Blood transfusion in cardiac surgery: Primum non nocere

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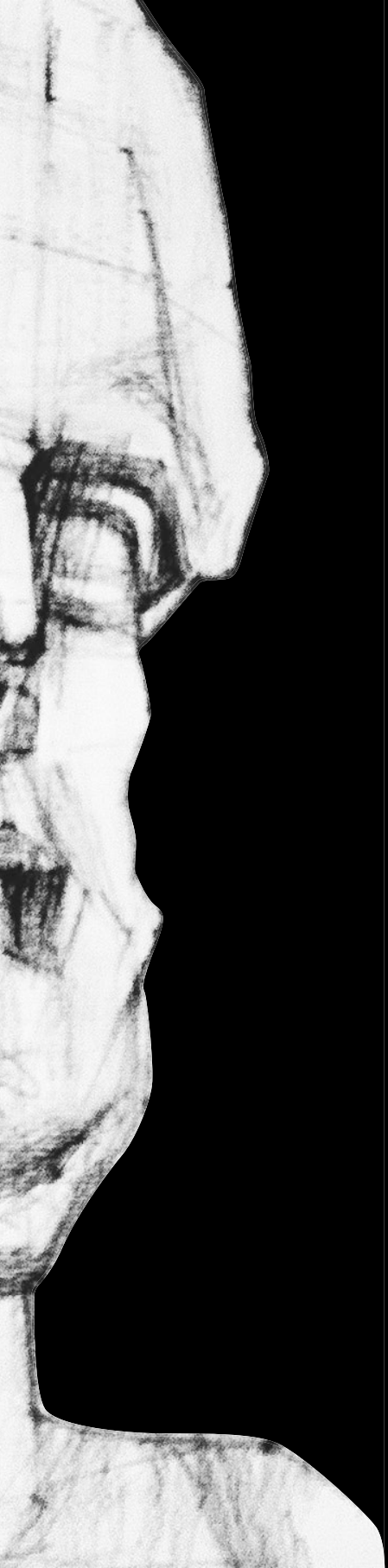


General introduction

CHAPTER 1

General Introduction

Cardiac surgery and blood transfusion

In the Netherlands, sixteen hospitals, including eight university hospitals, perform cardiac surgery on a daily basis. In the last 20 years, over 200.000 cardiac surgeries have been performed and the number of procedures keeps increasing every year.[1] For example, in 2006, 14.013 open cardiac procedures were performed in the Netherlands whereas in 2015 this number was 16.346 in a population of 17 million people.[2] This rise in numbers can be explained by the higher life expectancy, less invasive surgical techniques and improved peri-operative care. It is expected that these and other factors will continue to influence both the frequency and the outcomes of cardiac surgery in the future.[3]

Cardiac surgery has always been a field of medicine in which a fair share of blood products is used. This is because cardiac surgery can go with substantial blood loss. Moreover, the use of heart-lung machines causes hemodilution and the patients undergoing cardiac surgery need a relatively high hemoglobin concentration due to impaired oxygen delivery.[4] The consumption of blood products in cardiac surgery decreased over the last decades.[5] When the heart- lung machine first enabled cardiac surgery, the duration of surgery could extent up to ten hours and the heart-lung machines were much bigger than the modern ones (requiring a larger volume often primed with blood products). Nowadays, most cardiac surgeries take about four to six hours and heart-lung machines are much smaller and more efficient, often primed with a mix of colloids and crystalloids. This makes that less blood products are required than in the past.[6] Still cardiac surgery remains a major consumer of blood products, approximately 10-15% of the overall supply of donor blood is consumed by cardiac surgery patients.[7,8]

In many cases it remains unclear when and if a patient benefits from the transfusion of blood products and there is still much uncertainty about the possible benefits and harms of blood transfusion in patients undergoing cardio- thoracic surgery.

Risk models in cardiac surgery, the EuroSCORE II

One of the most used risk models in cardiac surgery is the EuroSCORE. The first EuroSCORE became available in 1999 and provided a simple additive and logistic model.[9] The EuroSCORE was designed to predict in-hospital mortality in cardiac surgery patients, and for years it did so with great accuracy. However, over the years it became clear that the calibration of this model became less accurate; the mortality risk was increasingly overestimated.[10–12] This overestimation was caused by substantial improvements in cardiac surgery, which in turn substantially decreased mortality rates.[13] Therefore, the EuroSCORE was modified and renamed EuroSCORE II in 2011. In this new risk model adjustments in the choice of prognostic variables were made and the model was re-calibrated. When a new risk model is launched it is important to externally validate the model in the local population before it is implemented in clinical practice to prevent over- or underestimation of peri-operative risks.[14,15] After the presentation of the EuroSCORE II a number of validation studies have been performed. The EuroSCORE II was compared with its predecessor the EuroSCORE I and with other cardiac surgery risk models, like the Society of Thoracic Surgeons score (STS-score).[16–18] Results of these validation studies were conflicting, although the EuroSCORE II was often the best performing model.[16,17]

To examine if the EuroSCORE II is a better fitting risk model for cardiac surgery patients in the Netherlands than its predecessor, the EuroSCORE I, we performed a prospective validation study comparing both risk models. This validation study is presented in **chapter two** of this thesis.

Transfusion triggers

Over the last decade transfusion practices regarding red blood cells have been subjected to major changes, especially in patients undergoing cardiac surgery.[19–21] Both anemia as well as red blood cell transfusions can cause serious adverse events and the risks of both are put well forward in literature.[22–25] Over the last few years, as the awareness of the risks of red blood cell transfusions increased, research concentrated on finding the lowest hemoglobin level that was tolerated in patients. In these studies, in search of a more restrictive transfusion strategy a transfusion threshold of seven g/dL was studied extensively.[26,27]

The results of these studies resulted in a decrease in the use of red blood cell transfusions, without an apparent effect on 30-day mortality.[28] But although these studies showed no inferiority of a restricted transfusion threshold in cardiac surgery patients, other studies found more adverse outcome using a restrictive transfusion trigger and expressed their concern whether a hemoglobin level as low as seven g/dL is safe for patients with a predisposition of cardiac ischemia.[29,30]

Current transfusion guidelines, like the guidelines of the American Association of Anesthesiologists (ASA) or the Dutch transfusion guidelines, use relatively fixed transfusion thresholds.[4,31] These guidelines provide in a higher transfusion threshold in more severely ill patients (based on their ASA classification).[4] But although age and severity of disease is taken into account in transfusion guidelines, the relative amount of hemoglobin decrease during surgery is ignored. In 2008 a study analyzed the effect of relative hemoglobin decrease during cardiac surgery.[30] A more than 50 percent hemoglobin decrease was associated with a higher occurrence of the composite endpoint consisting of in-hospital mortality, stroke and/or kidney failure. This suggests that the magnitude of hemoglobin decrease may also play a role in postoperative morbidity and/or mortality. Until now, no other studies confirmed or refuted these remarkable findings. **Chapter three** of this thesis shows a study examining the influence of a relative (> 50% decrease) hemoglobin decrease on adverse postoperative outcome.

Jehovah's Witnesses, anemia and red blood cell transfusion

As mentioned above both anemia and red blood cell transfusion can cause morbidity and mortality.[22–25] In cardiac surgery, there is no consensus regarding the intra-operative hemoglobin level at which the beneficial effects of red blood cell transfusions outweigh the risks.[5,30] To study the effect of uncorrected anemia (i.e. without the confounding interference of red blood cell transfusions) one can study a population like Jehovah's witnesses, who refuse blood transfusions on account of their religious beliefs. A disadvantage of studying Jehovah's witnesses is the possible introduction of selection bias. Caution is warranted when designing a study which includes Jehovah's witnesses to avoid this pitfall.

Previous studies show that selected Jehovah's witnesses can undergo bloodless cardiac surgery with the same results as non-Jehovah's witnesses, although it is not known whether this is true for Jehovah's witnesses who develop intra-operative anemia.[32–37] Blood sparing measures like

isovolemic hemodilution, administration of tranexamic acid and (if the patient consents) cell saver systems can be used during surgery to decrease blood loss as much as possible.[33] In addition to that, many Jehovah's witnesses are subjected to a pre-operative preparation regime in which erythropoietin, iron supplements and/or folic acid are administered when deemed necessary to achieve an optimal Hb.[38,39] All these measures in combination with extended coagulation during surgery make it possible to perform major surgery without using any blood products.[40]
Some studies have compared Jehovah's witnesses with patients who did receive red blood cell transfusion during surgery.[34,36,41] Although these studies show no differences in the postoperative outcome between Jehovah's witnesses and non-Witnesses, one cannot deduce from these studies that the patients who were transfused received their red blood cell redundantly, because they could have been worse off if they did not receive the transfusion. In the **fourth chapter** of this thesis we examine the effect of uncorrected anemia in Jehovah's witnesses and the role of a single red blood cell transfusion using Jehovah's witnesses as well as transfused and non-transfused non-Witnesses who suffer from an intra-operative anemia.

Red blood cell allo-immunisation

One of the unwanted effects of red blood cell transfusion is the formation of allo-antibodies against incompatible donor antigens. These allo-antibodies could lead to delayed and acute hemolytic transfusion reactions which could be fatal. Also, logistic inconvenience trying to find a matching red blood cell unit for a patient with allo-antibodies can be challenging and time consuming. In cardiac surgery 2-10% of the patients form allo-antibodies to red blood cell transfusion after a single transfusion event.[42–45]
Red blood cell transfusions which are ABO-D compatible, but are incompatible for additional blood group systems do not always lead to the formation of allo-antibodies. So, unraveling possible causes of the formation of these antibodies is important to develop preventive strategies. Genetic, environmental and pro-inflammatory factors have been studied as possible causes of the formation of allo-antibodies.[46–48] It has been hypothesized that the storage time of red blood cells also influences this process.[49,50]
The effect of red blood cell storage time is unclear and has been widely debated. During storage red blood cells undergo a series of morphological and biochemical changes known as the storage lesion.[51] Some studies reported adverse outcomes after transfusion of 'older' red blood cell units on account of this storage lesion while others did not.[52–55] One study, performed in a mouse model, showed an association between storage time and the formation of allo-antibodies.[56] Two (observational) studies have assessed the effect of red blood cell storage time on the formation of allo-antibodies.[49,50] Both studies suggested that storage time did not affect allo- immunization, but this may have been due to limitations in the design. Both studies lacked information on the exact red blood cell unit carrying the cognate incompatible antigen (i.e. the red blood cell unit which caused the formation of allo-antibodies). In the **fifth chapter** of this thesis we present a study analyzing the influence of red blood cell storage time on the formation of allo-antibodies in which we did identify the red blood cell unit deemed responsible for the allo-immunization. To achieve this we focused our study on the Kell-antigen. Because this antigen has a relatively low frequency in Caucasian populations, the probability that a patient receives multiple incompatible

K-positive units, each with a different storage interval, during a transfusion event is low.[57] Therefore it was possible to determine the exact storage time of the red blood cell unit which caused immunization. Also the storage times of the concomitantly transfused K-negative units were analyzed because one could hypothesize that those units could play an enhancing or dampening role in the formation of allo-antibodies.

Safety of platelet transfusions in cardiac surgery

When prescribing red blood cells the benefits and adverse effects of transfusion should be weighted carefully.

The same applies to platelet concentrates. In cardiac surgery excessive bleeding is not uncommon due to both surgical and hemostatic causes.[58–60] Among the hemostatic causes of bleeding, platelet dysfunction plays an important role. The use of cardiopulmonary bypass and/or pre-operative anti-platelet drug therapy are well known causes for an impaired platelet function during and after cardiac surgery.[27,61] To treat or prevent bleeding which is presumed to be the result of platelet dysfunction, platelet transfusions are often prescribed in cardiac surgery patients.[59] Also, because an increasing number of patients is having cardiac surgery while they are still on anti- platelet medication or anti-coagulants, prophylactic platelet transfusions are more and more prescribed.[62–64] Despite the current guidelines, transfusion policies regarding platelet concentrates remain divergent which is shown by the wide variety of platelet use among different hospitals.[65,66]

The efficacy of platelets remains unclear and studies that analyzed the safety of platelet concentrates show conflicting results[67–71] Some studies found associations between platelet transfusion and vasoplegia, renal failure, infections and trombo-embolic complications like myocardial infarction or stroke.[68,70,71] Others examining the same associations found none.[67,69] In the **sixth chapter** of this thesis we examine the safety as well as the efficacy of a single platelet concentrate by comparing patients who received one platelet concentrate intra-operatively with matched patients who received no blood products at all.

In this thesis we address the question when the transfusion of blood products is in the best interest of the patient undergoing cardiac surgery. We specifically study risk models, does the EuroSCORE II perform better than its predecessor? Transfusion triggers, is an addition to the absolute transfusion trigger that is used now feasible for certain patient categories undergoing cardiac surgery? We also look at bloodless surgery and the effects of a single red cell transfusion as well as platelet transfusions and the postoperative effects of a single platelet transfusion and antibody formation and the possible role of storage time.

Reference List

1 Siregar S, Groenwold RH, Versteegh MI, et al. Data Resource Profile: adult cardiac surgery database of the Netherlands Association for Cardio-Thoracic Surgery. Int J Epidemiol. 2013;42(1):142-149. doi:10.1093/ije/dys241 [doi].

2 society of thoracic surgery D. Registratie Begeleidings commissie hartinterventies Nederland. 2016.

3 Whitson BA, Lima B. Surgery for acquired cardiac disease: An evolving paradigm with a promising future. J Thorac Cardiovasc Surg. 2016;151(6):1466-1469. doi:10.1016/j.jtcvs.2016.01.009 [doi].

4 de Vries R, Haas F, working group for revision of the Dutch Blood Transfusion Guideline 2011. English translation of the dutch blood transfusion guideline 2011. Clin Chem. 2012;58(8):1266-1267. doi:58/8/1266 [pii].

5 Vonk AB, Meesters MI, van Dijk WB, et al. Ten-year patterns in blood product utilization during cardiothoracic surgery with cardiopulmonary bypass in a tertiary hospital. Transfusion. 2014;54(10 Pt 2):2608-2616. doi:10.1111/trf.12522 [doi].

6 2nd EAH. A Brief History of Cardiopulmonary Bypass. Semin Cardiothorac Vasc Anesth. 2014;18(2):87-100. doi:10.1177/1089253214530045 [doi].

7 Anderson L, Quasim I, Soutar R, Steven M, Macfie A, Korte W. An audit of red cell and blood product use after the institution of thromboelastometry in a cardiac intensive care unit. Transfus Med. 2006;16(1):31-39. doi:TME645 [pii].

8 Tinegate H, Chattree S, Iqbal A, et al. Ten-year pattern of red blood cell use in the North of England. Transfusion. 2013;53(3):483-489. doi:10.1111/j.1537-2995.2012.03782.x [doi].

9 Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg. 1999;16(1):9-13. doi:S1010794099001347 [pii].

10 Parolari A, Pesce LL, Trezzi M, et al. Performance of EuroSCORE in CABG and off-pump coronary artery bypass grafting: single institution experience and meta-analysis. Eur Heart J. 2009;30(3):297-304. doi:10.1093/eurheartj/ehn581 [doi].

11 Lebreton G, Merle S, Inamo J, et al. Limitations in the inter-observer reliability of EuroSCORE: what should change in EuroSCORE II? Eur J Cardiothorac Surg. 2011;40(6):1304-1308. doi:10.1016/j.ejcts.2011.02.067 [doi].

12 Yap CH, Reid C, Yii M, et al. Validation of the EuroSCORE model in Australia. Eur J Cardiothorac Surg. 2006;29(4):6; discussion 446. doi:S1010-7940(06)00019-4 [pii].

13 Nashef SA, Roques F, Sharples LD, et al. EuroSCORE II. Eur J Cardiothorac Surg. 2012;41(4):5. doi:10.1093/ejcts/ezs043 [doi].

14 Nashef SA, Sharples LD, Roques F, Lockowandt U. EuroSCORE II and the art and science of risk modelling. Eur J Cardiothorac Surg. 2013;43(4):695-696. doi:10.1093/ejcts/ezs468 [doi].

15 Collins GS, Altman DG. Design flaws in EuroSCORE II. Eur J Cardiothorac Surg. 2013;43(4):871. doi:10.1093/ejcts/ezs562 [doi].

16 Kunt AG, Kurtcephe M, Hidiroglu M, et al. Comparison of original EuroSCORE, EuroSCORE II and STS risk models in a Turkish cardiac surgical cohort. Interact Cardiovasc Thorac Surg. 2013;16(5):625-629. doi:10.1093/icvts/ivt022 [doi].

17 Wang L, Han QQ, Qiao F, et al. Performance of EuroSCORE II in patients who have undergone heart valve surgery: a multicentre study in a Chinese population. Eur J Cardiothorac Surg. 2014;45(2):359-364. doi:10.1093/ejcts/ezt264 [doi].

18 Wang TK, Choi DH, Stewart R, Gamble G, Haydock D, Ruygrok P. Comparison of four contemporary risk models at predicting mortality after aortic valve replacement. J Thorac Cardiovasc Surg. 2015;149(2):443-448. doi:10.1016/j.jtcvs.2014.04.032 [doi].

19 Song HK, von Heymann C, Jespersen CM, et al. Safe application of a restrictive transfusion protocol in moderate-risk patients undergoing cardiac operations. Ann Thorac Surg. 2014;97(5):1630-1635. doi:10.1016/j.athoracsur.2013.12.025 [doi].
20 Goda TS, Sherrod B, Kindell L. An Interdisciplinary Education Initiative to Promote Blood Conservation in Cardiac Surgery. J Healthc Qual. 2017;39(3):e33-e41. doi:10.1097/01.JHQ.0000462687.63006.48.
21 Khan JH, Green EA, Chang J, et al. Blood and Blood Product Conservation: Results of Strategies to Improve Clinical Outcomes in Open Heart Surgery Patients at a Tertiary Hospital. J Extra Corpor Technol. 2017;49(4):273-282.
22 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(5):471-479. doi:CIRCULATIONAHA.106.653501 [pii].
23 Munoz M, Gomez-Ramirez S, Campos A, Ruiz J, Liumbruno GM. Pre-operative anaemia: prevalence, consequences and approaches to management. Blood Transfus. 2015;13(3):370-379. doi:10.2450/2015.0014-15 [doi].
24 Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. Crit Care Med. 2008;36(9):2667-2674. doi:10.1097/CCM.0b013e3181844677 [doi].
25 Banbury MK, Brizzio ME, Rajeswaran J, Lytle BW, Blackstone EH. Transfusion increases the risk of postoperative infection after cardiovascular surgery. J Am Coll Surg. 2006;202(1):131-138. doi:S1072-7515(05)01430-4 [pii].
26 Samolyk KA. State-of-the-art blood management in cardiac surgery. Semin Cardiothorac Vasc Anesth. 2009;13(2):118-121. doi:10.1177/1089253209339510 [doi].
27 Goodnough LT, Levy JH, Murphy MF. Concepts of blood transfusion in adults. Lancet (London, England). 2013;381(9880):1845-1854. doi:10.1016/S0140-6736(13)60650-9 [doi].
28 Roubinian NH, Escobar GJ, Liu V, et al. Trends in red blood cell transfusion and 30-day mortality among hospitalized patients. Transfusion. 2014;54(10 Pt 2):2678-2686. doi:10.1111/trf.12825 [doi].
29 Carson JL, Brooks MM, Abbott JD, et al. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. Am Heart J. 2013;165(6):971.e1. doi:10.1016/j.ahj.2013.03.001 [doi].
30 Karkouti K, Wijeysundera DN, Yau TM, McCluskey SA, van Rensburg A, Beattie WS. The influence of baseline hemoglobin concentration on tolerance of anemia in cardiac surgery. Transfusion. 2008;48(4):666-672. doi:10.1111/j.1537-2995.2007.01590.x [doi].
31 of Anesthesiologists Task Force on Perioperative Blood Transfusion AS, Therapies A. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Anesthesiology. 2006;105(1):198-208. doi:00000542-200607000-00030 [pii].
32 Pattakos G, Koch CG, Brizzio 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):1154-1160. doi:10.1001/archinternmed.2012.2449 [doi].
33 Vaislic CD, Dalibon N, Ponzio O, et al. Outcomes in cardiac surgery in 500 consecutive Jehovah's Witness patients: 21 year experience. J Cardiothorac Surg. 2012;7:95. doi:10.1186/1749-8090-7-95 [doi].
34 Stamou SC, White T, Barnett S, Boyce SW, Corso PJ, Lefrak EA. Comparisons of cardiac surgery outcomes in Jehovah's versus Non-Jehovah's Witnesses. Am J Cardiol. 2006;98(9):1223-1225. doi:S0002-9149(06)01372-5 [pii].
35 Jassar AS, Ford PA, Haber HL, et al. Cardiac surgery in Jehovah's Witness patients: ten-year experience. Ann Thorac Surg. 2012;93(1):19-25. doi:10.1016/j.athoracsur.2011.06.029 [doi].
36 Bhaskar B, Jack RK, Mullany D, Fraser J. Comparison of outcome in Jehovah's Witness patients in cardiac surgery: an Australian experience. Heart Lung Circ. 2010;19(11):655-659. doi:10.1016/j.hlc.2010.07.010 [doi].

37 Emmert MY, Salzberg SP, Theusinger OM, et al. How good patient blood management leads to excellent outcomes in Jehovah's witness patients undergoing cardiac surgery. Interact Cardiovasc Thorac Surg. 2011;12(2):183-188. doi:10.1510/icvts.2010.242552 [doi].

38 Casati V, D'Angelo A, Barbato L, et al. Perioperative management of four anaemic female Jehovah's Witnesses undergoing urgent complex cardiac surgery. Br J Anaesth. 2007;99(3):349-352. doi:aem170 [pii].

39 McCartney S, Guinn N, Roberson R, Broomer B, W hite W , Hill S. Jehovah's W itnesses and cardiac surgery: a single institution's experience. Transfusion. 2014;54(10 Pt 2):2745-2752. doi:10.1111/trf.12696 [doi].

40 Garcia JH, Coelho GR, Neto BAF, Nogueira EA, Teixeira CC, Mesquita DF. Liver transplantation in Jehovah's Witnesses patients in a center of northeastern Brazil. Arq Gastroenterol. 2013;50(2):138-140. doi:S0004-28032013000200138 [pii].

41 Marshall L, Krampl C, Vrtik M, et al. Short term outcomes after cardiac surgery in a Jehovah's Witness population: an institutional experience. Heart Lung Circ. 2012;21(2):101-104. doi:10.1016/j.hlc.2011.10.003 [doi].

42 van de Watering L, Hermans J, Witvliet M, Versteegh M, Brand A. HLA and RBC immunization after filtered and buffy coat-depleted blood transfusion in cardiac surgery: a randomized controlled trial. Transfusion. 2003;43(6):765-771. doi:trf390 [pii].

43 Fluit CR, Kunst VA, Drenthe-Schonk AM. Incidence of red cell antibodies after multiple blood transfusion. Transfusion. 1990;30(6):532-535.

44 Ness PM, Shirey RS, Thoman SK, Buck SA. The differentiation of delayed serologic and delayed hemolytic transfusion reactions: incidence, long-term serologic findings, and clinical significance. Transfusion. 1990;30(8):688-693.

45 Redman M, Regan F, Contreras M. A prospective study of the incidence of red cell allo-immunisation following transfusion. Vox Sang. 1996;71(4):216-220.

46 Seyfried H, Walewska I. Analysis of immune response to red blood cell antigens in multitransfused patients with different diseases. Mater medica Pol J Med Pharm. 1990;22(1):21-25.

47 Noizat-Pirenne F, Tournamille C, Bierling P, et al. Relative immunogenicity of Fya and K antigens in a Caucasian population, based on HLA class II restriction analysis. Transfusion. 2006;46(8):1328-1333. doi:TRF00900 [pii].

48 Hendrickson JE, Desmarets M, Deshpande SS, et al. Recipient inflammation affects the frequency and magnitude of immunization to transfused red blood cells. Transfusion. 2006;46(9):1526-1536. doi:TRF00946 [pii].

49 Yazer MH, Triulzi DJ. Receipt of older RBCs does not predispose D-negative recipients to anti-D alloimmunization. Am J Clin Pathol. 2010;134(3):443-447. doi:10.1309/AJCP2J8SVWOXRLRB [doi].

50 Zalpuri S, Schonewille H, Middelburg R, et al. Effect of storage of red blood cells on alloimmunization. Transfusion. 2013;53(11):2795-2800. doi:10.1111/trf.12156 [doi].

51 Flegel WA, Natanson C, Klein HG. Does prolonged storage of red blood cells cause harm? Br J Haematol. 2014;165(1):3-16. doi:10.1111/bjh.12747 [doi].

52 Eikelboom JW, Cook RJ, Liu Y, Heddle NM. Duration of red cell storage before transfusion and in- hospital mortality. Am Heart J. 2010;159(5):743.e1. doi:10.1016/j.ahj.2009.12.045 [doi].

53 Robinson SD, Janssen C, Fretz EB, et al. Red blood cell storage duration and mortality in patients undergoing percutaneous coronary intervention. Am Heart J. 2010;159(5):876-881. doi:10.1016/j.ahj.2010.02.018 [doi].

54 Naidech AM, Liebling SM, Duran IM, Ault ML. Packed red blood cell age does not impact adverse events or outcomes after subarachnoid haemorrhage. Transfus Med. 2011;21(2):130-133. doi:10.1111/j.1365-3148.2010.01048.x [doi].

55 McKenny M, Ryan T, Tate H, Graham B, Young VK, Dowd N. Age of transfused blood is not associated with increased postoperative adverse outcome after cardiac surgery. Br J Anaesth. 2011;106(5):643- 649. doi:10.1093/bja/aer029 [doi].

56 Hendrickson JE, Hod EA, Spitalnik SL, Hillyer CD, Zimring JC. Storage of murine red blood cells enhances alloantibody responses to an erythroid-specific model antigen. Transfusion. 2010;50(3):642-648. doi:10.1111/j.1537-2995.2009.02481.x [doi].

57 Reid ME, Mohandas N. Red blood cell blood group antigens: structure and function. Semin Hematol. 2004;41(2):93-117. doi:S0037196304000022 [pii].

58 Gorlinger K, Shore-Lesserson L, Dirkmann D, Hanke AA, Rahe-Meyer N, Tanaka KA. Management of hemorrhage in cardiothoracic surgery. J Cardiothorac Vasc Anesth. 2013;27(4 Suppl):20. doi:10.1053/j.jvca.2013.05.014 [doi].

59 Cobain TJ, Vamvakas EC, Wells A, Titlestad K. A survey of the demographics of blood use. Transfus Med. 2007;17(1):1-15. doi:TME709 [pii].

60 Levy JH, Despotis GJ. Transfusion and hemostasis in cardiac surgery. Transfusion. 2008;48(1 Suppl):2995.2007.01572.x. doi:10.1111/j.1537-2995.2007.01572.x [doi].

61 Thiele RH, Raphael J. A 2014 Update on Coagulation Management for Cardiopulmonary Bypass. Semin Cardiothorac Vasc Anesth. 2014;18(2):177-189. doi:10.1177/1089253214534782 [doi].

62 Horvath KA, Acker MA, Chang H, et al. Blood transfusion and infection after cardiac surgery. Ann Thorac Surg. 2013;95(6):2194-2201. doi:10.1016/j.athoracsur.2012.11.078 [doi].

63 Drews S, Bolliger D, Kaiser C, et al. Prasugrel increases the need for platelet transfusions and surgical reexploration rates compared with clopidogrel in coronary artery bypass surgery. Thorac Cardiovasc Surg. 2015;63(1):28-35. doi:10.1055/s-0034-1373901 [doi].

64 Juergens CP, Yeung AC, Oesterle SN. Routine platelet transfusion in patients undergoing emergency coronary bypass surgery after receiving abciximab. Am J Cardiol. 1997;80(1):74-75. doi:S0002914997002877 [pii].

65 Bennett-Guerrero E, Zhao Y, O'Brien SM, et al. Variation in use of blood transfusion in coronary artery bypass graft surgery. Jama. 2010;304(14):1568-1575. doi:10.1001/jama.2010.1406 [doi].

66 Snyder-Ramos SA, Mohnle P, Weng YS, et al. The ongoing variability in blood transfusion practices in cardiac surgery. Transfusion. 2008;48(7):1284-1299. doi:10.1111/j.1537-2995.2008.01666.x [doi].

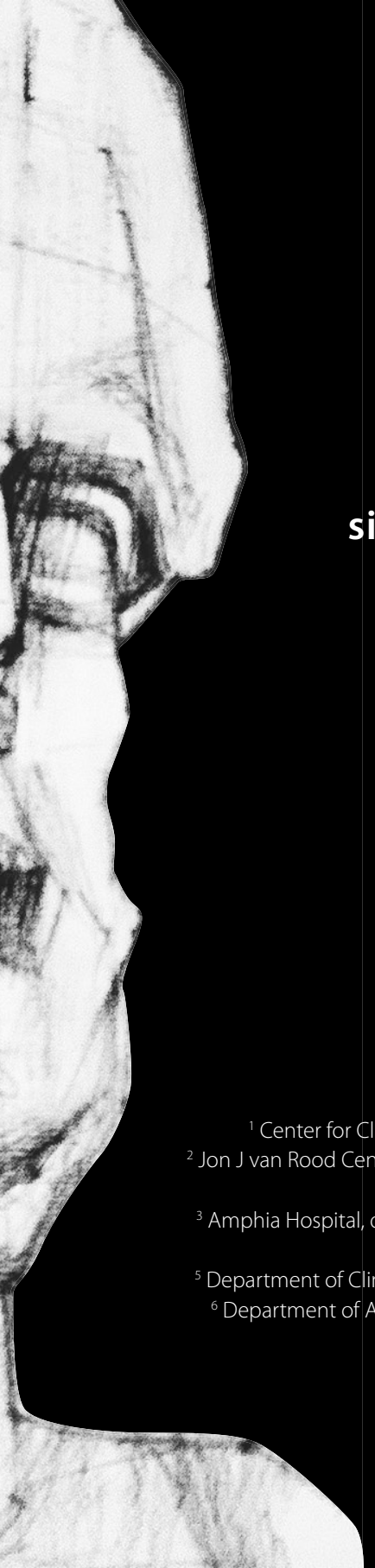
67 Sreeram GM, Welsby IJ, Sharma AD, Phillips-Bute B, Smith PK, Slaughter TF. Infectious complications after cardiac surgery: lack of association with fresh frozen plasma or platelet transfusions. J Cardiothorac Vasc Anesth. 2005;19(4):430-434. doi:S1053-0770(05)00194-1 [pii].

68 Spiess BD, Royston D, Levy JH, et al. Platelet transfusions during coronary artery bypass graft surgery are associated with serious adverse outcomes. Transfusion. 2004;44(8):1143-1148. doi:10.1111/j.1537-2995.2004.03322.x [doi].

69 Karkouti K, Wijeysundera DN, Yau TM, et al. Platelet transfusions are not associated with increased morbidity or mortality in cardiac surgery. Can J Anaesth. 2006;53(3):279-287. doi:53/3/279 [pii].

70 Mikkola R, Gunn J, Heikkinen J, et al. Use of blood products and risk of stroke after coronary artery bypass surgery. Blood Transfus. 2012;10(4):490-501. doi:10.2450/2012.0119-11 [doi].

71 Alfirevic A, Xu M, Johnston D, Figueroa P, Koch CG. Transfusion increases the risk for vasoplegia after cardiac operations. Ann Thorac Surg. 2011;92(3):812-819. doi:10.1016/j.athoracsur.2011.04.020 [doi].



Prospective validation of the EuroSCORE II risk model in a single Dutch cardiac surgery center

CHAPTER 2

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Abstract

Objective

The EuroSCORE I was one of the most frequently used pre-operative risk models in cardiac surgery. In 2011 it was replaced by its successor the EuroSCORE II. This study aims to validate the EuroSCORE II and to compare its performance with the EuroSCORE I in a Dutch hospital.

Methods

The EuroSCORE II was prospectively validated in 2296 consecutive cardiac surgery patients between April 1th 2012 and January 1th EuroSCORE I and EuroSCORE II and the Area Under the Curve was calculated to assess discriminative power. Calibration was assessed by comparing observed versus expected mortality. Additionally, analyses were performed in which we stratified for type of surgery and for elective versus emergency surgery.

Results

The observed mortality was 2.4% (55 patients). The discriminative power of the EuroSCORE II surpassed that of the EuroSCORE I (area under the curve EuroSCORE II 0.871 95%, Confidence interval 0.832-0.911, area under the curve additive EuroSCORE 0.840, CI 0.798-0.882, area under the curve logistic EuroSCORE I 0.761, CI 0.695-0.828). Both the additive and the logistic EuroSCORE I overestimated mortality (predictive mortality additive EuroSCORE I median 5.0%, inter quartile range 3.0-8.0%, logistic EuroSCORE I 10.7%, inter quartile range 5.8-13.9), while the EuroSCORE II underestimated mortality (median 1.6%, inter quartile range 1.0-3.5). In most stratified analyses the EuroSCORE II performed better.

Conclusion

Our results show that the EuroSCORE II produces a valid risk prediction and outperforms the EuroSCORE I in elective cardiac surgery patients.

Introduction

In a growing population of patients undergoing cardiac surgery (including older and more vulnerable patients), an accurate pre-operative risk assessment has become indispensable.1 An often-used method for risk assessment in cardiac surgery is the European System for Cardiac Operative Risk Evaluation better known as the EuroSCORE (ES). The first ES became available in 1999 and provided a simple additive and logistic risk calculation model based on European adult cardiac surgery patients, and was widely implemented.[2] The ESI was validated in the Netherlands for both short as long term mortality and morbidity.[3] Over time, it became clear that the EuroSCORE I (ESI) overestimated the 30-day and 90-day mortality risk.[4,5] This overestimation was caused by improvements in peri-operative patient care resulting in substantially reduced mortality rates and evoked the need for a renewed risk model.[1]
In 2011 the successor, the EuroSCORE II (ESII), was presented. As with all new risk models it is important to externally validate this model in patients other than the sampled patient population from which the risk model was developed.[6] Differences in patient populations influence risk models' performance and determines whether or not the model is fit for use in a particular population.[7]
Validation studies that have been published so far show ambiguous results when comparing the ESII with other risk models like the ESI and the Society of Thoracic Surgery score.[8,9] Furthermore, several studies used data which were collected before the ESII was developed and several studies validated the study for surgical procedures for which the ESII was not intended.[10–12]
In 2003 we performed the first study validating the ESI in cardiac surgery patients in the Netherlands.[3] In succession of that, the present study aims to validate the ESII risk model in patients undergoing cardiac surgery in the Netherlands and also compare ESII performance with the performance of the additive and logistic ESI.

Materials and Methods

Data collection

The analyses were performed with data from the Amphia Cardiac Surgery Blood Management Study. Details of this study have been described earlier.[13] In this ongoing cohort study, peri-operative data are prospectively collected of all consecutive cardiac surgery patients since 1997. Data are collected in a distributed proprietary database during the complete peri-operative course. Variables regarding pre-operative co-morbidities, drug therapy, routine pre-, intra- and postoperative lab analysis, complications and postoperative outcome are collected in the Amphia hospital, Breda, the Netherlands. The Amphia hospital is a non-university hospital with the possibility of transferring special patient categories to tertiary hospitals.
All variables necessary to calculate both the ESI and the ESII are present in the database. After publication of the ESII the data-dictionary was updated to reflect ESII additions and changes. The ESII update was implemented from April 2012 on. The database is compliant with the Dutch National Cardiac Surgery Registry and the Dutch National Intensive Care Registry.[14]
Data collection took place between April 1st 2012 and January 1th 2014.

Patient sample and analyses

All consecutive patients who underwent cardiac surgery were included regardless their type of surgery. For each patient the additive and logistic ESI as well as the ESII were calculated using the formula's available at the EuroSCORE website (www.euroscore.org). The discriminative power of each risk model was assessed by plotting the Receiver Operator Curves (ROC curves) of the different ES on in-hospital mortality, and comparing the Area Under the Curve (AUC). The calibration of the different risk models was examined comparing the observed versus the expected values for in-hospital mortality rates. This way we could assess whether the ES (low or high) corresponded with the observed mortality. We performed the same analyses in subgroups according to type of surgery in 4 categories: Coronary Artery Bypass Graft (CABG), CABG combined with other surgery, valve surgery, miscellaneous procedures and according to the urgency of the procedure: emergency versus elective surgery. Emergency surgery was defined as surgery which had to be performed as soon as possible but at least within 24 hours after admittance.

Results

Patient characteristics

Our cohort consisted of 2296 patients; pre- and intra-operative patient characteristics are shown in table 1. A total of 662 patients (28.8%) were female, the median age was 70 years (interquartile range [IQR] 63-76). The overall mortality in our cohort was 2.4% (55 patients).

