Patient Blood Management

The Intraoperative Period

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The 3 Pillars of PBM – Intraoperative

- Optimize erythropoiesis
  - Schedule surgery with red cell mass in consideration
  - Intravenous iron for acute alteration of risk

- Will not discuss at this lecture

The 3 Pillars of PBM – Intraoperative

- Minimize blood loss
  - Anesthetic blood sparing techniques
  - Acute normovolemic hemodilution
  - Cell salvage
  - Pharmacological therapies (Tranexamic acid)
  - POC-based coagulation management algorithms

The 3 Pillars of PBM – Intraoperative

- Manage anemia
  - Improve tolerance of anemia
  - Evidence-based transfusion thresholds

Practical criteria for adoption of modalities

1. Has to be effective
2. Has to be at least as safe as transfusion
3. Costs should be reasonable

Anesthetic blood sparing techniques

- Permissive hypotension
  - Lowering of blood pressure to mean ~ 50–60 mmHg
  - Objectives:
    - Reducing blood loss
    - Improving visibility in surgical field
  - Techniques:
    - Anesthetic depth, vasodilators, beta-blockers, fluid restriction
  - Risks:
    - Organ hypoperfusion and injury

Anesthetic blood sparing techniques

- Permissive hypotension
  - Evidence:
    - Supported by meta-analysis
      - Specific types of surgeries: Sinus, Orthopedics, Spine, Liver, Prostate
      - Based on small, low-quality, outdated studies
        - Do not account for improvements in surgical technique
      - Safety not adequately assessed

Neuraxial Anesthesia

- Mechanism:
  - **Sympathetic blockade → reduced arterial pressure**
    → reduced venous pressure
    → reduced surgical stress
    → stabilization of clotting factors
    → reduced fibrinolysis
  - Evidence:
    - Conflicting
      - Older, lower quality evidence positive
      - Newer, higher quality evidence negative

Acute normovolemic hemodilution

- Removal of 3-4 units of blood before surgery and simultaneous replacement with crystalloids or colloids
  - Theoretical example:
    - if Hct = 0.40 and EBL = 1L → RBC Loss = 400 cc
    - if Hct = 0.25 and EBL = 1L → RBC Loss = 250 cc
    - RBC conserved = 150 cc or ~ 2/3 of a unit of PRBC
- Effectiveness questionable and not properly assessed
- Safety questionable and not properly assessed

