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

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Objective: The objectives of this consensus conference were to evaluate the evidence for the efficacy and safety of perioperative drugs, technologies, and techniques in reducing allogeneic blood transfusion for adults undergoing cardiac surgery and to develop evidence-based recommendations for comprehensive perioperative blood management in cardiac surgery, with emphasis on minimally invasive cardiac surgery.

Methods: The consensus panel short-listed the potential topics for review from a comprehensive list of potential drugs, devices, technologies, and techniques. The process of short-listing was based on the need to prioritize and focus on the areas of highest importance to surgeons, anesthesiologists, perfusionists, hematologists, and allied health care involved in the management of patients who undergo cardiac surgery whether through the conventional or minimally invasive approach. MEDLINE, Cochrane Library, and Embase databases were searched from their date of inception to May 2011, and supplemental hand searches were also performed. Detailed methodology and search strategies are outlined in each of the subsequently published systematic reviews. In general, all relevant synonyms for drugs (antifibrinolytic, aprotinin, ε-aminocaproic acid, tranexamic acid [TA], desmopressin, anticoagulants, heparin, antiplatelets, anti-Xa agents, adenosine diphosphate inhibitors, acetylsalicylic acid [ASA], factor VIIa [FVIIa]), technologies (cell salvage, miniaturized cardiopulmonary bypass (CPB) circuits, biocompatible circuits, ultrafiltration), and techniques (transfusion thresholds, minimally invasive cardiac or aortic surgery) were searched and combined with terms for blood, red blood cells, fresh-frozen plasma, platelets, transfusion, and allogeneic exposure. The American Heart Association/American College of Cardiology system was used to label the level of evidence and class of each recommendation.

Results and Recommendations: Database search identified more than 6900 articles, with 4423 full-text randomized controlled trials assessed for eligibility, and the final 125 systematic reviews and meta-analyses were used in the consensus conference. The results of the consensus conference, including the evidence-based statements and the recommendations, are outlined in the text, with references given for the relevant evidence that formed the basis for the statements and recommendations.

Recommendations for Antifibrinolytics:

- The lysine analogs ε-aminocaproic acid (Amicar) and tranexamic acid (TA) reduce exposure to allogeneic blood in patients undergoing on-pump cardiac surgery. These agents are recommended to be used routinely as part of a blood conservation strategy especially in patients at risk of undergoing on-pump cardiac surgery (Class I, Level A).
- It is importarnt not to exceed maximum TA total dosages (50–100 mg/kg) because of potential neurotoxicity in the elderly and open-heart procedures (Class IIb, Level C).

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- Aprotinin is not recommended in adult cardiac surgery until further studies on its safety profile have been performed (Class III, Level A).

Recommendations for TA in Off-Pump Coronary Artery Bypass:

- Tranexamic acid may be recommended as part of a blood conservation strategy in high risk patients undergoing off-pump coronary artery bypass (OPCAB) surgery (Class I, Level A).
- Tranexamic acid dosing in OPCAB surgery needs further study particularly with regard to possible neurotoxicity such as seizures. In addition, the benefit-risk ratio in OPCAB needs further elucidation because of the lower inherent risk for bleeding in this group (Class IIb, Level C).

Recommendations for DDAVP:

- DDAVP can be considered for prophylaxis in coronary artery bypass grafting (CABG) surgery, in particular, for patients on ASA within 7 days or prolonged CPB more than 140 minutes (Class IIa, Level A).
- Caution should be used with the DDAVP infusion rate to avoid significant systemic hypotension (Class I, Level A).

Recommendations for Topical Hemostatics:

- The routine use of topical antifibrinolytics in cardiac surgery is not recommended (Class IIa, Level A).
- Topical fibrin sealants may be considered in clinical situations where conventional approaches of surgical and medical improvement of hemostasis are not effective, that is, with bleeding problems more local than generalized, bearing in mind the black box warning of bovine thrombin by the US Food and Drug Administration (Class IIb, Level C).

Recommendations for FVIIa:

- Prophylactic use of FVIIa cannot be recommended because of a significant increase in the risk of thromboembolic events and stroke (Class IIa, Level A).
- Factor VIIa may be considered in clinical situations where conventional approaches of surgical and pharmacologic hemostasis have failed and uncontrollable hemorrhage poses a high risk of severe and life-threatening outcomes (Class IIb, Level B).

Recommendations for Erythropoietin Plus Iron:

- It is reasonable to administer erythropoietin preoperatively to increase red blood cell mass in patients who are anemic or refuse blood products (such as for Jehovah's Witness faith) or who are likely to have postoperative anemia (Class IIa, Level A).

Recommendations for Antiplatelets Before Cardiac Surgery:

- Acetylsalicylic acid may be continued until surgery (Class IIa, Level B)
- For stable elective CABG procedures with no drug-eluting stent, stop clopidogrel 5 days before surgery (Class I, Level A).
- For stable elective CABG procedures with drug-eluting stents less than 1 year old, consider continuing clopidogrel or heparin as a bridge to surgery (Class IIb, Level C).
- Direct-acting P2Y12 receptor antagonists may be a better alternative than clopidogrel in acute coronary syndrome patients undergoing CABG surgery (Class IIa, Level B).

Recommendations for Antiplatelets After Cardiac Surgery:

- In stable CABG surgery (non–acute coronary syndrome patients), the routine use of postoperative clopidogrel with ASA is not warranted (Class IIb, Level B).

Recommendations for Acute Normovolemic Hemodilution:

- Acute normovolemic hemodilution can be considered in selected patients with adequate preoperative hemoglobin to reduce post-CPB bleeding (Class IIa, Level A).
- The routine use of acute normovolemic hemodilution is not recommended (Class IIb, Level B).

Recommendations for Retrograde Autologous Priming:

- Retrograde autologous priming is recommended as a blood conservation modality to reduce allogeneic blood transfusion for on-pump cardiac surgery (Class I, Level A).

Recommendations for Cell Salvage:

- Routine use of cell salvage is recommended in operations where an increased blood loss is expected (Class 1, Level A).
- Cell salvage should be used throughout the entire operation and not merely as a replacement for CPB cardiotomy suction (Class IIa, Level A).

Recommendations: Biocompatible CPB Circuits:

- The routine use of biocompatible coated CPB circuitry *may be considered* as part of a multimodal blood conservation program. However, the heterogeneity of surface-modified products, anticoagulation management, and CPB technique does not significantly impact surgical blood loss and transfusion needs (Class IIb, Level A).

Recommendations for Miniaturized Extracorporeal Cardiopulmonary Circuit Versus Conventional Extracorporeal Cardiopulmonary Circuit:

- Miniaturized extracorporeal cardiopulmonary circuit can be considered as a blood conservation technique to reduce allogeneic blood exposure (Class IIa, Level A); however, issues related to heparinization management and biocompatible coatings remain to be clarified.

Recommendations for Ultrafiltration (Continuous or Modified):

- Ultrafiltration may be considered for blood conservation (Class IIb, Level A); however, the impact on clinically relevant outcomes remains unknown.

Recommendations for Platelet Plasmapheresis:

- It is reasonable to recommend platelet plasmapheresis for blood management in cardiac surgery (Class IIa, Level A), although the impact on clinically relevant outcomes remains unknown.