Table 1: Patient characteristics (n=2296)

Pre-operative variables:*	**Missing:**	
Age (years)	-	70 (63-76)
Female gender	-	662 (28.8)
Weight (kg)	-	80 (71-90)
Previous cardiac surgery	-	171 (7.4)
Previous myocardial infarction	-	311 (13.5)
NYHA class:	-	
- I		942 (41.0)
- II		694 (30.2)
- III		484 (21.1)
- IV		176 (7.7)
LMCA > 50% occluded	4	299 (13.0)
Left ventricle hypertrophy	24	536 (23.3)
Pulmonary artery pressure > 40 mmHg	-	58 (2.5)
Atrial fibrillation	1	399 (17.4)
Extra cardiac arteriopathy	-	311 (13.5)
Hypertension	8	1445 (62.9)
Pre-operative Hb level (g/dL)	-	13.7 (12.6-14.8)
Creatinine level (micromol/L)	-	84 (72-100)
Creatinine clearance	-	80 (60-101)
Ejection Fraction:	-	
- good		1758 (76.6)
- moderate		377 (16.4)
- poor		136 (5.9)
- very poor		25(1.1)
Smoking	19	366 (15.9)
Insulin dependent diabetes	-	284 (12.4)
Endocarditis	-	28 (1.2)
Chronic renal failure**	-	50 (2.2)
COPD	-	267 (11.6)
Poor mobility	-	167 (7.3)
Pre-operative use of inotropic agents	-	25 (1.1)
Respiratory insufficiency	-	65 (2.8)
Jehovah's witnesses	2	32 (1.4)
Emergency surgery	-	261 (11.4)
Aortic valve pathology	-	793 (34.5)
Mitral valve pathology	-	469 (20.4)
Type of surgery:	-	
- CABG		1059 (46.1)
- CABG + other surgery		319 (13.9)
- Valve		615 (26.8)
- Miscellaneous surgery		303 (13.2)
Off-pump procedure	-	139 (6.1)
Additive EuroSCORE I	-	5 (3-8)
Logistic EuroSCORE I	-	10.7 (5.8-13.9)
EuroSCORE II	-	1.6 (1.0-3.5)
Intra-operative variables:		
Time in surgery (min)	11	215 (180-255)
CPB time (min)	-	83 (61-117)
Clamp time (min)	-	54 (36-78)
Intra-operative nadir Hb (g/dL)	15	9.7 (8.4-10.8)

*** Variables are presented as number (%) or median (IQR)**
****Creatinine level above 177 mmol/L**

Performance of the EuroSCORE II

We observed that although the discriminative power of both the additive as well as the logistic ESI was good, it was surpassed by the ES II (AUC additive ESI 0.840, 95% Confidence Interval (CI) 0.798-0.882, logistic ESI 0.761, CI 0.695-0.828, AUC ESII 0.871, CI 0.832-0.911). ROC curves are

displayed in Figure I. The ESII underestimated observed mortality while the additive and the logistic mortality overestimated mortality (ESII observed versus expected (O/E) ratio 1.50 vs ESI additive 0.48 vs ES logistic 0.22, results are displayed in table 2).

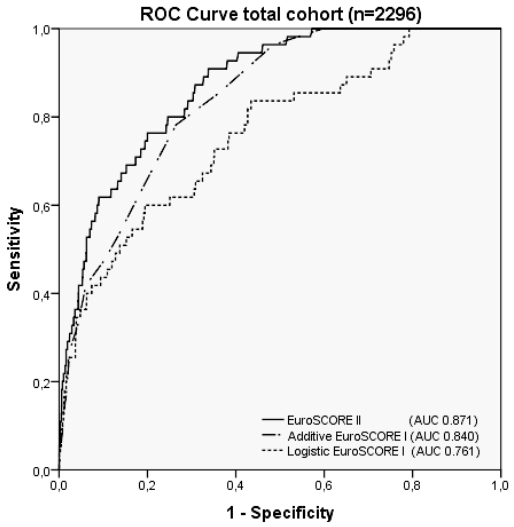


Figure 1. *ROC-curves for the additive and logistic ESI and the ESII*

Table 2: Discrimination and calibration parameters in total cohort (n=2296)

	Area Under the Curve	Observed mortality Number (%)	Expected mortality Median (IQR)*	O/E ratio**
Additive EuroSCORE I	0.840 (0.798-0.882)	55 (2.4)	5.0 (3.0-8.0)	0.48
Logistic EuroSCORE I	0.761 (0.695-0.828)	55 (2.4)	10.7 (5.8-13.9)	0.22
EuroSCORE II	0.871 (0.832-0.911)	55 (2.4)	1.6 (1.0-3.5)	1.50

* **IQR - Inter Quartile Range**
** **Observed versus Expected ratio**

EuroSCORE II performance in different types of surgery

A total of 1059 patients underwent a CABG, 319 patients underwent a CABG in combination with another procedure, 615 patients underwent surgery regarding one or more heart valves and 303 patients underwent miscellaneous kinds of cardiac surgery. Table 3 shows the observed versus expected mortality for the different surgical procedures, the ROC curves are presented in figure 2.

Table 3: Discrimination and calibration according to surgical procedure

	Area Under the Curve	Observed mortality	Expected mortality	O/E ratio**
		Number (%)	Median (IQR)*	
CABG (n=1059)				
Additive EuroSCORE I	0.900 (0.838-0.962)	13 (1.2)	4.0 (3.0-6.0)	0.30
Logistic EuroSCORE I	0.691 (0.536-0.846)	13 (1.2)	10.6 (4.8-13.7)	0.11
EuroSCORE II	0.884 (0.809-0.958)	13 (1.2)	1.4 (0.93-2.6)	0.86
CABG + other procedure (n=319)				
Additive EuroSCORE I	0.739 (0.648-0.831)	14 (4.4)	7.0 (5.0-9.0)	0.63
Logistic EuroSCORE I	0.812 (0.695-0.929)	14 (4.4)	10.3 (5.5-13.8)	0.43
EuroSCORE II	0.693 (0.566-0.820)	14 (4.4)	3.4 (2.0-6.5)	1.29
Valve (n=615)				
Additive EuroSCORE I	0.833 (0.722-0.943)	13 (2.1)	7.0 (5.0-9.0)	0.30
Logistic EuroSCORE I	0.755 (0.594-0.917)	13 (2.1)	11.2 (8.8-14.2)	0.19
EuroSCORE II	0.866 (0.768-0.964)	13 (2.1)	1.5 (1.0-3.1)	1.40
Miscellaneous procedures (n=303)				
Additive EuroSCORE I	0.819 (0.732-0.907)	15 (5.0)	5.0 (2.0-9.0)	1.00
Logistic EuroSCORE I	0.784 (0.692-0.876)	15 (5.0)	10.3 (4.5-14.2)	0.49
EuroSCORE II	0.912 (0.862-0.962)	15 (5.0)	1.5 (0.7-4.7)	3.33
Discrimination and calibration according to urgency				
Elective surgery (n=2035)				
Additive EuroSCORE I	0.827 (0.779-0.875)	30 (1.5)	5.0 (3.0-7.0)	0.30
Logistic EuroSCORE I	0.720 (0.621-0.818)	30 (1.5)	10.5 (5.2-13.7)	0.14
EuroSCORE II	0.839 (0.784-0.894)	30 (1.5)	1.5 (0.92-2.9)	1.00
Emergency surgery (n=261)				
Additive EuroSCORE I	0.726 (0.616-0.836)	25 (9.6)	10.0 (7.0-13.0)	0.96
Logistic EuroSCORE I	0.729 (0.631-0.826)	25 (9.6)	12.9 (9.2-17.5)	0.74
EuroSCORE II	0.816 (0.736-0.896)	25 (9.6)	5.9 (2.2-13.2)	1.63

*** IQR - Inter Quartile Range**
**** Observed versus Expected ratio**

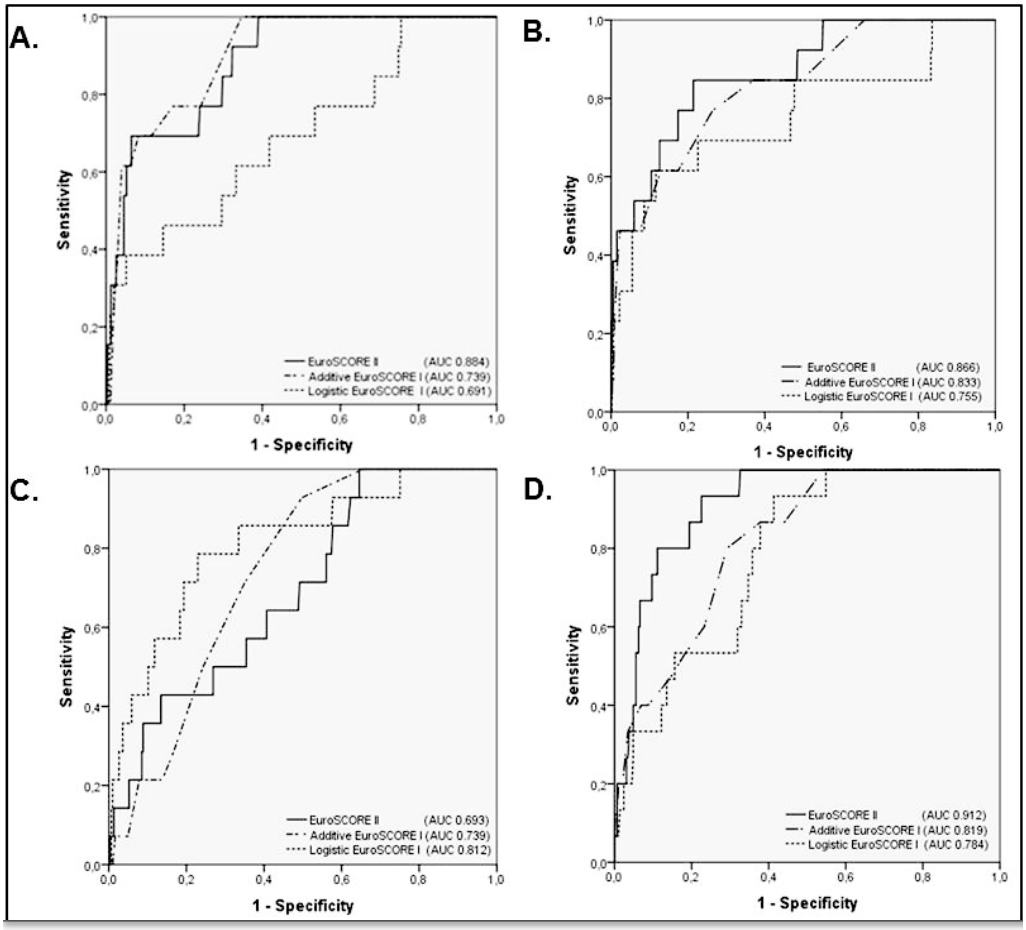


***Figure 2**. Receiver Operator Characteristic curves for the additive and logistic EuroSCORE I and the EuroSCORE II. A. Patients undergoing a CABG (n=1059). B. Patients undergoing valve surgery(n=615). C. Patients undergoing a CABG in combination with any other procedure (n=319). D. Patients undergoing miscellaneous cardiac surgical procedures (n=303).*

In patients who underwent a CABG in-hospital mortality was 1.2%. The additive ESI had the best discriminative power (AUC 0.900, CI 0.838-0.962) and the ESII was the best calibrated risk model (O/E ratio ESII 0.86). In patients who underwent a CABG in combination with other surgery in-hospital mortality was 4.4%. Discriminative power of the logistic ESI was highest (AUC 0.812, CI 0.695-0.929). Although mortality was underestimated by the ES II, the ESI overestimated the mortality even more therefore the ESII provided a better calibration (O/E ratio ESII 1.29).
In the patients who underwent isolated valve surgery the mortality was 2.1%. The ESII had the highest discriminative power and was best calibrated (AUC 0.866, CI 0.768-0.964, O/E ratio 1.40).

In patients who underwent miscellaneous cardiac surgery, mortality was 5.0%. The ESII showed best discrimination (AUC 0.912, CI 0.862-.962).Best calibration was performed by the additive ESI (O/E ratio 1.00)

EuroSCORE II performance in emergency surgery

A total of 261 patients underwent emergency surgery and 2035 patients underwent elective surgery. Table 3 shows the observed versus expected mortality in patients who underwent elective or emergency surgery (ROC curves are displayed in figure 3). In patients who underwent elective surgery the ESII had the highest discriminative power and was best calibrated (AUC 0.839, CI 0.784-0.894, O/E ratio1.00). In patients who underwent emergency surgery the ESII had the highest discriminative power but the additive ESI was better calibrated (ESII AUC 0.816, CI 0.736-0.896, O/E ratio 1.63 and ESI AUC 0.726, CI 0.616-0.836, O/E ratio 0.96).

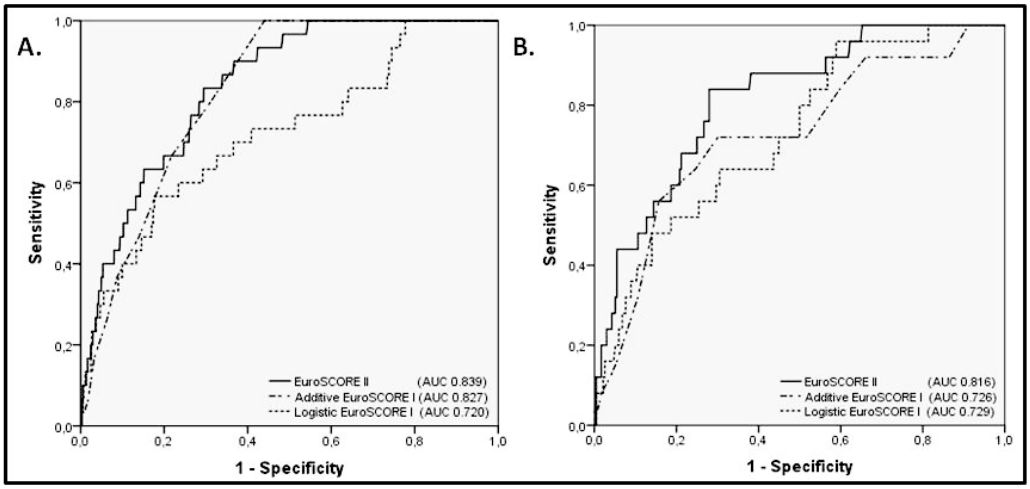


Figure 3. Receiver Operator Characteristic curves for the additive and logistic EuroSCORE I and the EuroSCORE II. A. Patients undergoing elective surgery (2035). B. Patients undergoing emergency surgery (261).

Discussion

Main Findings

In this validation study, we found that the ESII is a well-calibrated risk model with a good predictive value. The ESII underestimated the mortality in some subgroups while the ESI overestimated the observed mortality. Nevertheless the expected mortality of the ESII approached the observed mortality more closely than the ESI and therefore the ESII outperformed the ESI in most patients. Whether this is also true for patients who underwent CABG surgery in combination with another procedure, miscellaneous surgery or emergency surgery in this study is not certain due to small sample size of the subgroups.

Limitations and Strengths

A limitation of our study is that it is a single centre study, which could impair the generalizability of our results. There is little reason to believe that the patient population in the Amphia hospital will differ a lot from other peripheral hospitals in the Netherlands. Nevertheless bias due to population differences could not be ruled out. Furthermore, sample sizes of some subcategories used in our subgroup analyses (CABG in combination with another procedure, miscellaneous surgery and emergency surgery) might be too small to exclude random error. Also, validating the ESII for 30-day and 90-day mortality was not possible with our present data.

Strengths of this validation study are that our data were collected prospectively after the implementation of the ESII in clinical practice. The database used is accurate and contained very few missing data.

In order to validate a risk model like the ESII, validation studies must satisfy certain requirements. In this study we avoided pitfalls which could lead to biased results. For example, the ESII was developed based on data collected in a 12 week period in 2010 and was intended for prospective use.[1] Some studies have validated the ESII based on data acquired before 2010, and some studies included patients over an extended period of time.

This could lead to biased results because of changes and improvements made in daily practice.[15] An example of this bias is illustrated in a study, which validates the ESII in two different time periods. First, the ESII was validated in patients who had surgery between 2003 and 2012. The results from the analyses showed that although the ESII had the highest discriminative power, the STS score had a better calibration. After this analysis, the ESII was validated in a subgroup of patients who had surgery between 2008 and 2012. Results from these analyses show that the ESII (based on patient data collected in 2010) was the best overall risk model.[16] Also, there are studies in which the ESII has been validated in surgical procedures for which the ESII was never intended (for example in trans-catheter aortic valve implantation). This also could lead to suboptimal performance.[17] And third, some validation studies present incomplete data or use inaccurate statistical methods.

For example basing their conclusions solely on a non-significant Hosmer-Lemeshow test, instead of showing the complete data.[17] In this present study we avoided these known pitfalls.

Comparison with other EuroSCORE II validation studies

The observed in-hospital mortality in our study (2.4%) differed slightly with the overall mortality of cardiac surgery procedures in the Netherlands (3.0%) or in neighboring countries like the UK (2.7%).[18,19] Baseline characteristics of our cohort and the patient sample on which the original ESII was based were nearly identical. The only variable that differed between our study and the original sample was insulin-dependent diabetes (12.4% in our cohort versus 7.6%). The mortality rates of the original patient sample (3.9%) and the mortality rates in our cohort differed 1.5%.

Ever since the publication of the ESII in 2012, more than 50 studies concerning the ESII have been published with varying results. Our results agree with a majority of these studies.[20–24] Two studies also analyzed the performance of the ESII according to type of surgery using the same categories we used. Curiously, although the ESII performed well, these studies found that the ES I was the overall best performing risk model in elective surgery.[25,26] This is due to a higher mortality rate

than in our cohort. Why the mortality of these two cohorts differ with ours is not precisely known, but these differences could be due to different population characteristics like NYHA class and gender.
In a previous study, focusing solely on the performance of the ESII in patients who had emergency surgery, the ESII outperformed the ESI, although both the ES showed a poor calibration and discrimination.[27] In our cohort the overall performance of the models was worse in patients who underwent emergency surgery than in patients who did not. In our cohort of emergency patients the ESII had a good discriminative power but a rather poor calibration, while the additive ES I had a good calibration. It is possible that other logistic factors, like for example, time to diagnosis or time it takes to get a patient to a specialized centre play a more important role in the risk evaluation of emergency patients than factors included the ES.
One study retrospectively evaluated the performance of the ESII in the Netherlands with similar results as we found.[24] However this was a small study examining only one hundred patients who underwent CABG surgery combined with mitral- or aortic valve surgery.

Implications for practice and future research

Before implementing a risk model in daily practice it is important to externally validate the model in local populations.[6] Our findings show that the ESII is a good risk predictor which outperforms its predecessor. Based on the results in our cohort we recommend using the ESII as standard tool for risk prediction in patients undergoing cardiac surgery. A significant part of our cohort existed of patients undergoing an isolated CABG with relatively short CPB times. Therefore we also recommend that all hospitals using or planning to use ESII should validate the ESII in their setting because for example differences in CPB time or operation type could influence the predictive value of the ESII.
Another topic of future research should be identifying other variables that could increase the accuracy of the ESII, especially with regards to emergency surgery and/or high risk patients because it seems the ESII has the least predictive value in those populations.
In conclusion, the ESII is a good predictive model of short term mortality in cardiac surgery and it is better calibrated than its predecessor the ESI in patients undergoing elective surgery.

Reference List

1 Nashef SA, Roques F, Sharples LD, et al. EuroSCORE II. Eur J Cardiothorac Surg. 2012;41(4):5. doi:10.1093/ejcts/ezs043 [doi].

2 Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg. 1999;16(1):9-13. doi:S1010794099001347 [pii].

3 Huijskes RVHP, Wesselink RMJ, Noyez L, et al. Predictive models for thoracic aorta surgery. Is the Euroscore the optimal risk model in the Netherlands? Interact Cardiovasc Thorac Surg. 2005;4(6):538- 542. doi:10.1510/icvts.2005.108761.

4 Parolari A, Pesce LL, Trezzi M, et al. Performance of EuroSCORE in CABG and off-pump coronary artery bypass grafting: single institution experience and meta-analysis. Eur Heart J. 2009;30(3):297-304. doi:10.1093/eurheartj/ehn581 [doi].

5 Yap CH, Reid C, Yii M, et al. Validation of the EuroSCORE model in Australia. Eur J Cardiothorac Surg. 2006;29(4):6; discussion 446. doi:S1010-7940(06)00019-4 [pii].

6 Collins GS, Altman DG. Design flaws in EuroSCORE II. Eur J Cardiothorac Surg. 2013;43(4):871. doi:10.1093/ejcts/ezs562 [doi].

7 Nashef SA, Sharples LD, Roques F, Lockowandt U. EuroSCORE II and the art and science of risk modelling. Eur J Cardiothorac Surg. 2013;43(4):695-696. doi:10.1093/ejcts/ezs468 [doi].

8 Kunt AG, Kurtcephe M, Hidiroglu M, et al. Comparison of original EuroSCORE, EuroSCORE II and STS risk models in a Turkish cardiac surgical cohort. Interact Cardiovasc Thorac Surg. 2013;16(5):625-629. doi:10.1093/icvts/ivt022 [doi].

9 Wang L, Han QQ, Qiao F, et al. Performance of EuroSCORE II in patients who have undergone heart valve surgery: a multicentre study in a Chinese population. Eur J Cardiothorac Surg. 2014;45(2):359-364. doi:10.1093/ejcts/ezt264 [doi].

10 Goetzenich A, Deppe I, Schnoring H, et al. EuroScore 2 for identification of patients for transapical aortic valve replacement--a single center retrospective in 206 patients. J Cardiothorac Surg. 2012;7:89. doi:10.1186/1749-8090-7-89 [doi].

11 Carnero-Alcazar M, Silva Guisasola JA, Reguillo Lacruz FJ, et al. Validation of EuroSCORE II on a single-centre 3800 patient cohort. Interact Cardiovasc Thorac Surg. 2013;16(3):293-300. doi:10.1093/icvts/ivs480.

12 Kuwaki K, Inaba H, Yamamoto T, et al. Performance of the EuroSCORE II and the Society of Thoracic Surgeons Score in patients undergoing aortic valve replacement for aortic stenosis. J Cardiovasc Surg (Torino). 2015;56(3):455-462. doi:R37Y2015N03A0455 [pii].

13 Hogervorst E, Rosseel P, Van Der Bom J, et al. Tolerance of intraoperative hemoglobin decrease during cardiac surgery. Transfusion. 2014;54(1). doi:10.1111/trf.12654.

14 Koetsier A, Peek N, de Keizer N. Identifying types and causes of errors in mortality data in a clinical registry using multiple information systems. Stud Health Technol Inform. 2012;180:771-775.

15 Hickey GL, Grant SW, Bridgewater B. Validation of the EuroSCORE II: should we be concerned with retrospective performance? Eur J Cardiothorac Surg. 2013;43(3):655. doi:10.1093/ejcts/ezs547 [doi].

16 Osnabrugge R, Head S, Birim O. Combining the new euroscore ii and syntax score provides excellent risk-stratification of patients undergoing coronary artery bypass grafting for left main disease. In: 26th Annual Meeting of the Meeting of the European Association for Cardio- Thoracic Surgery. Interactive Cardiovascular and Thoracic Surgery; 2012:1.

17 Sergeant P, Meuris B, Pettinari M. EuroSCORE II, illum qui est gravitates magni observe. Eur J Cardiothorac Surg. 2012;41(4):729-731. doi:10.1093/ejcts/ezs057.

18 Siregar S, Groenwold RH, Versteegh MI, et al. Data Resource Profile: adult cardiac surgery database of the Netherlands Association for Cardio-Thoracic Surgery. Int J Epidemiol. 2013;42(1):142-149. doi:10.1093/ije/dys241 [doi].

19 Bridgewater B, Hickey GL, Cooper G, Deanfield J, Roxburgh J. Publishing cardiac surgery mortality rates: lessons for other specialties. BMJ. 2013;346:f1139.

20 Barili F, Pacini D, Capo A, et al. Does EuroSCORE II perform better than its original versions? A multicentre validation study. Eur Heart J. 2013;34(1):22-29. doi:10.1093/eurheartj/ehs342.

21 Borracci RA, Rubio M, Celano L, Ingino CA, Allende NG, Ahuad Guerrero RA. Prospective validation of EuroSCORE II in patients undergoing cardiac surgery in Argentinean centres. Interact Cardiovasc Thorac Surg. 2014;18(5):539-543. doi:10.1093/icvts/ivt550.

22 Biancari F, Vasques F, Mikkola R, Martin M, Lahtinen J, Heikkinen J. Validation of EuroSCORE II in patients undergoing coronary artery bypass surgery. Ann Thorac Surg. 2012;93(6):1930-1935. doi:10.1016/j.athoracsur.2012.02.064.

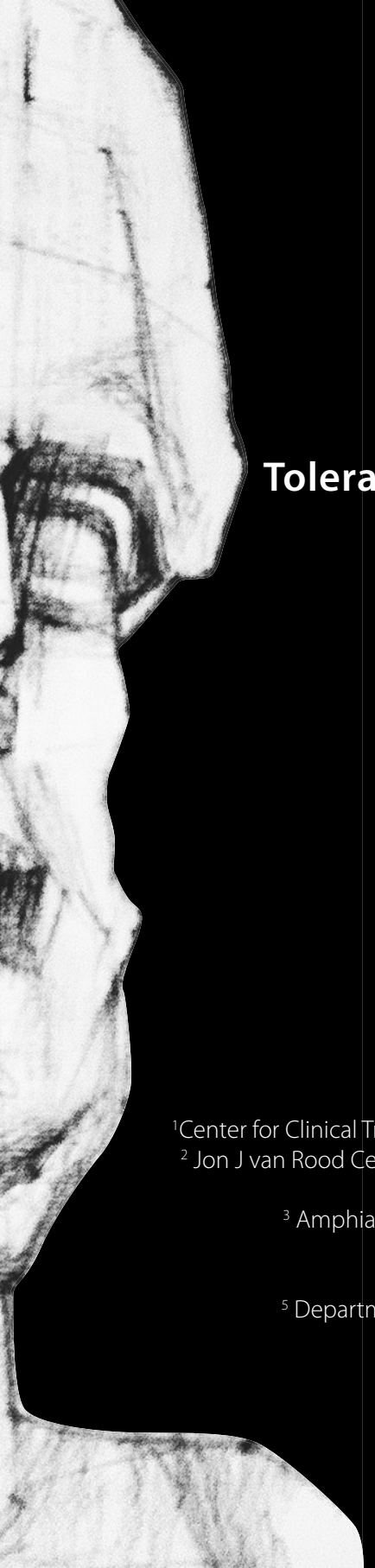
23 Chalmers J, Pullan M, Fabri B, et al. Validation of EuroSCORE II in a modern cohort of patients undergoing cardiac surgery. Eur J Cardiothorac Surg. 2013;43(4):688-694. doi:10.1093/ejcts/ezs406.

24 Noyez L, Kievit PC, van Swieten HA, de Boer M-J. Cardiac operative risk evaluation: The EuroSCORE II, does it make a real difference? Neth Heart J. 2012;20(12):494-498. doi:10.1007/s12471-012-0327-1.

25 Arnaiz-Garcia ME, Gonzalez-Santos JM, Lopez-Rodriguez J, Dalmau-Sorli MJ, Bueno-Codoner M, Arevalo-Abascal A. Survival after major cardiac surgery: performance and comparison of predictive ability of EuroSCORE II and logistic EuroSCORE in a sample of Mediterranean population. Thorac Cardiovasc Surg. 2014;62(4):297-298. doi:10.1055/s-0034-1376255.

26 Velicki L, Cemerlic-Adjic N, Pavlovic K, et al. Clinical performance of the EuroSCORE II compared with the previous EuroSCORE iterations. Thorac Cardiovasc Surg. 2014;62(4):288-297. doi:10.1055/s-0034-1367734.

27 Grant SW, Hickey GL, Dimarakis I, et al. Performance of the EuroSCORE models in emergency cardiac surgery. Circ Qual outcomes. 2013;6(2):178-185. doi:10.1161/CIRCOUTCOMES.111.000018 [doi].



Tolerance of intraoperative hemoglobin decrease during cardiac surgery

CHAPTER 3

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Abstract

Background

It has been suggested that a decrease of at least 50% from the preoperative hemoglobin (Hb) level during cardiac surgery is associated with adverse outcomes even if the absolute Hb level remains above the commonly used transfusion threshold of 7.0 g/dL. In this study the relation between intraoperative Hb decline of at least 50% and a composite endpoint was analyzed.

Study Design and Methods

This single-centre study comprised 11,508 patients who underwent cardiac surgery and had normal preoperative Hb levels (12.0-16.0 g/dL in women, 13.0-18.0 g/dL in men) between January 2001 and December 2011. Logistic regression modeling was used. The composite endpoint comprised in-hospital mortality, stroke, myocardial infarction and renal failure.

Results

Patients whose Hb did not decrease at least 50% and remained above 7 g/dL were used as reference (n=9672). A total of 363 (3.2%) patients had an intraoperative Hb of less than 7 g/dL during surgery but a Hb decrease less than 50%; 876 patients (7.4%) showed both a nadir Hb less than 7g/dL and a Hb decrease of at least 50%, while 597 (5.2%) had a Hb decrease of at least 50% and a nadir Hb of at least 7 g/dL. In this last group the incidence of the composite endpoint was higher than in patients in the reference group (adjusted odds ratio,1.27; 95 % confidence interval,1.14-1.41).

Conclusions

Our findings show that a decrease at least 50% from baseline Hb during cardiac surgery is associated with adverse outcomes, even if the absolute Hb level remains above the commonly used transfusion threshold 7.0 g/dL.

Introduction

Cardiac surgery is associated with intraoperative blood loss and hemoglobin (Hb) decrease, which can lead to an anemic state. Anemia is a recognized risk factor for operative mortality; additionally serious and invalidating postoperative morbidity like stroke, myocardial infarction, and renal failure have been described.[1–4] Transfusions with red cells (RBCs) serve to prevent the occurrence of anemia-related complications, but have also been associated with severe side effects.[5,6] Therefore, it is sometimes unclear whether an anemic patient will benefit from a RBC transfusion or not.

Measuring tissue oxygen delivery would be the best way to measure a critically low Hb level that may benefit from a RBC transfusion, but since this is not yet possible surrogate indications for transfusion are used. In cardiac surgery often a transfusion threshold of 7.0 g/dL is used. It has been suggested that the extent of an acute decrease in Hb might pose a greater risk for postoperative complications than a Hb decreasing below 7.0 g/dL.[7]

This could imply that a relative transfusion threshold might be more useful in preventing ischemia-related complications than an absolute transfusion trigger. This would especially be the case in patients with a 'higher' preoperative Hb level, because they must tolerate a larger Hb decrease before being transfused with RBCs when a fixed transfusion trigger is used. In the literature, the use of a relative transfusion trigger of 50% Hb decrease has led to fewer postoperative adverse events.[7]

Our primary objective was to examine the association between intraoperative acute anemia - defined as a Hb decrease of 50% or more – on a composite endpoint of postoperative complications. Our secondary objective was to analyze the relation between RBC transfusions and the composite endpoint in patients with an intraoperative Hb decrease of 50% or more with a nadir Hb of higher than 7 g/dL.

Materials and Methods

This study complied with the Declaration of Helsinki (2012-2013 revision. The local research ethics committee approved this study and the need for informed consent was waived.

Study population

We performed a single-centre cohort study that included 11,580 consecutive patients who underwent cardiac surgery in the Amphia Hospital in Breda, the Netherlands.

Annually, approximately 1500 patients undergo cardiac surgery at the Amphia Hospital. After surgery, patients were admitted at a 26-bed, level III intensive care unit.

Patients undergoing all types of on-pump cardiac surgery from January 1, 2001 until December 31, 2011 were included. To avoid bias of preexistent anemia and polycytemia, we excluded patients with an abnormal Hb level. Therefore, we only included patients with a preoperative Hb between 12.0 and 16.0 g/dL in women and 13.0 and 18.0 g/dL in men according to the definition of the World Health Organization (WHO).[8] All RBC transfusions prescribed to patients were allogeneic and leukoreduced. Patients of whom no perioperative Hb levels were available were excluded.

Decisions regarding patient care or perioperative transfusions were left to the attending anesthesiologist and/or surgeon, according to the transfusion guidelines of the American Association of Anesthesiologists and the Dutch transfusion guideline.[9,10]
On the intensive care unit and the ward, transfusions were prescribed by the attending physician based on the assumed cardio and respiratory status of the patient. This Dutch guideline stated that RBC transfusion is usually indicated when the Hb level is < 7 g/dL and rarely higher than 9 g/dL. In case of Hb levels between 7 and 9 g/dL cardiopulmonary reserve, age, comorbidity and blood loss determines the transfusion threshold. In practice a transfusion trigger of 7 g/dL was applied.

Data collection

Data collection for this cohort started January 1, 1997. Intraoperative Hb data were not collected until 2001. To answer our specific research question, patients who underwent cardiac surgery prior to January 1, 2001, were therefore excluded. Thus, our cohort comprised patients who underwent on-pump cardiac surgery from January 1, 2001, until December 31, 2011. Data collection was compliant with the National Cardiac Surgery Registry and the National Intensive Care Registry.[11] All data were acquired from pre-, intra-, and postoperative routine blood draws and medical files.

Measurements

The preoperative Hb level was routinely measured in all patients and the last preoperatively measured Hb level was used as preoperative Hb in our study. Intraoperative Hb was measured at the induction of anesthesia, 30 minutes after the start of cardiopulmonary bypass (CPB), and after heparin reversal before chest closure. Additional Hb measurements were left to the discretion of the attending anesthesiologist and/or surgeon and were mostly performed when the patient's condition required strict monitoring. The lowest intraoperative Hb was taken as the nadir Hb. Only patients whose pre- as well as intraoperative Hb level were available were included in the present analysis.
The Hb decrease in percentage was calculated as: [(preoperative Hb – nadir Hb)/preoperative Hb] x 100.

Outcome definitions

Our primary aim was to analyze the effect of a Hb decrease of 50% or more during cardiac surgery on a composite endpoint of possible anemia-related complications comprising in-hospital death and/or stroke and/or acute kidney failure and/or myocardial infarction. Stroke was defined as a new persistent cerebrovascular event leading to neurological defaults and was diagnosed by a neurologist. Acute kidney failure was defined as the
need for postoperative renal replacement therapy when this was not indicated before and/or an increase in serum creatinine of more than 100%. The diagnosis postoperative myocardial infarction was made based on either the occurrence of new Q waves on the electrocardiogram or ischemic ST changes in combination with abnormal postoperative troponin T levels (troponin T level > 0.5 μ/L for coronary artery bypass grafting (CABG) surgery, troponin T level > 0.8 μ/L for valve surgery and troponin T level > 1.0 μ/L for combined CABG and valve procedures). Both serum

creatinine and troponin T were routinely measured in every patient postoperatively. A secondary aim was to analyze the association between RBC transfusion and the composite endpoint in the four different categories independently, in particular because we were interested in the effect of RBC transfusion in patients with a Hb decrease of 50% or more.

Statistical analyses

We divided our cohort in four categories based on absolute and relative Hb decrease using the cut off points described previously. Specifically, we analyzed the association between a 50% Hb decrease or more and the composite endpoint in the presence and in the absence of a Hb level of less than 7 g/dL as this is a commonly used transfusion trigger.

The first (reference) category consisted of patients who had an intraoperative Hb decrease less than 50% and whose intraoperative nadir Hb remained higher than 7 g/dL. Furthermore, the categories consisted of patients who only had a Hb level of less than 7 g/dL (second category), only an intraoperative Hb decrease of 50% or more (third category), and both an intra-operative Hb level of less than 7 g/dL and a Hb decrease of 50% or more (fourth category).

Multivariable logistic regression models were used and crude as well as adjusted results are presented. Covariates were included in the adjusted analysis if they were considered a risk factor for the composite endpoint and their incidence differed between the four categories. Because of the etiological nature of our research question we also included covariates related to the exposure and the outcome irrespectively if there were differences between the four categories.[12] We adjusted for the following pre- and intra-operative variables;

Preoperative variables

Preoperative variables included age (as a continuous variable), sex, current smoking, preoperative Hb (g/dL), vascular disease (defined as having previous vascular surgery and/or intermittent claudication), liver cirrhosis (diagnosed by a positive biopsy and documented portal hypertension or previous periods of upper gastrointestinal bleeding due to portal hypertension or previous episodes of liver failure, coma or encephalopathy), hematologic malignancy (as diagnosed by a hematologist), left ventricle hypertrophy (diagnosed on echocardiography), atrial fibrillation, endocarditis (according to the Duke criteria), hypertension (diagnosis retrieved from patient's history and/or treatment with antihypertensive drug therapy), chronic obstructive pulmonary disease (COPD; diagnosis retrieved from patient's history and treatment with bronchodilators and/or corticosteroids), diabetes (defined as receiving any antidiabetic drug therapy), myocardial infarction (as diagnosed by the referring cardiologist), aspirin use, clopidogrel use, use of anticoagulant drugs (heparin, low-molecular-weight heparin, coumarines or a combination), creatinine clearance (as a continuous variable), fibrinogen (g/dl; as categorical variable; <2 / > 2 g/dl), New York Heart association (NYHA) class, respiratory failure (defined as the need for mechanical ventilation), previous cardiac surgery, emergency surgery, type of surgery (CABG, CABG plus valve surgery, CABG plus other, valve surgery or other), cardiopulmonary resuscitation (CPR) 24h before surgery.

Intra-operative variables

Intraoperative variables included use of antifibrinolytics (aprotinin, tranexamic acid, other), lowest intraoperative temperature (as continuous variable), CPB duration and operation duration (both as continuous variables), fresh frozen plasma (FFP) and platelet (PLT) transfusion (as binary variables), circulatory arrest, number of coronary arteries affected and cell-saver blood returned to patient (as binary variable). Missing data in the database were
imputed using a multiple imputations model.[13]
RBC transfusions were not included in the overall model because the relationship between RBC transfusions and the composite endpoint in the four patient groups was analyzed separately.
Effect modification occurs when the magnitude of the effect of the primary exposure on an outcome differs depending on the level of a third variable. In this situation, computing an overall estimate of association has little meaning. One common way of dealing with effect modification is to examine the association separately for each
level of the third variable.[14,15] To analyze if there was any effect modification present in our study sample we did separate analyses, stratifying sex and type of surgery, for all patients with a Hb decrease of at least 50%.

Results

Characteristics of the study population

Data of 16,352 patients were collected of which 11,508 patients were included in the analysis. Figure 1 presents a flow chart of patient exclusions and number of patients available for analysis. Perioperative Hb data were missing for 3341 patients, so they were excluded. A total of 181 patients were excluded because of missing intraoperative Hb data. An additional 1322 were excluded because they underwent off-pump surgery. A total of 1473 (12.8%) patients had a Hb decrease of 50% or more.