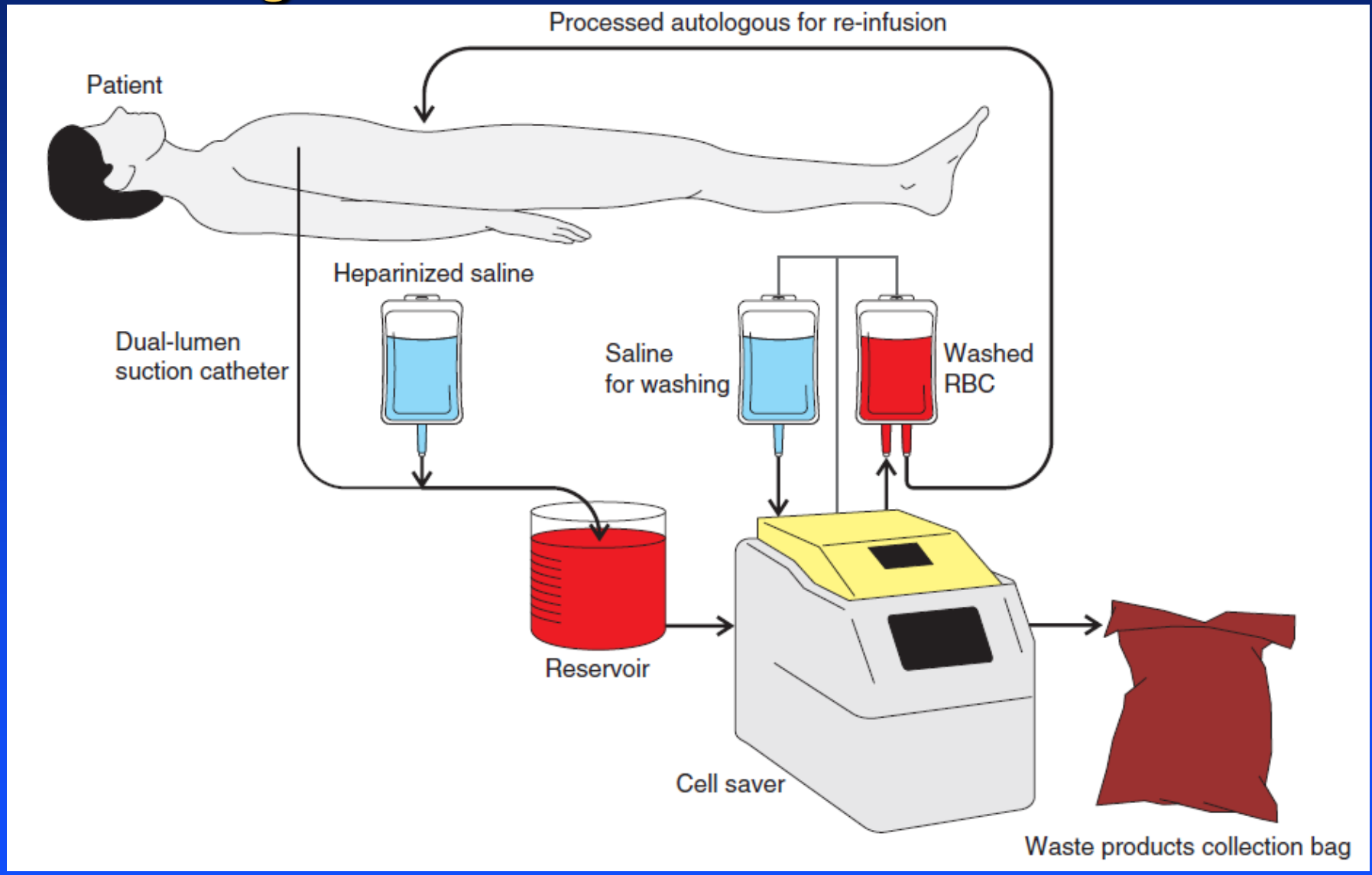
Anesthetic blood sparing techniques / Neuraxial anesthesia / ANH

1. Has to be effective X
2. Has to be at least as safe as transfusion ?
3. Costs should be reasonable ✓

Anesthetic blood sparing techniques / Neuraxial anesthesia / ANH

- New versus old study dichotomy:
  - Surgical techniques have improved substantially
    - Faster, less invasive (e.g., prostate / orthopedics)
- Current status of anesthetic blood sparing techniques:
  - Modest benefit on blood loss itself
  - Major benefit is improved visibility in surgical field
    - **↓ length of surgery + surgical control of bleeding = ↓ blood loss**
  - Driving factor is surgical rather than PBM
  - Neuraxial techniques / fluid restriction / permissive hypotension

Cell Salvage



Cell Salvage

- Complications are rare
  - Hemolysis, air embolism, incomplete washing, infections
  - Safer than allogeneic blood
    - Lower AE rates (0.027% versus 0.14%)
    - Better quality (fresh versus old blood)
- Indications
  - Anticipated blood loss > 500 mL (ASA guidance)
  - Anemia, antibodies or rare blood types, JW

Ashworth et al. BJA 2010;105:401-416

Cell Salvage

- Benefits
  - Reduce RBC exposure
    - **On average, ↓0.7 units; ↑avoidance ~40%**
    - Much more effective in MBH
  - Other blood products: ?
- Contra-indications
  - Sepsis; Contaminated surgery; Malignance
    - **Leukocyte depletion filter → 99% reduced bacterial contamination**
    - Reinfused tumour cells do not have metastatic potential