Recommendations for Point-of-Care Monitoring:

- The evidence is too premature to recommend point-of-care technology for routine use because its use has not been shown to impact clinical outcome (Class IIb, Level A).

Recommendations for Surgical Techniques for OPCAB, Minimally Invasive Sternotomy for Aortic Valve Surgery, Minimally Invasive Sternotomy for Mitral Valve Surgery, and Transcatheter Aortic Valve Implantation:

- Although these minimally invasive procedures are not primarily selected for the purpose of blood management, the reduced allogeneic blood exposure should be considered in the balance of benefits and risks when selecting the appropriate surgery for patients.

Key Words: Blood management, Cardiac surgery, Consensus statements.

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RATIONALE

Blood loss during and after cardiac surgery is one of the most common causes of allogeneic blood product use.[1–3] Blood transfusions are administered during cardiac surgery to manage or prevent hemodynamic instability and ischemia-related injury to the heart, kidneys, brain, and other vital organs. Administration of red blood cells (RBCs) may improve oxygen delivery when the existing RBC mass has been depleted. Other blood product fractions including plasma, cryoprecipitate, and platelets may reduce coagulopathies.[4–7]

However, oxygen delivery and coagulopathies are not hard outcomes per se, and it is the prevention of clinically relevant adverse outcomes such as death, stroke, myocardial infarction, renal failure, infection, and blood loss requiring intervention that would be of greater clinical relevance. Whether transfusions adequately prevent these clinically relevant outcomes to a degree that matter, and with sufficient magnitude that the benefits outweigh the inherent risks that accompany blood product transfusion, remains a relevant and timely question.[7,8]

A myriad of studies (observational studies and randomized trials) have demonstrated an adverse and dose-related association between blood product transfusion and serious morbidity and mortality in surgical and critical care patients.[7,9–11] As a result, uncertainty remains regarding the rightful place for blood product transfusions (in whom, at what threshold, and after failing which alternatives?).[12–14] Clearly, the risks of blood product administration, considered together with the uncertain benefits, significant costs, and limited supply of blood products, suggest that blood administration should not be considered lightly and conservation practices need to be ascertained and agreed on.

Whereas the clinically appropriate place of blood product transfusion has been uncertain in the world of conventional cardiac surgery, it remains even less certain within the world of minimally invasive cardiac surgery where the risk for blood loss and hemodilution is likely to be inherently less than in conventional surgery. The International Society of Minimally Invasive Cardiothoracic Surgery (ISMICS) sponsored this consensus conference to specifically address the evidence for blood conservation in cardiac surgery, with special emphasis on minimally invasive cardiac surgery. This consensus statement was convened to add to existing guidelines on cardiac surgical blood management strategies[7,15–20] because previous guidelines have not specifically addressed blood management for minimally invasive cardiac surgery.

OBJECTIVES

The objectives of this consensus conference were twofold:

1. To evaluate the evidence for efficacy and safety of perioperative drugs, technologies, and techniques to reduce allogeneic blood transfusion for adults undergoing cardiac surgery, with emphasis on minimally invasive cardiac surgery.
2. To develop evidence-based recommendations for perioperative blood management in cardiac surgery, with emphasis on minimally invasive cardiac surgery.

The methodology used to support the evidence identification, retrieval, synthesis, and interpretation for this consensus panel was similar to previous published ISMICS consensus conferences.[21–29] This represents the eighth consensus conference supported by ISMICS. Previous consensus statements are freely available at www.ismics.org.

SEARCH STRATEGY AND EVIDENCE RETRIEVAL

For each aspect of perioperative blood management to be addressed during the consensus conference, we searched for existing high-quality systematic reviews of the literature to objectively inform the consensus panel. If high-quality published systematic reviews were not found or if they did not include the most recent studies, de novo systematic reviews were performed by members of the group for publication in the peer-reviewed literature. The de novo systematic reviews were performed in accordance with recent guidelines for evidence synthesis.[30] MEDLINE, Cochrane Library, and Embase databases were searched from their date of inception to May 2011, and supplemental hand searches were also performed. Detailed methodology and search strategies are outlined in each of the subsequently published systematic reviews. In general, all relevant synonyms for drugs (antifibrinolytic, aprotinin [AP], ε-aminocaproic acid [EACA], tranexamic acid [TA], desmopressin, anticoagulants, heparin, antiplatelets, anti-Xa agents, adenosine diphosphate inhibitors, acetylsalicylic acid [ASA, aspirin], factor VIIa [FVIIa]), technologies (cell salvage [CS], miniaturized cardiopulmonary bypass [CPB] circuits, biocompatible circuits, ultrafiltration), and techniques (transfusion thresholds, minimally invasive cardiac or aortic surgery) were searched and were combined with terms for blood, RBCs, fresh-frozen plasma (FFP), platelets, transfusion, and allogeneic exposure.

Identification, selection, and quality assessment of relevant studies (meta-analyses, systematic reviews, randomized trials, and if needed, based on lack of higher levels of evidence, observational studies) was performed by at least two reviewers based on predefined inclusion criteria (published in any language, with relevant patient population, intervention, comparator, and outcomes for the prespecified clinical questions). Noncomparative studies were not considered. Data were extracted and double checked by a team of systematic reviewers. Meta-analysis was performed using the random effects model when heterogeneity across studies was expected to be significant or using the fixed effect model when heterogeneity was not statistically significant. Using Review Manager 5, Stata, or Comprehensive Meta-Analysis v2.0, the weighted mean differences (WMDs) and 95% confidence intervals (95% CIs) for continuous data and the rate ratio (95% CI) for dichotomous data were calculated. Meta-regressions were performed when dose-response relationships were in question or when time-dependent outcomes were in question. Heterogeneity across studies was estimated using the I^2 statistic, whereby an I^2 exceeding 50% was considered moderately heterogeneous and I^2 exceeding 75% was considered highly heterogeneous.

LEVELS OF EVIDENCE AND GRADES OF RECOMMENDATIONS

As described in previous ISMICS consensus statements,[21–29] the evidence used in consideration for each respective clinical question and any related subquestions was classified according to the American Heart Association (AHA)/American College of Cardiology (ACC) levels of evidence and grades of recommendation (Tables 1 and 2). The AHA/ACC classification categorizes evidence levels primarily based on considerations of study design where the highest level of evidence (Level A) consists of two or more randomized controlled trials. We also include meta-analyses of randomized trials as Level A evidence. The higher the level of evidence has presumably, the lesser the likelihood for bias caused by trial design limitations.[31,32] However, it is also important to consider that there are additional forms of bias beyond the study design alone,

which should be considered when applying evidence to make recommendations.[32]

While other systems of grading evidence exist, the AHA/ACC system was used to maintain consistency with previous consensus statements[21–29] and to allow comparability with other AHA/ACC statements in the field of cardiology and cardiac surgery. Labeling the level of evidence for each statement and classifying the recommendations derived from the evidence statements were performed collaboratively with the consensus panel using a democratic process after full discussion of the strengths and limitations of the evidence. The highest existing level of evidence was considered when making recommendations to inform the clinical questions, whereby systematic reviews and meta-analyses of randomized trials (Level A) were considered preferentially over singular randomized trials or observational studies (Level B). When no relevant clinical trials could be found after systematically reviewing the literature, expert opinion from the consensus panel was considered but was labeled explicitly as such so the reader will interpret it flexibly in full light of the lack of evidence and reliance on opinion (Level C evidence). Recommendations with highest levels of evidence should be interpreted with more confidence than recommendations based on lower levels of evidence. The former recommendations may represent a list of priorities for implementation into practice after consideration of local contextual factors, whereas the latter (Level B and Level C) should be considered to be important priorities for future research programs to clarify the existing gaps in the evidence to move beyond reliance on opinion.