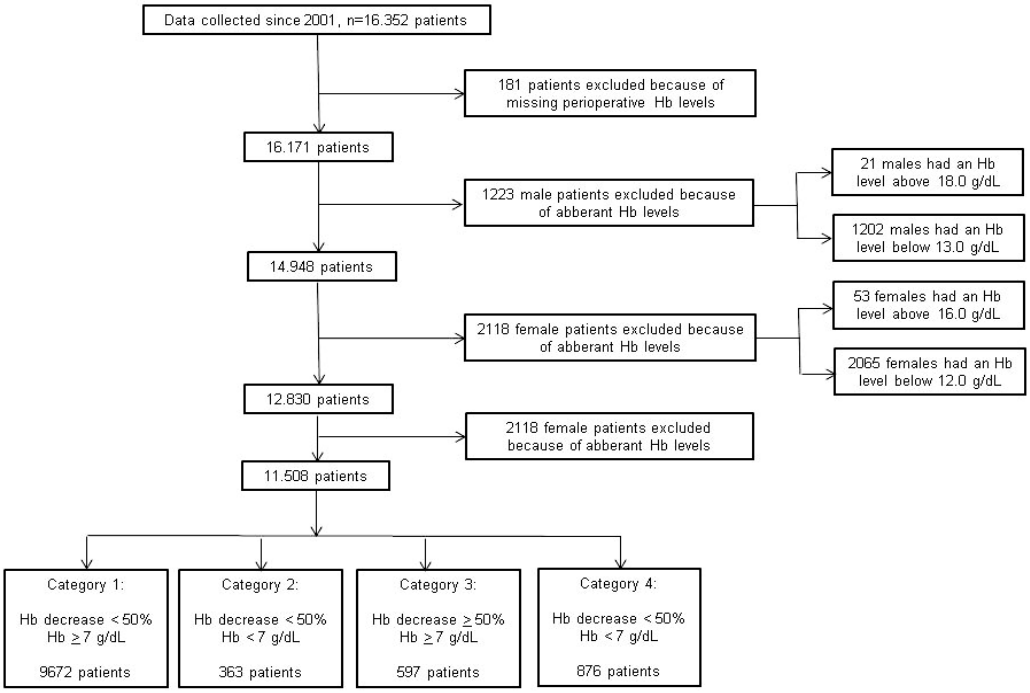


Figure 1. *In- and exclusion flowchart*

Perioperative characteristics of the included patients according to Hb loss of 50% or more and/or nadir Hb below 7 g/dL are shown in Table 1. As expected comorbidities, demographics, and risk factors differed between patients with different amounts of blood loss. For example patients with an intraoperative Hb loss of 50% or more and a nadir Hb of higher than 7 g/dl were more often male, had less often emergency surgery performed, had a higher preoperative Hb and were less frequently transfused. Also, they received less inotropic drugs.

Blood loss and anemia-related complications

Overall, anemia-related complications occurred in 2322 (20.7%) patients, of who 254 (2.2%) died, 952 (8.3%) had a stroke, 569 (5.0%) developed postoperative renal failure requiring renal replacement therapy and/or an increase in serum creatinine of more than 100% and 1176 (10.3%) suffered a postoperative myocardial infarction. Some patients suffered more than one complication.

Compared to patients who did not lose 50% or more of their Hb and who remained higher than 7 g/dl (reference group, Category 1), patients in Category 3 with a Hb loss of 50% or more whose intraoperative nadir Hb remained higher than 7 g/dL did suffer more anemia-related complications (adjusted OR [aOR], 1.26; 95% Confidence Interval [CI] 1.13-1.41; table 2). In patients who had a Hb decrease of 50% or more and an intraoperative nadir Hb of less than 7 g/dL there

was also a positive association with the composite endpoint (aOR 1.12; 95% CI 1.02-1.22).
Patients who had a Hb decrease of less than 50% but who did experience a nadir Hb of less than 7 g/dL during surgery had roughly the same odds to suffer from the composite endpoints as the patients in the reference category (aOR, 0.93; 95% CI, 0.82-1.06).

Effect modification and stratification

To examine potential effect modification by sex and type of surgery, we performed stratified analyses for males and females as well as for type of surgery (CABG and CABG in combination with other surgical procedures vs. remaining non-CABG surgeries). Patients with an isolated Hb level of less than 7 g/dL despite less than 50% Hb decrease were more often female (85%), which is often a cause of a different profile of comorbidities and outcomes. When we stratified our analysis for sex, a more distinct association between a Hb decrease of at least 50% and the composite endpoint was found in women. This could be explained by the fact that for a woman to reach a Hb decrease of 50% or more, it means that a much lower nadir Hb must be reached compared to men, even though, this association was not statistical significant (aOR, 1.40; 95% CI, 1.09-1.81). When we examined CABG or combined surgery with CABG combined versus other surgical procedures, no apparent modifications of the effect of Hb decrease on the composite endpoint were found. These results are displayed in table 2A.

Table 1. Patient characteristics (N= 11508)

	Total	Missing	Hb decrease <50% & Hb > 7 g/dL (n=9672)	Hb decrease <50% & Hb < 7 g/dL (n=363)	Hb decrease >50% & Hb > 7 g/dL (n=597)	Hb decrease >50% & Hb < 7 g/dL (n=876)
Pre-operative variables:						
Female, N (%)	3202 (27.8)	-	2304 (23.8)	310 (85.4)	86 (14.4)	502 (57.3)
Age (year), median (IQR)	67 (59-73)	-	67 (59-73)	71 (64-77)	65 (57-71)	69 (61-74)
Weight (kg), median (IQR)	80 (71-89)	1	81 (72-90)	70 (63-79)	79 (73-87)	72 (64-81)
Aspirin use, N (%)	6489 (57.3)	182	5445 (57.0)	208 (59.1)	360 (62.2)	476 (56.7)
Clopidogrel use, N (%)	2183(17.1)	58	1950 (17.9)	59(16.3)	72(12.0)	102(11.6)
Anticoagulant drug use, N (%)*	3476 (30.3)	35	3009 (31.2)	99 (27.3)	126 (21.2)	242 (27.8)
Pre-operative fibrinogen level <2, N (%)	26 (0.5)	6068	23 (0.5)	1 (0.8)	1 (0.8)	1 (0.6)
Diabetes	2085 (18.2)	19				
Diabetes I, N (%)	365 (3.2)		296 (3.1)	19 (5.2)	12 (2.0)	38 (4.3)
Diabetes II, N (%)	1720 (15.0)		1415 (14.7)	82 (22.6)	77 (12.9)	146 (16.7)
Hypertension, N (%)	6494 (56.4)	3	5449 (56.4)	229 (63.1)	318 (53.3)	498 (56.8)
Cerebro-vascular disease (history of stroke, transient ischaemic attack, other), N (%)	1089 (9.5)	7	878 (9.1)	53 (14.6)	58 (9.7)	100 (11.4)
Hematological malignancy, N (%)	29 (0.3)	7	23 (0.2)	2 (0.6)	2 (0.3)	2 (0.2)
Atrial fibrillation, N (%)	1392 (12.1)	15	1220 (12.6)	46 (12.7)	49 (8.2)	77 (8.8)
History of myocardial infarction, N (%)	1894 (19.7)	1916	1698 (20.8)	40 (12.7)	55 (12.4)	101 (14.9)
Left ventricular hypertrophy, N (%)	2815 (24.6)	68	2368 (24.6)	99 (27.3)	119 (20.0)	229 (26.4)
Previous cardiac surgery, N (%)	747 (6.5)	1	573 (5.9)	22 (6.1)	46 (7.7)	106 (12.1)
No. coronary arteries affected, median (IQR)	3 (1-3)	26	3 (1-3)	3 (0-3)	3 (2-3)	3 (2-3)
Ejection Fraction, N (%)		187				
- >50%	8896 (78.6)		7443 (78.2)	287 (80.2)	486 (82.9)	680 (79.5)
- 25-50%	1928 (17.0)		1637 (17.2)	59 (16.5)	84 (14.3)	148 (17.3)
- < 25%	497 (4.4)		442 (4.6)	12 (3.4)	16 (2.7)	27 (3.2)
Creatinine clearance (ml/min), median (IQR)	82 (65-102)	20	84 (67-104)	64 (50-78)	82 (66-102)	68 (55-86)
Chronic renal failure (creatinine> 177), N (%)	131 (1.1)	3	93 (1.0)	12 (3.3)	4 (0.7)	22 (2.5)
Acute renal failure N (%)	99 (0.9)	7	86 (0.9)	1 (0.3)	2 (0.3)	10 (1.1)
Type of surgery, N (%)		-				
- CABG	7028 (61.1)		5885 (60.8)	187 (51.5)	419 (70.2)	537 (61.3)
- CABG + valve	1584 (13.8)		1276 (13.2)	78 (21.5)	68 (11.4)	162 (18.5)
- CABG + other	87 (0.8)		67 (0.7)	4 (1.1)	4 (0.7)	12 (1.4)
- Valve replacement	2397 (20.8)		2123 (21.9)	84 (23.1)	82 (13.7)	108 (12.3)
- Other	412 (3.6)		321 (3.3)	10 (2.8)	24 (4.0)	57 (6.5)
Emergency surgery, N (%)	672 (5.8)	3	562 (5.8)	22 (6.1)	18 (3.0)	70 (8.0)
Euroscore I, median (IQR)	5 (3-7)		5 (3-7)	7 (5-9)	4 (2-6)	6 (4-9)

Table 1. Patient characteristics (N= 11508)						
Intra-operative variables:						
Time in surgery in minutes, median (IQR)	240 (205-281)	14	235 (205-275)	252 (210-305)	245 (207-295)	270 (225-340)
CPB duration (min), median (IQR)	97 (78-125)	-	95 (77-122)	104 (80-136)	99 (79-127)	111 (85-160)
Circulatory arrest, N (%)	141 (1.2)		86 (0.9)	5 (1.4)	12 (2.0)	38 (4.3)
IABP, N (%)	485 (4.2)	-	379 (3.9)	16 (4.4)	19 (3.2)	71 (8.1)
Inotropic drug use, N (%)	4494 (39.4)	88	3786 (39.5)	156 (43.1)	161 (27.1)	391 (44.8)
Anti-fibrinolytic drug use, N (%)	7671 (67.2)	92	6774 (70.5)	213 (59.7)	269 (45.5)	415 (48.0)
Cellsaver blood returned during surgery, N (%)	11495 (99.9)	-	9666 (99.9)	362 (99.7)	595 (99.7)	872 (99.5)
≥ 1 unit RBC during surgery, N (%)	1300 (11.3)	1	703 (7.3)	157 (43.3)	47 (7.9)	393 (44.9)
≥ 1 unit FFP during surgery, N (%)	598 (5.2)	-	395 (4.1)	22 (6.1)	39 (6.5)	142 (16.2)
≥ 1 unit platelets during surgery, N (%)	569 (4.9)	-	373 (3.9)	24 (6.6)	43 (7.2)	129 (14.7)
Hb measurements:						
Pre-operative Hb (g/dl), median (IQR)	14.3 (13.5-15.1)	-	14.3 (13.7-15.1)	12.7 (12.4-13.0)	15.5 (15.0-16.1)	13.8 (13.2-14.5)
Lowest Hb during surgery (g/dl), median (IQR)	8.5 (7.6-9.3)	-	8.7 (8.1-9.7)	6.7 (6.6-6.9)	7.4 (7.2-7.7)	6.4 (6.0-6.7)
Hb at hospital discharge, median (IQR)	10.5 (9.7-11.4)	220	10.5 (9.7-11.4)	10.3 (9.7-10.9)	10.6 (10.0-11.6)	10.5 (9.7-11.3)
In hospital mortality, N (%)	254 (2.2)	-	167 (1.7)	17 (4.7)	11 (1.8)	59 (6.7)
Acute kidney injury, N (%) †	569 (5.0)	236	435 (4.6)	23 (6.5)	27 (4.6)	84 (9.8)
Stroke, N (%) ‡	952 (8.3)	14	759 (7.9)	34 (9.4)	52 (8.7)	107 (12.2)
Acute myocardial infarct, N (%)	1176 (10.3)	1916	953 (9.9)	38 (10.5)	63 (10.6)	122 (14.0)
Composite endpoint, N (%)	2322 (20.7)	303	1865 (19.8)	85 (24.2)	124 (21.2)	248 (29.2)

** Heparin, low molecular weight heparin (LMWH), coumarines or a combination*

† Defined as the postoperative need for renal replacement therapy or a creatinine rise > 100%

‡ Defined as a new persistent cerebro-vascular event leading to neurological defaults.

Table 2. Composite endpoint in relation to intraoperative Hb decrease (N = 11508)

Patient category	Number	Hb decrease ≥ 50%	Hb < 7 g/dL	OR (crude)	95% CI	p value	OR* (adjusted)	95% CI	p value
1 (ref)	9672	–	–	1			1		
2	363	–	+	1.28	1.16-1.42	<0.001	0.93	0.82-1.06	0.309
3	597	+	–	1.08	0.99-1.17	0.064	1.26	1.13-1.41	<0.001
4	876	+	+	1.65	1.55-1.75	<0.001	1.12	1.02-1.22	0.017

**Adjusted for acetylsalicylic acid, clopidogrel and anticoagulant drug use, preoperative fibrinogen of less than 2 g/dL, hematologic malignancy, antifibrinolytic use, cell-saver blood returned to patient, lowest temperature intraoperative, previous cardiac surgery, preoperative Hb (g/dL), emergency surgery, CPB duration, operation duration, type of surgery, FFP and PLT transfusion during surgery, liver cirrhosis, preoperative circulation arrest, number of coronaries affected, age, sex, creatinine clearance, NYHA class, left ventricle hypertrophy, respiratory failure, smoking, atrial fibrillation, endocarditis, hypertension, COPD, diabetes, vascular disease, preoperative myocardial infarction, and CPR 24 hours before surgery.*

Table 2A: Patients with more than 50% Hb decrease in relation to the composite endpoint stratified for gender & type of surgery

Intra-operative Hb:		N	Hb decrease >50%	Hb < 7 g/dl	OR (crude)	95% CI	P-value	OR* (adjusted)	95% CI	P-value
Category 3	Male	511	+	-	1.12	1.02-1.22	0.016	1.22	1.08-1.39	0.002
Category 4	Male	374	+	+	1.67	1.51-1.83	<0.001	1.13	0.98-1.31	0.092
Category 3	Female	86	+	-	1.04	0.84-1.27	0.735	1.40	1.09-1.81	0.009
Category 4	Female	502	+	+	1.44	1.32-1.57	<0.001	1.05	0.93-1.19	0.444
Category 3	CABG	491	+	-	1.07	0.97-1.19	0.170	1.24	1.07-1.43	0.003
Category 4	CABG	711	+	+	1.46	1.34-1.59	<0.001	1.10	0.97-1.24	0.153
Category 3	Non-CABG	106	+	-	1.19	1.03-1.37	0.015	1.26	1.05-1.51	0.013
Category 4	Non-CABG	165	+	+	1.95	1.77-2.14	<0.001	1.19	1.04-1.36	0.014

** Adjusted for: acetylic salicylic acid, clopidogrel and anti-coagulant drug use, preoperative fibrinogen <2 g/dl, haematological malignancy, anti-fibrinolytic use, cell saver blood returned to patient, lowest temperature intra-operative, previous cardiac surgery, pre-operative Hb (g/dL) emergency surgery, CPB duration, operation duration, type of surgery, FFP and platelet transfusion during surgery, liver cirrhosis, preoperative circulation arrest, number of coronaries affected, age, sex, creatinine clearance, NYHA class, left ventricle hypertrophy, respiratory failure, smoking, Atrial fibrillation, endocarditis, hypertension, COPD, diabetes, vascular disease, preoperative myocardial infarction, CPR 24h before surgery.*

Red cell transfusions

As shown in Table 1, 7.3 and 7.9% of patients in categories 1 and 3 received red blood cell transfusions though their nadir Hb remained higher than 7 g/dl. This is most often the result of clinical judgment by the attending physician or intraoperative events, which indicated the need of a blood transfusion despite the Hb level higher than the transfusion trigger of 7 g/dl. Table 3 presents the association between RBC transfusions and the composite endpoint within each of the four categories of Hb decrease. In Category 1 where there was neither a Hb decrease of at least 50 % nor a Hb level of less than 7 g/dL, the adjusted odds of acquiring the composite endpoint was

1.51 (95% CI, 1.38-1.66) in transfused patients compared with non-transfused patients. In patients from Categories 2 and 4, 43.3 and 44.9% received red cell transfusions. Among these patients transfusion was associated with a decreased odds of developing the composite endpoint (aOR 0.57, 95% CI 0.42-0.77, for Category 2; and aOR 0.95, 95% CI 0.78-1.16 for Category 4).
Among patients who had a Hb decrease of more than 50% but had an intraoperative nadir Hb of more than 7 g/dL, 47 (7.9%) patients received RBC transfusions. Among these patients transfusion was associated with a nonsignificant lower odds of developing composite endpoints (aOR, 0.88; 95% CI, 0.55-1.41).

Table 3: Composite endpoint in relation to RBC transfusion (n=11,508)

RBC transfusion	Number	Number (%) transfused	Hb decrease ≥ 50%	Hb < 7 g/dL	OR crude	95% CI	P value	OR* adjusted	95% CI	P value
Category 1	9672	703 (7.3)	–	–	2.67	2.50-2.86	<0.001	1.26	1.17-1.36	<0.001
Category 2	363	157 (43.3)	–	+	0.91	0.74-1.11	0.348	0.57	0.42-0.77	<0.001
Category 3	597	47 (7.9)	+	–	3.00	2.33-3.86	<0.001	0.88	0.55-1.41	0.590
Category 4	876	393 (44.9)	+	+	1.64	1.45-1.84	<0.001	0.95	0.78-1.16	0.618

** Adjusted for acetylsalicylic acid, clopidogrel and anticoagulant drug use, preoperative fibrinogen of less than 2 g/dL, hematologic malignancy, antifibrinolytic use, cell-saver blood returned to patient, lowest temperature intraoperative, previous cardiac surgery, preoperative Hb (g/dL), emergency surgery, CPB duration, operation duration, type of surgery, FFP and PLT transfusion during surgery, liver cirrhosis, preoperative circulation arrest, number of coronaries affected, age, sex, creatinine clearance, NYHA class, left ventricle hypertrophy, respiratory failure, smoking, atrial fibrillation, endocarditis, hypertension, COPD, diabetes, vascular disease, preoperative myocardial infarction, and CPR 24 hours before surgery.*

Discussion

In our cohort of cardiothoracic surgery patients an intraoperative Hb decrease of 50% or more was associated with a higher incidence of postoperative complications including in-hospital mortality and/or stroke and/or kidney failure and/or myocardial infarction, even if their Hb concentration remained higher than 7 g/dL. Males with higher preoperative Hb were overrepresented in this category , but when the analysis was stratified for gender these findings also applied to females with a higher preoperative Hb.
This finding is in agreement with a previous study performed by Karkouti and colleagues who analyzed the degree of acute anemia that patients can safely tolerate during cardiac surgery.[7] That study also showed that a Hb decrease of more than 50% during surgery was associated with in-hospital mortality, stroke and kidney failure (OR 1.53, 95% CI, 1.12-2.08).[7] In this study we combined two cut-off points creating four categories. This way we were able to analyze the association between absolute and relative Hb loss in more detail. We chose a broader definition of the composite endpoint; in addition to in-hospital mortality and/or stroke and/or renal failure our endpoint also comprised postoperative myocardial infarction.
Approximately 8% of the patients with more than 50% Hb loss were transfused RBCs despite Hb levels above 7 g/dL. In these patients, as well in patients who reached a nadir Hb below 7g/dL,

transfusion was associated with fewer postoperative complications, suggesting that transfusion might be efficacious in these patients. Yet, given the limited number of transfused patients in this subgroup and the lack of statistical significance, these findings have to be interpreted with caution.

To appreciate these findings, some issues need to be discussed. One of the strengths of our study was the large number of consecutive patients. The outcome variables of all patients were known and therefore selection bias was avoided. Also, due to the large amount of detailed covariates we were able to correct thoroughly for possible confounding caused by differences in preoperative patient characteristics. While seeking causal inferences between exposure and outcome, we chose to adjust for risk factors for the outcome and differences in baseline patient characteristics independent of their significance.[12]

A limitation of our study was that we only took intra-operative Hb and transfusion into account; this does not allow us to convey the conclusions to the whole perioperative period. The complexity of unravelling whether the complications that occur after cardiac surgery are caused by blood loss or by the events leading to excessive blood loss is well recognized. Although we tried to be as thorough as possible (for instance, by excluding re- sternotomies from our analysis) we cannot distinguish between the cause of Hb loss more than 50% and the acute anemia itself to explain the increased risk for the composite endpoint in this category.

A further limitation is that the number and timing of Hb measurements during surgery were not documented (besides the four standard measurements). Additional Hb measurements were performed on request by the attending anesthesiologist when deemed needed. This meant that the 'correct' lowest intraoperative Hb level might have been missed and that patients could have been misclassified. The risk of missing the 'correct' nadir Hb is a general problem in this type of study, since continuous measurement of Hb is not accurate enough for clinical use, especially in patients who have a low perfusion state.[16,17]

Our findings are biologically plausible, because it is known that an acute decrease in Hb level could have adverse consequences on end-organ function, especially on oxygen dependent organs as the kidney, heart and brain.[18]

An acute reduction in Hb level will be sensed on a cellular level which leads to adaptive cardiovascular and respiratory responses to optimize tissue oxygen delivery.[13,18–21] These adaptive responses include an increase in cardiac output, a reduction in systemic vascular resistance with organ specific vasodilatation, and an increase in tissue oxygen extraction.[18] Although these adaptive mechanisms can keep homeostatic balance intact for some time, depending on the extent and timing of Hb loss adaptive mechanisms may fail and eventually lead to end-organ damage.

The amount of Hb decrease that can be safely tolerated is highly debated. As long as cellular oxygen content measurements cannot be applied routinely to define whether or not a RBC transfusion is indicated, it is of great importance to define the most beneficial transfusion policy. In critically ill patients and in patients undergoing cardiothoracic surgery, a restrictive transfusion strategy is propagated, with the purpose of reducing the risks associated with the (inappropriate) transfusion of RBCs, as those risks are well put forward in literature.[22–25]

Interestingly, a pilot trial in patients with symptomatic coronary artery disease, comparing

a restrictive (8 g/dL) versus a liberal (10 g/dL) transfusion threshold, showed that the liberal transfusion strategy was associated with a trend for fewer major cardiac events and deaths.[26] This underscores that the optimal transfusion threshold depends on the clinical situation and therefore differs for individual patients, which is corroborated by the results of an international forum in which 38 hospitals answered a questionnaire regarding their transfusion triggers and the use of guidelines. In those hospitals, target Hb on CPB differed, ranging from 6.0 till 8.0 g/dL.[25,27,28]

Also the appropriate acceptable amount of hemodilution is uncertain. Several studies have addressed the adverse effects of a low nadir Hct.[29–31] But if and when exactly volume and/or Hb replacement during cardiac surgery is indicated needs to be addressed in future studies.[18,32]

The results of our study imply that a fixed transfusion trigger might not be in the best interest of patients with a 'higher' preoperative Hb. Patients with a high preoperative Hb level must lose a greater Hb volume before reaching the transfusion triggers currently described in the guidelines.[9,10] Therefore, these patients are more likely to suffer from anemia-related complications. It is unknown whether RBC transfusions decrease the risk of anemia-related complications in patients with an intraoperative Hb decrease of 50% or more. In our study we found that RBC transfusions were associated with a lower incidence of the composite endpoint in patients with a Hb decrease of 50% while their nadir Hb remained higher than 7 g/dL. The previously mentioned questionnaire shows that the transfusion threshold described in guidelines or local protocols is not the leading reason for transfusions, as additional variables also serve as important triggers.[28] Taken into account the results of our study, a Hb decrease of 50% or more poses one of these additional variables.

In conclusion, patients with an intraoperative Hb decrease of 50% or more may suffer from anemia-related complications even if their Hb remains higher than 7 g/dL.

Reference List

1 Munoz M, Gomez-Ramirez S, Campos A, Ruiz J, Liumbruno GM. Pre-operative anaemia: prevalence, consequences and approaches to management. Blood Transfus. 2015;13(3):370-379. doi:10.2450/2015.0014-15 [doi].

2 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(5):471-479. doi:CIRCULATIONAHA.106.653501 [pii].

3 van Straten AH, Hamad MA, van Zundert AJ, Martens EJ, Schonberger JP, de Wolf AM. Preoperative hemoglobin level as a predictor of survival after coronary artery bypass grafting: a comparison with the matched general population. Circulation. 2009;120(2):118-125. doi:10.1161/CIRCULATIONAHA.109.854216 [doi].

4 Ranucci M, Baryshnikova E, Castelvecchio S, Pelissero G, Surgical, Group COR (SCORE). Major bleeding, transfusions, and anemia: the deadly triad of cardiac surgery. Ann Thorac Surg. 2013;96(2):478-485. doi:10.1016/j.athoracsur.2013.03.015 [doi].

5 Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. Jama. 2010;304(14):1559-1567. doi:10.1001/jama.2010.1446 [doi].

6 Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. Crit Care Med. 2008;36(9):2667-2674. doi:10.1097/CCM.0b013e3181844677 [doi].

7 Karkouti K, Wijeysundera DN, Yau TM, McCluskey SA, van Rensburg A, Beattie WS. The influence of baseline hemoglobin concentration on tolerance of anemia in cardiac surgery. Transfusion. 2008;48(4):666-672. doi:10.1111/j.1537-2995.2007.01590.x [doi].

8 McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993-2005. Public Health Nutr. 2009;12(4):444-454. doi:10.1017/S1368980008002401.

9 of Anesthesiologists Task Force on Perioperative Blood Transfusion AS, Therapies A. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Anesthesiology. 2006;105(1):198-208. doi:00000542-200607000-00030 [pii].

10 de Vries R, Haas F, working group for revision of the Dutch Blood Transfusion Guideline 2011. English translation of the dutch blood transfusion guideline 2011. Clin Chem. 2012;58(8):1266-1267. doi:58/8/1266 [pii].

11 Koetsier A, Peek N, de Keizer N. Identifying types and causes of errors in mortality data in a clinical registry using multiple information systems. Stud Health Technol Inform. 2012;180:771-775.

12 Zalpuri S, Middelburg RA, van de Watering L, Vamvakas E, Zwaginga JJ, van der Bom JG. Association vs. causality in transfusion medicine: understanding multivariable analysis in prediction vs. etiologic research. Transfus Med Rev. 2013;27(2):74-81. doi:10.1016/j.tmrv.2013.02.002.

13 Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol. 2006;59(10):1087-1091. doi:10.1016/j.jclinepi.2006.01.014.

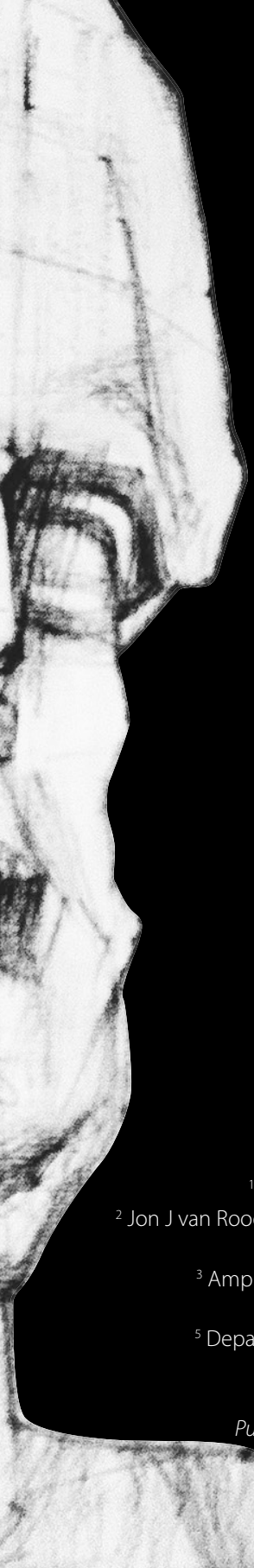
14 14. Boston University School of Public Health. Multivariable methods. http://sphweb.bumc.bu.edu/otlt/MPH- Modules/BS/BS704_Multivariable/BS704_Multivariable7.html. Published 2013. Accessed March 27, 2014.

15 VanderWeele TJ. On the distinction between interaction and effect modification. Epidemiology. 2009;20(6):863-871. doi:10.1097/EDE.0b013e3181ba333c.

16 Isosu T, Obara S, Hosono A, et al. Validation of continuous and noninvasive hemoglobin monitoring by pulse CO-oximetry in Japanese surgical patients. J Clin Monit Comput. 2013;27(1):55-60. doi:10.1007/s10877-012-9397-2.

17 Joseph B, Hadjizacharia P, Aziz H, et al. Continuous noninvasive hemoglobin monitor from pulse ox: ready for prime time? World J Surg. 2013;37(3):525-529. doi:10.1007/s00268-012-1871-y.

18 Hare GMT, Freedman J, David Mazer C. Review article: risks of anemia and related management strategies: can perioperative blood management improve patient safety? Can J Anaesth. 2013;60(2):168-175. doi:10.1007/s12630-012-9861-y.
19 Shander A, Javidroozi M, Ozawa S, Hare GMT. What is really dangerous: anaemia or transfusion? Br J Anaesth. 2011;107 Suppl 1:i41-59. doi:10.1093/bja/aer350.
20 Hare GMT, Tsui AKY, McLaren AT, Ragoonanan TE, Yu J, Mazer CD. Anemia and cerebral outcomes: many questions, fewer answers. Anesth Analg. 2008;107(4):1356-1370. doi:10.1213/ane.0b013e318184cfe9.
21 Weiskopf RB, Viele MK, Feiner J, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. JAMA. 1998;279(3):217-221.
22 Rao S V, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. Jama. 2004;292(13):1555-1562. doi:292/13/1555 [pii].
23 Hebert PC, Wells G, Martin C, et al. A Canadian survey of transfusion practices in critically ill patients. Transfusion Requirements in Critical Care Investigators and the Canadian Critical Care Trials Group. Crit Care Med. 1998;26(3):482-487.



Intraoperative anemia and single red blood cell transfusion during cardiac surgery: An assessment of postoperative outcome including patients refusing blood transfusion

CHAPTER 4

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Abstract

Objectives
Increasing evidence suggests benefits from restrictive red blood cell transfusion (RBC) thresholds in major surgery and critically ill patients. However, these benefits are not obvious in cardiac surgery patients with intraoperative anemia. The authors examined the association between uncorrected hemoglobin (Hb) levels and selected postoperative outcomes as well as the effects of RBCs.

Design
Cohort study with prospectively collected data from a cardiac surgery registry.

Setting
A major cardiac surgical hospital within the Netherlands, which is also a referral center for Jehovah's Witnesses.

Participants
Patients (23,860) undergoing cardiac surgery between 1997 and 2013.

Interventions
Comparisons were done in patients with intraoperative nadir Hb of 8 g/dL and/or an Hb decrease > 50%. Comparison (A) between Jehovah's Witnesses (Witnesses) and matched non-Jehovah's Witnesses (non- Witnesses) transfused with 1 unit of RBC, and comparison (B) between patients given1unit of RBC intraoperatively versus matched non-transfused patients.

Measurements and Main Results
Postoperative outcomes were myocardial infarction, renal replacement therapy, stroke, and death. With propensity matching, the authors optimized exchangeability of the compared groups. Adverse outcomes increased with a decreasing Hb both among Witnesses and among non-Witnesses. The incidence of postoperative complications did not differ between Witnesses and matched non-Witnesses who received RBC (adjusted odds ratio1.44, 95% confidence interval 0.63- 3.29). Similarly, postoperative complications did not differ between patients who received a red cell transfusion and matched patients who did not (adjusted odds ratio 0.94, 95% confidence interval 0.72-1.23).

Conclusion
Intraoperative anemia is associated with adverse outcomes after cardiac surgery, and a single RBC transfusion does not seem to influence these outcomes
Introduction

Introduction

Both low intraoperative hemoglobin (Hb) concentration and red blood cell (RBC) transfusions have been associated with adverse outcomes after cardiac surgery.[1–4] Results from randomized controlled trials performed in patients with various medical conditions, usually using 7.0 or 8.0 g/dL as a restrictive transfusion threshold, suggested no beneficial effects of a more liberal transfusion strategy.[5–7] Clinical guidelines increasingly promote lower transfusion triggers despite insufficient evidence in cardiac surgery regarding the intraoperative Hb level at which the beneficial effects of RBC transfusions outweigh the risks.[8–13]

The interpretation of the association between Hb concentrations and clinical outcomes is hampered by the effect of RBC transfusions, since with decreasing Hb concentrations more patients will be treated with transfusions. RCTs cannot investigate this topic in severely anemic patients as withholding transfusion in these patients is widely considered unethical. Patients who decline transfusion for whatever reason (for example Jehovah's Witnesses, further abbreviated as Witnesses) enable clinicians to study the association between Hb decrease and relevant postoperative outcomes in the absence of RBC transfusions. Comparing anemic Witnesses with transfused anemic non-Jehovah's Witnesses (non-Witnesses) undergoing cardiac surgery can provide valuable information about the consequences of uncorrected anemia or the benefits of transfusion.

Previous studies with Witnesses showed an increase in morbidity when the Hb level decreased below 8g/dL, and an increased mortality when the Hb level decreased below 7 g/dL.[4,14] However, cardiac surgery was not specially addressed in these studies. Cardiac surgery studies including Witnesses underscored the good outcome and similar mortality and morbidity rates as in non-Witnesses, provided Hb levels were optimized.[15–17]

However, the postoperative outcomes of Witnesses undergoing cardiac surgery and suffering from an intraoperative Hb decrease below 8 g/dL (and thus reaching a possible harmful Hb level) have not been reported. The authors hypothesized that uncorrected anemia would lead to more postoperative complications and that RBC transfusions would help decrease these complications. The authors' objectives were to describe the association between intraoperative Hb and postoperative adverse events among patients who received no RBC transfusions during cardiac surgery in both Witnesses and non-Witnesses. Furthermore, Witnesses who, based on intraoperative anemia (intraoperative nadir Hb <8 g/dL and/or Hb decrease >50%), would be eligible for RBC transfusion were compared to similar anemic non-Witnesses who received a single RBC transfusion. Because unidentified differences in preoperative selection and intraoperative treatment between Witnesses and non- Witnesses may have occurred, the authors composed an additional (non-Witness only) study cohort of anemic patients in which they compared non-transfused patients with patients who received 1 unit of RBC.

Methods of Study and Design

This study complied with the Declaration of Helsinki (10th version, 2012-2013). The local research ethics committee approved this study, and the need for informed consent was waived.

Study Setting

The analyses were performed with data of a single-center cardiac surgery registry. Details of this registry have been described earlier.[13] In this registry, perioperative data, including morbidity and process as well as outcome indicators, from all consecutive patients who undergo cardiac surgery in the Amphia Hospital, Breda, the Netherlands are collected. Data collection for the present analysis took place between January 1, 1997 and January 1, 2013 and was compliant with the Dutch National Cardiac Surgery Registry (BHN) and the Dutch National Intensive Care Registry (NICE, instituted since 1996).[18] All data were acquired from preoperative, intraoperative, and postoperative routine blood collections and medical files. Data regarding blood transfusion were obtained from the hospital laboratory information system.

Since 2006, a Patient Blood Management Program (PBMP) is in place covering the complete perioperative period (including ICU and ward). This PBMP is compliant with the transfusion guidelines of the American Society of Anesthesiologists, the Dutch transfusion guidelines and, more specifically, the guidelines from the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists (STS and SCA guidelines published in 2006 and updated in 2011).[19–21] Intraoperatively, an Hb trigger of 8.0g/dL is used. During cardiopulmonary bypass, Hb above 7.0 g/L is maintained either by transfusion or hemoconcentration, whatever is most appropriate according to the attending anesthesiologist.

Since 2009, this PBMP was further expanded with more elaborated coagulation monitoring and component therapy (Point-of-Care Coagulation, Rotem ®, TEM, Inc.). Within the Netherlands, the Amphia Hospital is a major referral center for Witnesses undergoing cardiac surgery. Witnesses are operated according to a local protocol prohibiting any transfusion of blood products. The differences between PBMP in Witnesses and non-Witnesses are presented schematically in the Scheme 1.

	Management/ measure	Witnesses	Non-Witnesses before 2006	Non Witnesses 2006 - 2009 (Introduction of PBMP)	Non Witnesses after 2009 (Addition of Point of Care Tromboelastography and Coagulation protocol to PBMP)
Pre-operative optimisation	Replacement of oral anticoagulants with heparin or LMWH.	+	+	+	+
	Stopping platelet inhibiting agents 5 days before surgery in stable patients only.	+	+	+	+
	Iron supplements, Folic acid and Recombinant Erythropoietin if anemia or suboptimal Hb	+	-	-	-
	Treatment under is continued in selected patients postoperatively	+	-	-	+
Minimizing blood loss	Meticulous surgical care	+	-	+	+
	Acute autologous blood donation (ABD) if sufficiently high preoperative Haemoglobin,	+	-	+	-
	Routine administration of antifibrinolytics, either tranexamic acid (2x2gr pre and post bypass) or aprotinin (before 2009)	+	-	+	+
	Minimal Extracorporeal Circulation (MECC) priming volume	+ after 2006	-	+	+
	Retrograde drainage of priming fluid.	+ after 2006	-	+ in selected patients	+ in selected patients
	Intra-operative cell salvage; cell saver is routinely available.	+	-	+	+
	In case of ABD and cell salvage, contact between the ABD or cell saver device tubing and the patient was maintained at all times as required by the JW.	+	-	-	-
	Normothermia or light hypothermia and active rewarming up to 36-36.5 °C core temp before coming	+	-	+	+

	Management/ measure	Witnesses	Non-Witnesses before 2006	Non Witnesses 2006 - 2009 (Introduction of PBMP)	Non Witnesses after 2009 (Addition of Point of Care Tromboelastography and Coagulation protocol to PBMP)
	off bypass.				
	After ECC reversal with protamine.	+	+	+	+
	Minimizing blood sampling volume for lab measurement	+	-	-	-
In case of excessive post-operative blood loss	Desmopressin acetate in case of prior acetylsalicylate of phenopyridine exposure	+	-	+	+
	Repeat administration of Tranexamic acid 2 gr intravenously	+	+	+	+
	Rapid decision for resternotomy in case of chest drain loss exceeding 100ml/h for more than 1-3 hours.	+	-	+	+
	No transfusion of blood products	+	-	-	-
	Routine use of dynamic Coagulation testing	+ (since 2009)	-	-	+
	Introduction of Therapy with Fibrinogen and Prothrombin Complex Concentrate (PCC; Coagulation Factors II, VII, IX and X) in Coagulation management protocol	+ (since 2009)	-	-	+

Scheme 1. *Highlights of the PBM protocol for Witnesses and non-Witnesses*

Study Population

To study the association between intraoperative Hb and adverse postoperative outcomes, all patients who underwent cardiac surgery between 1997 and 2013 (Witnesses and non-Witnesses) were included.

