BÖLÜM 2

KARDİYAK VASKÜLER CERRAHİDE KAN KORUMA STRATEJİLERİ

İlker Hasan KARAL[1]

GİRİŞ

1950 lerden itibaren konjenital kalp defektlerinin cerrahi olarak düzeltilmesi ile başlayan, sonraki dönemde kapak cerrahisi ve koroner baypas greftleme ile devam eden kalp cerrahisinin gelişim süreciyle beraber yüksek miktarlarda kan transfüzyon ihtiyacı ortaya çıkmıştır. Bu dönemlerde allojenik kan ürünlerinin yaygın ve yüksek miktarlarda kullanımı bu alanda hızlı bir gelişmenin önünü açmıştır.

Açık kalp cerrahisi ile yüksek miktarlarda kan kaybı ve transfüzyon gerekliliği arasındaki ilişki çeşitli çalışmalarla desteklenmiştir. Açık kalp cerrahisinde hasta popülasyonunun %70 inde kan transfüzyonu gerektiği ve hasta başına 2-4 donör hazırlığı yapıldığı bildirilmiştir.[1-2] Hatta kalp cerrahisi kan ürünlerinin en büyük tüketicisi durumundadır. Amerika Birleşik Devletlerinde kan ürünlerinin %20 si kardiyak cerrahi girişimlerinde kullanılmaktadır ve tüm dünyada da benzer oranlar bildirilmektedir.[3] Son yıllarda kan transfüzyon sayısında azalma olmasına rağmen kardiyak cerrahi hastalarında bu oran yeniden yükselerek %34 e ulaşmıştır.[4] Kalp cerrahisi sonrası bu yüksek transfüzyon oranlarının sebebi sıklıkla kardiyoplumoner baypasa bağlı ortaya çıkan koagülopati, trombosit disfonksiyonu ve çeşitli derecelerde gerçekleşen eritrosit hemolizi sorumlu tutulmaktadır.[5-7] Kanamanın ve transfüzyon gerekliliğinin diğer sebepleri arasında doğuştan veya kazanılmış trombosit disfonksiyonları, yüksek doz antikoagülan kullanımı, koagülasyon faktör eksiklikleri ve artmış fibrinolizis gibi etiyolojik faktörler sayılabilir.[8]

Ateş ve ürtiker gibi sık görülen transfüzyon reaksiyonları genellikle kolayca tedavi edilirken daha nadir görülen transfüzyon ilişkili akut akciğer hasarı (TRALI) gibi ciddi komplikasyonlar kritik durumdaki hastalar için yüksek mortalite riski(%35-58)[9,10] taşımaktadır. Bu komplikasyonlar nedeniyle mümkün olan her durumda kan ürünü transfüzyonundan kaçınılmalıdır.

Kan ürünü transfüzyonunun kesin endikasyonu hayatı tehdit eden kanamalardır, bununla birlikte oksijen taşıma kapasitesinin arttırılması, organ iskemisinin düzeltilmesi veya engellenmesi için de kan ürünü transfüzyonu yapılabilmektedir. Kritik hastalarda kan transfüzyonunun organ oksijenasyonu üzerindeki olumlu etkilerine rağmen kardiyak cerrahide kan ürünlerinin serbest ve fazla miktarda kullanımını destekleyen yeterli kanıt yoktur. Tam tersine kan ürünü transfüzyonunun mortalite ve morbiditeyi arttırdığını gösteren yayınların sayısı gün geçtikçe artmaktadır.[11-13] Uzamış yoğun bakım süresi, kısa ve uzun dönem sağkalım sonuçlarında kötüleşme, tedavi maliyetlerinde artış kan ürünü verilmesi ile ilişkili isten-

[1] Dr. İlker Hasan KARAL, SBÜ, Samsun Eğitim Araştırma Hastanesi, Kalp ve Damar Cerrahisi Bölümü ilkerkaral@gmail.com

sayısı ve fonksiyonu için bir eşik değeri sunan çalışma yoktur.

ÖZET ÖNERİLER

Erişkin kalp cerrahisi sırasında kan korunma yöntemleri arasında hemodülisyonun azaltılması, antifibrinolitiklerin rutin kullanımı, sabit bir hemoglobin seviyesinden ziyade hastanın klinik durumuna göre kan transfüzyonu kararı verilmesi ve multidisipliner yaklaşım mutlaka önerilmektedir. Bununla beraber KABG öncesi aspirinin devamı, ototransfüzyon, modifiye UF kullanımı ve retrograd otolog priming yapılması, heparin seviyesinin ölçümü veya ACT'ye göre heparin tedavisi uygulaması, protamin/heparin dozunun >1:1 olarak ayarlanması kanıt düzeyi yüksek öneriler içerisindedir. Bu programlarda preoperatif eritrosit süspansiyonu transfüzyonu, topikal yapıştırıcıların rutin kullanımı, KPB sonrası kanamayı azaltmak için AT uygulaması, proflaktik TDP, fibrinojen, Dezmopressin veya rFVIIa verilmesi kesinlikle önerilmemektedir.[248]

KİLİT NOKTALAR

- Kardiyak cerrahide kan ürünlerinin serbest ve rutin kullanımını destekleyen kanıtlar kısıtlıdır.
- Kapsamlı bir kan koruma programı allojenik kan transfüzyonu oranlarını azaltacak en etkili strateji olarak görünmektedir.
- Cerrah, anestezist, hemşire, perfüzyonist ve kan bankasını içeren multidisiliner yaklaşım bu programın kalitesini ve başarısını arttıracaktır.
- Kanamayı ve kan transfüzyon oranlarını azaltan ve preoperatif uygulamalar arasında riskli hastaların tespiti, koagülapatiye neden olan ilaçların kesilmesi, preoperatif kırmızı hücre kitlesinin eritropoietin, demir ilavesi veya preoperatif otolog kan hazırlığı ile arttırılması vardır.
- Akut normovolemik hemodilüsyon, ototransfüzyon, Retro-antegrad priming ,mini devreler ve modifiye ultrafiltrasyon gibi kardiyopulmoner baypas tekniklerinin kullanımının arttırılması kan kaybını ve kan transfüzyon ihtiyacının azaltılması açısından anlamlıdır.
- Antifibrinolitik ilaçlar ve topikal hemostatik ajanlar kan koruma yöntemleri arasındadır.
- Hastanın mevcut klinik durumu postoperatif dönemde kan verme kararı açısından sabit bir eşik değerine göre daha iyi bir göstergedir.
- Milli kan koruma programları, yeni cerrahi tekniklerin, yeni ilaç ve kan ürünlerinin, ilerleyen teknolojinin katılımıyla iyi dizayn edilmiş kanıt düzeyi yüksek çalışmalara dayandırılmalıdır.

