. 2007;
116(5): 471–9. Published Abstract | Publisher Full Text | F1000 Recommendation

14. Rodriguez RM, Corwin HL, Gettinger A, et al.: Nutritional deficiencies and
blunted erythropoietin response as causes of the anemia of critical illness.
J Crit Care. 2001; 16(1): 36–41. Published Abstract | Publisher Full Text

15. Corwin HL, Parsonnet KC, Gettinger A: RBC transfusion in the ICU. Is there a
reason? Chest. 1996; 108(3): 767–71. Published Abstract | Publisher Full Text

16. Littenberg B, Corwin H, Gettinger A, et al.: A practice guideline and decision aid
for blood transfusion. Immunohematology. 1995; 11(3): 88–94. Published Abstract

17. Lako A, Bliti S, Memojshi S, et al.: The impact of blood use on patients
undergoing coronary artery bypass surgery: a prospective study. G Chir. 2014;
35(1–2): 20–6. Published Abstract | Publisher Full Text | Published Full Text | F1000 Recommendation

18. Westenbrink BD, Kleijn L, de Boer RA, et al.: Sustained postoperative anemia
is associated with an impaired outcome after coronary artery bypass graft surgery:
signs from the IMAGINE trial. Heart. 2011; 97(19): 1590–6. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

19. Patel NN, Avlonitis VS, Jones HE, et al.: Indications for red blood cell
transfusion in cardiac surgery: a systematic review and meta-analysis. Lancet
Haematol. 2015; 2(12): e543–50. Published Abstract | Publisher Full Text | F1000 Recommendation

20. Murphy GJ, Reeves BC, Rogers CA, et al.: Increased mortality, postoperative
morbidty, and cost after red blood cell transfusion in patients having cardiac
surgery. Circulation. 2007; 116(22): 2544–52. Published Abstract | Publisher Full Text | F1000 Recommendation

21. Litmanie J, Boeken U, Feindt P, et al.: Predictors of homologous blood
transfusion for patients undergoing open heart surgery. Thorac Cardiovasc
Surg. 2003; 51(1): 17–21. Published Abstract | Publisher Full Text

22. Pattakos G, Koch CG, Brizio ME, et al.: Outcome of patients who refuse
transfusion after cardiac surgery: a natural experiment with severe blood
conservation. Arch Intern Med. 2012; 172(15): 1154–60. Published Full Text | Publisher Full Text | F1000 Recommendation

23. Loor G, Li L, Sabib JK, et al.: Nadir hematocrit during cardiopulmonary bypass:
ed-end organ dysfunction and mortality. J Thorac Cardiovasc Surg. 2012;
144(3): 654–662.e4. Published Abstract | Publisher Full Text | F1000 Recommendation

24. Shaw RE, Johnson CK, Ferrari G, et al.: Impact of preoperative anemia on outcome
in uncomplicated cardiac surgery patients. Eur J Cardiothorac Surg. 2011;
39(3): 621–6. Published Abstract | Publisher Full Text | Free Full Text

25. Kuduvalli M, Oo AY, Newall N, et al.: Effect of peri-operative red blood cell
transfusion on 30-day and 1-year mortality following coronary artery bypass
surgery. Eur J Cardiothorac Surg. 2005; 27(4): 592–8. Published Abstract | Publisher Full Text

26. Engoren MC, Habib RH, Zacharias A, et al.: Effect of blood transfusion on long-
term survival after cardiac operation. Ann Thorac Surg. 2002; 74(4): 1180–6. Published Abstract | Publisher Full Text

27. Moehrle P, Snyder-Ramos SA, Miao Y, et al.: Postoperative red blood cell
transfusion and morbidity outcome in uncomplicated cardiac surgery patients.
Intensive Care Med. 2011; 37(1): 97–109. Published Abstract | Publisher Full Text

28. Loor G, Rajeewaraj J, Li L, et al.: The least of 3 evils: exposure to red blood cell
transfusion, anemia, or both? J Thorac Cardiovasc Surg. 2013; 146(6):
1480–1487.e7. Published Abstract | Publisher Full Text | Free Full Text