To assess the possible effect of RBC transfusion on postoperative outcome, the authors performed 2 separate analyses. First, they compared Witnesses with transfused non-Witnesses (Comparison A); second, they compared transfused with non-transfused non-Witnesses in a different study cohort (Comparison B).

Comparison A

All anemic Witnesses who, according to current guidelines, could have benefitted from intraoperative RBC transfusion were identified. For that purpose the authors defined anemia as an intraoperative Hb < 8 g/dL and/or an Hb decrease > 50%. The authors chose this double threshold based on current literature and because a previous study of their research group showed that patients who had an Hb decrease of 50% or more had a significantly higher chance of adverse outcome. The authors assumed that patients with an intraoperative Hb decrease of > 50% would equally benefit from an RBC transfusion as patients with an Hb level below 8 g/dL.[13] Witnesses were matched to non-Witnesses who received 1 RBC unit intraoperatively. The authors selected patients who received 1 RBC unit because comparability between patients who receive none and patients who receive multiple RBC is poor. To prevent selection bias, all non-Witnesses receiving a single RBC were considered possible matches regardless of whether they had received platelet/FFP transfusion or not. If the authors only included non-Witnesses who had received one RBC and no other blood products, they would have ignored the fact that Witnesses also could have been in need of a transfusion with additional blood products. Since the introduction of the PBMP in 2006, basic intraoperative blood- sparing measures in non-Witnesses have become similar to those in Witnesses. However, the authors acknowledge that Witnesses may undergo a more careful preoperative selection and preparation while, intraoperatively and postoperatively, the cardiac surgical team may work more cautiously to limit blood loss. This may introduce bias or other unidentified benefits that compromises the comparability of Witnesses and non-Witnesses.[15–17,22–24]

Comparison B

In order to cope with these identified and unidentified biases when comparing Witnesses, the authors designed an additional comparison of non-Witnesses. Here, the authors compared non-transfused patients with propensity- matched patients who received a single intraoperative RBC transfusion in the absence of any additional blood products (because in this cohort this would not introduce a selection bias). Data were available on whether the RBC transfusions had been administered during surgery, in the ICU, or on the surgical ward. This information, however, did not allow a distinction between intraoperative RBC transfusion during the primary cardiac operation and a possible subsequent re-sternotomy. The authors, therefore, excluded patients who had undergone a resternotomy.

Exposure and Outcome Definitions

The lowest intraoperative Hb was taken as the nadir Hb. The Hb decrease in percent was calculated as follows: [(preoperative Hb - nadir Hb) / preoperative Hb] x 100. Intraoperative Hb was measured routinely according to institution protocol after induction of anesthesia, 30 minutes after the start of cardiopulmonary bypass (CPB), after cardioplegia, and after heparin reversal before chest closure. Additional Hb measurements were left to the discretion of the attending anesthesiologist and perfusionist.

The postoperative outcomes of interest were myocardial infarction, acute kidney injury, stroke, ICU length of stay, duration of postoperative mechanical ventilation, in-hospital mortality, and a composite endpoint of serious adverse outcomes consisting of myocardial infarction, the need for renal replacement therapy, stroke, and in hospital mortality.

The diagnosis of postoperative myocardial infarction was made based upon either the occurrence of new Q waves on the electrocardiogram (ECG) or new ischemic ST changes in combination with abnormal postoperative troponin T levels (troponin T level 40.5 m/L for CABG surgery, troponin T level 40.8 m/L for valve surgery, and troponin T level above 1.0 m/L for combined CABG and valve procedures). Both serum creatinine and troponin T were measured routinely in every patient postoperatively. Acute kidney failure was defined as the need for postoperative renal replacement therapy excluding patients on preoperative renal dialysis or replacement therapy and/or a rise in serum creatinine of more than 100% as compared to preoperative creatinine. Stroke was defined as a new cerebrovascular event leading to neurologic deficit lasting at least 24 hours and diagnosed by a neurologist. ICU length of stay (ICU LOS) as well as mechanical ventilation time were measured in hours.

Statistical Analyses

To describe the association between the intraoperative nadir Hb and postoperative adverse outcome for all Witnesses as well as for all non-Witnesses who had not received RBC transfusions, the nadir Hb was categorized and plotted against the composite endpoint. No significance tests were performed because the authors studied the trend in decreasing Hb in relation to the composite endpoint and did not use a specific cut-off value.

To analyze the effect of a single unit of RBC transfused during surgery on postoperative adverse outcomes, all Witnesses who reached an intraoperative nadir Hb < 8 g/dL and/or an intraoperative Hb decrease > 50% were selected and propensity matched 1:1 with non-Witnesses who received 1unit of red cells (Comparison A). Also, all non-Witnesses who had an intraoperative nadir Hb < 8 g/dL and/or an intraoperative Hb decrease > 50% and who received 1 unit of RBC during surgery (and no other blood products) were identified. These patients were propensity matched 1:1 with non-Witnesses who did not receive any blood products (Comparison B).

The propensity score for comparison A was developed for matching Witnesses to non-Witnesses who received one unit of RBC. The propensity score for comparison B was developed to match anemic non-Witnesses who were not transfused with anemic non-Witnesses who received one RBC during surgery. The propensity scores were composed using binary regression modeling and included 37 variables. The matching technique used was nearest neighbor.

In addition to propensity score matching, the authors performed a multi variable analysis adjusting for variables, which were distributed unequally between transfused and non- transfused patients, using binary logistic regression modeling.

Results

Patient Characteristics

A total of 23,860 consecutive patients were included during a study period of 15 years, of whom 270 patients were Witnesses. Among the Witnesses, 79 (29%) patients were female, and the median age was 68 (interquartile range [IQR] 60-74) years. Most of these patients underwent an isolated CABG (65%). The median EuroSCORE I was 5 (IQR3-7). In total, 48 (18%) of the Witnesses and 17% of the non-transfused, non-Witnesses developed the composite endpoint complications. Intraoperative nadir Hb concentration in relation to the composite endpoint in Witnesses is shown in Figure 1.

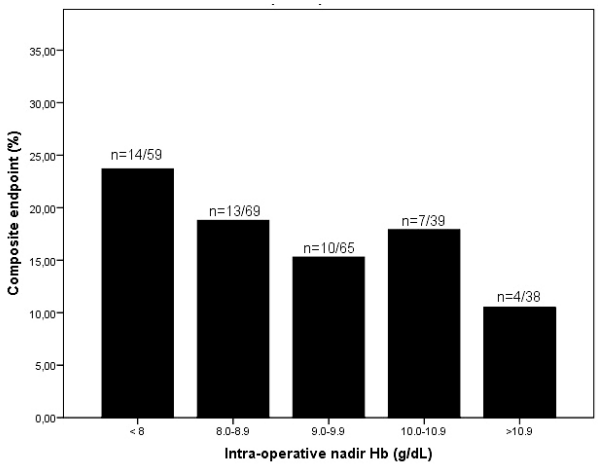


Figure 1. *Distribution of intraoperative nadir Hb (g/dL) in the total Witnesses population (n = 270) in relation to the composite endpoint.*

Postoperative complications increase with decreasing intraoperative Hb concentrations. The largest increase in incidence of the composite endpoint was seen when the nadir Hb decreased below 8 g/dL. Among Witnesses with a nadir Hb below 8 g/dL, the composite endpoint was seen in 24% of the patients. In non-Witness patients who did not receive transfusions the association between Hb and clinical outcomes showed a similar pattern. Among this group of patients with a nadir Hb below 8 g/dL, the composite endpoint was seen in 21% of the patients (Figure 2).

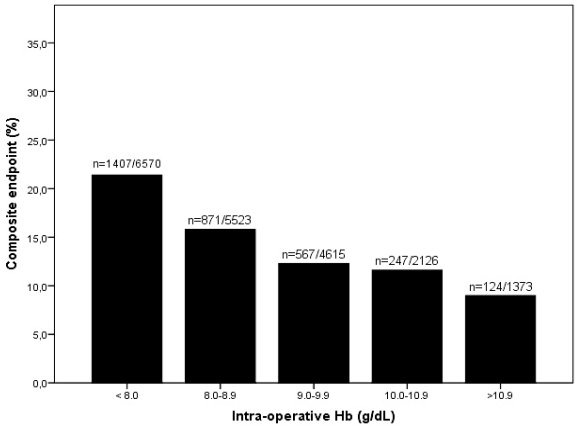


Figure 2. *Distribution of intra-operative nadir Hb (g/dL) in the non-transfused non-JW population (n=20207) in relation to the composite endpoint.*

Clinical Outcomes in Anemic Witnesses Compared to Transfused Anemic Non-Witnesses (Comparison A)

Figure 3 presents the flow chart of patient exclusions and number of patients available for this analysis. A total of 61 Witnesses with an intraoperative Hb level <8 g/dL and/or an Hb decrease >50% were matched with non-Witness patients who had received 1 unit of red cells.

Perioperative characteristics of these matched patients are shown in Table 1. The comorbidities, demographics, and risk factors between Witnesses and non-Witnesses largely were similar. After matching, slight differences were found; for example, in age and gender.

Propensity scores were similar in both groups. About a third of the non-Witnesses transfused with 1 unit of RBC received additional blood products; 33% received fresh frozen plasma (FFP), and 31% received additional platelet concentrates. The intraoperative nadir Hb was slightly higher among the Witnesses than among the other patients. Witnesses had a median Hb of 7.6 g/dL (IQR 7.2 - 7.9 g/dL), and non-Witnesses had a median Hb of 7.3 (IQR 6.6 - 7.6 g/dL). Table 2 presents postoperative outcomes. Witnesses and non-Witnesses had similar composite outcomes. Furthermore, Witnesses required a shorter mechanical ventilation time. Witnesses: median 11 h IQR 8-22; non- Witnesses: median 17 h IQR 10-30, p value 0.024.

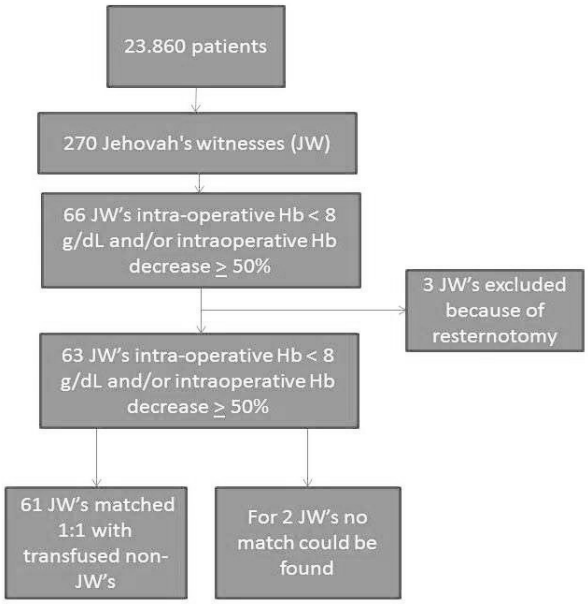


Figure 3. *flowchart of patient exclusions and number of JW available for analysis*

Table 1: Characteristics of patients with an intraoperative Hb < 8 g/dL and/or an intraoperative Hb decrease of ≥ 50%

	Total (N=122)	Jehovah's witnesses (N=61)	Transfused Patients (1 unit) (N=61)
Pre-operative variables			
Propensity score, median (IQR)	0.0164(0.0078-0.0292)	0.0164(0.0076-0.0293)	0.0164(0.0076-0.0292)
Age, median (IQR)	67(61-75)	64(57-73)	68(64-85)
Female, N (%)	66(54.1)	28(45.9)	38(62.3)
Weight (kg), median (IQR)	75(65-85)	78(67-86)	73(65-85)
Year of surgery, median (IQR)	2002(1998-2004)	2002(1998-2004)	2001(1998-2005)
Previous cardiac surgery, N (%)	11(9.0)	5(8.2)	6(9.8)
Smoking, N (%)	9(7.4)	5(8.2)	4(6.6)
Pre-operative Hb level, g/dl, median (IQR)	14.2(13.2-14.9)	14.5(13.4-15.1)	13.7(13.0-14.5)
Hypercholesterolemia, N (%)	72(59.0)	35(57.4)	37(60.7)
Creatinine, median (IQR)	87(70-99)	86(73-95)	88(69-101)
Vascular disease, N (%)	18(14.8)	7(11.5)	11(18.0)
Left ventricle hypertrophy, N (%)	34(27.9)	17(27.9)	17(27.9)
Atrial fibrillation, N (%)	12(9.8)	6(9.8)	6(9.8)
Hypertension, N (%)	57(46.7)	29(47.5)	28(45.9)
COPD, N (%)	18(14.8)	7(11.5)	11(18.0)
Diabetes, N (%)			
- type I	11(9.0)	4(6.6)	7(11.5)
- type II	16(13.1)	7(11.5)	9(14.8)
n. coronary arteries affected, median (IQR)	3(0-3)	3(0-3)	3(0-3)
> 50% LAD occlusion, N (%)	16(13.1)	8(13.1)	8(13.1)
Myocardial infarction, N (%)	27(22.1)	14(23.0)	13(21.3)
Ejection Fraction, N (%)			
- good	94(77.0)	48(78.7)	46(75.4)
- moderately depressed	16(13.1)	9(14.8)	7(11.5)
- severely depressed	8(6.6)	3(4.9)	5(8.2)
Aortic valve disease, N (%)	42(34.4)	22(36.1)	20(32.8)
Mitral valve disease, N (%)	22(18.0)	11(18.0)	11(18.0)
NYHA class IV, N (%)	8(6.6)	3(4.9)	5(8.2)
Cardiovascular insufficiency,* N (%)	19(15.6)	9(14.8)	10(16.4)
Respiratory insufficiency,† N (%)	2(1.6)	1(1.6)	1(1.6)
Aspirin use, N (%)	58(47.5)	32(52.5)	26(42.6)
Clopidogrel use, N (%)	3(2.50	2(3.3)	1(1.6)
Anti-coagulant drug use,‡ N (%)	22(18.0)	13(21.3)	9(14.8)
Calcium antagonist use, N (%)	58(47.5)	29(47.5)	29(47.5)
Beta blocker use, N (%)	82(67.2)	44(72.1)	38(62.3)
Nitrate use, N (%)	62(50.8)	31(50.8)	31(50.8)
Inotropic drug use, N (%)	1(0.8)	1(1.6)	0(0)
Emergency surgery, N (%)	4(3.3)	3(4.9)	1(1.6)
Type of Surgery, N (%)			
- CABG	62(50.8)	32(52.5)	30(49.2)
- CABG + valve	23(18.9)	11(18.0)	12(19.7)
- CABG + other	0(0)	0(0)	0(0)
- Valve	24(19.7)	13(21.3)	11(18.0)
- Other	13(10.7)	5(8.2)	8(13.1)
EuroSCORE I, median (IQR)	5(4-7)	5(2-7)	6(4-7)
Intra-operative variables			
Time in Surgery (min), median (IQR)	283(250-332)	283(245-321)	282(253-347)
CPB duration (min), median (IQR)	124(99-165)	123(102-158)	125(94-182)
Intra-operative circulatory arrest, N (%)	7(5.7)	2(3.3)	5(8.2)
Cellsaver blood returned during surgery, N (%)	34(27.9)	20(32.8)	14(23.0)
Intra-operative nadir Hb (g/dL), median (IQR)	7.4(6.9-7.8)	7.6(7.2-7.9)	7.3(6.6-7.6)
Intra-operative nadir Hb < 8 g/dL, N (%)	120(98.4)	59(96.7)	61(100)
Hb decrease ≥ 50%, N (%)	37(30.3)	18(29.5)	19(31.1)
FFP transfusion during surgery, N (%)	20(16.4)	0(0)	20(32.8)
Platelet transfusion during surgery, N (%)	19(15.6)	0(0)	19(31.1)
Lowest temperature in surgery (C), median (IQR)	30.3(29.0-33.2)	31(30-34)	30(28-32)

** Defined as: NYHA class IV and/or preoperative nitrate i.v and/or heparin i.v. and/or IABP*

† Defined as the need for mechanical ventilation

‡ Defined as the use of heparin, low molecular weight heparin, coumarines or a combination

Transfusions and Clinical Outcomes in Anemic Non- Witnesses (Comparison B)

A total of 831 non-Witnesses with an intraoperative Hb <8 g/dL and/or an Hb decrease >50% who received 1 RBC and no other blood products were matched with the same number of patients who received no blood products. Figure 4 presents the flow chart of patient exclusions and number of patients available for analysis. Perioperative characteristics of these patients are shown in Table 3. Table 4 shows the postoperative outcomes of the selected non-Witnesses. After reviewing baseline characteristics, additional adjustment was made with regard to time in surgery (min), time on CPB (min), intra-operative circulatory arrest (min), cell-saver blood returned during surge as a binary variable), and intraoperative nadir Hb (g/dL) in the multivariable analysis. The composite endpoint was seen in 149 non-transfused patients (18%) and in 144 transfused patients (17%) (aOR 0.94, CI 0.72-1.23).

Table 2: Postoperative Outcomes in patients with an intra-operative nadir Hb < 8 g/dL and or an intra-operative Hb decrease ≥ 50%

	Jehovah's Witnesses (N =61)	Transfused patients (1unit) (N =61)	Crude OR (95% CI)	aOR* (95% CI)
Myocardial infarction, N (%)	12(19.7)	13(21.3)	1.11(0.46-2.67)	1.18(0.47-2.96)
Acute kidney injury, N (%)	5(8.2)	6(9.8)	1.22(0.35-4.24)	0.77(0.19-3.06)
CVVH de novo, N (%)	2(3.3)	6(9.8)	3.22(0.62-16.62)	3.68(0.69-19.73)
Stroke, N (%)	2(3.3)	2(3.3)	1.00(0.14-7.34)	0.83(0.10-7.03)
ICU length of stay (hours), median (IQR)	24(22-58)	48(23-91)		
ICU length of stay > 48 hours, N (%)	22(36.1)	30(49.2)	1.72(0.83-3.54)	1.89(0.88-4.06)
Mechanical ventilation time (hours), median (IQR)	11(8-22)	17(10-30)		
Mechanical ventilation > 24 hours, N (%)	11(18.0)	19(31.1)	2.06(0.88-4.80)	2.13(0.88-5.16)
In hospital mortality, N (%)	1(1.6)	2(3.3)	2.03(0.18-23.0)	0.81(0.05-13.51)
Hb level at discharge (g/dL), median (IQR)	10.8(10.4-11.3)	10.6(10.0-10.8)		
Composite endpoint,† N (%)	15(24.6)	20(32.8)	1.50(0.68-3.30)	1.44(0.63-3.29)

** Adjusted for: intra-operative nadir Hb (g/dL)*

† Composite endpoint consisting of: Myocardial infarction, CVVH, Stroke, in hospital mortality

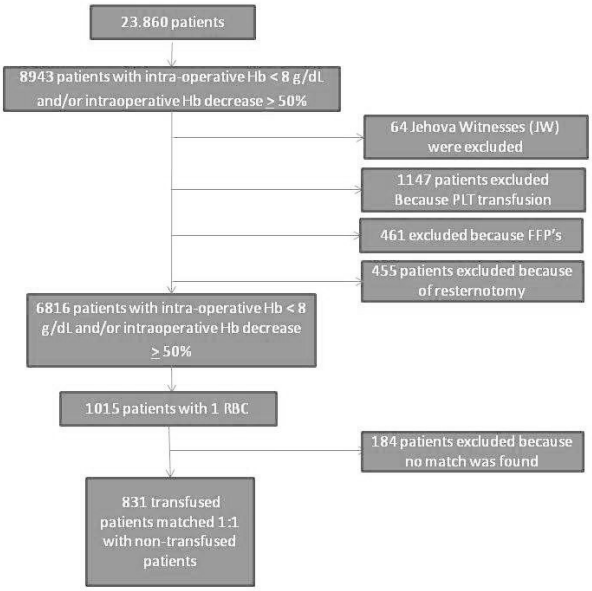


Figure 4. *Flow chart of patient exclusions and number of non-JW transfused with one RBC available for analysi*

Table 3: Patient Characteristics in patients with an intra-operative Hb < 8 g/dL and/or a intra-operative Hb decrease of ≥ 50%

	Total	Non-Transfused Patients	Transfused Patients (1 unit)
	(N=1662)	(N=831)	(N=831)
Pre-operative variables			
Propensity score, median (IQR)	0.2653(0.1630-0.3966)	0.2654(0.1629-0.3967)	0.2653(0.1630-3966)
Age, median (IQR)	72(65-77)	72(65-77)	72(65-77)
Female, N (%)	1075(64.7)	537(64.6)	538(64.7)
Weight (kg), median (IQR)	71(63-80)	71(64-80)	70(63-80)
Year of surgery, median (IQR)	2005(2002-2008)	2005(2002-2008)	2005(2001-2009)
Previous cardiac surgery, N (%)	127(7.6)	65(7.8)	62(7.5)
Smoking, N (%)	236(14.2)	123(14.8)	113(13.6)
Pre-operative Hb level, g/dl, median (IQR)	12.6(11.8-13.4)	12.6(11.8-13.4)	12.6(11.8-13.4)
Hypercholesterolemia, N (%)	1049(63.1)	521(62.7)	528(63.5)
Creatinine, median (IQR)	84(71-102)	82(70-102)	85(72-103)
Vascular disease, N (%)	305(18.4)	150(18.1)	155(18.7)
Left ventricle hypertrophy, N (%)	466(28.0)	232(27.9)	234(28.2)
Atrial fibrillation, N (%)	218(13.1)	108(13.0)	110(13.2)
Hypertension, N (%)	979(58.9)	487(58.6)	492(59.2)
COPD, N (%)	306(18.4)	151(18.2)	155(18.7)
Diabetes, N (%)			
- type I	75(4.5)	35(4.2)	40(4.8)
- type II	326(19.6)	160(19.3)	166(20.0)
n. coronary arteries affected, median (IQR)	3(0-3)	3(0-3)	3(1-3)
> 50% LAD occlusion, N (%)	272(16.4)	143(17.2)	129(15.5)
Myocardial infarction, N (%)	596(35.9)	289(34.8)	307(36.9)
Ejection Fraction, N (%)			
- good	1215(73.1)	615(74.0)	600(72.2)
- moderately depressed	302(18.2)	142(17.1)	160(19.3)
- severely depressed	147(8.8)	74(8.9)	73(8.8)
Aortic valve disease, N (%)	510(30.7)	258(31.0)	252(30.3)
Mitral valve disease, N (%)	407(24.5)	210(25.3)	197(23.7)
NYHA class IV, N (%)	271(16.3)	130(15.6)	141(17.0)
Cardiovascular insufficiency,* N (%)	345(20.8)	177(21.3)	168(20.2)
Respiratory insufficiency,† N (%)	90(5.4)	41(4.9)	49(5.9)
Aspirin use, N (%)	873(52.5)	440(52.9)	433(52.1)
Clopidogrel use, N (%)	244(14.7)	113(13.6)	131(15.8)
Anti-coagulant drug use,‡ N (%)	555(33.4)	272(32.7)	283(34.1)
Calcium antagonist use, N (%)	492(29.6)	245(29.5)	247(29.7)
Beta blocker use, N (%)	1218(73.3)	603(72.6)	615(74.0)
Nitrate use, N (%)	600(36.1)	298(35.9)	302(36.3)
Inotropic drug use, N (%)	45(2.7)	23(2.8)	22(2.6)
Emergency surgery, N (%)	147(8.8)	81(9.7)	66(7.9)
Type of Surgery, N (%)			
- CABG	956(57.5)	470(56.6)	486(58.5)
- CABG + valve	290(17.4)	145(17.4)	145(17.4)
- CABG + other	14(0.8)	8(1.0)	6(0.7)
- Valve	355(21.4)	182(21.9)	173(20.8)
- Other	46(2.8)	25(3.0)	21(2.5)
EuroSCORE I, median (IQR)	6(4-9)	7(4-9)	6(4-9)
Intra-operative variables			
Time in Surgery (min), median (IQR)	240(205-284)	235(201-275)	245(205-290)
CPB duration (min), median (IQR)	99(78-128)	97(76-124)	101(80-131)
Intra-operative circulatory arrest, N (%)	25(1.5)	16(1.9)	9(1.1)
Cellsaver blood returned during surgery, N (%)	739(44.5)	364(43.8)	375(45.1)
Intra-operative nadir Hb (g/dL), median (IQR)	7.2(6.8-7.6)	7.4(6.9-7.7)	7.1(6.4-7.6)
Intra-operative nadir Hb < 8 g/dL, N (%)	1659(99.8)	828(99.6)	831(100.0)
Hb decrease ≥ 50%, N (%)	303(18.2)	102(12.3)	201(24.2)
Lowest temperature in surgery (C), median (IQR)	34(32-34)	33(32-34)	34(32-35)

** Defines as: NYHA class IV and/or preoperative nitrate i.v and/or heparin i.v. and/or IABP*

† Defined as the need for mechanical ventilation

‡ Defined as the use of heparin, low molecular weight heparin, coumarines or a combination

Table 4: Postoperative Outcomes in patients with an intra-operative nadir Hb < 8 g/dL and or an intra-operative Hb decrease ≥ 50%

	Non-Transfused patients (N =831)	Transfused patients (1 units) (N =831)	Crude OR (95% CI)	aOR* (95% CI)
Myocardial infarction, N (%)	83(10.0)	88(10.6)	1.07(0.78-1.47)	1.03(0.74-1.42)
Acute kidney injury, N (%)	64(7.7)	84(10.1)	1.35(0.96-1.89)	1.29(0.91-1.84)
CVVH de novo, N (%)	42(5.1)	43(5.2)	1.03(0.66-1.59)	0.89(0.56-1.40)
Stroke, N (%)	15(1.9)	18(2.4)	1.20(0.60-2.41)	1.33(0.65-2.68)
ICU length of stay (hours), median (IQR)	24(20-48)	24(21-63)		
ICU length of stay > 48 hours, N (%)	206(24.8)	233(28.0)	1.18(0.95-1.47)	1.14(0.91-1.43)
Mechanical ventilation time (hours), median (IQR)	10(7-14)	10(7-16)		
Mechanical ventilation > 24 hours, N (%)	96(11.6)	112(13.5)	1.19(0.89-1.60)	1.21(0.90-1.64)
In hospital mortality, N (%)	30(3.6)	20(2.4)	0.66(0.37-1.17)	0.64(0.34-1.19)
Hb level at discharge (g/dL), median (IQR)	10.0(9.3-10.8)	10.1(9.5-10.9)		
Composite endpoint†, N (%)	149(17.9)	144(17.3)	1.04(0.81-1.34)	0.94(0.72-1.23)

** Adjusted for: time in surgery, CPB duration, intra-operative circulatory arrest, cellsaver blood returned during surgery, intra-operative nadir Hb (g/dL)*

† Composite endpoint consisting of: Myocardial infarction, CVVH, Stroke, in hospital mortality

Discussion

Main Findings

In both Witnesses and non-transfused non-Witnesses who underwent cardiac surgery, lower intraoperative Hb was associated with a higher incidence of adverse postoperative events. Postoperative outcomes of anemic Witnesses and matched non-Witnesses who had received, intraoperatively, 1 unit of RBC were similar, with the exception that Witnesses had a shorter duration of mechanical ventilation than the patients who received blood products. In order to cope with biases when comparing Witnesses, comparison B showed that postoperative outcome in transfused and non-transfused anemic non-Witnesses also revealed no differences.

Strengths and Limitations

Many studies have shown that Witnesses can safely undergo cardiac surgery. To the authors' knowledge, however, this study is the first to focus on Witnesses with moderate-to-severe anemia by comparing anemic Witnesses with a matched group of anemic non-Witnesses who received, intraoperatively, 1 RBC. The authors' study indirectly suggested that a single packed cell transfusion did not impact outcome in moderately severe anemia in cardiac surgery.

To appreciate the authors' results, some issues need to be discussed. The authors examined anemia and the role of RBC on clinical endpoints using Witnesses as a non-transfused control group. Despite all the authors' efforts, they cannot ensure the absence of residual confounding in their study as not all possible preoperative and intraoperative variables were measured.[25,26]

Analyzing the postoperative outcomes of Jehovah's witnesses was an important part of the authors' study because Witnesses can provide valuable information about the course of uncorrected anemia. However, surgeons and anesthesiologists may work more cautiously during

surgery on Witnesses to limit blood loss and avoid a low Hb. This effect of caution during surgery could not be measured, and therefore the authors could not adjust for it. Additionally, Witnesses were compared to transfused patients who received 1 RBC. However, one-third of these non-Witnesses received additional blood products during surgery, possibly influencing postoperative outcomes.[27,28]

In an attempt to rule out possible confounding associated with patient selection and surgical caution to prevent blood loss in Witnesses and to maximize comparability between patients who received an RBC transfusion and patients who did not, the authors performed analyses in an additional formed cohort comparing transfused non-Witnesses with non-transfused non-Witnesses. This cohort included different patients and could not be compared with the cohort formed with Jehovah's Witnesses. In these additional analyses, the authors compared non-Witnesses receiving only 1 RBC intraoperatively (and no additional blood products) with non-Witnesses receiving no blood products at all. While the 2 separate analyses cannot be compared with regard to absolute outcomes because both cohorts differed in baseline characteristics, both approaches failed to show any differences between transfused and non-transfused patients.

Because comparability between patients who received multiple RBC transfusions and patients who received no RBC transfusions was low, the authors chose to match non-transfused patients with patients who received only 1 RBC. This limited the generalizability of the authors' findings to patients who received only 1 RBC intraoperatively. Another limitation of the authors' study was that they ignored the duration of time each patient remained on their nadir Hb. The nadir Hb typically is reached during bypass. Besides transfusion, other measures may have been undertaken to restore oxygen delivery. As the authors did not measure the duration of anemia before treatment restored Hb, it might be speculated that the impact of anemia may not have been long enough to discriminate for the possibly beneficial effects of transfusion.

Comparison with Previous Studies

There was convincing evidence that bloodless cardiac surgery could be performed with results equivalent to cardiac surgery in (low-risk) non-Witnesses.[15–17,22–24] The authors' results showed that this was also true in Witnesses who experienced intra-operative moderate-to-severe anemia (nadir Hb level < 8 g/dL). Both in Witnesses and in non- Witnesses, the authors observed that a lower Hb level was associated with a higher incidence of the composite endpoint. This was in agreement with previous studies showing a significant association with morbidity and mortality, especially when postoperative Hb levels decreased below 5-7.5 g/dL.[11,29]

The authors did not find a significant beneficial or adverse effect of 1 RBC transfusion. In previous studies, both beneficial and adverse effects of RBC transfusions in cardiac surgery patients have been reported.[13,30–33]

Several studies reported worse outcome in cardiac surgery patients who received 1 and 2 units of RBC; other studies, like a recently performed RCT, showed that restrictive transfusion regimens may increase cardiogenic shock.[34–39] In the authors' cohort, they observed that Witnesses had a shorter ventilation time when compared to non-Witnesses who received blood products. The same result has been found in several other studies.[15] Whether this was due to blood products or due to another cause could not be concluded from the authors' study.

Clinical Implications

Perioperative anemia is associated with adverse outcomes after cardiac surgery. Previous studies have reported on the deleterious effect of anemia on end-organ function of organs that depend on a relatively high oxygen extraction ratio like the kidneys, the heart, and the brain.[1,2,40] Treating or preventing anemia with RBC transfusions has its own merits. In literature, many adverse effects of RBC transfusions were described, varying from antibody formation to increased postoperative morbidity like cerebrovascular accidents and acute kidney injury. Keeping the above in mind, the authors formulated clinical endpoints assessing the effect of anemia on the function of end-organ systems that are most dependent on sufficient oxygen delivery. Therefore, if any effects of anemia and/or RBC transfusion could be seen, the authors expected it to be seen in the endpoints formulated.

In this cardiac surgical population, including patients with moderate-to-severe blood loss, low intraoperative Hb is associated with more postoperative complications. The authors were reluctant to conclude that this may have consequences for settings of a transfusion threshold. They found a single RBC appeared not to affect postoperative outcomes.

The authors' results could imply that in anemic patients, transfusion of a single unit of RBC generally would not affect postoperative outcome and potentially could be avoided. However, they could not exclude that in the individual patient transfusion could either be beneficial or disadvantageous. Whether or not this is the case depends on the clinical profile of the patient.10

In conclusion, in this cardiac surgical population, including patients with moderate-to-severe blood loss, low intraoperative Hb was associated with more postoperative complications, but transfusion of a single RBC appeared not to affect them.

Reference List

1 Munoz M, Garcia-Erce JA, Leal-Noval SR. Perioperative transfusion in anaemic patients undergoing coronary artery bypass. Lancet (London, England). 2002;360(9343):8. doi:S0140673602113821 [pii].

2 Ranucci M, Baryshnikova E, Castelvecchio S, Pelissero G, Surgical, Group COR (SCORE). Major bleeding, transfusions, and anemia: the deadly triad of cardiac surgery. Ann Thorac Surg. 2013;96(2):478-485. doi:10.1016/j.athoracsur.2013.03.015 [doi].

3 Karkouti K, Wijeysundera DN, Yau TM, McCluskey SA, van Rensburg A, Beattie WS. The influence of baseline hemoglobin concentration on tolerance of anemia in cardiac surgery. Transfusion. 2008;48(4):666-672. doi:10.1111/j.1537-2995.2007.01590.x [doi].

4 Carson JL, Noveck H, Berlin JA, Gould SA. Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. Transfusion. 2002;42(7):812-818.

5 Carson JL, Stanworth SJ, Roubinian N, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane database Syst Rev. 2016;10:CD002042. doi:10.1002/14651858.CD002042.pub4 [doi].

6 Hebert 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(2):227-234.

7 Curley GF, Shehata N, Mazer CD, Hare GMT, Friedrich JO. Transfusion triggers for guiding RBC transfusion for cardiovascular surgery: a systematic review and meta-analysis*. Crit Care Med. 2014;42(12):2611-2624. doi:10.1097/CCM.0000000000000548.

8 Vonk AB, Meesters MI, van Dijk WB, et al. Ten-year patterns in blood product utilization during cardiothoracic surgery with cardiopulmonary bypass in a tertiary hospital. Transfusion. 2014;54(10 Pt 2):2608-2616. doi:10.1111/trf.12522 [doi].

9 Hebert PC, Wells G, Martin C, et al. A Canadian survey of transfusion practices in critically ill patients. Transfusion Requirements in Critical Care Investigators and the Canadian Critical Care Trials Group. Crit Care Med. 1998;26(3):482-487.

10 Vincent JL, Baron J-F, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. JAMA. 2002;288(12):1499-1507.

11 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):91-99. doi:10.1111/j.1537-2995.2011.03236.x.

12 Murphy GJ, Pike K, Rogers CA, et al. Liberal or restrictive transfusion after cardiac surgery. N Engl J Med. 2015;372(11):997-1008. doi:10.1056/NEJMoa1403612 [doi].

13 Hogervorst E, Rosseel P, Van Der Bom J, et al. Tolerance of intraoperative hemoglobin decrease during cardiac surgery. Transfusion. 2014;54(1). doi:10.1111/trf.12654.

14 Shander A, Javidroozi M, Naqvi S, et al. An update on mortality and morbidity in patients with very low postoperative hemoglobin levels who decline blood transfusion (CME). Transfusion. 2014;54(10 Pt 2):2688-95; quiz 2687. doi:10.1111/trf.12565.

15 Pattakos G, Koch CG, Brizzio 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):1154-1160. doi:10.1001/archinternmed.2012.2449 [doi].

16 Vaislic CD, Dalibon N, Ponzio O, et al. Outcomes in cardiac surgery in 500 consecutive Jehovah's Witness patients: 21 year experience. J Cardiothorac Surg. 2012;7:95. doi:10.1186/1749-8090-7-95 [doi].

17 Jassar AS, Ford PA, Haber HL, et al. Cardiac surgery in Jehovah's Witness patients: ten-year experience. Ann Thorac Surg. 2012;93(1):19-25. doi:10.1016/j.athoracsur.2011.06.029 [doi].

18 Koetsier A, Peek N, de Keizer N. Identifying types and causes of errors in mortality data in a clinical registry using multiple information systems. Stud Health Technol Inform. 2012;180:771-775.

19 Anesthesiologists Task Force on Perioperative Blood Transfusion AS, Therapies A. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Anesthesiology. 2006;105(1):198-208. doi:00000542-200607000-00030 [pii].

20 of Thoracic Surgeons Blood Conservation Guideline Task Force S, Ferraris VA, Brown JR, 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):944-982. doi:10.1016/j.athoracsur.2010.11.078 [doi].

21 de Vries R, Haas F, working group for revision of the Dutch Blood Transfusion Guideline 2011. English translation of the dutch blood transfusion guideline 2011. Clin Chem. 2012;58(8):1266-1267. doi:58/8/1266 [pii].

22 Stamou SC, White T, Barnett S, Boyce SW, Corso PJ, Lefrak EA. Comparisons of cardiac surgery outcomes in Jehovah's versus Non-Jehovah's Witnesses. Am J Cardiol. 2006;98(9):1223-1225. doi:S0002-9149(06)01372-5 [pii].

23 Bhaskar B, Jack RK, Mullany D, Fraser J. Comparison of outcome in Jehovah's Witness patients in cardiac surgery: an Australian experience. Heart Lung Circ. 2010;19(11):655-659. doi:10.1016/j.hlc.2010.07.010 [doi].

24 Emmert MY, Salzberg SP, Theusinger OM, et al. How good patient blood management leads to excellent outcomes in Jehovah's witness patients undergoing cardiac surgery. Interact Cardiovasc Thorac Surg.2011;12(2):183-188. doi:10.1510/icvts.2010.242552 [doi].