SELECTION OF TOPICS FOR REVIEW

The consensus panel short-listed the topics for review from a comprehensive list of potential drugs, devices, technologies, and techniques. The process of short-listing was based on the practical need to prioritize and focus on the areas of highest importance to cardiac surgeons, anesthesiologists, perfusionists, hematologists, and allied health care involved in the management of patients who undergo cardiac surgery whether through the conventional or the minimally invasive approach. The purpose of this consensus conference was to give an overview of the role of drugs, technologies, and techniques for blood management in the setting of minimally invasive and conventional cardiac surgery.

RESULTS

Database search identified more than 6900 articles, with 4423 full-text randomized controlled trials (RCTs) assessed for eligibility, and the final 125 systematic reviews and meta-analyses were used in the consensus conference. The results of the consensus conference, including the evidence-based statements and the recommendations, are outlined below, with references given for the relevant evidence that formed the basis for the statements and recommendations. Readers are encouraged to consult the original publications for the systematic reviews and meta-analyses for the detailed discussion of outcomes and implications for each of the drugs, technologies, and techniques discussed below.

TABLE 1. Levels of Evidence

Level of Evidence A	Data derived from multiple randomized clinical trials
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts

TABLE 2. Classes of Recommendations

Class I	Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III	Conditions for which there is evidence and/or general agreement that the procedure/treatment is NOT useful/effective and, in some cases, may be harmful

DRUGS

The following categories of drugs were addressed: systemic antifibrinolytics, desmopressin, topical hemostatics.

Systemic Antifibrinolytics: AP, TA, EACA

Relevant Evidence

Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, Ker K. Antifibrinolytic agents for use in minimising allogeneic blood transfusion [Review]. *Cochrane Database Syst Rev.* 2011 Mar 16;(3):CD001886.

Gagne J, Griesdale DE, Schneeweiss S. Aprotinin and risk of death and renal dysfunction in patients undergoing cardiac surgery: a meta-analysis of epidemiologic studies. *Pharmacoepi Drug Saf*. 2009;18:259–268.

Ma SC, Brindle W, Burton G, Gallacher S, Cheng Hong F, Manelius I, 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.

Statements for Antifibrinolytics in Cardiac Surgery

1. Antifibrinolytics reduce the risk of allogeneic blood transfusion (Level A) in patients undergoing on-pump cardiac surgery.
2. Aprotinin may increase the risk of in-hospital all-cause mortality compared with TA/EACA (relative risk [RR], 1.39; 95% CI, 1.02–1.89; Level A) in patients undergoing cardiac surgery.
3. Aprotinin may increase short-term (RR, 1.39; 95% CI, 1.02–1.89; Level A) and longer term mortality versus TA/EACA (hazard ratio [HR], 1.22; 95% CI, 1.08–1.39; Level B) in patients undergoing cardiac surgery.
4. Meta-analysis of RCTs suggests no increase in risk of renal dysfunction with AP versus placebo (Level A) in patients undergoing cardiac surgery, although non-RCT evidence has been contradictory.
5. Tranexamic acid reduces the risk of allogeneic blood exposure (RR, 0.67; 95% CI, 0.52–0.86), and EACA reduces the risk of

TABLE 3. Summary of Recommendations

Lysine Analogs in Cardiac Surgery
The lysine analogs ε-aminocaproic acid (Amicar) and tranexamic acid (TA) reduce exposure to allogeneic blood in patients undergoing CPB cardiac surgery. These agents are recommended routinely as part of a blood conservation strategy in patients undergoing cardiac surgery (Class I, Level A).
It is important not to exceed maximum recommended TA dosages (50–100 mg/kg) because of potential neurotoxicity, particularly in elderly and open-heart procedures (Class IIb, Level C).
Aprotinin is not recommended in adult cardiac surgery until further studies on its safety profile (Class III, Level A).
TA for OPCAB
TA is recommended as part of a blood conservation strategy in patients undergoing OPCAB surgery (Class I, Level A).
TA dosing in OPCAB surgery needs further study particularly with regard to possible neurotoxicity such as seizures (Class IIb, Level C).
Desmopressin
DDAVP may be considered for prophylaxis in CABG surgery, in particular, for patients on ASA within 7 days or prolonged CPB more than 140 minutes (Class IIa, Level A).
Use caution with DDAVP infusion rate to avoid significant hypotension (Class I, Level A).
Topical Hemostatics
Routine use of topical antifibrinolytics in cardiac surgery is not recommended (Class IIa, Level A).
Topical fibrin sealant may be considered in clinical situations where conventional approaches of surgical and medical improvement of hemostasis are not effective, that is, with bleeding problems more local than generalized (Class IIb, Level C).
FVIIa
Prophylactic use of FVIIa cannot be recommended because of a significant increase in the risk of thromboembolic events and stroke (Class IIa, Level A).
FVIIa may be considered in clinical situations where conventional approaches of surgical/pharmacologic hemostasis failed and uncontrollable hemorrhage poses a high risk of adverse outcome (Class IIb, Level B).
EPO + Iron
It is reasonable to administer EPO preoperatively (2–4 weeks) to increase red blood cell mass in patients who are anemic or refuse blood products (Jehovah's Witness) or as a blood management strategy (Class IIa, Level A).
Antiplatelet Agents Before Cardiac Surgery
ASA may be continued until surgery (Class IIa, Level B).
In stable elective CABG with no DES, clopidogrel should be discontinued 5 days preoperatively (Class I, Level A).
In stable elective CABG with DES less than 1 year old, consider continuing clopidogrel or heparin as a bridge to surgery (Class IIb, Level C).
Direct-acting P2Y12 receptor antagonist may be a better alternative than clopidogrel in ACS patients undergoing CABG surgery (Class IIa, Level B).
Antiplatelet Agents After Cardiac Surgery
In stable CABG surgery (non-ACS patients), the routine use of postoperative clopidogrel with ASA is not warranted (Class IIb, Level B).
ANH
ANH can be considered in selected patients (adequate preoperative hemoglobin level) to reduce post-CPB bleeding (Class IIa, Level A).
Routine use of ANH in unselected patients cannot be recommended (Class IIb, Level B).
RAP
RAP can be recommended as a blood conservation modality to reduce allogeneic blood transfusion in cardiac surgery (Class I, Level A).
CS
Routine use of CS is recommended in operations where an increased blood loss is expected (Class I, Level A).
CS should be used throughout the entire operation and not merely as a replacement for CPB cardiotomy suction (Class IIa, Level A).
Biocompatible Coated CPB Circuit
The routine use of biocompatible coated CPB circuitry *may be considered* as part of a multimodal blood conservation program. However, the heterogeneity of surface-modified products, anticoagulation management, and CPB technique does not significantly impact surgical blood loss and transfusion needs (Class IIb, Level A).
Miniaturized CPB Circuit
MECC can be considered as a blood conservation technique to reduce allogeneic blood exposure (Class IIa, Level A); however, issues related to heparinization management and biocoat remain to be clarified.
Ultrafiltration
The use of ultrafiltration may be considered for blood conservation; however, impact on clinically relevant outcomes remains unproven and issues related to different technologies and timing of ultrafiltration remain to be clarified (Class IIb, Level A).
Platelet Plasmapheresis
It is reasonable to consider platelet plasmapheresis for blood management in cardiac surgery (Class IIa, Level A).
POC Technology
The evidence is too premature to recommend POC technology for routine use because its use has not been shown to impact clinical outcome (Class IIb, Level A).
Minimally Invasive Techniques
Whereas minimally invasive cardiac procedures are not primarily selected for blood management, the reduced allogeneic blood exposure should be considered in the balance of benefits and risks when selecting the appropriate surgery for the patients (Class IIa, Level A).