KAYNAKLAR

1- Belisle S, Hardy JF, et al:Hemorrhage and the use of blood products after adult cardiac operations:myths and realities. Ann Thorac Surg 1996;62:1908.
2- Goodnough LT, Despostis GJ, Hohue CW,et al:On the need for improved transfusion indicators in cardiac surgery. Ann Thorac Surg 1995;60:473.
3- Spiess BD:Transfusion and outcome in heart surgery. Ann Thorac Surg 2002;74:986
4- Stoicea N,Bergese SD, Ackermann W,et al:Current status of blood transfusion and antifibrinolytic therapy in orthopedic surgeries. Front Surg 2015;2:3.
5- Boyle EM, Verrier VD, Spiess BD,et al: The procoagulant response to injury. Ann Thorac Surg 1997;64:516.
6- Woodman RC, Harker LA: Bleeding complications associated with cardiopulmonary bypass.Blood 1990;76:1680.
7- Hunt BJ,Parratt RN,Segal HC, et al: Activation of coagulation and fibrinoyysis duringcardiothoracic operations. Ann Thorac Surg 1998;65:712
8- Despotis G, Avidan M, Eby C,et al: Prediction and management of bleeding in cardiac surgery.J Throm Haemost 2009;7(suppl 1):111.
9- Gajic O,Rana R,Winters JL,et al: Transfusion related acute lung injury in the critically ill:prospective nested case-control study.Am J Respir Crit Care Med 2007;176:886
10- Vlaar AP,Binnekade JM,Prins D,et al: Risk factors and outcome of transfusion-related acute lung injury in the critically ill:a nested case-control study. Crit Care Med 2010;38:771.
11- Surgenor SD,Kramer RS,Olmstead EM,et al: The association of perioperative red blood cell transfusions and decreased long-term survival after cardiac surgery. Aneth Analg 2009;108:1741.
12- Whitson BA,Huddleston SJ,Savik K,et al: Risk of adverse outcomes associated with blood transfusion after cardiac surgery depends on the amount of transfusion. J Surg Res 2010;158:20.
13- Veenith T,Sharples L, Gerrard C,et al: Survival and length of stay following blood transfusion in octogenarians following cardiac surgery. J Anesth 2010;65:331.
14- Koch CG, Li L,Duncan AI, et al: Transfusion in coronary artery bypass grafting is associated with reduced long term survival. Ann Thorac Surg 2006;81:1650.
15- Murphy GJ,Reeves BC,Rogers CA,et al: Increased mortality, postoperative morbidity and cost after red cell transfusion in patients having cardiac surgery. Circula-

tion 2007;116:2544.
16- Paone G, Likosky DS, Brewer R,et al: Transfusion of 1 or 2 units of red blood cells is associated with increased morbiity and mortality. Ann Thorac Surg 2014;97:87-93;discussion 93-4.
17- Scott BH, Seifort FC, Grimson R: Blood transfusion is associated with increased resource utilisation, morbiity and mortality in cardiac surgery. Ann Card Anaesth 2008;11:15.
18- 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;34:1608
19- Lacroix J, Hebert PC, Hutchison JS, et al: Transfusion strategies for patients in pediatric intensive care units. N Engl J Med 2007;356:1609.
20- Hajjar LA, Vincent JL, Galas FR,et al: Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. JAMA 2010;304:1559.
21- Alghamdi AA, Davis A, Brister S,et al: Development and validation of Transfusion Risk Understanding Scoring Tool (TRUST) to stratify cardiac surgery patients according to their blood transfusion needs.Transfusion 2006;46:1120-9.
22- Ranucci M, Aronson S, Dietrich W, et al: Patient blood management during cardiac surgery:do we have enough evidence for clinical practice? J Thorac Cardiovasc Surg 2011;142:249.e1-32.
23- Ferraris VA, Brown JR, Respotis GJ,et al: 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg 2011;91:944-82.
24- Shehata N, Naglie G, Alghamdi AA, et al: Risk factors for red cell transfusion in adults undergoing coronary artery bypass surgery:a systematic review. Vox Sang 2007;93:1.
25- Nalla BP, Freedman J, Hare GM, et al: Update on blood conservation for cardiac surgery. J Cardiothorac Vasc Anesth 2012;26:117.
26- Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. Br Med J 2002;324: 71–86.
27- Myles PS, Smith JA, Forbes A, et al. Stopping vs. continuing aspirin before coronary artery surgery. N Engl J Med 2016;374:728–37.
28- Deja MA, Kargul T, Domaradzki W, et al: Effects of preoperative aspirin in coronary artery bypass grafting: a double- blind, placebo-controlled, randomized trial. J Thorac Cardiovasc Surg 2012;144:204–9.
29- Yusuf S, Zhao F, Mehta SR, et al: Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494–502.
30- Wallentin L, Becker RC, Budaj A et al. Ticagrelor versus clopidogrel in patients with acute coronary syn-dromes. N Engl J Med 2009;361:1045–57.
31- Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute cor- onary syndromes. N Engl J Med 2007;357:2001–15.
32- Becker RC, Bassand JP, Budaj A, et al. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J 2011;32:2933–44.
33- Levine GN, Bates ER, Bittl JA et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016; 68:1082–115.
34- Fox KA, Mehta SR, Peters R et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coron- ary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. Circulation 2004;110:1202–8.
35- Held C, Asenblad N, Bassand JP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. J Am Coll Cardiol 2011; 57:672–84.
36- Tomsic A, Schotborgh MA, Manshanden JS, et al: Coronary artery bypass grafting-related bleeding complications in patients treated with dual antiplatelet treatment. Eur J Cardiothorac Surg 2016;50:849–56.
37- Pickard AS, Becker RC, Schumock GT,et al: Clopidogrel-associated bleeding and related complications in patients undergoing coronary ar- tery bypass grafting. Pharmacotherapy 2008;28:376–92.
38- Purkayastha S, Athanasiou T, Malinovski V,et al. Does clopidogrel affect outcome after coronary artery bypass grafting? A meta-analysis. Heart 2006;92:531–2.
39- Kolh P, Windecker S, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur J Cardiothorac Surg 2014;46:517–92.
40- 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;94:1761–81.
41- Wallentin L: P2Y(12) inhibitors: differences in properties and mechan- isms of action and potential consequences for clinical use. Eur Heart J 2009;30:1964–77.
42- Smith PK, Goodnough LT, Levy JH, et al. Mortality benefit with prasugrel in the TRITON-TIMI 38 coron- ary artery bypass grafting cohort: risk-adjusted retrospective data ana- lysis. J Am Coll Cardiol 2012;60:388–96.
43- Hansson EC, Jideus L, Aberg B, et al. Coronary artery bypass grafting-related bleeding complications in patients treated with ticagrelor or clopidogrel: a nationwide study. Eur Heart J 2016;37:189–97.
44- Gherli R, Mariscalco G, Dalen M, et al. Safety of preoperative use of ticagrelor with or without aspirin compared with aspirin alone in patients with acute coronary syndromes undergoing coronary artery bypass grafting. JAMA Cardiol 2016; 1:921–8.
45- Mahla E, Suarez TA, Bliden KP, et al. Platelet function measurement-based strategy to reduce bleeding and wa-

iting time in clopidogrel-treated patients undergoing coronary artery bypass graft surgery: the timing based on platelet function strategy to reduce clopidogrel-associated bleeding related to CABG (TARGET- CABG) study. Circ Cardiovasc Interv 2012;5:261–9.

46- Patrono C, Coller B, FitzGerald GA, et al: Platelet-active drugs: the relationships among dose, effectiveness, and side effects: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:234S–64S.

47- Dyke CM, Jennings LK, Maier G, et al: Preoperative platelet inhibition with eptifibatide during coronary artery bypass grafting with cardiopulmonary bypass. J Cardiovasc Pharmacol Ther 2007;12:54–60.