25 Middelburg RA, van de Watering LMG, van der Bom JG. Blood transfusions: good or bad? Confounding by indication, an underestimated problem in clinical transfusion research. Transfusion. 2010;50(6):1181-1183.doi:10.1111/j.1537-2995.2010.02675.x.

26 Zalpuri S, Middelburg RA, van de Watering L, Vamvakas E, Zwaginga JJ, van der Bom JG. Association vs. causality in transfusion medicine: understanding multivariable analysis in prediction vs. etiologic research. Transfus Med Rev. 2013;27(2):74-81. doi:10.1016/j.tmrv.2013.02.002.

27 Bilgin YM, van de Watering LM, Versteegh MI, van Oers MH, Vamvakas EC, Brand A. Postoperative complications associated with transfusion of platelets and plasma in cardiac surgery. Transfusion.2011;51(12):2603-2610. doi:10.1111/j.1537-2995.2011.03200.x [doi].

28 Gajic O, Dzik WH, Toy P. Fresh frozen plasma and platelet transfusion for nonbleeding patients in the intensive care unit: benefit or harm? Crit Care Med. 2006;34(5 Suppl):S170-3. doi:10.1097/01.CCM.0000214288.88308.26.

29 Carson JL. Risk of anemia and transfusion triggers: implications for bloodless care. Surg Infect (Larchmt).2005;6 Suppl 1:S17-21. doi:10.1089/sur.2005.6.s1-17.

30 Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. N Engl J Med. 2001;345(17):1230-1236. doi:10.1056/NEJMoa010615 [doi].

31 Banbury MK, Brizzio ME, Rajeswaran J, Lytle BW, Blackstone EH. Transfusion increases the risk of postoperative infection after cardiovascular surgery. J Am Coll Surg. 2006;202(1):131-138. doi:S1072-7515(05)01430-4 [pii].

32 Shimmer C, Hamouda K, Ozkur M, et al. Influence of storage time and amount of red blood cell transfusion on postoperative renal function: an observational cohort study. Hear lung Vessel. 2013;5(3):148-157.

33 Rao S V, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. Jama. 2004;292(13):1555-1562. doi:292/13/1555 [pii].

34 Murphy GJ, Reeves BC, Rogers CA, Rizvi SIA, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation.2007;116(22):2544-2552. doi:10.1161/CIRCULATIONAHA.107.698977.

35 Koch CG, Li 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(6):1608-1616. doi:10.1097/01.CCM.0000217920.48559.D8.

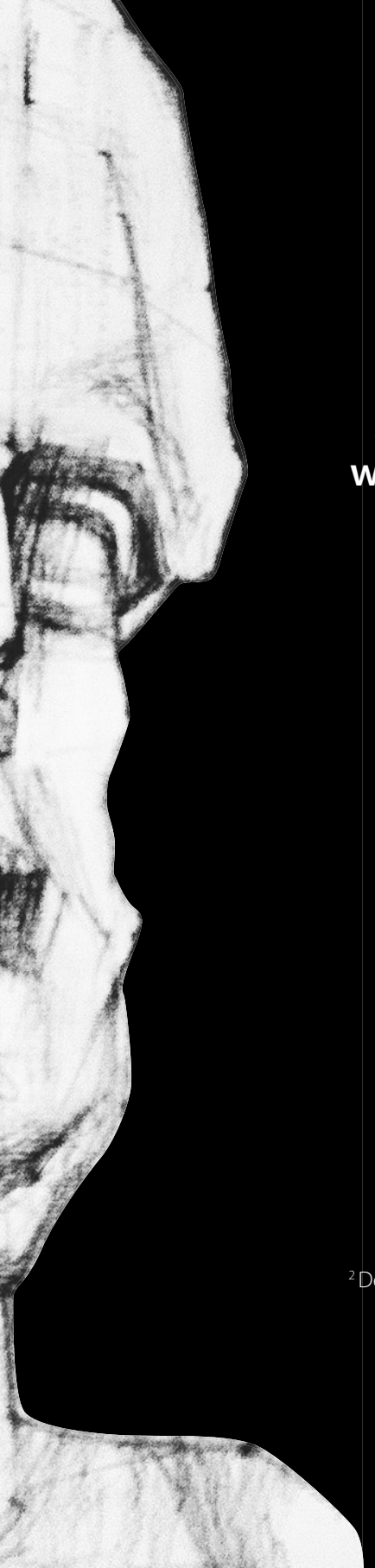
36 Surgenor SD, Kramer RS, Olmstead EM, et al. The association of perioperative red blood cell transfusions and decreased long-term survival after cardiac surgery. Anesth Analg. 2009;108(6):1741-1746. doi:10.1213/ane.0b013e3181a2a696.

37 Jakobsen C-J, Ryhammer PK, Tang M, Andreasen JJ, Mortensen PE. Transfusion of blood during cardiac surgery is associated with higher long-term mortality in low-risk patients. Eur J Cardiothorac Surg.2012;42(1):114-120. doi:10.1093/ejcts/ezr242.

38 Yun JJ, Helm RE, Kramer RS, et al. Limited blood transfusion does not impact survival in octogenarians undergoing cardiac operations. Ann Thorac Surg. 2012;94(6):2038-2045. doi:10.1016/j.athoracsur.2012.06.059.

39 Nakamura RE, Vincent J-L, Fukushima JT, et al. A liberal strategy of red blood cell transfusion reduces cardiogenic shock in elderly patients undergoing cardiac surgery. J Thorac Cardiovasc Surg.2015;150(5):1314-1320. doi:10.1016/j.jtcvs.2015.07.051.

40 Fowler AJ, Ahmad T, Phull MK, Allard S, Gillies MA, Pearse RM. Meta-analysis of the association between preoperative anaemia and mortality after surgery. Br J Surg. 2015;102(11):1314-1324. doi:10.1002/bjs.9861.



Anti-K formation is not associated with the storage time of transfused red blood cells

CHAPTER 5

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Abstract

Background

The formation of red blood cell (RBC) antibodies could be enhanced by the presence of inflammation caused by prolonged RBC storage, as was shown in animal studies. The low occurrence (<10%) of K-antigen in most populations often enables identification of the K+ RBC unit that triggered anti-K formation and determination of its storage time. This study aims to quantify the association of anti-K formation with RBC storage time.

Study designs and methods

K– patients who had not been previously transfused and received at least 1 K+ unit between January 2004 and August 2013 were identified. First, the influence of storage time of the K+ units was assessed as mean, maximum, and minimum storage times within one transfusion interval and at various cutoff points for old versus young blood (14, 18, and 21 days). Second, concomitantly transfused K– units were studied within different periods surrounding the K+ unit(s).

Results

Twenty-three patients formed anti-K, while 274 patients did not. The adjusted relative risks of anti-K formation for mean, maximum, and minimum storage time (days) ranged from 1.01 to 1.03 (95% confidence interval, 0.96-1.08). When analyzing the association between only "younger" and only "older" K+ units at various cutoff points, no association was found. Similarly, no association was found between storage time of the concomitantly transfused K– units and anti-K formation.

Conclusion

Within the range of storage times used in normal clinical practice in the Netherlands, no association could be found between RBC storage time and anti-K formation.

Introduction

The role of red blood cell (RBC) storage time on various (adverse) clinical outcomes in transfused patients is still elusive. Reports on an association between prolonged RBC storage and adverse clinical outcomes like a higher infection rate, prolonged hospital stay, or even mortality are conflicting.[1–4]

One of the most frequent adverse effects of RBC transfusions is the formation of alloantibodies against incompatible donor antigens. The consequences of these alloantibodies in transfusion medicine vary from logistic inconvenience finding compatible blood, to delayed and acute hemolytic reactions. Unraveling genetic and environmental, presumably pro-inflammatory, conditions enhancing RBC immunization is important to develop preventive strategies such as preemptive extended matching of RBC transfusions.[5–7] In a mouse model, it has been demonstrated that leukoreduced RBCs stored for 14 days resulted in higher alloantibody levels compared to fresh RBCs.[8] Two previous studies have addressed this subject in humans. Yazer and Triulzi found that multiple D+ units had the same mean storage time in patients who formed anti-D and in those who did not.[9] Zalpuri and colleagues10 analyzed storage time on any immunization, without differentiating between antigen immunogenicity, and also found no association.[10]

However, a limitation of both of these studies is that it was not known which RBC unit actually triggered immunization. The relative low frequency (<10%) of the K blood group antigen in most ethnic populations reduces the likelihood that patients receive multiple K+ units during a transfusion event.11 Therefore, it is often possible to identify the K+ RBC unit that triggered an antibody response and to determine the storage time of this unit.

The primary objective of this study was to quantify the association between the storage time of K+ RBC and anti-K formation in a new user cohort. Furthermore, to elucidate a potential role of antibody formation stimulating or dampening factors possibly present in concomitantly transfused units, the association of the storage time of concomitantly transfused K– units with anti-K formation was also quantified in various periods surrounding the K+ transfusion event.

Materials and Methods

Data collection and patients

In this single center, new user cohort study, K– patients who received at least one K+ RBC unit with or without concomitantly transfused K– units were included. Patients were selected from the Leiden University Medical Center in Leiden, the Netherlands, from January 2004 until August 2013. Data regarding age, sex, diagnosis, transfusion dates, and antibody follow-up were collected from hospital laboratory files. Donation dates and K blood group data of all transfused units were collected from the Dutch national blood bank (Sanquin Blood Supply) ePROGESA database (MAK-System International Group).

RBC storage time was defined as the number of days between donation and transfusion, with the day of donation defined as Day 0. A transfusion event was defined as a 7-day period in which the patient received K+ RBCs with Day 0 defined as the day of the first K+ transfusion. Storage times of all K+ RBC units and all concomitantly transfused K– units in a period of 30 days preceding and up to 30 days following a K+ transfusion event were collected. Transfusions outside this period were not included for analysis.

The antibody follow-up period started at the first K+ RBC transfusion and ended at seroconversion or at the last antibody test performed, which was always at least 30 days after the last K+ transfusion. In the Netherlands, women younger than 46 years and patients with congenital or acquired hemolytic disorders requiring regular transfusions routinely receive K-antigen (and c, E antigens) matched RBCs to reduce antibody formation.

Blood products

In the Netherlands, standard RBC units are non-irradiated, leukoreduced before storage, and stored in SAGM for a maximum of 35 days. Patients who underwent stem cell transplantations received irradiated RBCs with a maximum storage time of 14 days after irradiation. Before transfusion, screening for warm reacting clinically significant antibodies is routinely performed and retesting using a newly drawn serum for transfusion is mandatory every 72 hours.

Responders and nonresponders

Patients who developed anti-K during follow-up were defined as responders. When anti-K was detected within 2 weeks after transfusion of a K+ unit, a memory (booster) response could not be excluded and these patients were excluded. Nonresponders were defined as patients who received at least one K+ transfusion without anti-K seroconversion after a follow-up period of at least 30 days.

Statistical analyses of the storage time of K+ RBCs

The storage time of K+ RBC units was analyzed as a continuous (mean, maximum, minimum), a categorical (2-14 days as the reference category, 15-21 days, and longer than 21 days), and as a dichotomous variable (using different cutoff points: 14, 18, and 21 days defining "only older" vs. "only younger" blood).

Relative risks (RRs) and adjusted relative risks (aRRs) were estimated using Poisson regression models with robust standard errors and expressed with 95% confidence intervals (CIs).12 To adjust for confounding, the multivariable analysis was corrected for number of transfusions. Because of the nonlinearity of the relation between the number of transfusions and the outcome, the multivariable model was also adjusted for the number of transfusion as a quadratic term. A sensitivity analysis was performed including only patients who received only 1 K+ unit or 2 K+ units with the same storage time on the same day. This way, only patients of whom the storage time of the immunizing unit was certain were analyzed.

Statistical analyses of the storage time of K– RBC

Exploratory analyses of the storage time of concomitantly transfused K– units were performed for different periods surrounding the K+ transfusion event:

- Day 0 (transfusion date of the first K+ unit(s)).
- 30, 15, 7, and 1 day(s) before and after the K+ transfusion event.

To validly analyze the association between the storage time of K– RBCs and anti-K formation, within a given period of time surrounding a K+ transfusion, K– transfusions could be considered only once, that is, in one event. Therefore, only patients who received all K+ RBCs in a single

transfusion event were included in this analysis. The association between storage time of K– RBCs and anti-K formation was analyzed in the same way as the K+ units (i.e., mean, minimum, maximum storage time, as a categorical variable, and "only old" vs. "only young").

Results

Of the 297 patients included in this study, 124 patients received 1 K+ unit, 75 patients received 2, and 98 patients received 3 or more K+ units. A total of 23 patients (7.7%) seroconverted with anti-K during follow-up (responders) and 274 did not. In 18 patients (78%) anti-K was formed after one K-incompatible transfusion event and of these patients 15 had received only 1 K+ unit. The remaining five responders received 2 to 3 K+ RBC units during two transfusion events before seroconversion.

Baseline and transfusion characteristics for responders and nonresponders are presented in Table 1. Responders were older, were more often female, suffered less often from hematological malignancies, and received fewer solid organ transplantations. The storage time of the RBCs transfused, both K– and K+, ranged from 2 to 34 days, as displayed in Fig. 1.

Table 1. Characteristics of 297 patients with and without anti-K*

	Responders N=23	Nonresponders N=274
Female, N (%)	8 (34.8)	83 (30.3)
Age	62 (54-71)	58 (47-63)
Diagnosis,		
- Hematological malignancy	5 (21.7)	200 (73.0)
- Solid organ malignancies	7 (30.4)	9 (3.3)
- Transplantation	1 (4.3)	35 (12.8)
- Other	10 (43.5)	30 (10.9)
- nonsurgical	4 (40.0)	15 (50.0)
- Surgical	5 (50.0)	5 (16.7)
- Renal failure	1 (10.0)	10 (33.3)
Patients with non-K anti-bodies	9 (39.1)	26 (9.5)

** Data are reported as number (%) or median (interquartile range).*

Nonresponders had a longer follow-up time, received more (both K+ and K–) RBC transfusions and more antibody tests were performed in these patients. Non-K antibodies were formed by 35 (11.8%) patients: in two patients before anti-K, in seven patients together with or after anti-K, and in 26 patients without anti-K.

In anti-K responders, the mean, minimum, and maximum storage times of the K+ RBCs had a median of 15 days (interquartile range ranging from 12 to 20 days). In nonresponders the mean, maximum, and minimum storage times of K+ RBCs had a wider range. Results are displayed in Table 2.

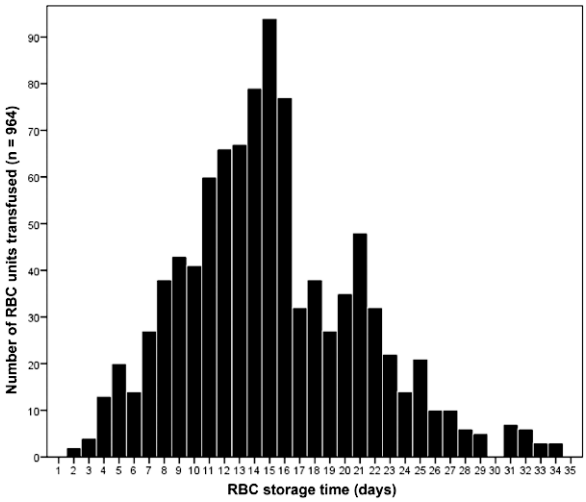


Figure 1. Storage time of all RBCs transfused (K+ and K– RBCs)

Table 2 Transfusion Characteristics of 297 patients with and without anti-K*

	23 Responders	274 Nonresponders
Total number of RBC units transfused	8 (5-14)	16 (6-24)
Number of K+ RBC units transfused	1 (1-2)	2 (1-3)
Storage time of K+ units (days)		
- Mean	15 (13-20)	16 (12-20)
- Minimum	15 (12-20)	13 (10-18)
- Maximum	15 (14-21)	18 (14-23)
Storage time of K- units (days)		
- Mean	15 (13-19)	15 (13-18)
- Minimum	11 (7-14)	9 (6-14)
- Maximum	19 (14-28)	22 (17-29)
Follow-up time (months)†	13 (4-34)	22 (7-48)
Number of antibody test during follow-up	2 (1-4)	15 (10-23)

** Data reported in median (interquartile range)*

† Follow-up time: from the first K+ transfusion until the positive antibody test for anti-K or the last antibody test performed

Anti-K formation was not associated with the mean, the maximum, or the minimum storage times of the K+ units (aRR mean storage time 1.02, 95% CI 0.96-1.08; aRR maximum storage time 1.01, 95% CI 0.96-1.07; and aRR minimum storage time 1.03, 95% CI 0.97-1.09). Also, no association was found when the storage time of K+ RBCs was analyzed as a categorical variable (with 2-14 days as reference category, 15-21 days, aRR 1.10, 95% CI 0.43-2.81; ≥22 days, aRR 1.18, 95% CI 0.36-3.43). Similarly, no association between anti-K formation and receiving only-old or only-young RBCs was found (aRR cutoff 14 days 1.00, 95% CI 0.43-2.35; aRR cutoff 18 days 1.02, 95% CI 2.55; aRR cutoff 21 days 1.21, 95% CI 0.07-5.88; Tables 3 and 4).

Table 3. Association between the storage time of K+ RBCs and the formation of anti-K in K- patients (n = 297, 23 responders, 274

	Crude			Adjusted*		
Storage time	**RR**	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
K+ RBCs						
Mean	1,02	0.96-1.10	0.498	1.02	0.96-1.08	0.492
Maximum	0.98	0.93-1.03	0.472	1.01	0.96-1.07	0.629
Minimum	1.06	1.00-1.12	0.037	1.03	0.97-1.09	0.399
Mean storage time K+ RBC in categories (days)						
2-14	1	Ref.	Ref.	1	Ref.	Ref.
15-21	1.08	0.42-2.76	0.870	1.10	0.43-2.81	0.838
≥ 22	1.30	0.40-3.75	0.627	1.18	0.36-3.43	0.752

** Adjusted for number of transfusions and for the numbers of transfusions square*

Table 4. Association between only "older" and "younger" K+ RBCs and anti-K formation

		Crude			Adjusted*		
Cut off point (days)	**number**	**RR**	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
2-14 vs. ≥ 15	217 (20 responders)	1.09	0.45-2.80	0.834	1.00	0.43-2.35	0.993
2-18 vs. ≥ 19	223 (20 responders)	1.14	0.46-2.83	0.780	1.02	0.36-2.55	0.964
2-21 vs. ≥ 22	268 (23 responders)	1.99	0.32-12.42	0.464	1.21	0.07-5.88	0.849

** Adjusted for number of transfusions and for the numbers of transfusions square*

The sensitivity analysis was performed in the subgroup of patients in which the immunizing K+ unit and its storage time was identified with certainty. The sensitivity analysis revealed similar results.

Sensitivity analysis I: Association between the storage time of K+ RBC and the formation of anti-K in patients who received 1 K+ RBC unit (N = 130, 16 responders)

Storage Time K-positive RBC:	**RR**	**95% CI**	**P-value**
Mean	1.05	0.98-1.11	0.156
Mean storage time K-positive RBC in categories:			
	RR	**95% CI**	**P-value**
2-14 days	1	-	-
15-21 days	1.54	0.49-5.19	0.437
≥ 22 days	1.95	0.48-7.36	0.285

Sensitivity Analysis II: Association between only 'older' and 'younger' K+ RBC and anti-K formation in patients who received 1 K-positive RBC unit (N = 130, 16 responders)

Cut off point (days)	**N**	**RR**	**95% CI**	**P-value**
2-14 vs ≥ 15	130	1.67	0.61-4.52	0.317
2-18 vs ≥ 19	130	1.40	0.54-3.58	0.483
2-21 vs ≥ 22	130	1.40	0.22-8.77	0.734

Storage time of concomitantly transfused K– units and anti-K formation

A total of 160 patients (18 responders and 142 nonresponders) had only one K+ transfusion event and were included in the exploratory analyses of the storage time of the concomitantly transfused K– units. The mean, maximum, and minimum storage times of the K– units that were transfused on the same day as the K+ units were not associated with anti-K formation (mean storage time aRR 1.02, 95% CI 0.95-1.10; maximum storage time aRR, 1.02, 95% CI 0.95-1.09; minimum storage time aRR 1.01, 95% CI 0.93-1.09). No association was observed when the storage time was analyzed categorically nor when analyzing only "older" versus only "younger" K– units (Tables 5 and 6). When these analyses were performed for K– units transfused in the periods 1, 7, 15, and 30 day(s) before and after the transfusion event, combined or separately no associations were found.

Table 5. anti-K in patients with one K+ transfusion episode (n = 131, 18 responders; K-RBCs transfused during the K+ transfusion episode)

	Crude			Adjusted*		
Storage time	**RR**	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
K- RBCs						
Mean	1.04	0.96-1.12	0.632	1.04	0.96-1.12	0.352
Maximum	1.03	0.96-1.10	0.467	1.03	0.96-1.10	0.427
Minimum	1.03	0.96-1.10	0.425	1.03	0.97-1.11	0.391
Mean storage time K- RBC in categories (days)						
2-14	1	Ref.	Ref.	1	Ref.	Ref.
15-21	1.43	0.53-4.00	0.446	1.42	0.53-3.98	0.448
≥ 22	1.01	0.15-4.17	0.991	1.03	0.15-4.27	0.971

** Adjusted for number of transfusions and for the numbers of transfusions square*

Table 6. Association between only "older" and "younger" K- RBCs and anti-K formation in patients with one K+ transfusion episode (K- RBCs transfused during the K+ transfusion episode)

		Crude			Adjusted*		
Cut off point (days)	**number**	**RR**	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
2-14 vs. ≥ 15	71 (10 responders)	1.16	0.36-3.76	0.802	1.11	0.35-3.50	0.859
2-18 vs. ≥ 19	88 (12 responders)	1.30	0.39-4.30	0.672	1.30	0.40-4.27	0.664
2-21 vs. ≥ 22	98 (13 responders)	0.82	0.12-5.63	0.824	0.84	0.11-6.36	0.866

** Adjusted for number of transfusions and for the numbers of transfusions square*

Table 7: Association between the storage time of K-negative RBC and the formation of anti-K in K-negative patients with one K-positive transfusion episode

	N = 160, 18 responders, 142 non responders 30 days before & after the K-positive transfusion episode						N =153, 17 responders, 136 non-responders 30 days before the K-positive transfusion episode						N = 154, 17 responders, 137 non responders 30 days after the K-positive transfusion episode					
Storage time K-negative RBC:	**Crude**			**Adjusted***			**Crude**			**Adjusted***			**Crude**			**Adjusted***		
	RR	**95% CI**	**P-value**	**RR**	**95% CI**	**P-value**	**RR**	**95% CI**	**P-value**	**RR**	**95% CI**	**P-value**	**RR**	**95% CI**	**P-value**	**RR**	**95% CI**	**P-value**
Mean	1.03	0.95-1.11	0.485	1.03	0.95-1.12	0.448	1.03	0.96-1.10	0.406	1.03	0.96-1.10	0.452	0.99	0.92-1.06	0.729	0.99	0.92-1.07	0.805
Maximum	1.01	0.94-1.08	0.773	1.02	0.95-1.08	0.645	1.01	0.94-1.08	0.817	1.01	0.94-1.08	0.840	1.00	0.93-1.08	0.955	1.01	0.95-1.08	0.700
Minimum	1.03	0.96-1.10	0.408	1.03	0.96-1.12	0.387	1.03	0.97-1.09	0.329	1.03	0.97-1.10	0.379	0.98	0.91-1.05	0.495	0.97	0.90-1.05	0.465
Mean storage time K-negative RBC in categories:							**Mean storage time K-negative RBC in categories:**						**Mean storage time K-negative RBC in categories:**					
2-14 days	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref
15-21 days	1.49	0.56-4.17	0.400	1.47	0.55-4.15	0.405	1.43	0.49-4.19	0.474	1.38	0.47-4.06	0.512	1.27	0.47-3.54	0.618	1.24	0.46-3.47	0.649
≥ 22 days	0.87	0.13-3.60	0.860	0.93	0.14-3.86	0.926	1.36	0.29-4.88	0.638	1.31	0.28-4.73	0.677	0.45	0.02-2.52	0.441	0.51	0.03-2.85	0.522
Only 'older' versus only 'younger' RBC:							**Only 'older' versus only 'younger' RBC:**						**Only 'older' versus only 'younger' RBC:**					
2-14 vs ≥ 15*	1.12	0.34-3.66	0.855	1.11	0.35-3.52	0.860	0.92	0.30-2.82	0.886	0.91	0.31-2.69	0.866	1.01	0.30-3.34	0.989	1.04	0.32-3.38	0.944
2-18 vs ≥ 19*	1.17	0.35-3.98	0.797	1.28	0.36-4.47	0.705	0.98	0.29-3.30	0.971	0.99	0.29-3.38	0.984	0.73	0.17-3.19	0.678	0.78	0.18-3.42	0.745
2-21 vs ≥ 22*	0.88	0.13-6.05	0.892	0.86	0.10-7.56	0.893	0.56	0.08-3.97	0.561	0.55	0.07-4.40	0.571	0.68	0.10-4.75	0.675	0.70	0.09-5.73	0.742

	N = 156, 18 responders, 138 non responders 15 days before & after the K-positive transfusion episode						N = 150, 17 responders, 133 non-responders 15 days before the K-positive transfusion episode						N = 150, 17 responders, 133 non responders 15 days after the K-positive transfusion episode					
Storage Time K-negative RBC:	**Crude**			**Adjusted***			**Crude**			**Adjusted***			**Crude**			**Adjusted***		
	RR	**95% CI**	**P-value**	**RR**	**95% CI**	**P-value**	**RR**	**95% CI**	**P-value**	**RR**	**95% CI**	**P-value**	**RR**	**95% CI**	**P-value**	**RR**	**95% CI**	**P-value**
Mean	1.03	0.96-1.11	0.385	1.03	0.96-1.12	0.386	1.04	0.97-1.11	0.305	1.04	0.97-1.11	0.323	1.01	0.94-1.08	0.896	1.00	0.93-1.08	0.919
Maximum	1.03	0.96-1.10	0.423	1.03	0.97-1.10	0.313	1.02	0.95-1.09	0.647	1.02	0.95-1.09	0.603	1.01	0.94-1.08	0.826	1.02	0.95-1.08	0.649
Minimum	1.02	0.95-1.10	0.599	1.02	0.94-1.11	0.597	1.03	0.97-1.10	0.329	1.03	0.96-1.10	0.387	0.99	0.93-1.06	0.757	0.98	0.92-1.05	0.629
Mean storage time K-negative RBC in categories:							**Mean storage time K-negative RBC in categories:**						**Mean storage time K-negative RBC in categories:**					
2-14 days	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref
15-21 days	1.77	0.66-5.20	0.241	1.74	0.64-5.16	0.238	1.69	0.59-5.13	0.303	1.65	0.57-5.02	0.314	1.39	0.50-4.15	0.508	1.31	0.47-3.94	0.582
≥ 22 days	1.05	0.15-4.54	0.954	1.09	0.16-4.71	0.917	1.54	0.33-5.85	0.514	1.51	0.32-5.74	0.530	1.11	0.16-4.80	0.897	1.13	0.17-4.91	0.879

Only 'older' versus only 'younger' RBC:

2-14 vs ≥ 15*	1.23	0.41-4.22	0.624	1.32	0.43-4.10	0.626	1.06	0.36-3.12	0.922	1.06	0.37-3.01	0.916	1.11	0.39-3.17	0.849	1.10	0.39-3.12	0.853
2-18 vs ≥ 19*	1.25	0.37-4.23	0.724	1.32	0.37-4.72	0.674	1.04	0.31-3.50	0.951	1.06	0.31-3.59	0.931	0.66	0.15-2.82	0.572	0.66	0.15-2.91	0.585
2-21 vs ≥ 22*	0.83	0.12-5.77	0.847	0.79	0.09-6.67	0.824	0.60	0.09-4.28	0.614	0.59	0.08-4.58	0.615	0.61	0.09-4.28	0.616	0.57	0.07-4.61	0.597

N = 152, 17 responders, 135 non responders
7 days before & after the K-positive transfusion episode

Storage time K-negative RBC:	Crude			Adjusted*		
	RR	95% CI	P-value	RR	95% CI	P-value
Mean	1.02	0.94-1.11	0.672	1.02	0.93-1.11	0.678
Maximum	1.01	0.94-1.10	0.742	1.02	0.95-1.10	0.631
Minimum	1.02	0.95-1.10	0.607	1.02	0.94-1.11	0.686

Mean storage time K-negative RBC in categories:

2-13 days	1	Ref	Ref	1	Ref	Ref
14-21 days	1.34	0.48-3.81	0.551	1.29	0.46-3.70	0.591
≥ 22 days	0.82	0.12-3.30	0.797	0.84	0.13-3.49	0.824

Only 'older' versus only 'younger' RBC:

2-14 vs ≥ 15*	0.91	0.34-2.47	0.860	0.89	0.34-2.32	0.805
2-18 vs ≥ 19*	0.85	0.25-2.83	0.785	0.87	0.26-2.97	0.825
2-21 vs ≥ 22*	1.10	0.27-4.42	0.897	1.10	0.25-4.78	0.903

N = 143, 16 responders, 127 non responders
1 day before & after the K-positive transfusion episode

Storage time K-negative RBC:	Crude			Adjusted		
	RR	95% CI	P-value	RR	95% CI	P-value
Mean	1.03	0.95-1.12	0.473	1.03	0.95-1.12	0.476
Maximum	1.03	0.96-1.11	0.364	1.04	0.97-1.11	0.288
Minimum	1.01	0.93-1.10	0.795	1.01	0.92-1.10	0.853

Only 'older' versus only 'younger' RBC:

2-14 vs ≥ 15*	1.06	0.36-3.12	0.922	1.06	0.37-3.01	0.916	1.11	0.39-3.17	0.849	1.10	0.39-3.12	0.853	1.23	0.41-4.22	0.624	1.32	0.43-4.10	0.626
2-18 vs ≥ 19*	1.04	0.31-3.50	0.951	1.06	0.31-3.59	0.931	0.66	0.15-2.82	0.572	0.66	0.15-2.91	0.585	1.25	0.37-4.23	0.724	1.32	0.37-4.72	0.674
2-21 vs ≥ 22*	0.60	0.09-4.28	0.614	0.59	0.08-4.58	0.615	0.61	0.09-4.28	0.616	0.57	0.07-4.61	0.597	0.83	0.12-5.77	0.847	0.79	0.09-6.67	0.824

N = 147, 17 responders, 130 non responders
7 days before the K-positive transfusion episode

Storage time K-negative RBC:	Crude			Adjusted*		
	RR	95% CI	P-value	RR	95% CI	P-value
Mean	1.02	0.94-1.09	0.674	1.02	0.94-1.10	0.703
Maximum	1.00	0.93-1.07	0.959	1.01	0.92-1.08	0.438
Minimum	1.02	0.96-1.09	0.462	1.02	0.95-1.10	0.545

Mean storage time K-negative RBC in categories:

2-13 days	1	Ref	Ref	1	Ref	Ref
14-21 days	2.75	0.94-9.92	0.089	2.64	0.89-9.56	0.091
≥ 22 days	1.68	0.23-8.63	0.528	1.68	0.23-8.59	0.539

Only 'older' versus only 'younger' RBC:

2-14 vs ≥ 15*	1.09	0.41-2.86	0.866	1.06	0.41-2.73	0.903	0.81	0.29-2.27	0.688	0.81	0.29-2.24	0.685	0.91	0.34-2.47	0.860	0.89	0.34-2.32	0.805
2-18 vs ≥ 19*	0.85	0.26-2.80	0.787	0.87	0.26-2.94	0.827	0.55	0.13-2.36	0.551	0.56	0.13-2.39	0.430	0.85	0.25-2.83	0.785	0.87	0.26-2.97	0.825
2-21 vs ≥ 22*	1.02	0.26-4.07	0.980	1.03	0.24-4.37	0.969	0.50	0.07-3.59	0.491	0.48	0.06-3.73	0.806	1.10	0.27-4.42	0.897	1.10	0.25-4.78	0.903

N = 137, 17 responders, 120 non responders
1 day before the K-positive transfusion episode

Storage time K-negative RBC:	Crude			Adjusted		
	RR	95% CI	P-value	RR	95% CI	P-value
Mean	1.02	0.95-1.09	0.684	1.01	0.94-1.09	0.729
Maximum	1.01	0.94-1.08	0.788	1.01	0.94-1.08	0.790
Minimum	1.02	0.95-1.09	0.660	1.01	0.94-1.09	0.738

N = 147, 16 responders, 131 non responders
7 days after the K-positive transfusion episode

Storage time K-negative RBC:	Crude			Adjusted*		
	RR	95% CI	P-value	RR	95% CI	P-value
Mean	0.99	0.92-1.07	0.793	0.99	0.91-1.07	0.751
Maximum	1.00	0.93-1.08	0.954	1.01	0.93-1.09	0.852
Minimum	0.98	0.91-1.06	0.624	0.97	0.90-1.05	0.518

Mean storage time K-negative RBC in categories:

2-13 days	1	Ref	Ref	1	Ref	Ref
14-21 days	1.10	0.38-3.22	0.85	1.07	0.37-3.14	0.887
≥ 22 days	0.81	0.12-3.34	0.780	0.82	0.12-3.39	0.795

Only 'older' versus only 'younger' RBC:

2-14 vs ≥ 15*	0.81	0.29-2.27	0.688	0.81	0.29-2.24	0.685	0.91	0.34-2.47	0.860	0.89	0.34-2.32	0.805	1.23	0.41-4.22	0.624	1.32	0.43-4.10	0.626
2-18 vs ≥ 19*	0.55	0.13-2.36	0.551	0.56	0.13-2.39	0.430	0.85	0.25-2.83	0.785	0.87	0.26-2.97	0.825	1.25	0.37-4.23	0.724	1.32	0.37-4.72	0.674
2-21 vs ≥ 22*	0.50	0.07-3.59	0.491	0.48	0.06-3.73	0.806	1.10	0.27-4.42	0.897	1.10	0.25-4.78	0.903	0.83	0.12-5.77	0.847	0.79	0.09-6.67	0.824

N = 143, 16 responders, 127 non responders
1 day after the K-positive transfusion episode

Storage time K-negative RBC:	Crude			Adjusted		
	RR	95% CI	P-value	RR	95% CI	P-value
Mean	0.99	0.92-1.07	0.858	0.99	0.92-1.07	0.819
Maximum	1.01	0.95-1.08	0.707	1.02	0.95-1.09	0.650
Minimum	0.97	0.90-1.04	0.970	0.96	0.89-1.04	0.354

Mean storage time K-negative RBC in categories:							**Mean storage time K-negative RBC in categories:**						**Mean storage time K-negative RBC in categories:**					
2-13 days	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref	1	Ref	Ref
14-21 days	1.21	0.40-3.75	0.722	1.13	0.37-3.53	0.814	1.14	0.41-3.26	0.782	1.07	0.38-3.07	0.890	0.97	0.33-2.83	0.948	0.92	0.31-2.71	0.866
≥ 22 days	1.48	0.31-5.60	0.555	1.52	0.32-5.78	0.511	0.89	0.13-3.67	0.874	0.89	0.13-3.68	0.873	0.82	0.12-3.38	0.790	0.84	0.13-3.46	0.813
Only 'older' versus only 'younger' RBC:							**Only 'older' versus only 'younger' RBC:**						**Only 'older' versus only 'younger' RBC:**					
2-14 vs ≥ 15*	1.06	0.40-2.80	0.906	1.05	0.40-2.72	0.928	1.04	0.40-2.74	0.934	0.99	0.38-2.59	0.984	0.93	0.34-2.52	0.886	0.91	0.34-2.43	0.843
2-18 vs ≥ 19*	0.84	0.25-2.87	0.778	0.87	0.26-2.94	0.824	0.73	0.22-2.43	0.613	0.75	0.23-2.46	0.630	0.52	0.12-2.22	0.377	0.54	0.13-2.30	0.404
2-21 vs ≥ 22*	1.12	0.27-4.57	0.877	1.12	0.26-4.72	0.883	0.98	0.25-3.93	0.980	0.98	0.24-3.96	0.975	0.50	0.07-3.59	0.491	0.48	0.06-3.69	0.479

** categorized time in days*

Discussion

In this study no association between the storage time of K+ or concomitantly transfused K– RBCs and the formation of anti-K was observed. Only two clinical studies analyzed the association between the storage time of RBCs and antibody formation. Zalpuri and coworkers found no association in a matched case-referent study between RBCs with a storage time of 1 to 4 weeks and any alloantibody formation.[10] However, this study included weak as well as strong immunogenic RBC antigens and could not conclude on the influence of storage time of RBCs with specific antigens and cognate antibody formation. Yazer and Triulzi performed a matched case-control study in D– patients receiving multiple D+ transfusions mainly in emergency situations.[9] In this study the D+ transfusions had different storage times and only the mean and median storage interval of D+ units in responders and nonresponders could be compared and no differences were found. In addition, both studies defined nonresponsiveness already after a follow-up of 13 or 20 days after transfusion, which may be too short to detect antibody formation in a proportion of patients.

The current study allowed us to compare the storage times of the actual immunizing K+ RBC in responders and in nonresponders with a follow-up time of at least 30 days. Furthermore we analyzed the storage time of the concomitantly transfused K– units because one could hypothesize that these units could dampen or enhance anti-K formation.

The assumption that a longer storage time of transfused RBC enhances immunization is based on the concept that concomitant danger signals are required for an immune response.[13] Such signals may be provided by pro-inflammatory cytokines accumulating during RBC storage.[8,14] In a mouse model, Hendrickson and colleagues demonstrated that a stronger alloantibody response after transfusion with "old" murine RBC (which had been stored for more than 14 days) was associated with increased levels of pro-inflammatory cytokines.[8] This response was blunted when mice were concomitantly transfused with antigen-expressing "young" RBCs that contained fewer pro-inflammatory cytokines.[8,15] Our study could not reproduce these associations, which may be explained by the difference in the murine and human RBC lifespan.[16] The natural lifespan of mouse RBCs is estimated to be 38 to 55 days.[8] A storage time of 14 days (which was the cutoff point in the mouse model) approximates human RBCs with a storage time over 35 days, which is the maximum allowed storage time in the Netherlands and rarely used in daily practice.[15,17] The K+ as well as the concomitantly transfused K– RBCs in our study may thus lack the metabolic changes that enhanced anti-K formation in the mouse. Also we did not observe a dampening of the antibody response associated with more fresh K– units during the same transfusion event as the K+ units.