ACS indicates acute coronary syndrome; ANH, acute normovolemic hemodilution; ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; CS, cell salvage; DES, drug-eluting stent; EPO, erythropoietin; FVIIa, factor VIIa; MECC, miniaturized extracorporeal circuit; OPCAB, off-pump coronary artery bypass; POC, point of care; TA, tranexamic acid; RAP, retrograde autologous priming;

blood exposure (RR, 0.70; 95% CI, 0.52–0.93) in patients undergoing cardiac surgery (Level A), although the impact versus placebo or no antifibrinolytic on clinically relevant outcomes such as thromboembolic, acute myocardial infarction (AMI), stroke, and death remains uncertain (Level A) in patients undergoing cardiac surgery.
6. Preliminary evidence from case series has raised considerations about potential neurotoxicity with TA (seizures, particularly exceeding the higher doses); further research about safe dosing levels remains to be addressed in valid studies (Level C).

Recommendations for Antifibrinolytics

- The lysine analogs EACA (Amicar) and TA (Cyklokapron) reduce exposure to allogeneic blood in patients undergoing on-pump cardiac surgery. These agents are recommended to be used routinely as part of a blood conservation strategy especially in patients at risk undergoing on-pump cardiac surgery (Class I, Level A).
- It is important not to exceed maximum TA dosages (50–100 mg/kg) because of potential neurotoxicity in the elderly and open-heart procedures (Class IIb, Level C).
- Aprotinin is not recommended in adult cardiac surgery until further studies on its safety profile (Class III, Level A).

Statements for TA in Off-Pump Coronary Artery Bypass

1. Tranexamic acid reduces RBC exposure (RR, 0.51; 95% CI, 0.36–0.71) and overall blood product exposure (RR, 0.47; 95% CI, 0.33–0.66) beyond the effect of CS compared with no TA or placebo in patients undergoing off-pump coronary artery bypass (OPCAB) (Level A). The impact of TA on AMI, stroke, or death is unknown (Level A).
2. Tranexamic acid has not been shown to increase thromboembolic rates (Level A), although the studies have been small and of short duration.

Recommendations for TA in OPCAB

- Tranexamic acid may be recommended as part of a blood conservation strategy in high-risk patients undergoing OPCAB surgery (Class I, Level A).
- Tranexamic acid dosing in OPCAB surgery needs further study particularly with regard to possible neurotoxicity such as seizures. In addition, the benefit-risk ratio in OPCAB needs further eludication because of the lower inherent risk for bleeding in this group (Class IIb, Level C).

Recommendations for Further Research

- ○ Does TA or EACA reduce the risk of clinically relevant outcomes such as death, stroke, MI, renal failure (RF), infections, and neurologic outcomes?
- ○ In which specific risk groups should antifibrinolytics be used?
- ○ What is the optimal dose for TA or EACA in on-pump bypass surgery?
- ○ What is the optimal dose for TA or EACA in off-pump bypass surgery?

Desmopressin

Relevant Evidence

Carless PA, Stokes BJ, Moxey AJ, Henry DA. Desmopressin use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev.* 2008;(1):CD001884.

Statements for DDAVP

1. DDAVP prophylaxis has been shown to reduce blood loss; however, its effect on need for blood transfusion does not reach conventional significance and the effect is heterogeneous across trials (Level A).
2. In coronary artery bypass grafting (CABG) surgery, DDAVP infusion reduces intraoperative and postoperative blood loss (WMD, −117 mL; 95% CI, −173 to −61), RBC unit transfused (WMD, −0.4 units; 95% CI, −0.8 to −0.01), and allogeneic blood exposure (RR, 0.85; 95% CI, 0.73-0.99; Level A).
3. In patients on ASA less than 7 days, DDAVP infusion reduces blood loss (WMD, −110 mL; 95% CI, −200 to −19; Level A), although it does not reduce blood transfusion rate.
4. In prolonged CPB more than 140 minutes, DDAVP infusion reduces blood loss (WMD, −345 mL; 95% CI, −479 to −211; Level A).
5. DDAVP infusion causes hypotension requiring intervention with fluid ± vasopressor (37% vs 10%; RR, 2.81; 95% CI, 1.50–5.27; Level A).

Recommendations for DDAVP

- DDAVP can be considered for prophylaxis in CABG surgery, in particular, for patients on ASA within 7 days or prolonged CPB more than 140 minutes (Class IIa, Level A).
- Use caution with DDAVP infusion rate to avoid significant hypotension (Class I, Level A).

Recommendations for Further Research

- ○ Is there a role for DDAVP for patients presenting for surgery while on antiplatelet agents?
- ○ Is there a role for DDAVP in patients with refractory active bleeding?

Topical Hemostatics

Relevant Evidence

Abrishami A, Chung F, Wong J. Topical application of antifibrinolytic drugs for on-pump cardiac surgery: a systematic review and meta-analysis. *Can J Anaesth*. 2009;56:202–212.

Carless DA, Henry PA, Anthony DM. Fibrin sealant use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev.* 2003:CD004171.

Statements for Topical Hemostatics

1. Topical antifibrinolytics (TA or AP) and topical fibrin sealants may reduce postoperative chest tube blood loss (~200 mL); however, the impact on RBC exposure did not reach conventional significance and there is significant heterogeneity across trials (Level A).
2. Impact on other clinically relevant outcomes (AMI, stroke, death) is unknown, and safety data are sparse.

Recommendations for Topical Hemostatics

- Routine use of topical antifibrinolytics in cardiac surgery is not recommended (Class IIa, Level A).
- Topical fibrin sealants may be considered in clinical situations where conventional approaches of surgical and medical improvement of hemostasis are not effective, that is, with bleeding problems more local than generalized, bearing in mind the black

box warning of bovine thrombin by the US Food and Drug Administration (Class IIb, Level C)

Recommendations for Further Research

- ○ Does topical fibrin sealant result in clinically significant impact on outcomes when systemic antifibrinolytics have been used?
- ○ What are the risks of using topical fibrin sealant?
- ○ Do the clinically meaningful benefits of topical fibrin sealant outweigh the risks? If so, in which patient risk groups?

FACTOR VIIA

Relevant Evidence

Ponschab M, Landoni G, Biondi-Zoccai G, Bignami E, Frati E, Nicolotti D, et al. Recombinant activated factor VII increased stroke in cardiac surgery: a meta-analysis. *J Cardiothorac Vasc Anesth*. 2011;25:804–810.

Lin Y, Stanworth S, Birchall J, Doree C, Hyde C. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database Syst Rev.* 201116;CD005011.