29. Schwamm TA, Habib JR, Khalifeh JM, et al.: Effects of Blood Transfusion on
Cause-Specific Late Mortality After Coronary Artery Bypass Grafting-Less Is
More. Ann Thorac Surg. 2016; 102(2): 465–73. Published Abstract | Publisher Full Text | F1000 Recommendation
30. Du Pont-Thibodeau G, Harrington K, Lacroix J. Anemia and red blood cell transfusion in critically ill cardiac patients. Ann Intensive Care. 2014; 4: 16. PubMed Abstract | Publisher Full Text | Free Full Text

31. Azarfarin R, Ashouri N, Totonchi Z, et al.: Factors influencing prolonged ICU stay after open heart surgery. Res Cardiovasc Med. 2014; 3(4): e20159. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

32. Mehta RH, Grab JD, O'Brien SM, et al.: Clinical characteristics and in-hospital outcomes of patients with cardiogenic shock undergoing coronary artery bypass surgery: insights from the Society of Thoracic Surgeons National Cardiac Database. Circulation. 2008; 117(7): 876–85. PubMed Abstract | Publisher Full Text | F1000 Recommendation

33. Acharya D, Gulack BC, Loyaga-Rendon RY, et al.: Clinical Characteristics and Outcomes of Patients With Myocardial Infarction and Cardiogenic Shock Undergoing Coronary Artery Bypass Surgery: Data From The Society of Thoracic Surgeons National Database. Ann Thorac Surg. 2016; 101(2): 558–66. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

34. Gundling F, Seid H, Gansera L, et al.: Early and late outcomes of cardiac operations in patients with cirrhosis: a retrospective survival-rate analysis of 47 patients over 8 years. Eur J Gastroenterol Hepatol. 2010; 22(12): 1466–73. PubMed Abstract

35. Engoren M, Scherran TA, Habib RH, et al.: The independent effects of anemia and transfusion on mortality after coronary artery bypass. Ann Thorac Surg. 2014; 97(2): 514–20. PubMed Abstract | Publisher Full Text | F1000 Recommendation

36. Jubeliner SJ, Mousa L, Reddy U, et al.: Coronary artery bypass grafting (CABG) in patients with immune thrombocytopenia (ITP): a community hospital experience and review of the literature. W V Med J. 2011; 107(6): 10–4. PubMed Abstract

37. Engoren M, Arslanian-Engoren C. Long-term survival in the intensive care unit after erythrocyte blood transfusion. Am J Crit Care. 2009; 18(2): 124–31; quiz 132. PubMed Abstract | Publisher Full Text

38. Vamvakas EC, Carven JH: RBC transfusion and postoperative length of stay in the hospital or the intensive care unit among patients undergoing coronary artery bypass graft surgery: the effects of confounding factors. Transfusion. 2000; 40(8): 832–9. PubMed Abstract | Publisher Full Text

39. Koster A, Zittermann A, Borgemann J, et al.: Transfusion of 1 and 2 units of red blood cells does not increase mortality and organ failure in patients undergoing isolated coronary artery bypass grafting. Eur J Cardiothorac Surg. 2016; 49(3): 931–6. PubMed Abstract | Publisher Full Text | F1000 Recommendation

40. Haanschoten MC, van Straten AH, Verstappen F, et al.: Reducing the immediate availability of red blood cells in cardiac surgery, a single-centre experience. Neth Heart J. 2015; 23(1): 28–32. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

41. Ferraris VA: Blood transfusion in cardiac surgery: who should get transfused? Lancet Haematol. 2015; 2(12): e510–1. PubMed Abstract | Publisher Full Text
Open Peer Review

Current Peer Review Status: ✔ ✔

Editorial Note on the Review Process

Faculty Reviews are review articles written by the prestigious Members of Faculty Opinions. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

1. Nina A Guzzetta
   Department of Anesthesiology, Emory University School of Medicine, Atlanta, USA
   Competing Interests: No competing interests were disclosed.

2. Fausto Biancari
   Department of Surgery, Oulu University Hospital, Oulu, Finland
   Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

• Your article is published within days, with no editorial bias
• You can publish traditional articles, null/negative results, case reports, data notes and more
• The peer review process is transparent and collaborative
• Your article is indexed in PubMed after passing peer review
• Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com