To appreciate the results of this study, some issues need to be discussed. The majority of responders developed anti-K after a single K-incompatible transfusion; this indicates that one RBC transfusion is sufficient to induce a prompt and strong immunoglobulin G response. Furthermore, the detection of RBC antibodies is dependent on the follow-up period and frequency of antibody testing. Differences in these characteristics in populations under study may influence the outcome. In the nonresponders the follow-up time after each K+ unit was at least 30 days and

total follow-up time and number of antibody test were sufficient to detect anti-K if it had been present. In this study, nonresponders had a longer follow-up time and received more RBCs. This explains the differences in ranges found between responders and nonresponders regarding the maximum and minimum storage time.[18]

There are a number of limitations of our study. Most important, with the differences in immunocompetence between responders and nonresponders one would prefer to stratify analyses according to diagnosis. Patients with a hematological malignancy and transplant patients using immunosuppressant drugs are low responders, with only 2.6% anti-K responders in our cohort, while surgical patients or patients with a solid tumor, previously identified as high responders, produced anti-K in 44%.[19,20] Unfortunately, our small sample size prohibited us to stratify according to diagnosis. Another limitation is that no standardized follow-up measurements were in place. Although patients with anti-K detected within 14 days after transfusion of the first K+ RBCs were excluded, not all seroconverted patients had been tested within 14 days after the first K+ transfusion. In theory, some of these patients may have had a booster reaction after prior pregnancies or unknown transfusions in other hospitals, instead of a primary anti-K response. And last, the storage times of the RBC units fell within a small interval and numbers of very fresh and end-of-shelf life units were insufficient to study the extremes.

In conclusion, in this study no association between anti-K formation and the storage time of K+ or concomitantly transfused K– RBCs was observed. The results are based on current transfusion practice with regard to storage time and make an association between storage time and anti-K alloimmunization less likely. Which factors are most important in the formation of alloantibodies in humans and if these factors contribute equally for the different RBC antigen specificities remains a subject for further research.

Reference List

1 Eikelboom JW, Cook RJ, Liu Y, Heddle NM. Duration of red cell storage before transfusion and in- hospital mortality. Am Heart J. 2010;159(5):743.e1. doi:10.1016/j.ahj.2009.12.045 [doi].

2 Robinson SD, Janssen C, Fretz EB, et al. Red blood cell storage duration and mortality in patients undergoing percutaneous coronary intervention. Am Heart J. 2010;159(5):876-881. doi:10.1016/j.ahj.2010.02.018 [doi].

3 Naidech AM, Liebling SM, Duran IM, Ault ML. Packed red blood cell age does not impact adverse events or outcomes after subarachnoid haemorrhage. Transfus Med. 2011;21(2):130-133. doi:10.1111/j.1365-3148.2010.01048.x [doi].

4 McKenny M, Ryan T, Tate H, Graham B, Young VK, Dowd N. Age of transfused blood is not associated with increased postoperative adverse outcome after cardiac surgery. Br J Anaesth. 2011;106(5):643-649. doi:10.1093/bja/aer029 [doi].

5 Seyfried H, Walewska I. Analysis of immune response to red blood cell antigens in multitransfused patients with different diseases. Mater medica Pol J Med Pharm. 1990;22(1):21-25.

6 Noizat-Pirenne F, Tournamille C, Bierling P, et al. Relative immunogenicity of Fya and K antigens in a Caucasian population, based on HLA class II restriction analysis. Transfusion. 2006;46(8):1328-1333. doi:TRF00900 [pii].

7 Hendrickson JE, Desmarets M, Deshpande SS, et al. Recipient inflammation affects the frequency and magnitude of immunization to transfused red blood cells. Transfusion. 2006;46(9):1526-1536. doi:TRF00946 [pii].

8 Hendrickson JE, Hod EA, Spitalnik SL, Hillyer CD, Zimring JC. Storage of murine red blood cells enhances alloantibody responses to an erythroid-specific model antigen. Transfusion. 2010;50(3):642-648. doi:10.1111/j.1537-2995.2009.02481.x [doi].

9 Yazer MH, Triulzi DJ. Receipt of older RBCs does not predispose D-negative recipients to anti-D alloimmunization. Am J Clin Pathol. 2010;134(3):443-447. doi:10.1309/AJCP2J8SVWOXRLRB [doi].

10 Zalpuri S, Schonewille H, Middelburg R, et al. Effect of storage of red blood cells on alloimmunization. Transfusion. 2013;53(11):2795-2800. doi:10.1111/trf.12156 [doi].

11 Reid ME, Mohandas N. Red blood cell blood group antigens: structure and function. Semin Hematol. 2004;41(2):93-117. doi:S0037196304000022 [pii].

12 Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004;159(7):702-706.

13 Matzinger P. The danger model: a renewed sense of self. Science. 2002;296(5566):301-305. doi:10.1126/science.1071059.

14 Zimring JC, Hendrickson JE. The role of inflammation in alloimmunization to antigens on transfused red blood cells. Curr Opin Hematol. 2008;15(6):631-635. doi:10.1097/MOH.0b013e328313695e.

15 Hendrickson JE, Hod EA, Hudson KE, Spitalnik SL, Zimring JC. Transfusion of fresh murine red blood cells reverses adverse effects of older stored red blood cells. Transfusion. 2011;51(12):2695-2702. doi:10.1111/j.1537-2995.2011.03197.x.

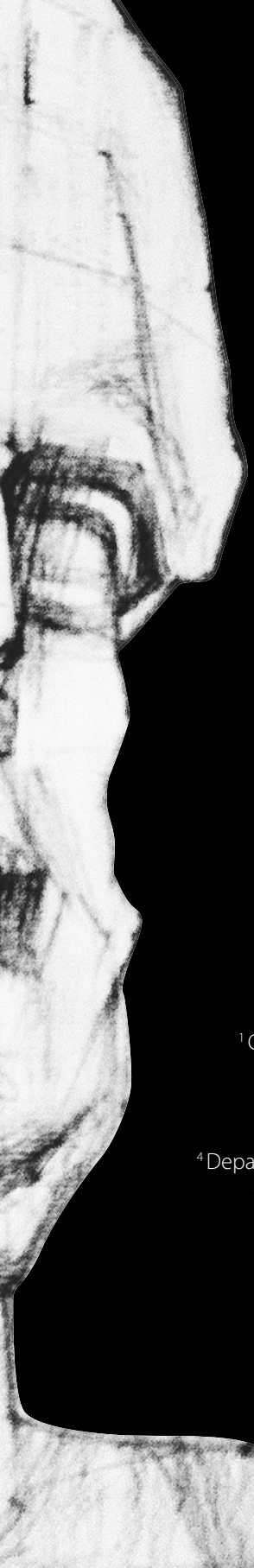
16 Mestas J, Hughes CCW. Of mice and not men: differences between mouse and human immunology. J Immunol. 2004;172(5):2731-2738.

17 Zimring JC, Smith N, Stowell SR, et al. Strain-specific red blood cell storage, metabolism, and eicosanoid generation in a mouse model. Transfusion. 2014;54(1):137-148. doi:10.1111/trf.12264.

18 van de Watering L, Lorinser J, Versteegh M, Westendord R, Brand A. Effects of storage time of red blood cell transfusions on the prognosis of coronary artery bypass graft patients. Transfusion. 2006;46(10):1712-1718. doi:10.1111/j.1537-2995.2006.00958.x.

19 Bauer MP, Wiersum-Osselton J, Schipperus M, Vandenbroucke JP, Briet E. Clinical predictors of alloimmunization after red blood cell transfusion. Transfusion. 2007;47(11):2066-2071. doi:10.1111/j.1537-2995.2007.01433.x.

20 Zalpuri S, Evers D, Zwaginga JJ, et al. Immunosuppressants and alloimmunization against red blood cell transfusions. Transfusion. 2014;54(8):1981-1987. doi:10.1111/trf.12639.



Does a platelet transfusion independently affect bleeding and adverse outcomes in cardiac surgery?

CHAPTER 6

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Abstract

Background
Conflicting results have been reported concerning the effect of platelet transfusion on several outcomes. The aim of this study was to assess the independent effect of a single early intraoperative platelet transfusion on bleeding and adverse outcomes in cardiac surgery patients.

Methods
For this observational study 23,860 cardiac surgery patients were analyzed. Patients who received one early (shortly after cardiopulmonary bypass while still in the operating room) platelet transfusion, and no other transfusions, were defined as the intervention group. By matching the intervention group 1:3 to patients who received no early transfusion with most comparable propensity scores, the reference group was identified.

Results
The intervention group comprised 169 patients and the reference group 507. No difference between the groups was observed concerning reinterventions, thromboembolic complications, infections, organ failure and mortality. However, patients in the intervention group experienced less blood loss and required vasoactive medication 139/169 (82%) versus 370/507 (74%), (odds ratio 1.65; 95%-confidence interval1.05-2.58); prolonged mechanical ventilation 92/169 (54%) versus 226/507 (45%) (1.47;1.03-2.11); prolonged intensive care 95/169 (56%) versus 240/507 (46%) (1.49;1.04-2.12); red cells 75/169 (44%) vs 145/507 (34%) (1.55;1.08-2.23), plasma 29/169 (17%) vs 23/507 (7.3%) (2.63;1.50-4.63) and platelets 72/169 (43%) vs 25/507 (4.3%) (16.4;9.3-28.9) more often compared to the reference group.

Conclusions
In this retrospective analysis, cardiac surgery patients receiving platelet transfusion in the operating room experienced less blood loss and more often required vasoactive medication; prolonged ventilation; prolonged intensive care and blood products postoperatively. However, early platelet transfusion was not associated with reinterventions, thromboembolic complications, infections, organ failure, or mortality.

Introduction

Patients undergoing cardiac surgery are at increased risk for excessive bleeding. Excessive bleeding may lead to surgical re-exploration. Both excessive blood loss and re-exploration are associated with increased postoperative mortality and morbidity.[1–3] Thus efficient prevention and treatment of the cause of bleeding is an important issue in cardiac surgery. As expected, part of the postoperative bleedings is due to surgically induced injury, but a significant proportion of the observed bleedings can be explained by acquired hemostatic defects.[4,5] Impaired platelet function, mainly due to cardiopulmonary bypass (CPB) and anti-platelet drug therapy, is considered one of the most important hemostatic factors leading to postoperative bleeding.[4–8] Platelet transfusions are thus commonly administered to treat bleeding.[9]

The platelet-transfusion rates vary greatly in cardiac surgery, both nationally and internationally, in spite of existing guidelines.[10,11] This wide variety in platelet transfusion use among cardiac surgery centres illustrates the lack of consensus on the indication for a platelet transfusion in certain clinical situations. Presumed platelet dysfunction in patients using platelet-inhibiting drugs is not always confirmed by a measurement before platelets are transfused. Furthermore, just as in other clinical areas, there is a lack of clinical evidence establishing the effectiveness of administering platelets in cardiac surgery.[12–14]

In addition, conflicting results have been reported concerning the effect of platelet transfusions on serious adverse events, like stroke, infections, vasoplegia and death in cardiac surgery.[15–22] The recently published results of a multicenter randomized controlled trial (Platelet Transfusion in Cerebral Haemorrhage trial) comparing standard care to standard care with platelet transfusion in patients using antiplatelet therapy before intracerebral hemorrhage, showed that platelet transfusions seemed inferior to standard care.[23]

Our hypothesis was that a single early platelet transfusion, in the absence of concomitant erythrocyte or plasma transfusion, is associated with less bleeding complications and is associated with more adverse events, in patients undergoing cardiac surgery.

Patients and methods

Data collection

The analyses were performed using data from the Amphia Cardiac Surgery Registry consisting of 23,860 patients who underwent cardiac surgery at the Amphia Hospital (Breda, The Netherlands) between 1997 and 2013.

Details of this database have been described previously.[24] In this ongoing cohort study detailed baseline and perioperative data of all consecutive patients undergoing cardiac surgery in the Amphia Hospital (Breda, The Netherlands) were collected. Data collection for the current analysis took place between January 1st 1997 and January 1th 2013 and was compliant with the definitions of the Dutch National Cardiac Surgery Registry and the Dutch National Intensive Care Registry (instituted in 1996).[25] All patient-care decisions were taken by the attending physician in accordance with transfusion and coagulation hospital guideline based protocols. Members of

our departmental review committee critically reviewed the analytical plan. The aim of the study, the inclusion and exclusion criteria, propensity score matching as the method to correct for confounding by indication, the postoperative endpoints, and logistic regression as the method to analyse the endpoints were determined before examination of the data. There was no a priori statistical power analysis calculation used to guide sample size. Sample size and analyses were based on the available data. The ratio and caliper of the propensity score matching were determined during examination of the data. An acknowledged Dutch medical ethical committee approved this study protocol and waived individual patient consent.

Patient sample

It was decided in advance to select only patients who received one early platelet transfusion, defined as one platelet transfusion after end of CPB while still in the operating room. Patients transfused with more than one unit of platelets were excluded presuming that these patients would not be comparable to patients who were not transfused with platelets. Also patients who received other blood products in the operating room were excluded aiming at studying the independent effect of an early platelet transfusion without the potential influence of erythrocyte or fresh frozen plasma (FFP) transfusions.

The platelet units transfused in this study consisted of 5 pooled buffy coats and contained approximately 300 x 10^9 platelets suspended in plasma with or without platelet additive solution. Since 2001, all platelet units were prestorage leukocyte reduced in The Netherlands and before 2001 platelet units were leukocyte reduced when indicated in the Amphia hospital (Breda, The Netherlands). The decision to transfuse platelets was made according to a cardiac surgery coagulation algorithm, with up scaling treatment modalities in which platelet transfusion is used as a last resort after considering other pharmacological strategies. Some degree of freedom was left to the discretion of the physicians, but platelet count lower than 50 x 10^9/L was an indication for platelet transfusion in any case. When platelet count was lower than 100 x 10^9/L and bleeding was present, this was also indication for transfusion of platelets. No specific platelet function test was available, but in recent years rotational thromboelastometry was included in the algorithm.

Patients who received an early platelet transfusion may differ in various ways from patients who received no early transfusion because there was a reason to administer the platelet unit (confounding by indication). To correct for this confounding we estimated a propensity score for these patients, representing the probability that the patient received platelets conditional on relevant covariates prior to the decision to transfuse platelets. The patients who received one early platelet transfusion and no other blood products, and were suitable for propensity score matching were defined as the intervention group. The intervention group was then matched to the reference group, consisting of patients who received no early transfusion and had the closest propensity scores. We hereby aimed at selecting an intervention and reference group with comparable baseline characteristics. We excluded patients in whom an intraoperative circulatory arrest was part of the surgical procedure because of their exceptional hemodynamic and hemostatic state. Furthermore, Jehovah's witnesses were excluded as they may be treated with different surgical and anesthesiological strategies.

Postoperative outcomes

As a result of numerous previous articles reporting contradictory results about the effect of platelet transfusion in cardiac surgery patients, the aim of our study was to obtain an overall picture of all potential consequences for a clinician who is considering an early platelet transfusion for a cardiac surgery patient. So before initiation of the analysis of this study we defined the outcomes we were interested in (based on previous literature and clinical knowledge). Our objective was to study not only the intended effects of an early platelet transfusion (preventing / treating bleeding complications), but also the possible adverse events associated with a platelet transfusion. We aimed at analysing all relevant factors, so both the potential beneficial effects and the potential undesired effects. We planned to study the following postoperative outcomes: amount of blood loss within 12h, early reexploration for bleeding and/or tamponade, late intervention for tamponade, stroke, myocardial infarction (MI), infections, systemic inflammatory response syndrome, shock, acute kidney injury, multi organ failure, in-hospital mortality, and a composite endpoint (consisting of myocardial infarction, stroke, acute kidney injury and in-hospital mortality). Definitions of postoperative myocardial infarction, acute kidney failure and stroke were described earlier.[21] Infection was categorized as pneumonia, mediastinitis, sepsis and other infections with the diagnoses requiring organisms isolated from culture(s) in combination with elevated temperature and white blood cell counts. Systemic inflammatory response syndrome was diagnosed if two or more of the following criteria were present: temperature greater than 38 or less than 36 degree Celsius; tachypnea (greater than 20 per minute) or hypocapnea (pCO_2 less than 32 mmHg); tachycardia (greater than 90 beats/min); or need of mechanical ventilation and leukocyte count greater than 12 or less than 4 x 10^9/L. Multiorgan failure was defined as simultaneous or sequential dysfunction or failure of two or more organ systems. Shock was defined as a syndrome in which the effective capillary and tissue perfusion declined to a level detrimental to cellular metabolism. Also we compared duration of postoperative mechanical ventilation and intensive care unit (ICU) stay (both in hours), requirement of postoperative inotropic or vasoactive drugs and erythrocyte, FFP and platelet transfusions in the ICU. Amount of blood loss, duration of mechanical ventilation, and ICU stay were analyzed as being high or low, with the median as the cutoff point.

Statistical analysis

The continuous baseline variables were summarized by medians and interquartile ranges and the categorical variables were summarized by frequencies and percentages. The propensity score was generated with logistic regression and the variables where the propensity score was based on were chosen based on previous knowledge of the subject, as suggested in earlier papers.[26–28] The following preoperative variables were included in the propensity score: age, gender, year of surgical procedure (per calendar year), previous cardiac surgery, history of MI, number of affected coronary arteries, left ventricular hypertrophy, acetylsalicylic acid or clopidogrel use (continued up to surgery, stopped preoperatively or never used), known vascular disease, chronic obstructive pulmonary disease, diabetes, atrial fibrillation, angina pectoris, active endocarditis, hemoglobin level, international normalized ratio, acute or chronic renal failure, left ventricular ejection

fraction, immunosuppressant drug use, type of surgery, non-elective surgery, cardiopulmonary resuscitation within 24 hour before surgery, respiratory insufficiency, off-pump surgery, CPB duration and European System for Cardiac Operative Risk Evaluation (EuroSCORE). It was not in all years part of standard care to determine fibrinogen level and platelet function before surgery and / or transfusion, so these measures were not available for analysis. Missing variables were imputed using single imputation strategies. For the propensity score matching we used the "psmatch2" function in Stata Statistical Software (Release 14; StataCorp LP, USA), nearest neighbour 1:3 matching with replacement. Only controls with a propensity score within 0.01 distance (caliper) of the propensity score of the case were selected.[29] To assess the balance in measured baseline characteristics after propensity score matching between treated and untreated patients, the standardized mean differences were determined. The matching procedure was optimized based on observed balance in baseline variables before examination of the outcome results. Comparisons of outcomes were made between the intervention and reference group with regard to odds ratios with 95% confidence intervals derived from multiple univariate logistic regression analyses. Given the fact that 1:3 matching with replacement was applied, the clustered pattern of the data was taken into account in the estimation procedure by using a robust (sandwich) estimator in the logistic regressions, specifying the patient identifying number. Additionally, we performed two sensitivity analyses. Firstly, we corrected the logistic models for baseline characteristics that remained unbalanced after the matching procedure. Secondly, we corrected the logistic regressions for a baseline characteristic with standardized difference below 10%, because of its high clinical relevance. No adjustments were made for testing multiple outcomes.

Results

Patient characteristics

The database comprised 23,860 patients in total, of whom 17,918 remained after application of the exclusion criteria (shown in figure 1).

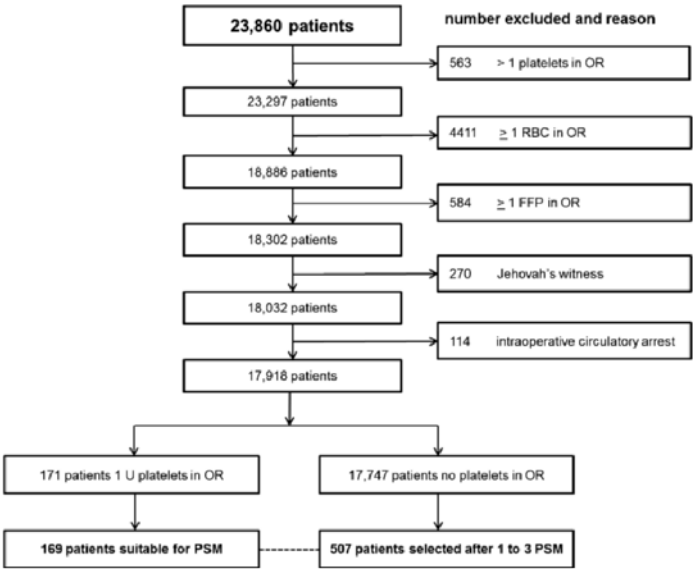


Figure 1. *Flow chart exclusions. FFP = fresh frozen plasma; OR = operating room; PSM = propensity score matching*

Several of the relevant baseline characteristics of the 171 patients who received an early platelet transfusion were evidently different from the ones of the 17,747 patients who received no early transfusions (shown on the left side of table 1). By propensity score matching, the patients were selected from the 17,747 patients who received no early transfusion and were most comparable with the patients who received an early platelet transfusion. Of the 171 patients who received one early platelet transfusion, 169 patients had propensity scores overlapping with the propensity scores of the patients who received no early transfusions (i.e. had the same "baseline risk" of receiving a platelet transfusion).

Table 1. Patient Characteristics Before and After Propensity Score Matching

	Before Propensity Score Matching			After Propensity Score Matching		
	One Early Platelet Transfusion N=171	No Early Transfusion N=17,747	SMD (%)	Intervention Group N=169	Reference Group N=507	SMD (%)
Pre-operative variables						
Female sex*	33(19.3)	4.107(23.1)	9.4	32(18.9)	97(19.1)	0.5
Age (yr)*	67(61-74)	66(59-73)	0.5	67(60-73)	67(58-73)	4.3
Weight (kg)	81(75-90)	80(72-90)	10.2	81(75-90)	80(73-90)	9.9
Year of surgery*	2003(1998-2008)	2004(2001-2009)	26.5	2003(1998-2008)	2003(1999-2007)	2.5
Previous cardiac surgery*	21(12.3)	1290(7.3)	16.9	21(12.4)	56(13.2)	2.7
History of MI*	83(48.5)	6.441(36.3)	24.9	81(47.9)	253(49.9)	4.0
Affected coronary arteries*	3(1-3)	3(1-3)	7.9	3(1-3)	3(1-3)	4.3
LV hypertrophy*	50(29.2)	3623(20.4)	20.5	50(29.6)	166(32.7)	7.3
LMCA occluded > 50%	30(17.5)	2661(15.0)	6.9	29(17.2)	95(18.7)	4.3
Acetylsalicylic acid use*						
- Continued up to surgery	21(12.3)	1133(6.4)	20,3	20(11.8)	60(11.8)	0.0
- Stopped before surgery	81(47.4)	9181(51.7)	8.7	81(47.9)	253(49.9)	3.9
- Never	69(40.4)	7433(41.9)	3.1	68(40.2)	194(38.3)	4.0
Clopidogrel use*						
- Continued up to surgery	20(11.7)	362(2.0)	38.8	19(11.2)	59(11.6)	1.6
- Stopped before surgery	32(18.7)	1974(11.1)	21.4	31(18.3)	101(19.9)	4.4
- Never	119(69.6)	15411(86.8)	42.6	119(70.4)	347(68.4)	4.9
Hypertension	85(49.7)	9433(53.2)	7.0	84(49.7)	251(49.5)	0.4
Hypercholesteremia	105(61.4)	11583(65.3)	8.0	105(62.1)	325(64.1)	4.1
Smoking	29(17.0)	3560(20.1)	8.0	28(16.6)	98(19.3)	7.1
Vascular disease*	26(15.2)	2558(14.4)	2.2	25(14.8)	76(15.0)	0.6
COPD*	21(12.3)	2485(14.0)	5.1	20(11.8)	53(10.5)	4.1
Diabetes mellitus*						
Diabetes mellitus I	3(1.8)	545(3.1)	8.6	3(1.8)	7(1.4)	2.6
Diabetes mellitus II	23(13.5)	2617(14.7)	3.7	23(13.6)	70(13.8)	0.6
Atrial fibrillation*	20(11.7)	2404(1313.5)	5.6	20(11.8)	53(10.5)	3.6
Endocarditis*	3(1.8)	84(0.5)	12.2	3(1.8)	9(1.8)	0.0
Pre-operative hemoglobin (g/dL)*	14.0(13.2-15.0)	14.2(13.2-15.0)	9.0	14.0(13.2-15.0)	14.2(13.0-15.0)	0.7
APTT, s	34(28-40)	32(28-38)	23.5	34(28-40)	33(28-40)	4.0
INR*						
• < 1.5	122(71.3)	13620(76.7)	12.3	122(72.2)	356(70.2)	4.5
• 1.5 - 2.5	38(22.2)	3472(19.6)	6.5	37(21.9)	120(23.7)	4.4
• > 2.5	11(6.4)	655(3.7)	12.5	10(5.9)	31(6.1)	0.9
Creatinine, μmol/l	88(76-101)	86(75-99)	7.2	88(76-101)	88(77-103)	1.8
Chronic renal failure*	2(1.2)	218(1.2)	0.5	2(1.2)	2(0.4)	7.2
Acute renal failure*	4(2.3)	130(0.7)	13.1	4(2.4)	12(2.4)	0.0
Left ventricular ejection fraction*						
• >50%	110(64.3)	13386(75.4)	24.3	108(63.9)	344(67.9)	8.6
• 25-50%	42(24.6)	2813(15.9)	21.7	42(24.9)	107(21.1)	9.4
• < 25%	19(11.1)	1548(8.7)	8.0	19(11.2)	56(11.1)	0.7
Immunosuppressive drugs*	8(4.7)	604(3.4)	6.5	7(4.1)	25(4.9)	4.0
Tricuspid valve pathology	6(3.5)	476(2.7)	4.8	6(3.6)	16(3.2)	2.3
Mitral valve pathology	33(19.3)	2449(13.8)	14.8	32(18.9)	88(17.4)	4.3
Aortic valve pathology	42(24.6)	3885(21.9)	6.3	42(24.9)	115(22.7)	5.1
Type of surgery*						
• Isolated CABG	115(67.3)	12532(70.6)	7.3	114(67.5)	351(69.2)	3.8
• Other than isolated CABG	56(32.7)	5215(29.4)	7.3	55(32.5	156(30.8)	3.8
EuroSCORE I*	6(3-9)	4(2-7)	50.5	6(3-9)	6(3-9)	6.7
NYHA class IV*	35(20.5)	2871(16.2)	11.1	34(20.1)	88(17.4)	7.1
Nonelective surgery*	42(24.6)	1089(6.1)	52.8	41(24.3)	114(22.5)	5.1
CPR in 24 h before surgery*	6(3.5)	128(0.7)	19.4	6(3.6)	16(3.2)	2.7
Intra-operative variables						
Surgical procedure time, min	251(208-310)	233(196-275)	30.0	251(208-307)	255(210-300)	4.4
Aortic occlusion time, min	69(47-95)	61(44-80)	37.0	69(48-95)	68(53-90)	0.2
CPB use*	163(95.3)	15653(88.2)	26.1	161(95.3)	488(96.3)	3.6
CPB time, min*	106(78-149)	91(69-116)	48.8	106(78-148)	104(83-136)	3.5
Cellsaver blood given, yes/no	64(37.4)	6203(35.0)	5.1	64(37.9)	166(32.7)	10.7
Nadir hemoglobin (g/dL)	8.6(7.7-9.5)	8.7(7.9-9.7)	11.1	8.6(7.8-9.5)	8.7(7.6-9.5)	10.5

Continuous variables are reported as median with interquartile range, and categorical variables are reported as counts with percentages. Standardized differences are reported in % for assessing balance.

**Marks variables that were used to calculate the propensity score.*

APTT = activated partial thromboplastin time; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; CPR = cardiopulmonary resuscitation; INR = international normalized ratio; LMCA = left main coronary artery; LV = left ventricle; MI = myocardial infarction; NYHA = New York Heart Association; SMD = standardized mean difference.

So these 169 patients were suitable for propensity score matching and thereby formed the intervention group. The reference group, which was formed after 1:3 propensity score matching, consisted of 507 patients (who had not received any blood product in the operating room). Considering the fact that matching with replacement was used control patients could be used multiple times: 444 controls were used once, 24 controls were used twice and 5 were used three times, summing up to 473 unique controls out of 507 controls in total.

The majority of patients were men (81%), the median age was 67 year, and about half the patients (49%) had a history of MI. Most patients underwent isolated coronary artery bypass graft (69%), and almost one quarter (23%) of all procedures was a nonelective procedure. As expected, the balance of multiple clinically important variables improved after propensity score matching. Among others the balance of gender, year of surgery, history of MI, clopidogrel use, type of surgery, EuroSCORE, nonelective surgery, cardiopulmonary resuscitation within 24 h before surgery and CPB time improved remarkably (shown on the right side of table 1). Standardized differences for the baseline characteristics are reported for the unmatched and matched groups. Two of the measured covariates, "cellsaver blood returned or not" and "nadir intraoperative hemoglobin", had standardized differences that slightly exceeded 10%, indicative of imbalance in these covariates between matched-treated and untreated patients. The second sensitivity analysis was not only corrected for variables with standardized differences above 10%, but also for a variable with better balance, but with high clinical relevance, namely the EuroSCORE.

Early platelet transfusion and outcomes

Patients in the intervention group less often experienced blood loss higher than 500mL than patients in the reference group (odds ratio 0.66, 95% CI, 0.46 to 0.94). However, the number of early reexplorations for bleeding and/or tamponade and number of late interventions for tamponade of patients in the intervention group did not significantly differ from that of patients in the reference group (table 2).

Table 2. Postoperative bleeding-related Outcomes

	Intervention Group, n=169	Reference Group, n=507	Odds Ratio (95% CI)	P-value
Blood loss > 500ml first 12 h	79(46.7)	290(57.2)	0.66(0.46-0.94)	0.021
Early reexploration for bleeding and/or tamponade	4(2.4)	23(4.5)	0.51(0.17-1.52)	0.227
Late intervention for tamponade	4(2.4)	6(1.2)	2.02(0.52-7.89)	0.309

The absolute numbers and percentages of patients in the intervention and the reference group are given, the regression derived odds ratios with 95% CI and exact P values.

Patients in the intervention group did not endure more stroke, MI, infection, systemic inflammatory response syndrome, shock, acute kidney injury, multiorgan failure, death or composite endpoint than patients in the reference group (table 3).

Table 3. Postoperative Adverse Outcomes

	Intervention Group n=169	Reference Group n=507	Odds Ratio (95% CI)	P value
Stroke*	5(3.0)	16(3.2)	0.94(0.32-2.71)	0.902
Myocardial infarction*	25(14.8)	57(11.2)	1.37(0.82-2.28)	0.226
Patients with postoperative infection	35(20.7)	88(17.4)	1.24(0.79-1.94)	0.340
- Mediastinitits	2(1.2)	1(0.2)	6.06(0.54-67.4)	0.143
- Superficial wound infection	1(0.6)	2(0.4)	1.50(0.14-16.7)	0.740
- Pneumonia	4(2.4)	13(2.6)	0.92(0.30-2.87)	0.887
- Sepsis	11(6.5)	23(4.5)	1.47(0.70-3.08)	0.313
- Other infections	27(16.0)	62(12.2)	1.36(0.82-2.27)	0.230
SIRS	13(7.7)	25(4.9)	1.61(0.79-3.25)	0.187
Shock	28(16.6)	67(13.2)	1.30(0.79-2.14)	0.296
CVVH de novo*	9(5.3)	19(3.7)	1.44(0.63-3.30)	0.383
Multiorgan failure	7(4.1)	16(3.2)	1.33(0.53-3.34)	0.549
In-hospital mortality*	7(4.1)	13(2.6)	1.64(0.64-4.19)	0.300
Composite Endpoint	34(20.1)	89(17.6)	1.18(0.76-1.85)	0.462
Ventilation > 11h	92(54.4)	227(44.8)	1.47(1.03-2.11)	0.034
ICU length of stay > 26 h	95(56.2)	235(46.4)	1.49(1.04-2.12)	0.030
Vasoactive drugs	139(82.2)	374(73.8)	1.65(1.05-2.58)	0.029
Erytrocyte transfusion in ICU	75(44.4)	172(33.9)	1.55(1.08-2.23)	0.017
FFP transfusion in ICU	29(17.2)	37(7.3)	2.63(1.50-4.63)	0.001
Platelet transfusion in ICU	72(42.6)	22(4.3)	16.4(9.3-28.9)	<0.001

The absolute numbers and percentages of patients in the intervention and the reference group are given, the regression derived odds ratios with 95% CI and exact P values.

**Marks endpoints that make up the composite endpoint.*

CVVH = continuous venovenous hemofiltration; FFP = fresh frozen plasma; ICU = intensive care unit; SIRS = systemic inflammatory response syndrome.

An early platelet transfusion was significantly associated with the need for postoperative vasoactive medication (odds ratio 1.65; 95% CI 1.05 to 2.58); long (above median) mechanical ventilation (odds ratio 1.47; 95% CI, 1.03 to 2.11) and long (above median) ICU stay (odds ratio 1.49; 95% CI, 1.04 to 2.12). Also, patients in the intervention group required erythrocyte (44.4 vs 33.9%), FFP (17.2 vs 7.3%) and platelet transfusion in the ICU (42.6 vs 4.3%) more often as compared to patients in the reference group (table 3). The sensitivity analyses yielded results similar to the original analyses.

Results of the first sensitivity analysis: Postoperative outcomes

	Intervention Group n=169	Reference group n=507	Odds ratio (95%CI)	P-value
Blood loss >500 mL first 12 h	79 (46.7)	290 (57.2)	0.68 (0.47-0.97)	0.033
Early reexploration for bleeding /tamponade	4 (2.4)	23 (4.5)	0.53 (0.17-1.59)	0.257
Late intervention for tamponade	4 (2.4)	6 (1.2)	1.94 (0.49-7.76)	0.346
Stroke	5 (3.0)	16 (3.2)	1.03 (0.38-2.81)	0.957
Myocardial infarction	25 (14.8)	57 (11.2)	1.40 (0.84-2.34)	0.195
Patients with postoperative infection	35 (20.7)	88 (17.4)	1.25 (0.80-1.96)	0.325
- Mediastinitis	2 (1.2)	1 (0.2)	7.09 (0.75-66.7)	0.087
- Superficial wound infection	1 (0.6)	2 (0.4)	1.48 (0.13-17.0)	0.753
- Pneumonia	4 (2.4)	13 (2.6)	0.87 0.28-2.69)	0.808
- Sepsis	11 (6.5)	23 (4.5)	1.47 (0.69-3.11)	0.318
- Other infections	27 (16.0)	62 (12.2)	1.39 (0.83-2.32)	0.206
SIRS	13 (7.7)	25 (4.9)	1.46 (0.71-3.00)	0.305
Shock	28 (16.6)	67 (13.2)	1.31 (0.79-2.17)	0.299
CVVH de novo	9 (5.3)	19 (3.7)	1.42 (0.61-3.30)	0.411
Multi organ failure	7 (4.1)	16 (3.2)	1.31 (0.53-3.27)	0.561
In hospital mortality	7 (4.1)	13 (2.6)	1.55 (0.61-3.95)	0.354
Composite endpoint	34 (20.1)	89 (17.6)	1.21 (0.77-1.90)	0.407
Ventilation >11h	92 (54.4)	227 (44.8)	1.53 (1.07-2.20)	0.021
ICU length of stay >26h	95 (56.2)	235 (46.4)	1.51 (1.06-2.17)	0.024
Vasoactive drugs	139 (82.2)	374 (73.8)	1.62 (1.04-2.55)	0.034
RBC transfusion in ICU	75 (44.4)	172 (33.9)	1.64 (1.13-2.38)	0.009
FFP transfusion in ICU	29 (17.2)	37 (7.3)	2.80 (1.56-5.00)	0.001
Platelet transfusion in ICU	72 (42.6)	22 (4.3)	18.8 (10.3-34.0)	<0.001

The results of the first sensitivity analysis in which the logistic regression was adjusted for the covariates "cellsaver blood returned or not" and "nadir intraoperative hemoglobin". The absolute numbers and percentages of patients in the intervention and the reference group are given, the regression derived odds ratios with 95% confidence interval and p-values.

CI confidence interval; CVVH Continuous Veno-Venous Hemofiltration; FFP fresh frozen plasma; ICU Intensive Care Unit; RBC red blood cell; SIRS systemic inflammatory response syndrome.

Results of the second sensitivity analysis: Postoperative outcomes				
	Intervention group n=169	Reference group n=507	Odds ratio (95%CI)	P-value
Blood loss >500 mL first 12 h	79(46.7)	290(57.2)	0.67(0.47-0.97)	0.032
Early reexploration for bleeding /tamponade	4(2.4)	23(4.5)	0.49(0.17-1.44)	0.196
Late intervention for tamponade	4(2.4)	6(1.2)	1.84(0.47-7.31)	0.384
Stroke	5(3.0)	16(3.2)	0.95(0.33-2.74)	0.924
Myocardial infarction	25(14.8)	57(11.2)	1.41(0.84-2.35)	0.195
Patients with postoperative infection	35(20.7)	88(17.4)	1.24(0.79-1.95)	0.359
- Mediastinitis	2(1.2)	1(0.2)	7.29(0.68-78.0)	0.101
- Superficial wound infection	1(0.6)	2(0.4)	1.28(0.11-14.4)	0.840
- Pneumonia	4(2.4)	13(2.6)	0.88(0.28-2.76)	0.820
- Sepsis	11(6.5)	23(4.5)	1.47(0.69-3.11)	0.317
- Other infections	27(16.0)	62(12.2)	1.36(0.81-2.29)	0.239
SIRS	13(7.7)	25(4.9)	1.33(0.63-2.83)	0.451
Shock	28 (16.6)	67 (13.2)	1.25(0.74-2.10)	0.399
CVVH de novo	9 (5.3)	19 (3.7)	1.12(0.45-2.83)	0.805
Multi organ failure	7 (4.1)	16 (3.2)	1.07(0.39-2.93)	0.902
In hospital mortality	7 (4.1)	13 (2.6)	1.31(0.47-3.61)	0.605
Composite endpoint	34 (20.1)	89 (17.6)	1.17(0.74-1.85)	0.511
Ventilation >11h	92 (54.4)	227 (44.8)	1.52(1.06-2.19)	0.024
ICU length of stay >26h	95 (56.2)	235 (46.4)	1.49(1.04-2.15)	0.030
Vasoactive drugs	139 (82.2)	374 (73.8)	1.63(1.04-2.57)	0.035
RBC transfusion in ICU	75 (44.4)	172 (33.9)	1.62(1.11-2.36)	0.012
FFP transfusion in ICU	29 (17.2)	37 (7.3)	2.74(1.52-4.94)	0.001
Platelet transfusion in ICU	72 (42.6)	22 (4.3)	19.9(10.6-37.2)	<0.001

The results of the second sensitivity analysis in which the logistic regression was adjusted for the covariate "EuroSCORE" besides for "cellsaver blood returned or not" and "nadir intraoperative hemoglobin". The absolute numbers and percentages of patients in the intervention and the reference group are given, the regression derived odds ratios with 95% confidence interval and p-values.