Statements for FVIIa

1. Factor VIIa reduces blood exposure in patients refractory to conventional hemostatic management (Level B).
2. Factor VIIa is associated with a significant increased risk stroke (odds ratio [OR], 3.69; 95% CI, 1.10–12.38; Level B), and there is a trend toward increased thromboembolic events (OR, 1.84; 95% CI, 0.82–4.09; Level B).
3. No impact on mortality has been shown (OR, 0.96; 95% CI, 0.50–1.86; Level B), but studies have largely been nonrandomized and retrospective and of short duration.

Recommendations for FVIIa

- ■ Prophylactic use of FVIIa cannot be recommended because of a significant increase in the risk of thromboembolic events and stroke (Class IIa, Level A).
- ■ Factor VIIa may be considered in clinical situations where conventional approaches of surgical and pharmacologic hemostasis have failed and uncontrollable hemorrhage poses a high risk of severe and life-threatening outcomes (Class IIb, Level B).

Recommendations for Further Research

- ○ In refractory hemorrhage, at what point along the continuum of risk toward life-threatening or severe adverse events is the benefit of FVIIa worthy of the risks?
- ○ What dose of FVIIa is recommended to maximize the benefit-risk ratio?

ERYTHROPOIETIN (PLUS IRON)

Relevant Evidence

Martin JE, Lal A, Bainbridge D, Cheng D. Does perioperative erythropoietin benefit patients undergoing cardiac surgery? A meta-analysis with meta-regression of randomized trials. Submitted 2012.

Alghamdi AA, Albanna MJ, Guru V, Brister SJ. Does the use of erythropoietin reduce the risk of exposure to allogeneic blood transfusion in cardiac surgery? A systematic review and meta-analysis. *J Card Surg*. 2006;21:320–326.

Statements for Erythropoietin Plus Iron

1. Erythropoietin (EPO) reduces the risk of allogeneic RBC exposure (OR, 0.26; 95% CI, 0.15–0.44; number needed to treat, 4) in cardiac surgery undergoing PAD and in patients not undergoing PAD for cardiac surgery (Level A); however, its impact on AMI, RF, cerebrovascular accident (CVA), and death is unknown.
2. Although the impact may be greater when EPO is initiated 2 to 4 weeks before surgery, emerging evidence suggests that EPO initiated on the day of surgery may also reduce the need for transfusion (Level A).
3. In OPCAB, EPO (high-dose, short-term) reduced the risk of RBC transfusion (Level B); however, its impact on AMI, RF, CVA, and death is unknown.
4. Reports of improvement in neurologic outcomes and reduced acute kidney injury (Level B) are encouraging, but more study is needed.

Recommendations for EPO Plus Iron

- ■ It is reasonable to administer EPO preoperatively to increase red blood cell mass in patients who are anemic or refuse blood products (such as for Jehovah's Witness faith) or who are likely to have postoperative anemia (Class IIa, Level A).

Recommendations for Further Research

- ○ Does EPO significantly reduce clinically relevant outcomes (reduced death, stroke, MI, kidney failure, and neurologic performance) without undue risk of adverse events?
- ○ Is the routine use of erythropoietin warranted, and if so, in which patient risk groups (elderly, small stature, preexisting renal dysfunction, severity of preoperative anemia)?
- ○ What is the optimal dose, route, time of initiation, and duration for EPO and accompanying iron supplementation? What should be the target hemoglobin or hematocrit level?
- ○ Does the role of EPO differ for on- versus off-pump cardiac surgery?

ANTIPLATELETS *BEFORE* CARDIAC SURGERY

Relevant Evidence

Sun JCJ, Whitlock R, Cheng J, Eikeboom JW, Thabane L, Crowther MA, Teoh KHT. The effect of preoperative aspirin on bleeding, transfusion, myocardial infarction, and mortality in coronary artery bypass surgery: a systematic review of randomized and observational studies. *Eur Heart J.* 2008;29:1058–1071.

Nijjer S. 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. *Euro Heart J.* 2011 (Epub ahead of print).

Held C, Asenblad N, Bassand JP, Becker RC, Cannon CP, Claeys MJ, Harrington RA, Horrow J, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndrome undergoing coronary artery bypass surgery. Results from the PLATO (Platelet inhibition and Patient Outcomes) Trial. *J Am Coll Cardiol*. 2011;57:672–684.

Statements for Antiplatelets Before Cardiac Surgery

1. Continuation of ASA up to the time of surgery (or D/C <7 days) increases blood loss (~100 mL on average) (Level A).
2. Increased reoperation for bleeding (Level A).
3. Continuation of clopidogrel + ASA in the week before surgery increases blood loss, need for transfusion, and reoperation for bleeding (Level B).
4. Optimal timing of discontinuation of clopidogrel in elective surgery is 5 days (Level B).
5. Ticagrelor (D/C 24–72 hours) compared with clopidogrel (D/C 5 days) is associated with a lower total mortality (4.7% vs 9.7%; HR, 0.49; 95% CI, 0.32–0.77) and cardiovascular mortality (4.1% vs 7.9%; HR, 0.52; 95% CI, 0.32–0.85) without excessive risk of bleeding in CABG surgery (Level B).

Recommendations for Antiplatelets Before Cardiac Surgery

- ASA may be continued until surgery (Class IIa, Level B).
- Stable elective CABG with no drug-eluting stent (DES), stop clopidogrel 5 days preoperatively (Class I, Level A).
- Stable elective CABG with DES less than 1 year old, consider continuing clopidogrel or heparin as a bridge to surgery (Class IIb, Level C).
- Direct-acting P2Y12 receptor antagonist may be a better alternative than clopidogrel in acute coronary syndrome (ACS) patients undergoing CABG surgery (Class IIa, Level B).

ANTIPLATELETS *AFTER* CARDIAC SURGERY

Relevant Evidence

Patel JH, Stoner JA, Owora A, Mathew ST, Thadani U. Evidence for using clopidogrel alone or in addition to aspirin post coronary artery bypass surgery patients. *Am J Cardiol*. 2009;103:1687–1693.

Statements for Antiplatelets After Cardiac Surgery

1. Post-CABG use of clopidogrel with ASA is associated with increased trend for major and minor bleeding but no clear benefits on clinical outcomes (MI, stroke, death) after CABG surgery in on-pump and OPCAB patients (Level B).

Recommendations for Antiplatelets After Cardiac Surgery

- In stable CABG surgery (non-ACS patients), the routine use of postoperative clopidogrel with ASA is not warranted (Class IIb, Level B).

Recommendations for Future Research on Antiplatelets after Cardiac Surgery

- What is the place of newer antiplatelet agents in patients undergoing on-pump cardiac surgery?
- What is the place of newer antiplatelet agents in patients undergoing off-pump cardiac surgery?

TECHNOLOGIES

The following were considered under the category of technologies used to prevent or reduce exposure to allogeneic blood product transfusion: acute normovolemic hemodilution (ANH), retrograde autologous priming (RAP), CS, biocompatible CPB circuit, miniaturized extracorporeal circuit (MECC), and point-of-care (POC) monitoring.

Acute Normovolemic Hemodilution

Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C. Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model. *Health Tech Assess*. 2006;10(44): iii–iv, ix–x, 1–210.