48- Boeken U, Litmathe J, Kurt M, et al. CABG-procedures in patients with pretreatment with the GPIIb/IIIa-receptor antagonist tiro- fiban (Aggrastat): modification of perioperative management? Int J Cardiol 2008;127:257–9.

49- Susan B McDonald , Maurizio Renna, Edward L Spitznagel,et al.Preoperative Use of Enoxaparin Increases the Risk of Postoperative Bleeding and Re-Exploration in Cardiac Surgery Patients. J Cardio Thorac Vasc Anesth, 2005;19(1):4-10.

50- Benjamin Medalion [1], George Frenkel, Paulina Patachenko,et al.Preoperative Use of Enoxaparin Is Not a Risk Factor for Postoperative Bleeding After Coronary Artery Bypass Surgery.J Thorac Surg 2003;126(6):1875-9.

51- Ashikhmina E, Tomasello N, Connors JM, et al. Type A aortic dissection in a patient on dabigatran: hemostasis post circulatory arrest. Ann Thorac Surg 2014;98:2215–6.

52- Stein P, Bosshart M, Brand B, et al. Dabigatran anticoagulation and Stanford type A aortic dissection: lethal coincidence: case report with literature review. Acta Anaesthesiol Scand 2014;58:630–7.

53- Crapelli GB, Bianchi P, Isgro Get al. A case of fatal bleeding following emergency surgery on an ascending aorta intramural hematoma in a patient taking dabigatran. J Cardiothorac Vasc Anesth 2016;30:1027–31

54- Lai A, Davidson N, Galloway SW, et al:Perioperative management of patients on new oral anticoagulants. Br J Surg 2014;101:742.

55- Junichiro Y, Path FRC, Yamada K, et al:Testing various herbs for antithrombotic effect. Nutrition 2005;21:580.

56- Buckley MS, Goff AD, Knapp WE:Fish oil interaction with warfarin. Ann Pharmacother 2004;38:50.

57- Valli G, Giardina E:Benefits, adverse effects and drug interactions of herbal therapies with cardiovascular effects. J Am Coll Cardiol 2002;39:1083.

58- Kilic A, Whitman GJ:Blood transfusionsin cardiac surgery:indications,risks, and conservation strategies. Ann Thorac Surg 2014;97:726.

59- Hogan M, Klein AA, Richards T. The impact of anaemia and intravenous iron replacement therapy on outcomes in cardiac surgery. Eur J Cardiothorac Surg 2015;47:218–26.

60- Engoren M, Schwann TA, Habib RH, et al. The independent effects of anemia and transfusion on mortality after coron- ary artery bypass. Ann Thorac Surg 2014;97:514–20.

61- von Heymann C, Kaufner L, Sander M, et al. Does the severity of preoperative anemia or blood transfusion have a stronger impact on long-term survival after cardiac surgery? J Thorac Cardiovasc Surg 2016;152:1412–20.

62- Donat R Spahn , Felix Schoenrath , Gabriela H Spahnet al. Effect of Ultra-Short-Term Treatment of Patients With Iron Deficiency or Anaemia Undergoing Cardiac Surgery: A Prospective Randomised Trial Lancet 2019;393(10187):2201-2212.

63- Seung Hyun Lee, Jae-Kwang Shim, Sarah Soh,et al. The Effect of Perioperative Intravenously Administered Iron Isomaltoside 1000 (Monofer®) on Transfusion Requirements for Patients Undergoing Complex Valvular Heart Surgery: Study Protocol for a Randomized Controlled Trial. Trials 2018 jul 4;19(1):350.

64- Kulier A, Levin J, Moser R, et al. Impact of preoperative anemia on outcome in patients undergoing coronary artery bypass graft surgery. Circulation 2007; 116:471–9.

65- Karkouti K, Wijeysundera DN, Beattie WS; Reducing Bleeding in Cardiac Surgery Investigators. Risk associated with preoperative anemia in cardiac surgery: a multicenter cohort study. Circulation 2008;117:478–84.

66- Kozek-Langenecker SA, Afshari A, Albaladejo P, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol 2013;30:270–382.

67- Menkis AH, Martin J, Cheng DC, et al. Drug, devices, technologies, and techniques for blood management in minimally invasive and conventional cardiothoracic surgery: a consensus statement from the International Society for Minimally Invasive Cardiothoracic Surgery (ISMICS) 2011. Innovations (Phila) 2012;7:229–41.

68- Weltert L, Rondinelli B, Bello R, et al. A single dose of erythropoietin reduces perioperative transfusions in cardiac surgery: results of a prospective single-blind randomized controlled trial. Transfusion 2015;55:1644–54.

69- Weltert L, D'Alessandro S, Nardella S, et al. Preoperative very short-term, high-dose erythropoietin administration diminishes blood transfusion rate in off-pump coronary artery bypass: a randomized blind controlled study. J Thorac Cardiovasc Surg 2010;139:621–6; discussion 6–7.

70- Yoo YC, Shim JK, Kim JC, et al. Effect of single recom- binant human erythropoietin injection on transfusion requirements in preoperatively anemic patients undergoing valvular heart surgery. Anesthesiology 2011;115:929–37.

71- Karkouti K, Wijeysundera DN, Yau TM, et al. Advance targeted transfusion in anemic cardiac surgical pa- tients for kidney protection: an unblinded randomized pilot clinical trial. Anesthesiology 2012;116:613–21.

72- Puskas JD, Martin J, Cheng DC, et al. ISMICS consensus conference and statements of randomized controlled trials of off-pump versus conventional coronary artery bypass surgery. Innovations (Phila) 2015;10:219–29.

73- Deppe AC, Arbash W, Kuhn EW, et al. Current evidence of coronary artery bypass grafting off-pump versus on-pump: a systematic review with meta-analysis of over 16, 900 patients investigated in randomized controlled trialsdagger. Eur J Cardiothorac Surg 2016;49:1031–41; discussion 41.