CI confidence interval; CVVH Continuous Veno-Venous Hemofiltration; FFP fresh frozen plasma; ICU Intensive Care Unit; RBC red blood cell; SIRS systemic inflammatory response syndrome

Discussion

Main findings

In this study, no statistically significant difference was observed with regard to reinterventions for bleeding, stroke, MI, infections, systemic inflammatory response syndrome, shock, acute kidney injury, multi organ failure, death or composite endpoint between patients who received a single early platelet concentrate and those that did not. However, patients in the intervention group experienced less blood loss and required postoperative vasoactive medication, long mechanical ventilation, long ICU stay, erythrocyte, FFP and platelet transfusion in the ICU more often as compared to patients in the reference group.

Interpretation

The observed correlations between early platelet transfusion and less blood loss; longer postoperative mechanical ventilation; longer intensive care stay and higher rate of administration of vasoactive drugs in the ICU, might be explained by a causal effect of the platelet transfusion. For example, the fact that patients in the intervention group experienced less blood loss postoperatively could be due to the perioperative platelet transfusion. In the case of the

vasoactive drugs, it may be possible that in the intervention group more patients suffered from vasoplegia, and therefore required vasoactive support more often compared to the reference group. Vasoplegia as the indication, and thus possible causal explanation, of the higher risk of vasoactive medication would be in agreement with previous findings of others. First of all it would be consistent with the finding that patients undergoing cardiac surgery with the use of CPB commonly encounter vasoplegia for which pharmacological support, in the form of vasoactive drugs, is needed.[30,31] More importantly it would be in agreement with the correlation, demonstrated by others, between platelet transfusion and an increased risk of vasoplegia after cardiac surgery.[16] In our data, the diagnoses shock, SIRS and sepsis, were equally distributed among the groups, and are therefore not a plausible explanation for the difference in vasoactive drug need. This presumed higher rate of vasoplegia may further explain our finding that intraoperative platelet transfusions are associated with longer mechanical ventilation and intensive care stay.

However, although propensity score matching resulted in comparable baseline characteristics of both groups, it is also possible that the observed association is due to residual confounding, which is not visible in the measured baseline characteristics. Moreover, most of the observed associations are not strong, so they might also be explained by random chance and then it would be incorrect to reject the null hypothesis (type I error). We did not adjust the p-values in tables 2 and 3 for multiple testing, although we analysed multiple endpoints. If Bonferroni correction had been used, the associations between an early platelet transfusion and amount of blood loss, postoperative mechanical ventilation; intensive care stay, vasoactive drugs and erythrocyte administration in the ICU would no longer be considered statistically significant. However, the associations between an early platelet transfusion and postoperative plasma and platelet transfusions in the ICU would remain statistically significant after Bonferroni correction. With considering the results of a Bonferroni correction, we reduce the chance on making type I errors, but risk missing subtle associations with potential clinical importance.

In our study, an early platelet transfusion did not seem to reduce the need for reinterventions for bleeding or tamponade, but was associated with a lower blood loss and a higher rate of erythrocyte, plasma and platelet transfusions in the ICU. The fact that no statistically significant association was observed between an early platelet transfusion and early re-exploration for bleeding and/or tamponade and late intervention for tamponade, might be explained by a lack of statistical power. A possible explanation for the higher rate of postoperative transfusions, is that once one transfusion has been administered, the threshold for subsequent transfusions is lowered. Theoretically, a difference in preferences and convictions of treating physicians regarding transfusions, resulting in comparable patients receiving different treatment, could explain the higher transfusion rate in the ICU. However, in practice physicians who made the decision to transfuse platelets in the OR were generally not responsible for the treatment in the ICU. Finally, in addition to all the above-mentioned considerations, it may also be the case that one postoperative endpoint influenced another postoperative endpoint, but this could not be verified in this database. For example, besides the early platelet transfusion, the plasma and platelet transfusions given in the ICU may also have contributed to the lower blood loss in the intervention group.

Comparison with previous studies

Several other studies have analyzed the association between platelet transfusions and morbidity and mortality in cardiac surgery with varying findings. Our results are in contrast with the studies that report that transfusion of platelets increases the risk of serious adverse outcomes.[17,20,21,32] There are various possible explanations for the discrepancy between the findings of these studies and our results. First, not in all studies appropriate and sufficient adjustment of potential confounding factors, like use of aprotinin or concomitant erythrocyte and plasma transfusions, was applied. Second, in contrast to these four studies, we aimed at analyzing patients who only received one platelet unit and no other blood product shortly after end of CPB while still in the operating room. We focused on these patients because in these patients the indication for the platelet transfusion can be debatable and because these patients are most comparable to patients who received no transfusion. Third, a considerable part of the platelet units examined in these studies was not leukocyte-reduced and the vast majority of the units we studied were leukocyte-reduced.

Our results are consistent with several studies that showed no correlation between platelet transfusion and adverse outcomes like infection, low cardiac output syndrome, MI, stroke, renal failure, sepsis, and mortality.[15,18,33] One study ascertained an association between perioperative platelet transfusion and an increased risk of surgical re-exploration for bleeding, which we did not observe. However the remaining results of this study, regarding postoperative mortality, composite endpoint, infectious, cardiac, renal, pulmonary and neurologic complications, were similar to ours.[19]

Strengths and limitations

To the best of our knowledge, this study is the first to analyze the effect of a single platelet transfusion in a broader cardiac surgery population, consisting both of patients who underwent coronary artery bypass graft and those undergoing (concomitant) valve procedures. Besides we report not only on adverse outcomes, but also the intended effect of the transfusion, which is to prevent and/or stop excessive bleeding. Hereby we aimed at obtaining the overall picture of all potential consequences for a clinician who is considering a platelet transfusion for a cardiac surgery patient. A potential concern of our study is the 16-yr period that was studied, because multiple developments occurred both in blood banking and in cardiac surgery and anesthesiology in this period. However, by including year of surgery in the propensity score we strongly reduced the potential confounding impact of the developments. Furthermore, to the extent of our knowledge, we are the first to study patients who received just a single early platelet transfusion in absence of concomitant transfusion of other blood products, which precludes potential influence of erythrocyte or FFP transfusions on the outcomes. Another strength of our study is that we adjusted for confounding by indication by propensity score matching. By using propensity score matching we were able to identify the patients, out of the 17,747 selected patients, who received no early transfusion who were most comparable to the patients transfused with a single early platelet concentrate. A limitation of our study is that despite accurate propensity score matching residual confounding, by unknown confounders, cannot be completely ruled out. The large comprehensive cohort of 23,860 patients allowed the analysis of sufficient patients

numbers after strict selection of the specific population of interest. Although for some endpoints the 95% confidence interval was relatively wide, which may be partially caused by a lack of power. Since the database was extensive and detailed, it was possible to include the factors that were considered relevant in the propensity score. Furthermore since the data had been collected prior to and therefore independently of the present study, information and selection bias are minimum.

In this study, cardiac surgery patients receiving platelet transfusion in the operating room experienced less blood loss and required vasoactive medication; prolonged ventilation; prolonged intensive care and blood products more often postoperatively. However, our findings further show that an early platelet transfusion was not associated with other serious adverse outcomes like thromboembolic complications, infections, organ failure, in-hospital mortality and reinterventions for bleeding.

Reference List

1 Vivacqua A, Koch CG, Yousuf AM, et al. Morbidity of bleeding after cardiac surgery: is it blood transfusion, reoperation for bleeding, or both? Ann Thorac Surg. 2011;91(6):1780-1790. doi:10.1016/j.athoracsur.2011.03.105.

2 Biancari F, Mikkola R, Heikkinen J, Lahtinen J, Airaksinen KEJ, Juvonen T. Estimating the risk of complications related to re-exploration for bleeding after adult cardiac surgery: a systematic review and meta-analysis. Eur J Cardiothorac Surg. 2012;41(1):50-55. doi:10.1016/j.ejcts.2011.04.023.

3 Christensen MC, Dziewior F, Kempel A, von Heymann C. Increased chest tube drainage is independently associated with adverse outcome after cardiac surgery. J Cardiothorac Vasc Anesth. 2012;26(1):46-51. doi:10.1053/j.jvca.2011.09.021.

4 Haneya A, Diez C, Kolat P, et al. Re-exploration for bleeding or tamponade after cardiac surgery: impact of timing and indication on outcome. Thorac Cardiovasc Surg. 2015;63(1):51-57. doi:10.1055/s-0034-1390154.

5 Levy JH, Despotis GJ. Transfusion and hemostasis in cardiac surgery. Transfusion. 2008;48(1 Suppl):2995.2007.01572.x. doi:10.1111/j.1537-2995.2007.01572.x [doi].

6 Despotis G, Eby C, Lublin DM. A review of transfusion risks and optimal management of perioperative bleeding with cardiac surgery. Transfusion. 2008;48(1 Suppl):30S. doi:10.1111/j.1537-2995.2007.01573.x [doi].

7 Fitchett D, Mazer CD, Eikelboom J, Verma S. Antiplatelet therapy and cardiac surgery: review of recent evidence and clinical implications. Can J Cardiol. 2013;29(9):1042-1047. doi:10.1016/j.cjca.2013.02.014.

8 Thiele RH, Raphael J. A 2014 Update on Coagulation Management for Cardiopulmonary Bypass. Semin Cardiothorac Vasc Anesth. 2014;18(2):177-189. doi:10.1177/1089253214534782 [doi].

9 Cobain TJ, Vamvakas EC, Wells A, Titlestad K. A survey of the demographics of blood use. Transfus Med. 2007;17(1):1-15. doi:TME709 [pii].

10 Snyder-Ramos SA, Mohnle P, Weng YS, et al. The ongoing variability in blood transfusion practices in cardiac surgery. Transfusion. 2008;48(7):1284-1299. doi:10.1111/j.1537-2995.2008.01666.x [doi].

11 of Thoracic Surgeons Blood Conservation Guideline Task Force S, Ferraris VA, Ferraris SP, et al. 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(5 Suppl):27. doi:S0003-4975(07)00495-X [pii].

12 Kumar A, Mhaskar R, Grossman BJ, et al. Platelet transfusion: a systematic review of the clinical evidence. Transfusion. 2015;55(5):1116-27; quiz 1115. doi:10.1111/trf.12943.

13 Kaufman RM, Djulbegovic B, Gernsheimer T, et al. Platelet transfusion: a clinical practice guideline from the AABB. Ann Intern Med. 2015;162(3):205-213. doi:10.7326/M14-1589.

14 Premaratne S, Razzuk AM, Premaratne DR, Mugiishi MM, Hasaniya NW, Behling AF. Effects of platelet transfusion on post cardiopulmonary bypass bleeding. Jpn Heart J. 2001;42(4):425-433.

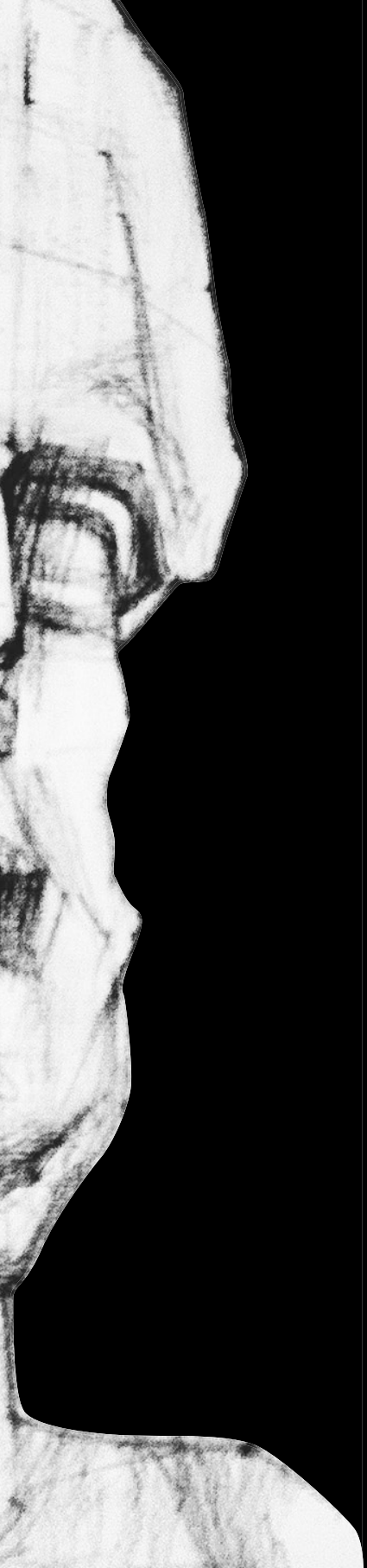
15 Kremke M, Hansen MK, Christensen S, Tang M, Andreasen JJ, Jakobsen CJ. The association between platelet transfusion and adverse outcomes after coronary artery bypass surgery. Eur J Cardiothorac Surg. 2015;48(5):102. doi:10.1093/ejcts/ezv297 [doi].

16 Alfirevic A, Xu M, Johnston D, Figueroa P, Koch CG. Transfusion increases the risk for vasoplegia after cardiac operations. Ann Thorac Surg. 2011;92(3):812-819. doi:10.1016/j.athoracsur.2011.04.020 [doi].

17 Bilgin YM, van de Watering LM, Versteegh MI, van Oers MH, Vamvakas EC, Brand A. Postoperative complications associated with transfusion of platelets and plasma in cardiac surgery. Transfusion. 2011;51(12):2603-2610. doi:10.1111/j.1537-2995.2011.03200.x [doi].

18 Karkouti K, Wijeysundera DN, Yau TM, et al. Platelet transfusions are not associated with increased morbidity or mortality in cardiac surgery. Can J Anaesth. 2006;53(3):279-287. doi:53/3/279 [pii].

19 McGrath T, Koch CG, Xu M, et al. Platelet transfusion in cardiac surgery does not confer increased risk for adverse morbid outcomes. Ann Thorac Surg. 2008;86(2):543-553. doi:10.1016/j.athoracsur.2008.04.051.
20 Mikkola R, Gunn J, Heikkinen J, et al. Use of blood products and risk of stroke after coronary artery bypass surgery. Blood Transfus. 2012;10(4):490-501. doi:10.2450/2012.0119-11 [doi].
21 Spiess BD, Royston D, Levy JH, et al. Platelet transfusions during coronary artery bypass graft surgery are associated with serious adverse outcomes. Transfusion. 2004;44(8):1143-1148. doi:10.1111/j.1537-2995.2004.03322.x [doi].
22 Sreeram GM, Welsby IJ, Sharma AD, Phillips-Bute B, Smith PK, Slaughter TF. Infectious complications after cardiac surgery: lack of association with fresh frozen plasma or platelet transfusions. J Cardiothorac Vasc Anesth. 2005;19(4):430-434. doi:S1053-0770(05)00194-1 [pii].
23 Baharoglu MI, Cordonnier C, Al-Shahi Salman R, et al. Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. Lancet (London, England). 2016;387(10038):2605-2613. doi:10.1016/S0140-6736(16)30392-0.
24 Hogervorst E, Rosseel P, van der Bom J, et al. Tolerance of intraoperative hemoglobin decrease during cardiac surgery. Transfusion. 2014;54(10 Pt 2):2696-2704. doi:10.1111/trf.12654 [doi].
25 Koetsier A, Peek N, de Keizer N. Identifying types and causes of errors in mortality data in a clinical registry using multiple information systems. Stud Health Technol Inform. 2012;180:771-775.
26 Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T. Variable selection for propensity score models. Am J Epidemiol. 2006;163(12):1149-1156. doi:10.1093/aje/kwj149.
27 Westreich D, Cole SR, Funk MJ, Brookhart MA, Sturmer T. The role of the c-statistic in variable selection for propensity score models. Pharmacoepidemiol Drug Saf. 2011;20(3):317-320. doi:10.1002/pds.2074.
28 Hernan MA, Hernandez-Diaz S, Werler MM, Mitchell AA. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. Am J Epidemiol. 2002;155(2):176-184.
29 Leuven E, Sianesi B. PSmatch2:stata module to perform full Mahalanobis and propensity score matching, common support graphing, and covariate imbalance testing, version 4.0.10 edition. https://ideas.repec.org/c/boc/bocode/s432001.html. https://ideas.repec.org/c/boc/bocode/s432001.html. Published 2003. Accessed June 16, 2016.
30 Levin MA, Lin H-M, Castillo JG, Adams DH, Reich DL, Fischer GW. Early on-cardiopulmonary bypass hypotension and other factors associated with vasoplegic syndrome. Circulation. 2009;120(17):1664-1671. doi:10.1161/CIRCULATIONAHA.108.814533.
31 Papadopoulos G, Sintou E, Siminelakis S, Koletsis E, Baikoussis NG, Apostolakis E. Perioperative infusion of low- dose of vasopressin for prevention and management of vasodilatory vasoplegic syndrome in patients undergoing coronary artery bypass grafting-A double-blind randomized study. J Cardiothorac Surg. 2010;5:17. doi:10.1186/1749-8090-5-17.
32 Mangano DT. Aspirin and mortality from coronary bypass surgery. N Engl J Med. 2002;347(17):1309-1317. doi:10.1056/NEJMoa020798.
33 Vamvakas EC. Platelet transfusion and postoperative infection in cardiac surgery. Transfusion. 2007;47(2):352-356. doi:10.1111/j.1537-2995.2007.01115.x.



General Discussion

CHAPTER 7

Summary and General Discussion

Preoperative risk assessment in cardiac surgery

- The EuroSCORE I, developed in 1999, has been used as an important risk model in cardiac surgery, its successor EuroSCORE II was presented in 2012
- We performed a validation study to assess whether or not the EuroSCORE II was a valid risk model in a Dutch cardiac surgery centre.
- The EuroSCORE II outperforms its predecessor in a Dutch single center validation study, with as exception emergency surgery

In **the second** chapter of this thesis we presented a prospective validation study of the EuroSCORE II. This study validated the EuroSCORE II in a complete cohort undergoing all types of cardiac surgery and also aimed at validating the EuroSCORE II in subgroups according to type of surgery and whether or not emergency surgery was performed.
Our results show that in a Dutch hospital, the EuroSCORE II had a more accurate calibration and discrimination than its predecessor the EuroSCORE I. An exception to this were patients who underwent emergency surgery.
In that category, the EuroSCORE II did not perform better than the EuroSCORE I, it underestimated mortality. This is in agreement with a meta-analysis of 22 studies involving 145,592 cardiac surgery procedures which also found that the EuroSCORE II performs less accurate in high risk patients and in emergency surgery.[1] Apparently in emergency surgery and in high risk patients, unknown patient variables which are not included, neither in the EuroSCORE I nor in the EuroSCORE II are more important for accurate prediction of peri-operative mortality. Future studies should therefore focus on identifying the patient variables most important for predicting outcome in emergency surgery and develop separate risk models for these high-risk patients.
In emergency surgery, factors predicting patient outcome could be of more logistical nature than in patients who undergo elective surgery. For example, the time to diagnosis, time from diagnosis until the moment of surgery, and the local experience with emergency surgery. To develop a valid risk model for emergency patients, these factors should be taken into account, as well as blood loss before surgery, the use of anti-coagulant drugs and cardio-pulmonary resuscitation and its duration. For high risk patients, a more comprehensive risk model with more attention for the severity of co-morbidities could improve prediction.
Until a valid risk model for emergency patients is developed, the EuroSCORE I as well as the EuroSCORE II should not be used in emergency patients neither to council patients nor to inform their next of kin because they are unreliable. Risk prediction of these patients should be based on their individual symptoms and co-morbidity until a more accurate risk model is in place.
Implementing risk models in daily practice before validating them in a local population should not occur as different genetic backgrounds, population lifestyles or local treatment regimens can intervene with the predictive ability of a risk model. If a risk model proves to be unreliable

in a particular patient population (assuming the validation study was carried out correctly), results should be published, and an adjusted risk model should be developed, designed to the peculiarities of the local population.
This is especially important because risk models are more and more used for patient counseling and as tools to assess if a particular patient is eligible for surgery and if open heart surgery or a trans-catheter procedure is more suited.[2,3]
It is also important to realize that a risk model is not finished when its first version is presented but that they require updating. Nowadays risk models are more and more used for comparing the quality of care providers by both patients as well as health care regulators and it is important that they stay accurate over time.[4] As seen with the EuroSCORE I model, the calibration and discriminative powers of a risk model will diminish over time, due to progress in medical techniques. Therefore, the performance of risk models like the EuroSCORE II model should be assessed regularly and if necessary adjustments should be made.
The EuroSCORE II and other risk models focus primarily on mortality as outcome measure, but post-operative morbidity is an equally important outcome as serious morbidity diminishes quality of life and is a known cost item. Separate risk models should be developed to predict the risk of different co-morbidity after cardiac surgery.

Transfusion thresholds in cardiac surgery

- In 2008 a study showed that a relative hemoglobin decrease of more than fifty percent was associated with adverse outcomes after cardiac surgery.
- These results were neither confirmed nor contradicted.
- Our results confirm that an intra-operative hemoglobin decrease of fifty percent or more is associated with more adverse outcomes after cardiac surgery.

In **the third chapter** of this thesis we presented a study in which we analyzed the effect of a hemoglobin decrease of fifty percent during cardiac surgery. We performed this study because in 2008 a Canadian study found that not only the absolute hemoglobin level but also the relative hemoglobin decrease should be taken into account when the decision to transfuse red cells is made and these results were never confirmed nor contradicted.[5]
Our results show that patients who do not reach the transfusion threshold of seven g/dL but do suffer from a hemoglobin decrease of more than fifty percent compared to their pre-operative hemoglobin indeed have worse postoperative outcome. Another study, similar in design, has also confirmed these results.[6] Results of these three studies imply that it might be beneficial to include this degree of intraoperative Hb decrease in the decision to transfuse.
Current transfusion thresholds in cardiac surgery patients are in the range of seven to eight g/dL depending on age and severity of co-morbidity.[7,8] It is not known in which situations the benefits of a transfusion outweigh the side effects. As this differs between individual patients and whether or not the patients suffer from acute or chronic coronary disease there is not one single 'optimum'

transfusion trigger for all patients. Accordingly, optimization of the transfusion trigger should take individual factors into account.[9,10]

An often used strategy in patients with acute coronary disease undergoing cardiac surgery is to transfuse until the hemoglobin level is above eight g/dL, if the patient remains symptomatic (hypotension, wall motion abnormalities on echography, elevated ST segments and/or other ECG deviations), then red cell transfusions up to a hemoglobin level of ten g/dL is advised.[11] The evidence base for this policy is limited and based on large observational studies. Future studies should be performed to establish individualized transfusion triggers for patients with acute coronary syndromes.[11,12]

For patients suffering from stable chronic coronary disease undergoing elective cardiac surgery a minimum hemoglobin level of seven to eight g/dL is deemed safe, as was shown in different randomized studies.[13–15] But in none of these studies the extent of the coronary lesions has been properly assessed and taken into account when determining the desired Hb level. The extent of coronary lesions is potentially also related to efficacy of red cell transfusions because it may be possible that more extensive coronary lesions impair the delivery of oxygen to tissues (DO2) in a more extended way, leading to a higher transfusion trigger in these patients.

Further optimization of personalized transfusion triggers could be achieved by including more patient characteristics besides the hemoglobin level and severity of co-morbidity. These characteristics could include smoking (because of the effects of chronic carbon monoxide exposure), ejection fraction (to take the adequacy of the DO2 into account), pre-operative coagulation parameters (because of the higher chance of extended bleeding while having an impaired coagulation), and the extent of the coronary disease. Future studies should look into the possibility of implementing these factors and other possible (bio-)markers in a transfusion trigger and evaluate whether or not this leads to improved transfusion policies with practical applicability.

Intra-operative anemia in cardiac surgery

- With decreasing intraoperative hemoglobin levels (compared to preoperative hemoglobin levels) during cardiac surgery, there is an increase in adverse events.
- A single red cell unit given to increase the hemoglobin level above 8 g/dL did not influence post-operative outcomes when compared with patients who did not receive a transfusion. This means that the transfusion in these patients was useless.

In **chapter four** we presented a study in which we evaluated anemia in Jehovah's witnesses and observed that with the decrease of hemoglobin levels an increase in adverse effects occurred. We composed a group of patients who received one red cell transfusion, matched and compared them with two similar groups of patients who did not receive a red cell transfusion. One group consisted of Jehovah's witnesses and the other one of non- Jehovah's witnesses. Our findings suggest that the transfusion of a single red cell unit did not affect the selected outcomes of these

patients compared to matched Jehovah's witnesses and to non-Jehovah's witnesses receiving no transfusion. This suggests that the red blood cell transfusion should have been avoided.
Studying the effects of anemia independently of red cell transfusions is difficult because the treatment of anemia consists of a red cell transfusion. Red cell transfusions are known to have adverse effects of their own and some of those adverse effects are comparable to the adverse effects of anemia.[6,16–18]
We tried to preclude this by examining intra-operative anemia among Jehovah's witnesses, because Jehovah's witnesses, due to their religious beliefs refuse to receive any blood products. But including Jehovah's witnesses in a study can introduce bias when they are compared to non-Jehovah's witnesses because Jehovah's witnesses often receive a more extensive pre-operative preparation, sometimes including erythropoietin and iron supplements. Also, the selection regarding which patient is eligible for surgery is stricter and the surgeon may operate with more caution to prevent blood loss during surgery. So, statistical analyses of these studies should be carried out with caution, the non-Jehovah's witnesses which are compared to Jehovah's witnesses should be carefully matched, which we did by using propensity scores.
Previous studies showed that Jehovah's witnesses can be operated on safely. Some findings suggest that patient outcomes are better after thoracic surgery without the use any of blood products (bloodless surgery).[19–21]
These previous results combined with our results suggest that bloodless cardiac surgery is safe in selected patients. Results regarding emergency surgery and/or surgery in which hemoglobin decrease exceeded 50% of the base line hemoglobin level in Jehovah's witnesses are lacking, although it is likely that the outcome in these cases is worse.

Formation of allo-antibodies and red cell storage time

- Allo-antibody formation is a side effect of red cell transfusion
- Genetic and environmental factors may increase RBC allo-immunization risks, including a possible role of storage interval of RBC.
- The formation of anti-K antibodies was not associated with duration of red blood cell storage time of K-positive transfusions to K-negative patients

In **chapter five** we presented a study examining the relation between allo-antibody formation after red cell transfusion and the storage time of the transfused red cells. Outside the human body red cells intended for transfusion are stored up to 35-42 days dependent on the storage solution. In our study we analyzed immunization against incompatible K positive red blood cells in a patient population with divergent disease entities. We identified the storage time of the immunizing and the non-immunizing K positive red cell units. We did not find an association between the storage time of red cells and allo-antibody formation.
Research into the origin of allo-antibodies is of utmost importance because alloimmunization as a side effect of red cell transfusion can cause serious complications like delayed and acute

hemolytic reactions. Also, the occurrence of alloimmunization is not a rare one as allo-antibody formation occurs in 2-10 % of all cardiac surgery patients.[22–25]
At least 30 RBC antigens can evoke antibodies after incompatible red cell transfusions, but some antigens such as Rh and K antigens are more immunogenic than others. A previous study showed no association between the storage time of red cells and the formation of anti-D antibodies in humans, but this study did not identify the 'immunizing' unit.[26] Therefore this study could not analyze the association between the storage time of the red blood cells which actually induce the allo-antibodies and the incidence of alloimmunization. In our study we were able to do so and found no association as was previously suggested in mouse models.[27]
Limitations of our study were that the amount of 'very old' units analyzed in our study was confined and so an association between 'very old' red blood cells and alloimmunization could not be excluded and the same is true for the 'very fresh' red cells.
Nevertheless, in agreement with a multitude of studies analyzing the effect of storage time on other clinical and in vitro outcomes we did not find an association between the storage time and adverse outcomes, making it unlikely that such an association exists.[28,29]

Platelet transfusion in cardiac surgery

- Platelet concentrates are relatively often transfused during cardiac surgery because of the use cardiopulmonary bypass and pre-operative antiplatelet drugs.
- Conflicting results have been reported regarding the effects of platelet concentrates on clinical outcomes.
- We found that patients who received one platelet concentrate experienced less blood loss, compared with similar patients who received none. Patients who received one platelet concentrate required more often vasoactive medication, prolonged ventilation, prolonged intensive care stay and more blood products postoperatively.

In **chapter six** we assessed the independent association between a single platelet transfusion, transfused during cardiac surgery, and bleeding and adverse postoperative outcomes. Our results show that a single platelet transfusion was not associated with more mortality, organ failure, infections, thromboembolic complications and re-interventions. Patients who did receive a single platelet transfusion experienced less postoperative blood loss compared with similar patients who received no platelets. However, they did require more vasoactive medication and received more erythrocytes and plasma postoperatively, also they stayed longer on the ICU and were longer on ventilatory support.
In contrast to red cell transfusions, in cardiac surgery there is no platelet count which serves as transfusion trigger for a platelet transfusion. If patients receive platelets it is often after being weaned from the cardiopulmonary bypass, and after neutralization of the heparin so damage by the extracorporeal circuit can be avoided. Platelets are generally administered when bleeding persists after a series of other measures to stop the bleeding such as: surgical hemostasis, fibrinogen

concentrates, tranexamic acid and plasma products (Fresh frozen plasma or Omniplasma, a solvent/detergent plasma). All of the above explains why platelet transfusion rates differ greatly between different centers.[30–34]

To assess whether or not a platelet transfusion is indicated during cardiac surgery, viscoelastic point of care tests like the TEG® or the Rotem® are often used. The advantage of these test above standard coagulation test is that they have a shorter turn-around time in a clinical setting where timely decision on coagulation interventions are a necessity.[35,36] A recent review showed that transfusion algorithms based on point of care testing lead to a reduction in the amount of blood products transfused with no adverse effects on mortality, stroke, prolonged intubation, emergency re-operation for bleeding or length of stay (both ICU as in-hospital).[37] This implies that current point of care testing may reduce the amount of blood products transfused.

With ameliorating techniques, the capabilities of point of care tests and thrombo-elastography will expand. Future techniques should be able to detect the nature of coagulopathies and specific clotting deficits even faster. Also, it could be feasible not only to perform viscoelastic point of care tests when a bleeding does occur but also as a routine monitoring tool during more difficult surgeries. This way deficiencies in clotting parameters could be treated before the bleeding occurred possibly resulting in a clinical benefit for the patients.

Not only the use of cardiopulmonary bypass but also the use of anti-platelet drugs by patients undergoing cardiac surgery increases platelet dysfunction and can contribute to bleeding necessitating more transfusions.[38]

Patients who use anti-coagulant drugs to prevent coronary artery blockage are more prone to platelet transfusions especially when these drugs are continued until surgery.[39] Over the last decade dual anti-platelet therapy (DAPT) has been prescribed to a growing patient population. DAPT treatment, existing of a regime with aspirin combined with an adenosine diphosphate P2Y12 receptor antagonist (P2Y12 inhibitors) like clopidogrel has been proven to be beneficial in patients with acute coronary syndromes and ischemic cardiomyopathies.[39]

Whether DAPT treatment should be (dis-) continued until the day of surgery is still uncertain. Continuing DAPT treatment could be beneficial because it is likely to prevent additional thrombotic events but it also can induce more bleeding complications during surgery. There is sufficient evidence proving that continuing aspirin alone during the peri-operative period does not lead to an increase in postoperative bleeding but could lead to more platelet transfusions.[40,41] With regard to P2Y12 inhibitors current guidelines, updated in 2012, advice that these drugs should be discontinued several days before cardiac surgery.[42] Nevertheless although some studies conclude that stopping these drugs is associated with reduced bleeding, blood transfusion and reoperation, others find that continuing P2Y12 inhibitors leads to les thrombotic complications. Maybe future studies can find more definite answers, until then continuing or stopping DAPT treatment should be evaluated for each individual patient.[42–44]

The future of research, transfusions and cardiac surgery

In this last section we address some aspects regarding the future of transfusion medicine and cardiac surgery. Cardiothoracic surgery is not without risk and patients can suffer from considerable blood loss due to the nature of surgery, the use of heart lung machines, pre-

existent and/or drug induced coagulation disorders, etc. This means that a notable part of the patients undergoing cardiac surgery receive blood products which have considerable side effects of their own. Future research should generate knowledge on how to prevent bleeding and how to optimize coagulation perioperatively. Topics which should be examined more closely are for example, the optimization of anticoagulant drug use perioperatively, further reduction of the volume of heart lung machines and a more effective use of point of care coagulation tests during surgery. Nevertheless, transfusion of blood products will remain necessary for a number of patients. Therefore, future research should also focus on identifying which patients will benefit from transfusions and further examine the most suitable transfusion trigger. Another issue that needs further investigation are the side effects of red cell transfusions like for example alloimmunization.

A possible solution to the side effects described above would be substitution of erythrocyte transfusion by artificial oxygen carriers. In the search for artificial oxygen carriers, three different concepts have been pursued over the years. Chemical O2 and CO2 transporters, only to use in mechanical ventilated patients, second artificially modified Hb derived from human, bovine, swine or even worm hemoglobin and third the ex vivo culture of erythrocytes lacking selected antigens.[45,46] Nowadays, only one (bovine) product suitable for humans is registered, and it is only registered in South Africa.[47] The use of this oxygen carrier comes with adverse effects on the cardiovascular system like vasospasms and/or vasoconstriction and therefore registration in the European Union and the United States of America has not been granted.[48] Biotechnical limitations which were difficult to overcome have slowed the research in this area for some time, but recently, the search of artificial blood products seems to flourish again.[45,49] Nevertheless, many challenges will be encountered before artificial oxygen carriers can replace red blood cell transfusions, and it is unlikely that complete replacement of allogenic red cell transfusions will be realized because there are too many disadvantages like for example the short lifespan of artificial oxygen carriers. But a supplemental role for artificial oxygen carriers should be further examined. They could be used for example in ex vivo perfusion of organ grafts before transplantation, as the first human liver transplantation after machine perfusion with artificial oxygen was recently performed.[50] Other uses, for example as a bridge to transfusion, or to surpass severe hemodilution should be further investigated.

Another topic of future research should be developing a better way to predict the need for red cell transfusions in individual patients. This could be achieved by composing a risk model using variables of which it is known that they influence oxygen delivery, such as pulmonary and cardiac conditions among others. In the past such risk models have been constructed, but the generalizability of these models did not suffice as these models were not constructed prospectively and thus based on deprecated data or were composed in a selected population which demised their generability.[51–53]

Identifying patients at risk of receiving a red cell transfusion during cardiac surgery has the advantage that some of these patients can be better prepared before surgery, for example in the same way that Jehovah witnesses are prepared. Iron supplements, erythropoietin and the emphasis on meticulous surgical coagulation could help prevent red cell transfusions in these patients. The annotation must be made that, the goal of the extended measures mentioned

above is improving the patient's clinical outcome and not reducing the number of transfusions per se. Treating cardiac surgery patients who have a greater chance at receiving a red cell transfusion with additional hemoglobin increasing therapies could be beneficial for some. But when implementing these therapies (for example as standard treatment in a PBM) one should realize that every treatment has its own side effects. For example, erythropoietin increases blood viscosity, and some studies report increased risk of infection in patients who are treated iron supplements.[54] So ideally a preemptive strategy to minimize the chance on red cell transfusion should be tailor made to the needs of the patient.

As with the preemptive measures mentioned above a 'tailor made' transfusion trigger could be more beneficial for patients then the current transfusion guidelines used. One can imagine that a more personalized transfusion threshold could prevent needless transfusions in patients who don't require them and also it could help determining which patients will benefit from blood products. Whether or not this will lead to better clinical outcomes should be assessed, preferably in a randomized control trial in which one group of patients will be transfused according to current transfusion guidelines and another group which will be transfused according to a personalized transfusion trigger. This personalized transfusion trigger should consist of information about the hemoglobin concentration of the patient complemented with patient characteristics mentioned when we discussed chapter three.

Furthermore, to improve a more individualized transfusion policy in the future it may be feasible to include advanced O2 measurements in transfusion algorithms. With the development of cerebral tissue oxygenation devices, like INVOS©, the oxygen saturation of the brain can be measured directly. Using these devices, red cell transfusion could be better adjusted to the actual oxygen demand during surgery. A randomized clinical trial published results which favored the use of these devices in guiding the decision making process with regard to red cell transfusions.[55] In this trial patients were randomized in one of two groups, the first group had a transfusion algorithm mostly based on cerebral oximetry values while the other group had a conventional algorithm based on hematocrit values. The results show that the in the cerebral oximetry group less red cell transfusions were prescribed perioperatively while there were no differences in outcome between both groups. Nevertheless when considering a red cell transfusion, values from cerebral oximetry always have to be interpreted with regards to the clinical situation of the patient.[56,57]

Maybe the best way to personalize the transfusion trigger lies in the development of a method in which intra- mitochondrial oxygen levels could be directly measured in the critical organs during surgery. This way oxygen delivery and the oxygen consumption could be best adjusted to each other. Such a device is currently under study in the LUMC, AMC and Erasmus MC.[58] This research focuses on validating this method of cellular O2 measurement and when proven beneficial, transfusions protocols should be adjusted accordingly.