Ashworth et al. BJA 2010;105:401-416

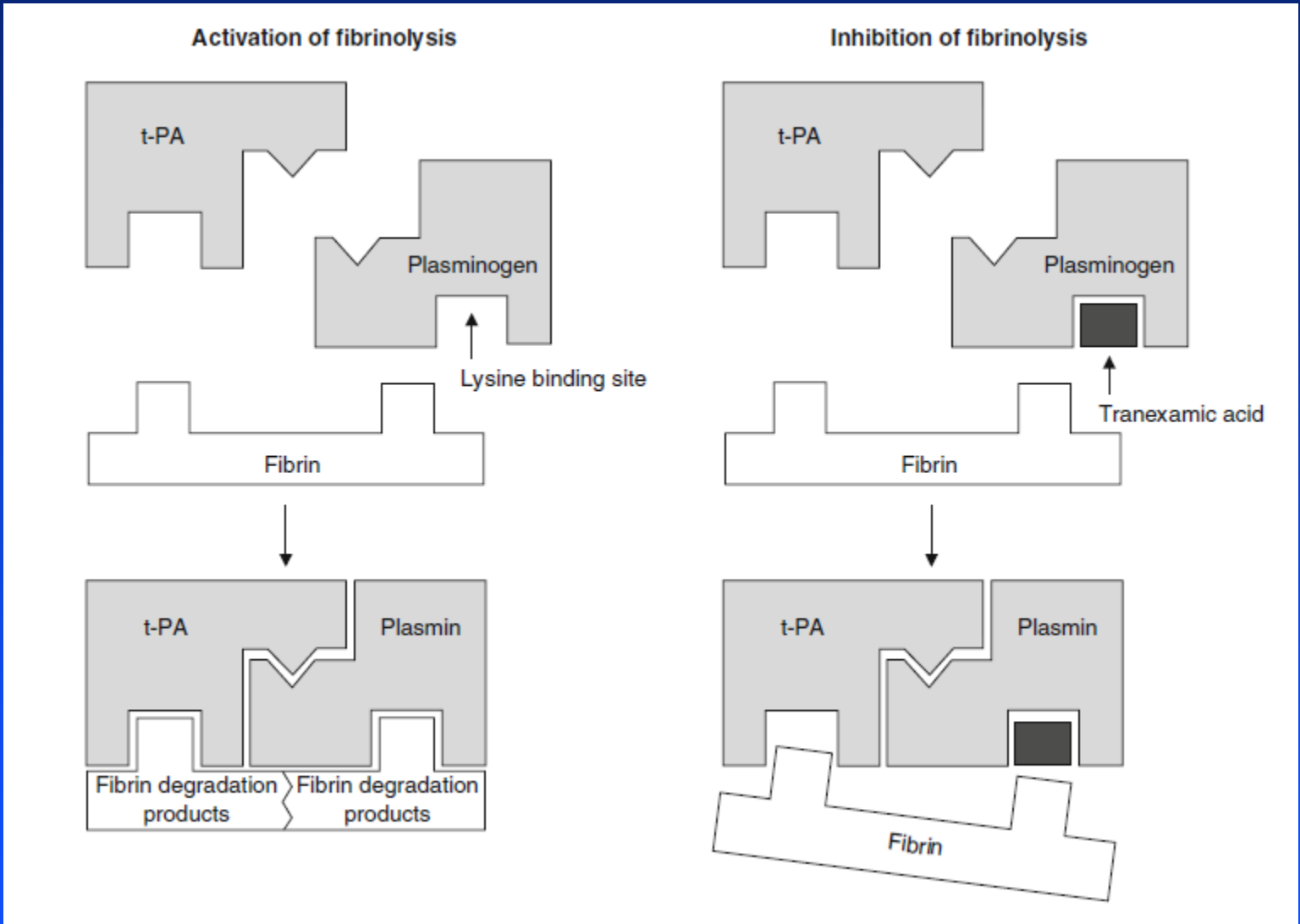
Cell Salvage

1. Has to be effective ✓
2. Has to be at least as safe as transfusion ✓
3. Costs should be reasonable ✓

Pharmacologic Agents

- Antifibrinolytics
- Desmopressin
- Prothrombin complex concentrate
- Fibrinogen concentrate
- rFVIIa