74- Lamy A, Devereaux PJ, Prabhakaran D, et al. Off-pump or on-pump coronary artery bypass grafting at 30 days. N Engl J Med 2012;366:1489–97.
75- Diegeler A, Borgermann J, Kappert U, et al. Off-pump versus on-pump coronary artery bypass grafting in elderly patients. N Engl J Med 2013;368:1189–98.
76- Anastasiadis K, Murkin J, Antonitsis P, et al. Use of minimal invasive extracorporeal circulation in cardiac surgery: principles, definitions and potential benefits. A position paper from the Minimal invasive Extra-Corporeal Technologies international Society (MiECTiS). Interact CardioVasc Thorac Surg 2016;22:647–62.
77- Anastasiadis K, Antonitsis P, Haidich AB, et al. Use of minimal extracorporeal circulation improves outcome after heart surgery; a systematic review and meta-analysis of randomized controlled trials. Int J Cardiol 2013;164: 158–69.
78- Harling L, Warren OJ, Martin A, et al. Do miniaturized extracorporeal circuits confer significant clinical benefit without compromising safety? A meta-analysis of randomized con- trolled trials. ASAIO J 2011;57:141–51.
79- Varghese R,Myers ML:Bloodconservation in cardiac surgery:let's get rstrictive.Semin Thorac Cardiovasc Surg 2010;22:121.
80- Remadi JP, Marticho P, Butoi I, et al: Clinical experience with the mini-extracorporeal circulation system:an evolution or a revolution? Ann Thorac Surg 2004;77:2172.
81- Assad H, Thomas P, Alois P, et al: Coronary Artery Bypass Grafting in Patients With Type 2 Diabetes Mellitus: A Comparison Between Minimized and Conventional Extracorporeal Circulation. ASAIO J 2011;57(6):501-6.
82- Puehler T,Haneya A, Philipp A,et al:Minimized extracorporeal circulation system in coronary artery bypass surgery: a 10-year single-center experience with 2243 patients. Eur J Cardiothorac Surg 2011;39:459.
83- Falk V, Cheng DC, Martin J, et al. Minimally invasive versus open mitral valve surgery: a consensus statement of the international society of minimally invasive coronary surgery (ISMICS) 2010. Innovations (Phila) 2011;6:66–76.
84- Sundermann SH, Sromicki J, Rodriguez Cetina Biefer H, et al. Mitral valve surgery: right lateral minithoracotomy or sternotomy? A systematic review and meta-analysis. J Thorac Cardiovasc Surg 2014;148:1989–95.e4.
85- Phan K, Xie A, Di Eusanio M,et al. A meta-analysis of minimally invasive versus conventional sternotomy for aortic valve replacement. Ann Thorac Surg 2014;98:1499–511.
86- Hall TS, Sines JC, Spotnitz AJ:Hemorrhage related reexploration follwing open heart surgery:the impact of pre-operative and post-operative coagulation testing. Cardiovasc Surg 2002;10:146.
87- Carless PA, Anthony DM,Henry DA:Systematic review of the use of fibrin sealent to minimize perioperative allogenic blood transfusion. Br J Surg 2002;89:695.
88- Schlag G,Seifert J: Fibrin sealent, aprotinin, and immune response in children undergoing operations for congenital heart disease. J Thorac Cardiovasc Surg 1998;116:1082.
89- Lamm P,Adelhard K,Juchem G,et al:Fibrin glue in coronary artery bypass grafting operations:casting out the Devil with Beelzebub? Eur J Cardiothorac Surg 2007;32:567.
90- Birmingham B:TEE diagnosis of mechanical AVR dysfunction associated with biological glue. Aneth Analg 2001;93:1627.
91- Passage J,Jalali H, Tam RK,et al:BioGlue surgical Adhesive -An appraisal of its indications in cardiac surgery. Ann Thorac Surg 2002;74:432
92- Coselli JS,Bavaria JE, Fehrenbacher J,et al: Propective randomized study of a protein based tissue adhesive used as a hemostatic and structural adjunt in cardiac and vascular anastomotic repair procedures. J Am Coll Surg 2003;197:243.
93- Carless PA, Henry DA, Anthony DM. Fibrin sealant use for minimising peri-operative allogeneic blood transfusion. Cochrane Database Syst Rev 2003;2:CD004171.
94- Abrishami A, Chung F, Wong J. Topical application of antifibrinolytic drugs for on-pump cardiac surgery: a systematic review and meta-ana- lysis. Can J Anaesth 2009;56:202–12.
95- Carless PA, Henry DA, Anthony DM. Fibrin sealant use for minimising peri-operative allogeneic blood transfusion. Cochrane Database Syst Rev 2003;2:CD004171.
96- Ker K, Beecher D, Roberts I. Topical application of tranexamic acid for the reduction of bleeding. Cochrane Database Syst Rev 2013; 7:D010562.
97- Gurian DB, Meneghini A, Abreu LC, et al. A randomized trial of the topical effect of antifibrinolytic epsilon amino- caproic Acid on coronary artery bypass surgery without cardiopulmonary bypass. Clin Appl Thromb Hemost 2014;20:615–20.
98- El-Sabbagh AM, Toomasian CJ, Toomasian JM, et al. Effect of air exposure and suction on blood cell activation and hemolysis in an in vitro cardiotomy suction model. ASAIO J 2013; 59:474–9.
99- Shigang W,Allen R K, John LM,et al. Comparison of Two Different Blood Pumps on Delivery of Gaseous Microemboli During Pulsatile and Nonpulsatile Perfusion in a Simulated Infant CPB Model. ASAIO 2008; 54(5):538-41.
100- Akimasa M,Atsushi N,Yasuyuki S, et al. Is Elimination of Cardiotomy Suction Preferable in Aortic Valve Replacement? Assessment of Perioperative Coagulation, Fibrinolysis and Inflammation Interact Cardiovasc Thorac Surg 2013; 17(3):507-14.
101- Lindholm L, Westerberg M, Bengtsson A, et al. A closed perfusion system with heparin coating and centrifugal pump improves cardiopulmonary bypass biocompatibility in elderly patients. Ann Thorac Surg 2004;78:2131–8; discussion 8.
102- Casalino S, Stelian E, Novelli E, et al. Reduced transfusion requirements with a closed cardiopulmonary by- pass system. J Cardiovasc Surg (Torino) 2008;49:363–9.
103- Ranucci M, Balduini A, Ditta A, et al. A systematic review of biocompatible cardiopulmonary bypass circuits and clinical outcome. Ann Thorac Surg 2009;87:1311–9.
104- Mahmood S, Bilal H, Zaman M, et al. Is a fully heparin-bonded cardiopulmonary bypass circuit superior to a standard cardiopulmonary bypass circuit? Interact CardioVasc Thorac Surg 2012;14:406–14.
105- Mirow N, Zittermann A, Koertke H, et al. Heparin-co-