Martin JE, Lal A, Bainbridge D, Cheng DC. Acute normovolemic hemodilution versus none in cardiac surgery. Submitted 2012.

Statements for ANH

1. Acute normovolemic hemodilution reduces bleeding and RBC volume transfused post-CPB (Level A), with a trend in reducing allogeneic RBC exposure (Level A).
2. No impact on AMI, CVA, and death has been shown. Issues of safety remain to be determined (hemodilution risks).

Recommendations for ANH

- Acute normovolemic hemodilution can be considered in selected patients (adequate preoperative hemoglobin) to reduce post-CPB bleeding (Class IIa, Level A).
- Routine use of ANH cannot be recommended (Class IIb, Level B).

Recommendations for Further Research

- Adequately powered RCTs comparing ANH versus none should be conducted in cardiac surgery settings, including in the minimally invasive setting, to determine whether ANH reduces the risk of clinically relevant adverse events without undue risk (ie, what is the risk of bleeding complications, RF, stroke, MI, death?).
- The role of colloids versus crystalloids for ANH and the appropriate dose and duration remain to be explored.

Retrograde Autologous Priming

Relevant Research

Martin JE, Lal A, Bainbridge D, Cheng DC. Retrograde autologous prime versus control: a meta-analysis and systematic review. Submitted 2012.

Statements for RAP

1. Retrograde autologous priming in cardiac surgery reduces the risk of allogeneic blood product exposure (RR, 0.31; 95% CI, 0.19–0.51; Level A).
2. Retrograde autologous priming reduces the mean volume of blood product exposure (−0.4 units; 95% CI, −0.6 to −0.2 units; Level A).

Recommendations for RAP

- Retrograde autologous priming is recommended as a blood conservation modality to reduce allogeneic blood transfusion for on-pump cardiac surgery (Class I, Level A).

Cell Salvage

Relevant Evidence

Carless PA, Henry DA, Moxey AJ, O'Connell D, Brown T, Fergusson DA. Cell salvage for minimising perioperative

allogeneic blood transfusion. *Cochrane Database Syst Rev.* 2010 Apr 14;(4):CD001888.

Wang G, Bainbridge D, Martin J, Cheng D. The efficacy of intraoperative cell saver during cardiac surgery: a meta-analysis of randomized trials. *Anesth Analg*. 2009;109: 320–330.

Statements for CS

1. The use of CS throughout cardiac surgery significantly reduces exposure to allogeneic RBC (OR, 0.63; 95% CI, 0.43–0.94; Level A). However, no impact on AMI, RF, infection rates, CVA, and death was shown (Level A).
2. The benefit for washed CS is greater than for unwashed blood salvaging technique (Level A).
3. Replacing cardiotomy suction with CS only has no significant impact on blood conservation and increases FFP need (Level A).

Recommendations for CS

- Routine use of CS is recommended in operations where an increased blood loss is expected (Class 1, Level A).
- Cell salvage should be used throughout the entire operation and not merely as a replacement for CPB cardiotomy suction (Class IIa, Level A).

Recommendations for Future Research

- The impact of CS on neurologic outcomes and on the risk of death, stroke, MI, and RF should be ascertained in adequately powered randomized trials.
- The risk-benefit of reinfusing washed or unwashed cells should be further addressed in future randomized trials.
- The cost-effectiveness of different forms of CS should be measured.

Biocompatible CPB Circuit

Relevant Evidence

Ranucci M, Balduini A, Ditta A, Boncilli A, Brozzi S. A systematic review of biocompatible cardiopulmonary bypass circuits and clinical outcome. *Ann Thorac Surg*. 2009;87: 1311–1319.

Statements for Biocompatible CPB Circuit

1. Using biocompatible CPB circuit has an uncertain impact on blood loss and transfusion needs (RR, 0.88; 95% CI, 0.72–1.1; Level A) and has not been shown to impact AMI, CVA, and death.

Recommendations: Biocompatible Coated CPB Circuits

- The routine use of biocompatible coated CPB circuitry *may be considered* as part of a multimodal blood conservation program. However, the heterogeneity of surface-modified products, anticoagulation management, and CPB technique does not significantly impact surgical blood loss and transfusion needs (Class IIb, Level A).

Recommendations for Future Research

- Randomized trials of homogeneously defined biocompatible circuits are required, with adequate power to measure clinically relevant outcomes such as death, stroke, MI, neurologic outcomes, and bleeding.
- A number of existing studies did not clearly define membrane "biocompatibility," and existing trials have tested heterogeneous biocompatible membranes. Studies need to clarify the membrane and the concomitant therapies (ie, coated oxygenator only or whole circuit? which biocoat? open vs closed reservoir? differences in heparinization?) and will need to adequately evaluate which characteristics provide best outcomes.

Minimized Extracorporeal Cardiopulmonary Circuit

Relevant Evidence

Harling L, Warren OJ, Martin A, Kemp PR, Evans PC, Darzi A, Athanasiou T. Do miniaturized extracorporeal circuits confer significant clinical benefit without compromising safety? A meta-analysis of randomized controlled trials. *ASAIO J.* 2011;57:141–151.

Zangrillo A, Garozzo FA, Biondi-Zoccai G, Pappalardo F, Monaco F, Crivellari M, Bignami E, Nuzzi M, Landoni G. Miniaturized cardiopulmonary bypass improves short-term outcome in cardiac surgery: a meta-analysis of randomized controlled studies. *J Thorac Cardiovasc Surg*. 2010;139: 1162–1169.

Harling L, Warren OJ, Rogers PL, Watret AL, Choong AM, Darzi A, Angelini GD, Athanasiou T. How minimalized extracorporeal circulation compares with the off-pump technique in coronary artery bypass grafting. *ASAIO J.* 2010;56: 446–456.

Statements for MECC Versus Conventional Extracorporeal Cardiopulmonary Circuit

MECC Versus Conventional Extracorporeal Cardiopulmonary Circuit

1. MECC (reservoir-less, coated circuits, reduced prime volume) for CABG significantly reduces risk of allogeneic blood exposure (OR, 0.42; 95% CI, 0.28–0.63; Level A). In addition, neurologic events have been shown to be reduced (OR, 0.30; 95% CI, 0.12-0.73; Level A). However, impact on AMI, stroke, and death is unproven.

MECC Versus OPCAB

1. Miniaturized extracorporeal cardiopulmonary circuit and OPCAB provide similar risks of blood loss and allogeneic transfusion. Clinical outcomes have not been shown to differ between MECC and OPCAB (Level A [two small RCTs; four observational studies]).

Recommendations for MECC Versus Conventional Extracorporeal Cardiopulmonary Circuit

- Miniaturized extracorporeal cardiopulmonary circuit can be considered as a blood conservation technique to reduce allogeneic blood exposure (Class IIa, Level A); however, issues related to heparinization management and biocoat remain to be clarified.

Recommendations for Future Research

- Does MECC have sufficient impact on clinically relevant outcomes (death, stroke, AMI, kidney failure, neurologic outcomes, severe bleeding) to warrant its routine use?
- There was significant heterogeneity in the biocoats used in trials of MECC. More research is required to determine the role of

MECC versus the role of the specific biocoat used within the MECC.
- There was significant heterogeneity in heparinization. More research is required to determine appropriate heparinization when using MECC.