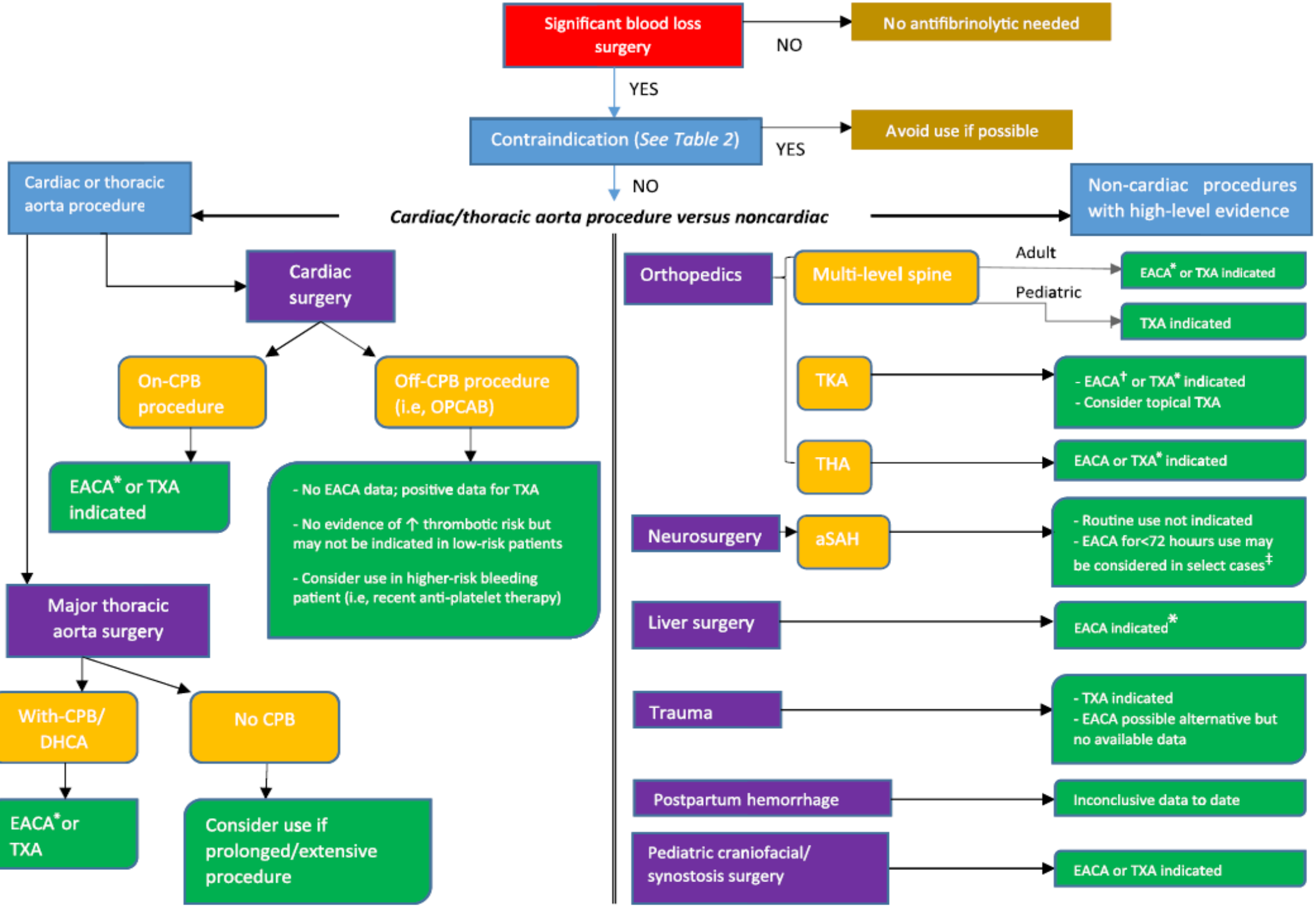
Mechanism of Action: Tranexamic Acid



McCormack PL. Drugs 2012;72:585-617

Current Status

- It definitely works … in some populations
  - Lots of high-level evidence in some areas, but not all
  - Overall, reduces blood loss and transfusions by one-third
  - Indications:
    - See figure
  - Benefits > Risks … but not in every case
    - Contraindications: Allergy, Hypercoagulable state
    - Caution: Seizure risk, renal failure, recent thromboembolic event, cirrhosis