ated extracorporeal circulation in combination with low dose systemic heparinization reduces early postoperative blood loss in cardiac surgery. J Cardiovasc Surg (Torino) 2008;49:277–84.
106- Paparella D, Scrascia G, Rotunno C, et al. A biocompatible cardiopulmonary bypass strategy to reduce hemostatic and inflammatory alterations: a randomized controlled trial. J Cardiothorac Vasc Anesth 2012;26:557–62.
107- Lorusso R, De Cicco G, Totaro P, et al. Effects of phosphorylcho- line coating on extracorporeal circulation management and postopera- tive outcome: a double-blind randomized study. Interact CardioVasc Thorac Surg 2008;8:7–11.
108- Marguerite S, Levy F, Quessard A, et al. Impact of a phosphorylcholine-coated cardiac bypass circuit on blood loss and platelet function: a prospective, randomized study. J Extra Corpor Technol 2012;44:5–9.
109- Hosoyama K, Ito K, Kawamoto S, et al. Poly-2-methoxyethylacrylate-coated cardiopulmonary bypass cir- cuit can reduce transfusion of platelet products compared to heparin- coated circuit during aortic arch surgery. J Artif Organs 2016;19:233–40.
110- Thiara AS, Mollnes TE, Videm V, et al. Biocompatibility and pathways of initial complement pathway ac- tivation with Phisio- and PMEA-coated cardiopulmonary bypass circuits during open-heart surgery. Perfusion 2011;26:107–14.
111- Carless PA, Henry DA, Moxey AJ, et al. Cell salvage for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2010;4:CD001888.
112- Carless PA, Henry DA, Moxey AJ, et al. Cell salvage for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2006;4:CD001888.
113- Said A,Madan MM, Maher JAB. Cell Salvage During Coronary Artery Bypass Surgery and Allogenic Blood Exposure. Asian Cardiovasc Thorac Ann 2015;23(8):913–6.
114- Meena N, Brielle T, Kimberlee G et al. A Red Cell Preservation Strategy Reduces Postoperative Transfusions in Pediatric Heart Surgery Patients. Paediatr Anaesth 2018;28(5):450457.
115- Wang G, Bainbridge D, Martin J, et al. The efficacy of an intraoperative cell saver during cardiac surgery: a meta-analysis of randomized trials. Anesth Analg 2009;109:320–30.
116- Weltert L, Nardella S, Rondinelli MB, et al. Reduction of allogeneic red blood cell usage during cardiac surgery by an integrated intra- and postoperative blood salvage strategy: results of a randomized comparison. Transfusion 2013;53:790–7.
117- Ferraris VA, Brown JR, Despotis GJ, et al. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg 2011;91:944–82.
118- Engels GE, van Klarenbosch J, Gu YJ, et al. Intraoperative cell salvage during cardiac surgery is associated with reduced postoperative lung injury. Interact CardioVasc Thorac Surg 2016;22:298–304.
119- Gabel J, Westerberg M, Bengtsson A, et al. Cell salvage of cardiot- omy suction blood improves the balance between pro- and anti- inflammatory cytokines after cardiac surgery. Eur J Cardiothorac Surg. 2013;44:506–11.
120- Damgaard S, Nielsen CH, Andersen LW, et al. Cell saver for on-pump coronary operations reduces systemic inflammatory markers: a randomized trial. Ann Thorac Surg 2010;89:1511–7.
121- Jewell AE, Akowuah EF, Suvarna SK, et al. A prospective randomised comparison of cardiotomy suction and cell saver for recycling shed blood during cardiac surgery. Eur J Cardiothorac Surg 2003;23:633–6.
122- Rubens FD, Boodhwani M, Mesana T, et al. The cardiotomy trial: a randomized, double-blind study to assess the effect of processing of shed blood during cardiopulmonary bypass on transfusion and neurocognitive function. Circulation 2007;116:I89–97.
123- A Z Al-Riyami, M Al-Khabori, Baskaran B, et al. Intra-operative Cell Salvage in Cardiac Surgery May Increase Platelet Transfusion Requirements: A Cohort Study. Vox Sang 2015;109(3):280–6.
124- Padhi S, Kemmis-Betty S, Rajesh S, Hill J, Murphy MF, Guideline Development Group. Blood transfusion: summary of NICE guidance. Br Med J 2015;351:h5832.
125- Liumbruno GM, Waters JH. Unwashed shed blood: should we transfuse it? Blood Transfus 2011;9:241–5.
126- Boodhwani M, Williams K, Babaev A, et al. Ultrafiltration reduces blood transfusions following cardiac surgery: a meta-analysis. Eur J Cardiothorac Surg 2006;30:892–7.
127- Danish N, Riaz AK, Abdul M, et al. Role of modified ultrafiltration in adult cardiac surgery:a prospective randomized control trial. J Ayub Med Coll Abbottabad 2016;28(1):22-5.
128- DeFoe GR,Ross CS, Olmstead EL,et al:Lowest hematocrit on bypass and adverse outcomes associated with coronary artery bypass surgery. Ann Thorac Surg 2001;71:769.
129- Karkouti K, Beattie WS, Wijeysundera DN,et al:Hemodulition during cardiopulmonary bypass is an independent risk factor for acute renal failure in adult cardiac surgery. J Thorac Cardiovasc Surg 2005;İ129:391.
130- E E Severdija, J H Heijmans, M Theunissen, et al. Retrograde Autologous Priming Reduces Transfusion Requirements in Coronary Artery Bypass Surgery. Perfusion 2011;26(4):315–21.
131- Sun P, Ji B, Sun Y, et al. Effects of retrograde autologous priming on blood transfusion and clinical outcomes in adults: a meta-analysis. Perfusion 2013;28:238–43.
132- Saczkowski R, Bernier PL, Tchervenkov CI, et al. Retrograde autologous priming and allogeneic blood transfusions: a meta-analysis. Interact CardioVasc Thorac Surg 2009;8:373–6.
133- Bikash S, Sandeep C ,Usha K, et al. Neurocognitive Function in Patients Undergoing Coronary Artery Bypass Graft Surgery With Cardiopulmonary Bypass: The Effect of Two Different Rewarming Strategies. J Cardiothorac Vasc Anesth 2009;23(1):14–21.
134- Suman R, Edward M, Jie N,et al. The Effects of Mild Perioperative Hypothermia on Blood Loss and Transfusion Requirement. Anesthesiology 2008; 108(1):71–7.
135- Karla M F S M P, Caroline S de A, Haulcionne N W L C, et al. Factors Associated With the Increased Bleeding in the Postoperative Period of Cardiac Surgery: A Cohort Study. J Clin Nurs 2019;28(5-6):850–61.