Ultrafiltration

Relevant Evidence

Martin J, Lal A, Cheng D. Does ultrafiltration improve outcomes in patients undergoing cardiac surgery? A meta-analysis of randomized trials. Submitted 2012.

Boodhwani M, Williams K, Babaev A, Gill G, Saleem N, Rubens FD. Ultrafiltration reduces blood transfusions following cardiac surgery: a meta-analysis. *Eur J CardioThorac Surg*. 2006;30:892–897.

Statements for Ultrafiltration (Continuous or Modified)

1. Ultrafiltration significantly reduces blood loss (−70 mL; 95% CI, −118 to −21 mL) and volume of blood product transfused (−0.73 units; 95% CI, −1.13 to −0.31 units) (Level A).

Recommendations for Ultrafiltration (Continuous or Modified)

■ Ultrafiltration may be considered for blood conservation (Class IIb, Level A); however, the impact on clinically relevant outcomes remains unknown.

Recommendations for Future Research

- Does ultrafiltration significantly reduce the risk of clinically relevant adverse outcomes (death, stroke, AMI, RF, and neurologic outcomes)?
- Does ultrafiltration add significantly to CS and antifibrinolytics?
- Which filtration approach is superior (continuous vs modified ultrafiltration)?

Platelet Plasmapheresis

Statements for Platelet Plasmapheresis

1. Platelet plasmapheresis significantly reduces exposure to allogeneic RBCs by 30% (RR, 0.70; 95% CI, 0.55–0.88) and platelets by 51% (RR, 0.49; 95% CI, 0.25–0.85) and also reduces volume of allogeneic RBCs (−0.44 units; 95% CI, −0.65 to −0.22 units) and allogeneic platelets transfused (−1.0 units; 95% CI, −1.6 to −0.4 units) (Level A).
2. Impact on AMI, stroke, RF, and death remains uncertain.

Recommendations for Platelet Plasmapheresis

■ It is reasonable to recommend platelet plasmapheresis for blood management in cardiac surgery (Class IIa, Level A), although the impact on clinically relevant outcomes remains unknown.

Recommendations for Future Research Related to Platelet Plasmapheresis

- Adequately powered randomized trials to measure clinically relevant outcomes for platelet plasmapheresis should be encouraged.
- The cost-effectiveness of routine or universal platelet plasmapheresis should be the focus of future studies in this area.

POC Monitoring

Relevant Evidence

Urwyler N, Trelle S, Theiler L, Juni P, Staub LP, Luyet C, Alberio L, Stricker L, Stricker K, Greif R. Does point of care prothrombin time measurement reduce the transfusion of fresh frozen plasma in patients undergoing major surgery? The POC-OP randomized-controlled trial [Study protocol] Trials. 2009;10:107–11.

Afshari A, Wikkelsø A, Brok J, Møller AM, Wetterslev J. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemotherapy versus usual care in patients with massive transfusion. *Cochrane Database Syst Rev.* 2011; 16;(3):CD007871.

Statements: POC Monitoring

1. Despite benefits shown for thromboelastography/thromboelastometry for reduced blood subcomponent transfusion, the results are heterogeneous and no benefit has been shown for clinically relevant outcomes (Level A).
2. The technologies for POC are still evolving, and adequate experience and evidence from clinical trials are required. In addition, the initial evidence that platelet testing impacts on decision making also requires confirmation of positive clinical impact (Level C).

Recommendations for POC Monitoring

■ The evidence is too premature to recommend POC technology for routine use because its use has not been shown to impact clinical outcome (Class IIb, Level A).

Recommendations for Future Research Related to POC Monitoring

- Randomized controlled trials that are adequately powered to measure clinically relevant outcomes such as death, stroke, MI, interventions for bleeding, and cost-effectiveness are required.
- Further studies should aim for consistency in which monitor is used and how they are used to direct decision making (ie, when and how frequently to measure platelet function perioperatively? When do the results add to standard anticoagulant monitoring? What actions should be taken based on the results of the POC monitoring?
- Is one monitoring system superior to another? How do the newer anticoagulants and antiplatelet agents impact the monitoring protocols?

SURGICAL TECHNIQUES

Because less invasive surgical procedures may reduce the risk of blood loss, the role of the following surgical techniques in blood management was considered: OPCAB; minimally invasive sternotomy for aortic valve surgery (mini-AVR); minimally invasive sternotomy for mitral valve surgery (mini-MVR); thoracic endovascular aortic regurgitation (TEVAR); transcatheter aortic valve implantation (TAVI). One overarching statement is provided for all techniques reviewed in this category.

OPCAB Surgery

Relevant Evidence

Puskas J, Cheng D, Knight J, Angelini G, Decannier D, Diegeler A, Dullum M, Martin J, Ochi M, Patel N, Sim E,

Trehan N, Zamvar V. Off-Pump versus conventional coronary artery bypass grafting: a meta-analysis and consensus statement from the 2004 ISMICS Consensus Conference. *Innovations*. 2005;1:3–27.

Cheng DC, Bainbridge D, Martin JE, Novick RJ; Evidence-Based Perioperative Clinical Outcomes Research Group. Does off-pump coronary artery bypass reduce mortality, morbidity, and resource utilization when compared with conventional coronary artery bypass? A meta-analysis of randomized trials. *Anesthesiology*. 2005;102:188–203.

Statements for OPCAB Versus Conventional CABG

1. Off-pump coronary artery bypass significantly reduces allogeneic blood exposure versus CABG across risk groups (OR, 0.42; 95% CI, 0.34–0.51; Level A). However, the impact on AMI, stroke, and death is less certain.
2. Off-pump coronary artery bypass suffers from lack of standardization of anticoagulation strategies (what should be the ACT target, protamine reversal dose) (Level C). Despite this, OPCAB has shown advantages in blood exposure reduction.

Minimally Invasive Sternotomy for Aortic Valve Replacement

Relevant Evidence

Brown ML, McKellar SH, Sundt TM, Schaff HV. Ministernotomy versus conventional sternotomy for aortic valve replacement: a systematic review and meta-analysis. *J Thorac Cardiovasc Surg*. 2009;137:670–679.

Statements for Mini-AVR

1. Mini-AVR reduces blood loss (WMD, −79 mL; 95% CI, −136 to −23 mL; Level A); however, impact on allogeneic blood exposure remains uncertain. Advantages for AMI, RF, stroke, and death have not been shown.

Minimally Invasive Sternotomy for Mitral Valve Replacement

Relevant Evidence

Cheng DCH, Martin J, Lal A, Diegler A, Folliguet TA, Nifong W, Perier P, Raanani E, Smith M, Seegurger J, Falk V. Minimally invasive versus conventional open mitral valve surgery: a meta-analysis and systematic review. *Innovations*. 2011;6:84–103.

Statements for Mini-MVR

1. Mini-MVR reduces RBC volume transfused (WMD, −1.85 units; 95% CI, −2.48 to −1.22; Level B).
2. However, impact on risk of allogeneic RBC exposure did not reach significance (OR, 1.00; 95% CI, 0.47–2.14; Level A).
3. Advantages for AMI, RF, and death have not been shown; the risk of stroke may be increased (OR, 1.79; 95%, 1.35–2.38; Level B)

Thoracic Endovascular Aortic Replacement

Relevant Evidence

Cheng D, Martin J, Dunning J, Shennib H, Muneretto C, Schueler S, von Segesser, Sergeant P, Turina M, on behalf of the ad hoc EACTS/ESCVS Committee. Endovascular versus open surgical repair of thoracic aortic disease: a systematic review and meta-analysis of comparative studies. *J Am Coll Cardiol*. 2010;55:986–995.