Some have implied that a prolonged storage time of red cells diminishes their quality and that a shorter storage time should be established to ensure the quality, effectivity and safety of transfused red cells. It is true that the quality of red cells alters over time because of changes that occur in the erythrocyte during storage, like a decrease of glucose, 2-3 diphosphoglycerate, adenosine triphosphate and an increase of potassium in the solvent. These changes combined

are called the storage lesion and is known to be partly reversible when the erythrocyte is 'back in vivo'.[59]

An extensive number of studies has been published about the clinical implication of the storage lesion. Most well executed studies however, did not find an association between storage time and increased morbidity and/or mortality.[28,29] In the recent years several large international randomized clinical trials, performed in different patient groups like as ICU patients, children and cardiac surgery patients published their results, also showing that prolonged storage time within the current ranges of storage is not associated with adverse clinical outcomes of transfusion recipients.[29]

It is hard to determine when there is enough evidence to accept that there is no causal effect of an intervention on patient outcomes but in the case of red cell storage time there is a convincing amount of evidence suggesting that there is no benefit when fresher red cells are transfused. Therefore, there is no need to perform more studies on the effect of storage time of red cells on clinical outcomes.

Other measures that could be taken to prevent bleeding complications and the transfusion of blood products in cardiac surgery patients are optimizing coagulation and minimalizing hemodilution. Optimizing coagulation can be achieved by meticulous surgical coagulation but also by sensible use of pro-coagulant drugs like desmopressin and anti-fibrinolytics like tranexamic acid. Future research must be done to find the optimal dose and timing of administration of these drugs, in order to be included in updated guidelines. The same goes for P2Y12 inhibitors and the interval before surgery in which they should be stopped. In clinical practice a wash out period of five to seven days is often used, but there is a large inter-individual variability in response to P2Y12 inhibitors. Point of care testing as a pre-operative screening tool could help to find the ideal timing to stop these drugs before surgery based on platelet reactivity.[43] Improving the current techniques for point-of-care coagulation testing and including these improved tests in transfusion algorithms could also lead to better clinical outcomes because it could accelerate diagnostics and proper treatment.

Hemodilution could be decreased if future heart lung machines will become available requiring a smaller extracorporeal volume.

To conclude, every well-constructed study has its importance if it is carried out correctly. Every reliable study contributes to better understanding of a problem, however small this contribution may be. For every acceptance or rejection of a hypothesis a growing body of evidence is formed to guide us in the right direction. Therefore, it is counterproductive to rely on personal clinical experience alone as this is restricted to a limited set of observations and important new evidence can be missed, which can lead to inferior and outdated treatment regimes.

The intent of this thesis was to shed light on when transfusing blood products is the right decision during cardiac surgery. As every blood transfusion has its risk on adverse events, every decision to transfuse must be based on reliable scientific evidence. Therefore, more research needs to be performed, more evidence needs to be gathered and more awareness regarding the risks of transfusions needs to be spread until we are certain that 'primum non nocere' is a fact with regard to transfusion medicine in cardiac surgery.

What is known?

- The EuroSCORE I (1999) has been an important risk model in cardiac surgery, its successor EuroSCORE II was presented in 2012
- Hemoglobin decrease > 50% during cardiac surgery is potential harmful, but current transfusion guidelines are based on absolute hemoglobin levels, gender and selective co-morbidity
- Extensive blood loss can be detrimental but on the other hand red cell transfusions can have detrimental side effects, which one is the cause of adverse clinical effects is almost impossible to determine
- Allo-antibody formation is a known side effect of red cell transfusions, approximately 5% of all cardiac surgery patients develop red cell antibodies
- Platelet concentrates are relatively often transfused during cardiac surgery because of the use of heart lung machines and the use of anti-platelet drugs before surgery.

What does this thesis add?

- The Euroscore II outperforms its predecessor in a Dutch single center validation study, both EuroSCORE I and II are not reliable enough in emergency surgery
- An intra-operative hemoglobin decrease of 50% or more leads to more adverse outcome after cardiac surgery
- Intra-operative anemia is associated with more adverse outcomes
- Transfusion of a single red blood cell concentrate does not seem to influence these outcomes
- It is not likely that there is a causal relationship between allo-antibody formation and storage time of red blood cells

Reference List

1 Guida P, Mastro F, Scrascia G, Whitlock R, Paparella D. Performance of the European System for Cardiac Operative Risk Evaluation II: a meta-analysis of 22 studies involving 145,592 cardiac surgery procedures. J Thorac Cardiovasc Surg. 2014;148(6):57.e1. doi:10.1016/j.jtcvs.2014.07.039 [doi].

2 Nashef SA, Roques F, Sharples LD, et al. EuroSCORE II. Eur J Cardiothorac Surg. 2012;41(4):5. doi:10.1093/ejcts/ezs043 [doi].

3 Kuwaki K, Inaba H, Yamamoto T, et al. Performance of the EuroSCORE II and the Society of Thoracic Surgeons Score in patients undergoing aortic valve replacement for aortic stenosis. J Cardiovasc Surg (Torino). 2015;56(3):455-462. doi:R37Y2015N03A0455 [pii].

4 Shahian DM, Blackstone EH, Edwards FH, et al. Cardiac surgery risk models: a position article. Ann Thorac Surg. 2004;78(5):1868-1877. doi:S0003-4975(04)01196-8 [pii].

5 Karkouti K, Wijeysundera DN, Yau TM, McCluskey SA, van Rensburg A, Beattie WS. The influence of baseline hemoglobin concentration on tolerance of anemia in cardiac surgery. Transfusion. 2008;48(4):666-672. doi:10.1111/j.1537-2995.2007.01590.x [doi].

6 Loor G, Li L, 3rd JFS, Rajeswaran J, Blackstone EH, Koch CG. Nadir hematocrit during cardiopulmonary bypass: end-organ dysfunction and mortality. J Thorac Cardiovasc Surg. 2012;144(3):662.e4. doi:10.1016/j.jtcvs.2012.03.058 [doi].

7 Docherty AB, O'Donnell R, Brunskill S, et al. Effect of restrictive versus liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting: systematic review and meta-analysis. BMJ. 2016;352:i1351.

8 Society of Thoracic Surgeons Blood Conservation Guideline Task Force S, Ferraris VA, Brown JR, 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):944-982. doi:10.1016/j.athoracsur.2010.11.078 [doi].

9 Kansagara D, Dyer E, Englander H, Fu R, Freeman M, Kagen D. Treatment of anemia in patients with heart disease: a systematic review. Ann Intern Med. 2013;159(11):746-757. doi:10.7326/0003-4819-159-11-201312030-00007 [doi].

10 Hovaguimian F, Myles PS. Restrictive versus Liberal Transfusion Strategy in the Perioperative and Acute Care Settings: A Context-specific Systematic Review and Meta-analysis of Randomized Controlled Trials. Anesthesiology. 2016;125(1):46-61. doi:10.1097/ALN.0000000000001162 [doi].

11 Carson J, Kleiman S. Indications and hemoglobin thresholds for red blood cell transfusion in the adult. March 2017. https://www-uptodate-com.proxy-ub.rug.nl/contents/indications-and-hemoglobin-thresholds- for-red-blood-cell-transfusion-in-the-adult?source=search_result&search=indications and hemoglobin thresholds&selectedTitle=1~150.

12 Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. N Engl J Med. 2001;345(17):1230-1236. doi:10.1056/NEJMoa010615 [doi].

13 Murphy GJ, Pike K, Rogers CA, et al. Liberal or restrictive transfusion after cardiac surgery. N Engl J Med. 2015;372(11):997-1008. doi:10.1056/NEJMoa1403612 [doi].

14 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):1070-1077.

15 Hajjar LA, Vincent JL, Galas FR, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. Jama. 2010;304(14):1559-1567. doi:10.1001/jama.2010.1446 [doi].

16 Habib RH, Zacharias A, Schwann TA, 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(8):1749-1756. doi:00003246-200508000-00012 [pii].

17 Koch C, Li L, Figueroa P, Mihaljevic T, Svensson L, Blackstone EH. Transfusion and pulmonary morbidity after cardiac surgery. Ann Thorac Surg. 2009;88(5):1410-1418. doi:10.1016/j.athoracsur.2009.07.020 [doi].
18 Loor G, Rajeswaran 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):1487.e6. doi:10.1016/j.jtcvs.2013.06.033 [doi].
19 Bhaskar B, Jack RK, Mullany D, Fraser J. Comparison of outcome in Jehovah's Witness patients in cardiac surgery: an Australian experience. Heart Lung Circ. 2010;19(11):655-659. doi:10.1016/j.hlc.2010.07.010 [doi].
20 Garcia JH, Coelho GR, Neto BAF, Nogueira EA, Teixeira CC, Mesquita DF. Liver transplantation in Jehovah's Witnesses patients in a center of northeastern Brazil. Arq Gastroenterol. 2013;50(2):138-140. doi:S0004-28032013000200138 [pii].
21 Issa K, Banerjee S, Rifai A, et al. Blood management strategies in primary and revision total knee arthroplasty for Jehovah's Witness patients. J Knee Surg. 2013;26(6):401-404. doi:10.1055/s-0033- 1353994 [doi].
22 van de Watering L, Hermans J, Witvliet M, Versteegh M, Brand A. HLA and RBC immunization after filtered and buffy coat-depleted blood transfusion in cardiac surgery: a randomized controlled trial. Transfusion. 2003;43(6):765-771. doi:trf390 [pii].
23 Fluit CR, Kunst VA, Drenthe-Schonk AM. Incidence of red cell antibodies after multiple blood transfusion. Transfusion. 1990;30(6):532-535.
24 Ness PM, Shirey RS, Thoman SK, Buck SA. The differentiation of delayed serologic and delayed hemolytic transfusion reactions: incidence, long-term serologic findings, and clinical significance. Transfusion. 1990;30(8):688-693.
25 Redman M, Regan F, Contreras M. A prospective study of the incidence of red cell allo-immunisation following transfusion. Vox Sang. 1996;71(4):216-220.
26 Yazer MH, Triulzi DJ. Receipt of older RBCs does not predispose D-negative recipients to anti-D alloimmunization. Am J Clin Pathol. 2010;134(3):443-447. doi:10.1309/AJCP2J8SVWOXRLRB [doi].
27 Hendrickson JE, Hod EA, Spitalnik SL, Hillyer CD, Zimring JC. Storage of murine red blood cells enhances alloantibody responses to an erythroid-specific model antigen. Transfusion. 2010;50(3):642-648. doi:10.1111/j.1537-2995.2009.02481.x [doi].
28 28. McKenny M, Ryan T, Tate H, Graham B, Young VK, Dowd N. Age of transfused blood is not associated with increased postoperative adverse outcome after cardiac surgery. Br J Anaesth. 2011;106(5):643-649. doi:10.1093/bja/aer029 [doi].
29 29. Shah A, McKechnie S, Brunskill SJ, Stanworth SJ. Fresh versus old red cell transfusions: what have the recent clinical trials found? Curr Opin Hematol. 2016;23(6):550-556. doi:10.1097/MOH.0000000000000283 [doi].
30 de Vries R, Haas F, working group for revision of the Dutch Blood Transfusion Guideline 2011. English translation of the dutch blood transfusion guideline 2011. Clin Chem. 2012;58(8):1266-1267. doi:58/8/1266 [pii].
31 Society of Thoracic Surgeons Blood Conservation Guideline Task Force S, Ferraris VA, Ferraris SP, et al. 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(5 Suppl):27. doi:S0003-4975(07)00495-X [pii].
32 Snyder-Ramos SA, Mohnle P, Weng YS, et al. The ongoing variability in blood transfusion practices in cardiac surgery. Transfusion. 2008;48(7):1284-1299. doi:10.1111/j.1537-2995.2008.01666.x [doi].
33 Shams Hakimi C, Fagerberg Blixter I, Hansson EC, Hesse C, W allen H, Jeppsson A. Effects of fibrinogen and platelet supplementation on clot formation and platelet aggregation in blood samples from cardiac surgery patients. Thromb Res. 2014;134(4):895-900. doi:10.1016/j.thromres.2014.05.023.

34 Gorlinger K, Shore-Lesserson L, Dirkmann D, Hanke AA, Rahe-Meyer N, Tanaka KA. Management of hemorrhage in cardiothoracic surgery. J Cardiothorac Vasc Anesth. 2013;27(4 Suppl):20. doi:10.1053/j.jvca.2013.05.014 [doi].

35 Bolliger D, Tanaka KA. Point-of-Care Coagulation Testing in Cardiac Surgery. Semin Thromb Hemost. 2017;43(4):386-396. doi:10.1055/s-0037-1599153.

36 Karkouti K, Callum J, Wijeysundera DN, et al. Point-of-Care Hemostatic Testing in Cardiac Surgery: A Stepped-Wedge Clustered Randomized Controlled Trial. Circulation. 2016;134(16):1152-1162. doi:CIRCULATIONAHA.116.023956 [pii].

37 Serraino GF, Murphy GJ. Routine use of viscoelastic blood tests for diagnosis and treatment of coagulopathic bleeding in cardiac surgery: updated systematic review and meta-analysis. Br J Anaesth. 2017;118(6):823-833. doi:10.1093/bja/aex100 [doi].

38 Despotis G, Eby C, Lublin DM. A review of transfusion risks and optimal management of perioperative bleeding with cardiac surgery. Transfusion. 2008;48(1 Suppl):30S. doi:10.1111/j.1537-2995.2007.01573.x [doi].

39 Helton TJ, Bavry AA, Kumbhani DJ, Duggal S, Roukoz H, Bhatt DL. Incremental effect of clopidogrel on important outcomes in patients with cardiovascular disease: a meta-analysis of randomized trials. Am J Cardiovasc Drugs. 2007;7(4):289-297. doi:746 [pii].

40 Myles PS, Smith JA, Forbes A, et al. Stopping vs. Continuing Aspirin before Coronary Artery Surgery. N Engl J Med. 2016;374(8):728-737. doi:10.1056/NEJMoa1507688 [doi].

41 Gielen CL, Bruggemans EF, Stijnen T, et al. Stopping antiplatelet medication before coronary artery bypass graft surgery: is there an optimal timing to minimize bleeding? Eur J Cardiothorac Surg. 2015;48(4):64. doi:10.1093/ejcts/ezv269 [doi].

42 Ferraris VA, Saha SP, Oestreich JH, et al. 2012 update to the Society of Thoracic Surgeons guideline on use of antiplatelet drugs in patients having cardiac and noncardiac operations. Ann Thorac Surg. 2012;94(5):1761-1781. doi:10.1016/j.athoracsur.2012.07.086 [doi].

43 Nijjer SS, Watson G, Athanasiou T, Malik IS. Safety of clopidogrel being continued until the time of coronary artery bypass grafting in patients with acute coronary syndrome: a meta-analysis of 34 studies. Eur Heart J. 2011;32(23):2970-2988. doi:10.1093/eurheartj/ehr151 [doi].

44 Gielen CL, Bruggemans EF, Stijnen T, et al. Stopping antiplatelet medication before coronary artery bypass graft surgery: is there an optimal timing to minimize bleeding? Eur J Cardiothorac Surg. 2015;48(4):64. doi:10.1093/ejcts/ezv269 [doi].

45 Simoni J. New approaches in commercial development of artificial oxygen carriers. Artif Organs. 2014;38(8):621-624. doi:10.1111/aor.12371.

46 Sakai H. Overview of Potential Clinical Applications of Hemoglobin Vesicles (HbV) as Artificial Red Cells, Evidenced by Preclinical Studies of the Academic Research Consortium. J Funct Biomater. 2017;8(1). doi:10.3390/jfb8010010.

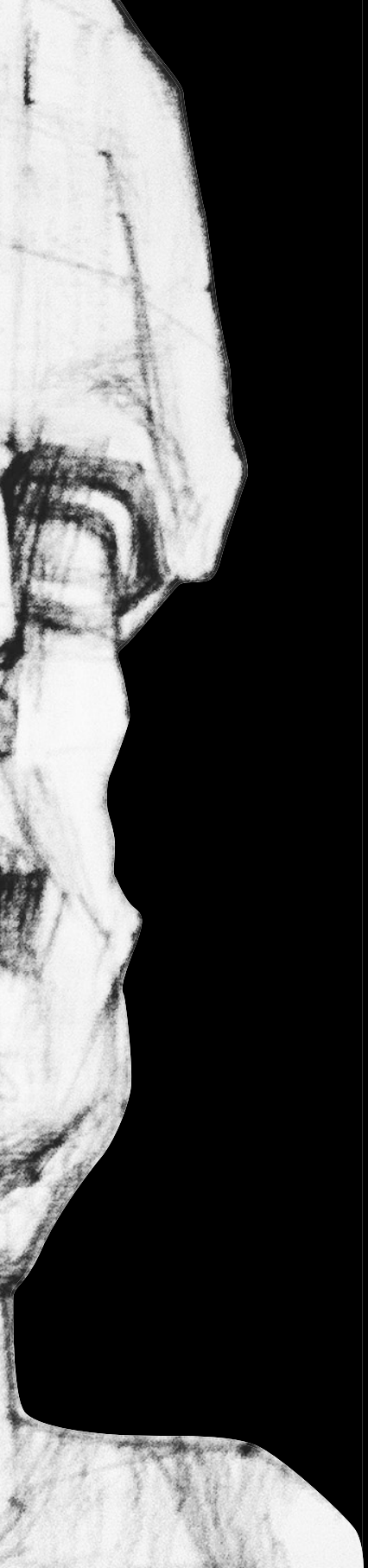
47 Simoni J. Artificial Oxygen Carriers: Exactly How Close Are We to an Ultimate Product? Artif Organs. 2017;41(4):316-318. doi:10.1111/aor.12939 [doi].

48 Mer M, Hodgson E, Wallis L, et al. Hemoglobin glutamer-250 (bovine) in South Africa: consensus usage guidelines from clinician experts who have treated patients. Transfusion. 2016;56(10):2631-2636. doi:10.1111/trf.13726.

49 Simoni J. Artificial Oxygen Carriers: Exactly How Close Are We to an Ultimate Product? Artif Organs. 2017;41(4):316-318. doi:10.1111/aor.12939 [doi].

50 Spahn DR. Artificial oxygen carriers: a new future? Crit Care. 2018;22(1):46. doi:10.1186/s13054-018-1949-5.

51 Al-Khabori M, Al-Riyami AZ, Mukaddirov M, Al-Sabti H. Transfusion indication predictive score: a proposed risk stratification score for perioperative red blood cell transfusion in cardiac surgery. Vox Sang 2014;107(3):269-275. doi:10.1111/vox.12163.
52 Litmathe J, Boeken U, Feindt P, Gams E. Predictors of homologous blood transfusion for patients undergoing open heart surgery. Thorac Cardiovasc Surg. 2003;51(1):17-21. doi:10.1055/s-2003-37281.
53 Alghamdi AA, Davis A, Brister S, Corey P, Logan A. Development and validation of Transfusion Risk Understanding Scoring Tool (TRUST) to stratify cardiac surgery patients according to their blood transfusion needs. Transfusion. 2006;46(7):1120-1129. doi:10.1111/j.1537-2995.2006.00860.x.
54 Roger SD. Practical considerations for iron therapy in the management of anaemia in patients with chronic kidney disease. Clin Kidney J. 2017;10(Suppl 1):i9-i15. doi:10.1093/ckj/sfx100.
55 Vretzakis G, Georgopoulou S, Stamoulis K, et al. Monitoring of brain oxygen saturation (INVOS) in a protocol to direct blood transfusions during cardiac surgery: a prospective randomized clinical trial. J Cardiothorac Surg. 2013;8:145. doi:10.1186/1749-8090-8-145 [doi].
56 Green DW, Kunst G. Cerebral oximetry and its role in adult cardiac, non-cardiac surgery and resuscitation from cardiac arrest. Anaesthesia. 2017;72 Suppl 1:48-57. doi:10.1111/anae.13740.
57 Vranken NPA, Weerwind PW, Sutedja NA, Severdija EE, Barenbrug PJC, Maessen JG. Cerebral Oximetry and Autoregulation during Cardiopulmonary Bypass: A Review. J Extra Corpor Technol. 2017;49(3):182-191.
58 Ubbink R, Bettink MA, Janse R, et al. A monitor for Cellular Oxygen METabolism (COMET): monitoring tissue oxygenation at the mitochondrial level. J Clin Monit Comput. December 2016. doi:10.1007/s10877-016-9966-x [doi].
59 Garcia-Roa M, Vicente-Ayuso MDC, Bobes AM, et al. Red blood cell storage time and transfusion: current practice, concerns and future perspectives. Blood Transfus. 2017;15(3):222-231. doi:10.2450/2017.0345-16 [doi].



Summary
Nederlandse Samenvatting

CHAPTER 8

Summary

Cardiac surgery is one of the fastest evolving fields in medicine. With improved techniques and the ever aging population, increasing numbers of patients with co-morbidities are undergoing cardiac surgery. Before cardiac surgery, it is important to weigh the benefits against the risks of surgery. The EuroSCORE I model had been an accurate tool to predict mortality after cardiac surgery. But over the years the accuracy of this model seemed to decrease. Therefore an updated version, the EuroSCORE II was created. In this thesis we validated the EuroSCORE II in a Dutch population of patients undergoing cardiac surgery and found that the EuroSCORE II model indeed outperformed its predecessor in the majority of patients. An exception to this was found in patients with very high preoperative risks and in emergency situations. For these patients the EuroSCORE did not predict mortality accurately and a new risk model would need to be developed for this category. For the remaining patient conditions the EuroSCORE II model is a reliable tool to predict mortality due to cardiac surgery.

Cardiac surgery can lead to significant blood loss which has led traditionally to high amounts of patients being treated with transfusion of allogeneic red blood cells. Over the past decades more conservative transfusion triggers have been implemented, trying to minimize the exposure to red cell transfusion and their possible side effects. But it is not known which Hb decrease can be safely tolerated and it is likely that this will differ between patients. A previous study in cardiac surgery patients assessed possible adverse events in patients with a Hb decrease of fifty percent or more during cardiac surgery. This study showed that such excessive hemoglobin decreases were associated with more postoperative adverse outcomes like acute kidney injury, myocardial infarction and mortality. The results of that study had not been confirmed nor contradicted.

We performed a study similar in design in a Dutch cohort. Our results also show that patients who did not reach the transfusion threshold of 7 g/dL but who did suffer from an intraoperative Hb decrease of fifty percent or more indeed had more postoperative adverse events compared to patients who had an intraoperative Hb decrease less than fifty percent. These results imply that it might be beneficial to include the degree of intraoperative Hb decrease in the decision when to transfuse so a more personalized transfusion trigger can be composed.

One of the hardest questions to answer in transfusion medicine is when do the benefits of a red cell transfusion outweigh its possible side-effects in patients suffering from anemia. Studying the effects of intraoperative anemia independently of red cell transfusions is difficult, not only because it is associated with many other detrimental factors but also because intraoperative anemia is treated with red cell transfusions which in itself also can cause adverse effects. With the aim to study the effect of red cell transfusion independent of the effects of anemia we examined Jehovah's witnesses with intraoperative anemia and compared them with matched non-Jehovah's witnesses (patients with similar characteristics) who did receive one red cell transfusion intra-operatively. There were no differences between the Jehovah's witnesses and the transfused

non-Jehovah's witnesses with regard to postoperative adverse events. This suggest that the red cell transfusion may have been redundant and that more red cell transfusions could be avoided if non-Jehovah's witnesses received the same pre- and intra-operative care as Jehovah's witnesses.

One of the possible adverse effects of red cell transfusions is the formation of allo-antibodies against red blood cells of the donor. The consequences of this so called red cell allo-immunisation can vary from logistic inconvenience when obtaining compatible blood to acute and delayed hemolytic transfusion reactions. Why one patient develops red cell antibodies to an incompatible red cell transfusion and another patient does not, is not known. One of the factors that could influence the formation of allo-antibodies is the storage time of red cells, as was the case in a mouse model. One could hypothesize that with a prolonged storage time red blood cells become more immunogenic and are more prone to causing allo-antibody formation. To assess whether this is true or not we compared the incidence of anti-K formation in patients who received K incompatible blood with different storage times (14, 18 and 21 days were used as cut off-point for 'old' versus 'fresh' red cells). We did not find any association between storage time and the formation of anti-K, which was also confirmed in the analysis in which we took the storage time of the concomitantly transfused K- red blood cells into account. Our results imply that the storage time of transfused red cells does not play a role in the formation of allo-antibodies. Which factors are most important in the formation of allo-antibodies and if these factors contribute equally for the different RBC antigen specificities remains a subject for further research.

Conflicting results have been reported on the effect of platelet transfusions in patients with various clinical conditions. In the last chapter of this thesis we analyzed the independent effects of a single platelet transfusion in patients undergoing cardiac surgery. We selected patients who received one platelet concentrate shortly after the cardiopulmonary bypass and no other blood products. These patients were matched 1:3, using propensity score matching, to patients who did not receive any blood products during surgery. We found that patients who received a platelet concentrate experienced less blood loss but more often required vasoactive medication, prolonged ventilation, prolonged intensive care stay, and other blood products postoperatively. In the literature vasoplegia has been mentioned as a possible side-effect of a platelet transfusion and vasoplegia could also be the cause for the use of more vaso-active medication, the longer ICU stay and the prolonged ventilation. The association between an early platelet concentrate and the need for more blood products postoperatively could be explained by a lowering of the transfusion threshold once one transfusion has been administered. An early platelet transfusion was not associated with reinterventions, thromboembolic complications, infections, organ failure, or mortality. So although platelet concentrates are a relative safe therapy in patients undergoing cardiac surgery, one should keep their side-effects and in particular the possibility of vasoplegia in mind.

Nederlandse Samenvatting

Thoraxchirugie is een van de snelst ontwikkelende specialismen binnen de geneeskunde. Met het ouder worden van de populatie zullen er steeds meer oudere patiënten met bijbehorende co- morbiditeit geaccepteerd worden voor een cardio-chirurgische ingreep. Een adequate peroperatieve risico inschatting is dan ook onontbeerlijk. Jarenlang werd het EuroSCORE I model hiervoor gebruikt, maar met het verstrijken van de tijd daalde de voorspellende waarde van dit model. Een opvolger van dit model, de EuroSCORE II werd hierom opgesteld.

In dit proefschrift valideren wij dit nieuwe EuroSCORE model in een Nederlandse populatie en onze resultaten laten zien dat het EuroSCORE II model het beter doet dan zijn voorganger. Echter, in de patiënten die spoed chirurgie ondergingen of patiënten die een zeer verhoogd preoperatief risico liepen vonden wij dat beiden modellen niet adequaat genoeg waren in het voorspellen van postoperatieve mortaliteit. Voor deze patiënten zal een nieuw model gecreëerd moeten worden. Voor de overige patiënten geldt dat preoperatieve risico inschatting het best gebeurt middels de EuroSCORE II.

In de afgelopen decennia werd er gepleit voor een meer restrictief beleid rondom erytrocyten transfusie, om zo de blootstelling aan eventuele bijwerkingen van bloedtransfusies te minimaliseren. Maar wat een acceptabele grens is voor een minimum Hb waarde is niet bekend en het is waarschijnlijk dat dit per patiënt verschilt. Een eerdere studie in cardio-chirurgische patiënten heeft het effect van een intra-operatieve Hb daling van vijftig procent of meer geanalyseerd en vond dat postoperatieve uitkomsten zoals acuut nierfalen, myocard infarct en mortaliteit meer voorkwamen in deze groep. De resultaten van deze studie waren nog niet bevestigd of verworpen.

Wij hebben een studie gedaan met een vergelijkbare studieopzet welke liet zien dat patiënten die een intra-operatieve Hb daling van meer dan 50 procent doormaken vaker een slechtere postoperatieve uitkomst hebben, zelfs als ze boven de veelgebruikte transfusiegrens van 7 g/dL blijven, in vergelijking met patiënten die een kleinere Hb daling hebben. Onze resultaten laten zien dat het bevorderlijk kan zijn voor de patiënt als men de grootte van de intra-operatieve Hb daling meeneemt als men een beslissing moet nemen om wel of niet te transfunderen, zo kan men een meer persoonlijke transfusie grens vaststellen.

Een van de moeilijkst te beantwoorden vragen binnen de transfusie geneeskunde is wanneer een erytrocyten transfusie meer voordeel oplevert voor de patiënt dan dat hij/zij hinder heeft van eventuele bijwerkingen. Het geïsoleerd bestuderen van de effecten van intra-operatieve anemie is bijna onmogelijk omdat de behandeling voor anemie bestaat uit erytrocyten transfusies en de bijwerkingen van erytrocyten transfusies weer erg kunnen lijken op de effecten van een anemie. We hebben geprobeerd dit probleem te omzeilen door intra-operatieve anemie te bestuderen in Jehova's getuigen, die geen bloedproducten gebruiken, en hebben deze Jehova's getuigen

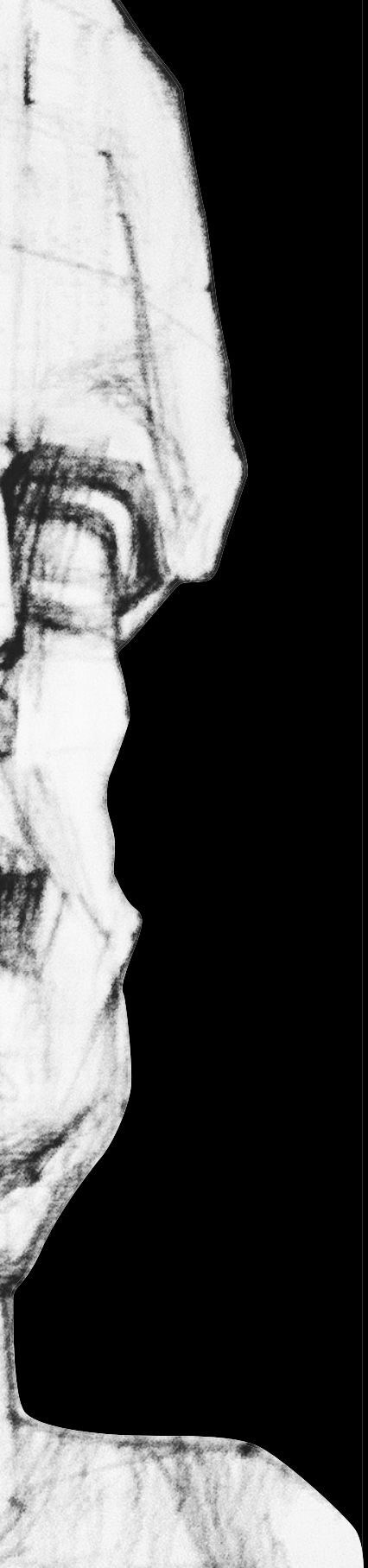
vergeleken met gematchte patiënten die 1 erytrocyten transfusie kregen. Er was geen verschil in postoperatieve uitkomst. Dit impliceert dat de erytrocyten transfusie misschien wel achterwege had kunnen blijven. Als alle patiënten die cardiochirurgie ondergaan dezelfde pre- en intra-operatieve behandeling zouden krijgen als Jehova's getuigen zou dit voor meer transfusies kunnen gelden.

Een van de bijwerkingen van een erytrocyten transfusie is de vorming van allo-antilichamen. De consequenties van allo-antilichamen varieert van logistieke problemen om compatibel bloed te verkrijgen tot acute en late transfusiereacties. Waarom de ene patiënt wel en de andere patiënt geen allo-antilichamen vormt na een incompatibele bloedtransfusies is onbekend. Als mogelijke factor die bijdraagt aan de vorming van allo-antilichamen wordt de opslagduur van erytrocyten genoemd, zoals eerder werd aangetoond in een muis model. De hypothese hierachter is dat 'ouder' bloed meer immunogeen zou zijn en zo dus zou bijdragen aan de vorming van allo-antilichamen.

Om te onderzoeken of dit waar is hebben we een studie gedaan waarin we de incidentie van anti-K vorming hebben geanalyseerd in patiënten die een incompatibele erytrocyten transfusie hebben gekregen en hebben we gekeken naar de opslagduur van deze erytrocyten. We hebben groepen gemaakt waarin we 'oude' met 'verse' incompatibele transfusies met elkaar hebben vergeleken (14, 18 en 21 dagen als afkappunt). Er werd geen associatie gevonden tussen opslagduur en de vorming van anti-K, zelfs niet toen we ook de opslagduur van de gelijktijdige K negatieve in de analyse betrokken. Onze resultaten doen vermoeden dat de opslagduur van erytrocyten geen rol speelt bij het ontstaan van allo-antilichamen. Welke factoren wel een rol spelen en hoe groot hun aandeel is zal uitgemaakt moeten worden door toekomstig onderzoek.

Als het om het effect van trombocyten transfusies gaat binnen de cardiochirurgie worden er conflicterende resultaten gepubliceerd. Daarom hebben we in het laatste hoofdstuk van dit proefschrift het onafhankelijke effect van een intra-operatief gegeven trombocyten concentraat geanalyseerd in patiënten die een cardio-chirurgische ingreep moesten ondergaan. Er werd een cohort geselecteerd van patiënten die een enkel trombocyten concentraat kregen nadat zij van de cardiopulmonale bypass geweaned waren en dit cohort werd vergeleken met een cohort van gematchte patiënten die geen trombocyten kregen toegediend. Het matchen gebeurde middels 1:3 propensity score matching. Onze resultaten lieten zien dat patiënten die een trombocyten transfusie kregen minder bloed verloren maar vaker vasoactieve medicatie nodig hadden, langer beademd moesten worden en langer op de intensive care moesten verblijven. Ook kregen deze patiënten vaker andere bloedproducten postoperatief. In de literatuur wordt beschreven dat vasoplegie een mogelijke bijwerking is van trombocyten transfusies. Dit zou kunnen passen bij de bevindingen dat patiënten na een trombocyten transfusie meer vasoactieve medicatie nodig hebben en langer aan de beademing en op de intensive care liggen. Het feit dat deze patiënten postoperatief meer bloedproducten kregen zou uitgelegd kunnen worden door een verlaagde drempel bij de behandelend artsen om nogmaals te transfunderen als dit eenmaal al

een keer gedaan is. Tevens vonden we dat een trombocyten transfusie niet geassocieerd was met re-interventies, trombo-embolische complicaties, infecties, orgaan falen of mortaliteit. Dus alhoewel een trombocyten transfusie relatief veilig is mag men nooit de mogelijke bijwerkingen uit het oog verliezen.



Publicatielijst
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CHAPTER 9

Publicatielijst

Tolerance of intra-operative Hb decrease
Hogervorst EK, Rosseel P, van der Bom J, Bentala M, Brand A, van der Meer N, van der Watering L.
Transfusion. 2014 Oct;54(10 Pt 2): 2696-704.

Anti-K formation is not associated with the storage time of transfused red cells
Hogervorst EK, Middelburg R, van de Watering L, Schonewille H.
Transfusion. 2015 Jun;55(6 Pt 2):1472-7.

Intraoperative Anemia and Single Red Blood Cell Transfusion During Cardiac Surgery: An assessment of Postoperative Outcome Including Patients refusing Blood Transfusion
Hogervorst EK, Rosseel PM, van de Watering LM, Brand A, Bentala M, van der Bom JG, van der Meer NJ.
J Cardiothorac Vasc Anesth. 2016 Apr;30(2):363-72.

Does a Platelet Transfusion independently affect bleeding and adverse outcomes in cardiac surgery?
van Hout FM, Hogervorst EK, Rosseel PM, van der Bom JG, Bentala M, van Dorp EL, van Geloven N, Brand A, van der Meer NJ, van de Watering LM.
Anesthesiology. 2017 mar;126(3):441-449.

Prospective validation of the EuroSCORE II risk model in a single Dutch cardiac surgery centre
Hogervorst EK, Rosseel PM, van de Watering LM, Brand A, Bentala M, van der Meer BJ, van der Bom, J. G.
Neth Heart J. 2018 nov;26(11):540-551

Curriculum Vitae

Esther Karlijn Hogervorst werd geboren op 26 september 1984 in Delft. In 2002 behaalde zij haar gymnasium diploma aan het Maerlant College te Brielle. Hierna heeft zij een jaar wijsbegeerte gestudeerd aan de Leidse Universiteit waarna zij aan haar geneeskunde studie begon aan de Vrije Universiteit te Amsterdam. Na het behalen van haar doctoraal examen heeft zij haar co-schappen en daarmee haar studie geneeskunde afgerond aan de Erasmus Universiteit te Rotterdam in 2009. Na het behalen van haar artsenbul heeft zij een jaar als ANIOS Intensive Care gewerkt in het Maasstad Ziekenhuis te Rotterdam (opleider Albert Grootendorst). Hierna is zij begonnen aan haar promotieonderzoek onder leiding van prof. Anneke Brand en prof. Anske van der Bom met als co-promotor Leo van de Watering aan het Center for Clinical Transfusion Research, Sanquin, Leiden. Hier heeft zij tezamen met Peter Rosseel en Nardo van der Meer van het Amphia ziekenhuis te Breda retrospectieve observationele studies uitgevoerd naar de effecten van bloedtransfusie bij cardio-chirurgische patiënten.
In 2015 kwam zij in opleiding tot anesthesioloog in het Universitair Medisch Centrum te Groningen (opleider prof. Götz Wietasch). Haar perifere tweede jaar van de opleiding heeft zij volbracht in het Tjongerschans Ziekenhuis te Heereveen (opleider dr. J. Petersen en dr. O. Beck). Momenteel zit zij in het laatste jaar van haar opleiding tot anesthesioloog waarna zij een fellowship Intensive Care zal gaan doen in het Universitair Medisch Centrum Groningen (opleider dr. Iwan van der Horst).

Dankwoord

Het proefschrift dat voor u ligt is niet van de een op de andere dag ontstaan maar dat maakt het resultaat er niet minder om. Ik heb de afgelopen jaren hulp en steun van zoveel mensen gehad bij het realiseren van dit proefschrift dat ik helaas niet iedereen bij naam kan noemen.

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