136- Vonk AB, Veerhoek D, van den Brom CE, et al. Individualized heparin and protamine management improves rotational thromboelastometric parameters and postoperative hemostasis in valve surgery. J Cardiothorac Vasc Anesth 2014;28:235–41.
137- Noui N, Zogheib E, Walczak K, et al. Anticoagulation monitoring during extracorporeal circulation with the Hepcon/HMS device. Perfusion 2012;27:214–20.
138- Wang J, Ma HP, Zheng H. Blood loss after cardiopulmonary bypass, standard vs titrated protamine: a meta-analysis. Neth J Med 2013; 71:123–7.
139- Hofmann B, Bushnaq H, Kraus FB, et al. Immediate effects of individualized heparin and protamine manage- ment on hemostatic activation and platelet function in adult patients undergoing cardiac surgery with tranexamic acid antifibrinolytic ther- apy. Perfusion 2013;28:412–8.
140- Aziz KA, Masood O, Hoschtitzky JA, et al. Does use of the Hepcon point-of-care coagulation monitor to optimise heparin and protamine dosage for cardiopulmonary bypass decrease bleeding and blood and blood product requirements in adult patients undergoing cardiac sur- gery? Interact CardioVasc Thorac Surg 2006;5:469–82.
141- Pappalardo F, Franco A, Crescenzi G,et al. Anticoagulation management in patients undergoing open heart surgery by activated clotting time and whole blood heparin concentration. Perfusion 2006;21:285–90.
142- Hoenicka M, Rupp P, Muller-Eising K, et al. Anticoagulation management during multivessel coronary artery bypass grafting: a randomized trial comparing individualized heparin management and conventional hemostasis management. J Thromb Haemost 2015;13:1196–206.
143- Avidan MS, Alcock EL, Da Fonseca J, et al. Comparison of structured use of routine laboratory tests or near-patient assessment with clinical judgement in the management of bleeding after cardiac surgery. Br J Anaesth 2004;92:178–86.
144- Slight RD, Buell R, Nzewi OC, et al. A comparison of activated coagulation time-based techniques for anticoagulation dur- ing cardiac surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2008;22:47–52.
145- Radulovic V, Laffin A, Hansson KM, et al. Heparin and protamine titration does not improve haemostasis after cardiac surgery: a prospective randomized study. PLoS One 2015; 10:e0130271.
146- Teoh KH, Young E, Blackall MH, et al. Can extra protamine eliminate heparin rebound following cardiopulmonary bypass surgery? J Thorac Cardiovasc Surg 2004;128:211–9.
147- Koster A, Borgermann J, Gummert J, et al: Protamine overdose and its impact on coagulation, bleeding, and transfusions after cardiopulmonary bypass: results of a randomized double-blind controlled pilot study. Clin Appl Thromb Hemost 2014; 20:290–5.
148- Meesters MI, Veerhoek D, de Lange F, et al: Effect of high or low protamine dosing on postoperative bleeding following heparin anticoagulation in cardiac surgery. A randomised clinical trial. Thromb Haemost 2016;116:251–61.
149- M S Avidan, J H Levy, H van Aken, et al. Recombinant Human Antithrombin III Restores Heparin Responsiveness and Decreases Activation of Coagulation in Heparin-Resistant Patients During Cardiopulmonary Bypass. J Thorac Cardiovasc Surg 2005;130(1):107–13.
150- Avidan MS, Levy JH, Scholz J, et al. A phase III, double-blind, placebo-controlled, multicenter study on the efficacy of recombinant human antithrombin in heparin-resistant patients scheduled to undergo cardiac surgery necessitating cardiopulmonary bypass. Anesthesiology 2005;102:276–84.
151- Ranucci M, Baryshnikova E, Crapelli GB, et al. Preoperative antithrombin supplementation in cardiac surgery: a randomized controlled trial. J Thorac Cardiovasc Surg 2013; 145:1393–9.
152- Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e495S–530S
153- Warkentin TE, Sheppard JA. Serological investigation of patients with a previous history of heparin-induced thrombocytopenia who are reexposed to heparin. Blood 2014;123:2485–93.
154- Lo GK, Sigouin CS, Warkentin TE. What is the potential for overdiagnosis of heparin-induced thrombocytopenia? Am J Hematol 2007;82: 1037–43.
155- Smedira NG, Dyke CM, Koster A, et al. Anticoagulation with bivalirudin for off-pump coronary artery bypass grafting: the results of the EVOLUTION-OFF study. J Thorac Cardiovasc Surg 2006;131:686–92.
156- Dyke CM, Aldea G, Koster A, et al. Off- pump coronary artery bypass with bivalirudin for patients with heparin-induced thrombocytopenia or antiplatelet factor four/heparin antibod- ies. Ann Thorac Surg 2007;84:836–9.
157- Dyke CM, Smedira NG, Koster A, et al. A comparison of bivalirudin to heparin with protamine reversal in patients undergoing cardiac surgery with cardiopulmonary bypass: the EVOLUTION-ON study. J Thorac Cardiovasc Surg 2006;131:533–9.
158- Koster A, Dyke CM, Aldea G, et al. Bivalirudin during cardiopulmonary bypass in patients with previous or acute heparin-induced thrombocytopenia and heparin antibodies: results of the CHOOSE-ON trial. Ann Thorac Surg 2007;83:572–7.
159- Palatianos G, Michalis A, Alivizatos P, et al. Perioperative use of iloprost in cardiac surgery patients diagnosed with heparin-induced thrombocytopenia-reactive antibodies or with true HIT (HIT-reactive antibodies plus thrombocytopenia): an 11-year experience. Am J Hematol 2015;90:608–17.
160- Koster A, Kukucka M, Meyer O, et al. Anticoagulation During Cardiopulmonary Bypass in Patients With Heparin-Induced Thrombocytopenia Type II and Renal Impairment Using Heparin and the Platelet Glycoprotein IIb-IIIa Antagonist Tirofiban. Anesthesiology 2001;94(2):245–51.
161- Welsby IJ, Um J, Milano CA, et al: Plasmapheresis and heparin reexposure as a management strategy for cardiac surgical patients with heparin-induced thrombocytopenia. Anesth Analg 2010; 110:30–5.

162- Warkentin TE, Sheppard JA, Chu FV, et al. Plasma exchange to remove HIT antibodies: dissociation between enzyme-immunoassay and platelet activation test reactivities. Blood 2015;125:195–8.

163- Osawa EA, Rhodes A, Landoni G, et al. Effect of perioperative goal-directed hemodynamic resuscitation therapy on outcomes following cardiac surgery: a randomized clinical trial and systematic review. Crit Care Med 2016;44:724–33.

164- Damen T, Reinsfelt B, Redfors B,et al. Pressure-dependent changes in haematocrit and plasma volume during anaesthesia, a randomised clinical trial. Acta Anaesthesiol Scand 2016;60:560–8.

165- Goepfert MS, Richter HP, Zu Eulenburg C, et al. Individually optimized hemodynamic therapy reduces complications and length of stay in the intensive care unit: a prospective, randomized controlled trial. Anesthesiology 2013; 119:824–36.

166- Kasper SM, Meinert P, Kampe S, et al. Large-dose hydroxyethyl starch 130/0.4 does not increase blood loss and transfusion requirements in coronary artery bypass surgery com- pared with hydroxyethyl starch 200/0.5 at recommended doses. Anesthesiology 2003;99:42–7.

167- Gurbuz HA, Durukan AB, Salman N, et al. Hydroxyethyl starch 6%, 130/0.4 vs. a balanced crystalloid solution in cardiopulmonary bypass priming: a randomized, prospective study. J Cardiothorac Surg 2013;8:71.

168- Min JOS, Ramzisham ARM, Zamrin MD. Is 6% hydroxyethyl starch 130/ 0.4 safe in coronary artery bypass graft surgery? Asian Cardiovasc Thorac Ann 2009;17:368–72.

169- Vanhoonacker J, Ongenae M, Vanoverschelde H, et al. Hydroxyethyl starch 130/0.4 versus modified fluid gelatin for cardiopul- monary bypass priming: the effects on postoperative bleeding and volume expansion needs after elective CABG. Acta Anaesthesiol Belg 2009; 60:91–7.

170- Hecht-Dolnik M, Barkan H, Taharka A, et al. Hetastarch increases the risk of bleeding complications in patients after off-pump coronary by- pass surgery: a randomized clinical trial. J Thorac Cardiovasc Surg 2009; 138:703–11.

171- Van der Linden PJ, De Hert SG, Deraedt D, et al. Hydroxyethyl starch 130/0.4 versus modified fluid gelatin for volume expansion in cardiac surgery patients: the effects on peri- operative bleeding and transfusion needs. Anesth Analg 2005;101:629–34.

172- Skhirtladze K, Base EM, Lassnigg A, et al. Comparison of the effects of albumin 5%, hydroxyethyl starch 130/0.4 6%, and Ringer's lactate on blood loss and coagulation after car- diac surgery. Br J Anaesth 2014;112:255–64.

173- Sandra D, Eugene D, Martin A, et al. Hemodilution and Surgical Hemostasis Contribute Significantly to Transfusion Requirements in Patients Undergoing Coronary Artery Bypass. J Thorac Cardiovasc Surg 2005; 130(3):654-61.

174- Robert H H, Anoar Z, Thomas A S, et al. Adverse Effects of Low Hematocrit During Cardiopulmonary Bypass in the Adult: Should Current Practice Be Changed?. Northern New England Cardiovascular Disease Study Group. J Thorac Cardiovasc Surg 2003;125(6):1438-50.