Statements for TEVAR

1. Thoracic endovascular aortic repair (may reduce risk of allogeneic RBC exposure (OR, 0.01; 95% CI, 0.002–0.04; Level B) and reexploration for bleeding (OR, 0.26; 95% CI, 0.11–0.62) compared with open thoracic aortic repair (Level B).
2. Thoracic endovascular aortic repair may reduce renal insufficiency (OR, 0.40; 95% CI, 0.25–0.63), early mortality (OR, 0.44; 95% CI, 0.33–0.59), and permanent paraplegia (OR, 0.30; 95% CI, 0.14–0.62; Level B) compared with open thoracic aortic repair, although the reduction in risk of stroke did not reach significance (OR, 0.75; 95% CI, 0.50–1.13) (Level B).
3. Survival benefit for TEVAR versus open repair beyond 1 year remains unproven (1-year mortality OR, 0.73; 95% CI, 0.53–1.02).

Transcatheter Aortic Valve Implantation

Relevant Evidence

Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187–2198.

Statements for TAVI

1. Transcatheter aortic valve implantation reduces a risk of major bleeding compared with open AVR (9.3% vs 19.5%; Level B; one RCT).
2. However, the balance of benefits and risks with respect to other clinically relevant outcomes is of key interest. There was similar 30-day and 1-year mortality but increased risk of stroke at 30 days (5.5% vs 2.4%) and 1 year (8.3% vs 4.3%) (Level B, one RCT).

Recommendations for Surgical Techniques for OPCAB, Mini-AVR, Mini-MVR, and TAVI

- Whereas these minimally invasive procedures are not primarily selected for the purpose of blood management, the reduced allogeneic blood exposure should be considered in the balance of benefits and risks when selecting the appropriate surgery for patients.

Recommendations for Future Research Related to OPCAB, Mini-AVR, Mini-MVR, and TAVI

- Further randomized studies with adequate power to measure clinically relevant outcomes beyond blood conservation should be encouraged for mini-AVR, mini-MVR, and TAVI.
- Future randomized evidence should explore the learning curve in minimally invasive surgery and its impact on the need for transfusions and clinically relevant outcomes.

DISCUSSION

A number of drugs, technologies, and techniques have been shown to reduce the need for allogeneic blood transfusion and should be routinely considered as part of a program to reduce exposure to allogeneic blood, including lysine analogs, discontinuing antiplatelets in non-ACS patients and in patients without recent DESs, RAP, and use of CS throughout surgery (see summary in Table 3). The benefits of other

strategies remain less clear, and definitive recommendations for routine use would be premature (ie, topical hemostatics, DDAVP, FVIIa in refractory bleeding, EPO, ANH, biocom patible CPB circuits, MECC, ultrafiltration, platelet plasmapheresis, POC platelet function testing). Furthermore, the role of the minimally invasive approach to surgery may be part of a program to reduce blood loss; however, there are more important considerations for choosing between minimally invasive and conventional approaches to cardiac surgery.

It is notable that none of these approaches to blood conservation has been proven in RCTs to significantly improve clinically important outcomes such as death, stroke, or organ failure in randomized trials. Furthermore, few of these approaches to blood conservation have been adequately addressed to determine their impact when applied singularly versus in combination as a multimodal approach to conservation. If the primary purpose of blood conservation strategies is to reduce the risk of clinically meaningful adverse events caused by blood exposure (presumably, increased risk of death, morbidities, immunologic reactions, and infections) while balancing the risk of anemia (death, stroke, MI, organ failure), then it is surprising that so few randomized trials have addressed these outcomes. Most RCTs have measured exposure to allogeneic blood, or volume of blood transfused, rather than measuring the ultimate outcomes that matter most to patients. While conserving blood because of limitations in supply is important, it is not the ultimate outcome per se, and future research is imperative to address whether strategies to reduce blood transfusion result in comparable or improved rates of death, stroke, MI, RF, neurologic function, graft patency, and overall serious adverse events.

If there has been a dearth of evidence for clinically relevant outcomes in conventional cardiac surgery, there has been an even greater lack of evidence addressing these important questions for minimally invasive cardiac surgery. The latter represents an important call to action for surgeons, anesthesiologists, perfusionists, intensivists, and other health care professionals to prioritize research on these most important questions. More than 1 million cardiac surgeries are performed globally every year, and still a paucity of research exists to support evidence-based decision making for patient care in safety and cost-effectiveness in blood management.

Areas Not Addressed

A number of important areas related to blood conservation were not addressed during this consensus conference, recognizing that future consensus processes may address these areas, such as the role of colloids versus crystalloids for fluid management, restrictive versus standard or liberal transfusion thresholds, role of transfusing different blood fractions (FFP, platelets, cryoprecipitate), role of different anticoagulation strategies (different doses of heparin, different ACT targets, protamine reversal strategies, and different classes of anticoagulants such as bivalirudin for anticoagulation during cardiac surgery, whether for on-pump or off-pump surgery). In addition, the role of formal blood management programs at the institutional and regional level was not specifically addressed during this consensus conference.[33–36]

Cost-effectiveness, Availability, and Local Contextual Considerations

This consensus panel did not specifically address issues of cost-effectiveness, and this should not be interpreted to suggest that costs and resource considerations are not important. Because cost-effectiveness and resource considerations are context-sensitive, these issues should be considered locally before decisions are made about the relative appropriateness of the different drugs, technologies, and techniques. In addition, local considerations regarding the availability of the drugs and technologies will be an important driver for deciding which is most important. Lastly, local expertise and skill sets should be considered carefully when deciding which type of surgical technique is appropriate, given that the learning curve can be a significant driver of adverse clinical outcomes, including a higher risk for bleeding.

CONCLUSIONS

A number of strategies have been shown to reduce the need for allogeneic blood transfusion in patients undergoing conventional cardiac surgery (antifibrinolytics such as lysine analogs, discontinuation of clopidogrel preoperatively in non-ACS patients without recent DESs, RAP, intraoperative CS), and these should be encouraged for routine blood conservation management. A number of strategies to conserve blood remain nondefinitive because of lack of consistent evidence (topical hemostatics, DDAVP, FVIIa in refractory bleeding, EPO, ANH, biocompatible CPB circuits, MECC, ultrafiltration, platelet plasmapheresis, POC platelet function testing). A number of strategies not addressed in this review should be the focus of future consensus, including anticoagulation strategies, colloids versus crystalloids, restrictive transfusion thresholds, transfusion protocols, and effective implementation of multifaceted blood conservation programs. Few blood management strategies have been specifically tested in minimally invasive cardiac surgery. The lack of high-level evidence to address the impact on clinical outcomes such as infection, incompatibility immunologic reactions, kidney failure, MI, stroke, and death remains a significant barrier to determining which drugs, technologies, and techniques provide worthy improvements in clinically important outcomes for patients undergoing cardiac surgery whether conventional or minimally invasive. Given the volume of cardiac surgery that is performed around the world and the significant consumption of blood that occurs during cardiac surgery, future large-scale research should be conducted to address these questions.

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