175- Tran MH, Lin DM, Wilcox T, et al. Effects of a multimodality blood conservation schema toward improvement of intraoperative hemoglobin levels and off-pump transfusions in coronary artery bypass graft surgery. Transfusion 2014;54:2769–74.

176- Vretzakis G, Kleitsaki A, Stamoulis K, et al. Intra-operative intravenous fluid restriction reduces perioperative red blood cell transfusion in elective cardiac surgery, especially in transfusion-prone patients: a prospective, randomized con- trolled trial. J Cardiothorac Surg 2010;5:7.

177- Dietrich W, Thuermel K, Heyde S, et al. Autologous blood donation in cardiac surgery: reduction of allogeneic blood transfusion and cost-effectiveness. J Cardiothorac Vasc Anesth 2005;19:589–96.

178- Lewis CE, Hiratzka LF, Woods SE, et al. Autologous blood transfusion in elective cardiac valve operations. J Card Surg 2005; 20:513–8.

179- Society of Thoracic Surgeons Blood Conservation Guideline Task Force, 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;91:944.

180- Varghese R,Myers ML:Blood conservation in cardiac surgery:let's get restrictive. Semin Thorac Cardiovasc Surg 2010;22:121

181- Kochamba GS,Pfeffer TA,Sintek CF, et al:Intraoperative autotransfusion reduces blood loss after cardiopulmonary bypass. Ann Thorac Surg 1996;61:900-3.

182- Jalali A,Naseri MH, Chalian M,et al:Acute normovolaemic hemodilution with crystalloids in coronary artery bypass graft surgery:a preliminary survey of haemostatic markers. Acta Cardiol 2008;63:335.

183- Segal JB,Blasco-Colmenares E,Norris EJ,et al:Preoperative acute normovolemic hemodilution:a meta-analysis. Transfusion 2004;44:632.

184- Höhn L,Schweiser A,Licker M,et al:Absence. of beneficial effect of acute normovolemic hemodilution combined with aprotinin on allogenic blood transfusion requirements in cardiac surgery.Anesthesiology 2002;96:276.

185- Casati V,Speziali G,D'Alessandro C,et al:Intraoperative low-volume acute normovolemic hemodilution in adult open-heart surgery.Anesthesiology 2002;97:367.

186- Barile L, Fominskiy E, Di Tomasso N, et al. Acute normovolemic hemodilution reduces allogeneic red blood cell transfusion in cardiac surgery: a systematic review and meta- analysis of randomized trials. Anesth Analg 2017;124:743–52.

187- Myles PS, Smith JA, Forbes A, et al. Tranexamic acid in patients undergoing coronary-artery surgery. N Engl J Med 2017;376:136–48.

188- Henry DA, Carless PA, Moxey AJ, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2011;3:CD001886.

189- Adler Ma SC, Brindle W, Burton G, et al. Tranexamic acid is associated with less blood transfusion in off-pump coronary artery bypass graft surgery: a systematic review and meta-analysis. J Cardiothorac Vasc Anesth 2011;25:26–35.

190- Ker K, Edwards P, Perel P, et al. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative

meta-analysis. Br Med J 2012;344:e3054.
191- Sharma V, Katznelson R, Jerath A, et al. The association between tranexamic acid and convulsive seizures after cardiac surgery: a multivariate analysis in 11529 patients. Anaesthesia 2014;69:124–30.
192- Nalla BP,Freedman J,Hare GM, et al:Update on blood conservation for cardiac surgery. J Cardiothorac Vasc Anesth 2012;26:117.
193- Society of Thoracic Surgeons Blood Conservation Guideline Task Force,Ferraris VA,Brown JR,et al:2011 update to The Society of Thoracic Surgeons and The Society of Crdiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg 2011;91:944.
194- Stanworth SJ, Brunskill SJ, Hyde CJ, et al. Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. Br J Haematol 2004;126:139–52.
195- Casbard AC, Williamson LM, Murphy MF,et al. The role of prophylactic fresh frozen plasma in decreasing blood loss and correcting coagulopathy in cardiac surgery. A systematic review. Anaesthesia 2004;59:550–8.
196- Yang L, Stanworth S, Hopewell S, et al. Is fresh-frozen plasma clinically effective? An update of a systematic review of randomized controlled trials. Transfusion 2012;52:1673–86; quiz.
197- Godje O, Gallmeier U, Schelian M, et al. Coagulation factor XIII reduces postoperative bleeding after coronary surgery with extracorporeal circulation. Thorac Cardiovasc Surg 2006;54:26–33.
198- Karkouti K, McCluskey SA, Syed S, et al. The influence of perioperative coagulation status on postoperative blood loss in complex cardiac surgery: a prospective observational study. Anesth Analg 2010;110:1533–40.
199- Ternstrom L, Radulovic V, Karlsson M, et al. Plasma activity of individual coagulation factors, hemodilution and blood loss after cardiac surgery: a prospective observational study. Thromb Res 2010;126:e128–33.
200- Godje O, Gallmeier U, Schelian M, et al. Coagulation factor XIII reduces postoperative bleeding after coronary surgery with extracorporeal circulation. Thorac Cardiovasc Surg 2006;54:26–33.
201- Bolliger D, Gorlinger K, Tanaka KA. Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. Anesthesiology 2010;113:1205–19.
202- Hiippala ST, Myllyla GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. Anesth Analg 1995;81:360–5.
203- Karkouti K, Callum J, Crowther MA, et al. The relationship between fibrinogen levels after cardiopulmonary bypass and large volume red cell transfusion in cardiac surgery: an observational study. Anesth Analg 2013;117:14–22.
204- Bolliger D, Gonsahn M, Levy JH, et al. Is preoperative fibrinogen predictive for postoperative bleeding after coronary artery bypass grafting surgery? Transfusion 2009;49:2006–7; author reply 7–8.
205- Jeppsson A, Walden K, Roman-Emanuel C, et al. Preoperative supplementation with fibrinogen concentrate in cardiac surgery: a randomized controlled study. Br J Anaesth 2016; 116:208–14.
206- Rahe-Meyer N, Solomon C, Hanke A, et al. Effects of fibrinogen concentrate as first-line therapy during major aortic replacement surgery: a randomized, placebo-controlled trial. Anesthesiology 2013;118:40–50.
207- Ranucci M, Baryshnikova E, Crapelli GB, et al. Randomized, double-blinded, placebo-controlled trial of fibrinogen concentrate supplementation after complex cardiac surgery. J Am Heart Assoc 2015;4:e002066.
208- Rahe-Meyer N, Levy JH, Mazer CD, et al. Randomized evaluation of fibrinogen vs placebo in complex cardiovascular surgery (REPLACE): a double-blind phase III study of haemostatic therapy. Br J Anaesth 2016;117:41–51.
209- Fassl J, Lurati Buse G, Filipovic M, et al. Perioperative administration of fibrinogen does not increase adverse cardiac and thromboembolic events after cardiac surgery. Br J Anaesth 2015;114:225–34.
210- Tanaka KA, Esper S, Bolliger D. Perioperative factor concentrate therapy. Br J Anaesth 2013;111(Suppl 1):i35–49.
211- Ghadimi K, Levy JH, Welsby IJ. Prothrombin complex concentrates for bleeding in the perioperative setting. Anesth Analg 2016;122: 1287–300.
212- Demeyere R, Gillardin S, Arnout J, et al. Comparison of fresh frozen plasma and prothrombin complex concentrate for the reversal of oral anticoagulants in patients undergoing cardiopulmonary bypass surgery: a randomized study. Vox Sang 2010;99:251–60.
213- Ortmann E, Besser MW, Sharples LD, et al. An exploratory cohort study comparing prothrombin complex concentrate and fresh frozen plasma for the treatment of coagulopathy after complex cardiac surgery. Anesth Analg 2015;121:26–33.
214- Arnekian V, Camous J, Fattal S, et al. Use of prothrombin complex concentrate for excessive bleeding after cardiac surgery. Interact CardioVasc Thorac Surg 2012;15:382–9.
215- Cappabianca G, Mariscalco G, Biancari F, et al. Safety and efficacy of prothrombin complex concentrate as first-line treatment in bleeding after cardiac surgery. Crit Care 2016; 20:5.
216- Carless PA, Henry DA, Moxey AJ, et al. Desmopressin for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2004;1:CD001884.
217- Wademan BH, Galvin SD. Desmopressin for reducing postoperative blood loss and transfusion requirements following cardiac surgery in adults. Interact CardioVasc Thorac Surg 2014;18:360–70.
218- Crescenzi G, Landoni G, Biondi-Zoccai G, et al. Desmopressin reduces transfusion needs after surgery: a meta-analysis of randomized clinical trials. Anesthesiology 2008; 109:1063–76.
219- Shaz BH, Stowell SR, Hillyer CD. Transfusion-related acute lung injury: from bedside to bench and back. Blood 2011;117:1463–71.
220- Vamvakas EC, Blajchman MA. Transfusion-related immunomodulation (TRIM): an update. Blood Rev 2007;21:327–48.
221- Blumberg N, Zhao H, Wang H, et al. The intention-to-treat principle in clinical trials and meta-analyses of leukoreduced blood transfusions in surgical patients. Transfusion 2007; 47:573–81.
222- Rohde JM, Dimcheff DE, Blumberg N, Saint S, Langa KM, Kuhn L et al. Health care-associated infection after

red blood cell transfusion: a systematic review and meta-analysis. JAMA 2014;311:1317–26.
223- Bilgin YM, van de Watering LM, Eijsman L, et al. Double-blind, randomized controlled trial on the effect of leukocyte-depleted erythrocyte transfusions in cardiac valve surgery. Circulation 2004;109:2755–60.
224- Steiner ME, Ness PM, Assmann SF, et al. Effects of red-cell storage duration on patients undergoing cardiac surgery. N Engl J Med 2015;372:1419–29.
225- Sartipy U, Holzmann MJ, Hjalgrim H, et al. Red blood cell concentrate storage and survival after cardiac surgery. JAMA 2015; 314:1641–3.
226- Kaufman RM, Djulbegovic B, Gernsheimer T, et al. Platelet transfusion: a clinical practice guideline from the AABB. Ann Intern Med 2015;162:205–13.
227- Alexander PE, Barty R, Fei Y, et al. Transfusion of fresher vs older red blood cells in hospitalized patients: a systematic review and meta-analysis. Blood 2016;127:400–10.
228- Lacroix J, Hebert PC, Fergusson DA, et al. Age of transfused blood in critically ill adults. N Engl J Med 2015; 372:1410–8.
229- Vamvakas EC. Relative safety of pooled whole blood-derived versus single-donor (apheresis) platelets in the United States: a systematic re- view of disparate risks. Transfusion 2009;49:2743–58.
230- Welsby IJ, Lockhart E, Phillips-Bute B, et al. Storage age of transfused platelets and outcomes after cardiac surgery. Transfusion 2010;50:2311–7.
231- Membe SK, Coyle D, Husereau D,et al. Octaplas Compared with Fresh Frozen Plasma to Reduce the Risk of Transmitting Lipid-Enveloped Viruses: An Economic Analysis and Budget Impact Analysis [Internet]. 2020.
232- Ranucci M, Baryshnikova E. Fibrinogen supplementation after cardiac surgery: insights from the Zero-Plasma trial (ZEPLAST). Br J Anaesth 2016;116:618–23.
233- Ogawa S, Szlam F, Bolliger D, et al. The impact of hematocrit on fibrin clot formation assessed by rotational thromboelastometry. Anesth Analg 2012;115:16–21.
234- Deppe AC, Weber C, Zimmermann J, et al. Point-of-care thromboelastography/thromboelastometry-based coagulation management in cardiac surgery: a meta-analysis of 8332 pa- tients. J Surg Res 2016;203:424–33.
235- Wikkelso A, Wetterslev J, Moller AM, et al. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treat- ment versus usual care in adults or children with bleeding. Cochrane Database Syst Rev 2016;8:CD007871.
236- Whiting P, Al M, Westwood M, et al. Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: a systematic review and cost- effectiveness analysis. Health Technol Assess 2015;19:1–228, v–vi.
237- Karkouti K, Stuart A McCluskey, Jeannie C, et al.Evaluation of a Novel Transfusion Algorithm Employing Point-Of-Care Coagulation Assays in Cardiac Surgery: A Retrospective Cohort Study With Interrupted Time-Series Analysis. Anesthesiology 2015;122(3):560-70.
238- 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; 97:1630–5.
239- Ranucci M, Aloisio T, Carboni G et al. Acute kidney injury and hemodilution during cardiopulmonary bypass: a changing scenario. Ann Thorac Surg 2015;100:95–100.
240- Fang WC, Helm RE, Krieger KH,et al: Impact of minimum hematocrit during cardiopulmonary bypass on mortality in patients undergoing coronary artery surgery. Circulation 1997;96:II194.
241- Beal AC Jr, Yow EM Jr, Bloodwell RD, et al: Open heart surgery without blood transfusion. Arch Surg 1967;94:567.
242- Hebert PC,Wells G,Blajchman MA,et al:Amulticenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in critical care investigators , Canadian Critical care trials group, N Engl J Med 1999;340:409
243- Patel NN, Avlonitis VS, Jones HE, et al. Indications for red blood cell transfusion in cardiac surgery: a systematic review and meta-analysis. Lancet Haematol 2015;2:e543–53.
244- Nakamura RE, Vincent JL, 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;150:1314–20.
245- Murphy GJ, Pike K, Rogers CA, et al. Liberal or restrictive transfusion after cardiac surgery. N Engl J Med 2015;372:997–1008.
246- von Heymann C, Sander M, Foer A, et al. The impact of an hematocrit of 20% during normothermic cardiopulmonary bypass for elective low risk coronary artery bypass graft sur- gery on oxygen delivery and clinical outcome–a randomized controlled study [ISRCTN35655335]. Crit Care 2006;10:R58.
247- Ranucci M, Conti D, Castelvecchio S, et al. Hematocrit on cardiopulmonary bypass and outcome after coronary surgery in nontransfused patients. Ann Thorac Surg 2010; 89:11–7.
248- Domenico Pagano, Milan Milojevic , Michael I. Meesters, et al; 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. European Journal Cardio-Thorac Surg 53 (2018) 79–111