Significant blood loss surgery
NO
No antifibrinolytic needed
YES
Contraindication (See Table 2)
YES
Avoid use if possible
NO
Cardiac or thoracic aorta procedure
Cardiac/thoracic aorta procedure versus noncardiac
Non-cardiac procedures with high-level evidence
Cardiac surgery
On-CPB procedure
Off-CPB procedure (i.e, OPCAB)
EACA* or TXA indicated
- No EACA data; positive data for TXA
- No evidence of ↑ thrombotic risk but may not be indicated in low-risk patients
- Consider use in higher-risk bleeding patient (i.e, recent anti-platelet therapy)
Major thoracic aorta surgery
With-CPB/ DHCA
No CPB
EACA* or TXA
Consider use if prolonged/extensive procedure
Orthopedics
Multi-level spine
Adult
Pediatric
EACA* or TXA indicated
TXA indicated
TKA
- EACA† or TXA* indicated
- Consider topical TXA
THA
EACA or TXA* indicated
Neurosurgery
aSAH
- Routine use not indicated
- EACA for<72 houurs use may be considered in select cases‡
Liver surgery
EACA indicated*
Trauma
- TXA indicated
- EACA possible alternative but no available data
Postpartum hemorrhage
Inconclusive data to date
Pediatric craniofacial/ synostosis surgery
EACA or TXA indicated

Uncertainties

- Dosing
  - **10 mg/kg IV → 10 mg/L in plasma → 80% inhibition fibrinolysis**
  - What dose for 100% inhibition?
- Studies used widely variable dosing
  - Recommendations based on studies rather than PK
  - Reasonable dose: 10 mg/kg bolus + 1 mg/kg/hour
- Indication:
  - NICE: Offer to adults for all surgical procedures with moderate (>500 mL) blood loss
  - Or more targeted approach?

Trauma

Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial

*CRASH-2 trial collaborators**

- N = 20,211
- Dose: 1g bolus + 1g infusion over 8 hours
- Primary outcome: 28-day in-hospital all-cause mortality

CRASH-2 Collaborators Lancet 2010;376:23-32

Trauma

	Tranexamic acid (n=10 060)	Placebo (n=10 067)	RR (95% CI)	p value (two-sided)
Any cause of death	1463 (14·5%)	1613 (16·0%)	0·91 (0·85–0·97)	0·0035
Bleeding	489 (4·9%)	574 (5·7%)	0·85 (0·76–0·96)	0·0077
Vascular occlusion*	33 (0·3%)	48 (0·5%)	0·69 (0·44–1·07)	0·096
Multiorgan failure	209 (2·1%)	233 (2·3%)	0·90 (0·75–1·08)	0·25
Head injury	603 (6·0%)	621 (6·2%)	0·97 (0·87–1·08)	0·60
Other causes	129 (1·3%)	137 (1·4%)	0·94 (0·74–1·20)	0·63

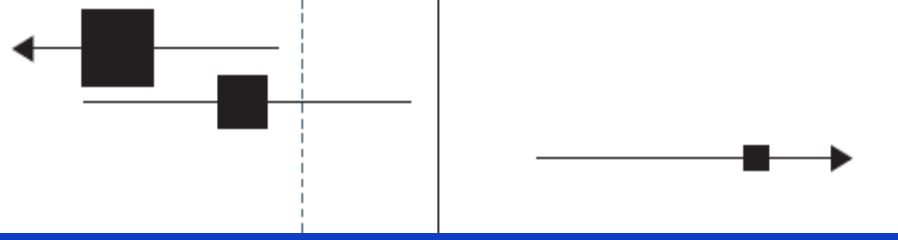
Data are number (%), unless otherwise indicated. RR=relative risk. *Includes myocardial infarction, stroke, and pulmonary embolism.

Table 2: Death by cause

CRASH-2 Collaborators Lancet 2010;376:23-32

Trauma

	Tranexamic acid allocated	Placebo allocated	Risk ratio (95% CI)
Time to treatment (h)			
≤1	198/3747 (5·3%)	286/3704 (7·7%)	0·68 (0·57–0·82)
>1–3	147/3037 (4·8%)	184/2996 (6·1%)	0·79 (0·64–0·97)
>3	144/3272 (4·4%)	103/3362 (3·1%)	1·44 (1·12–1·84)
χ^2=23·516; p<0·0000			



	≤1 h (n=7451)	>1–3 h (n=6033)	>3 h (n=6634)
Continents			
Asia	1213 (16·3%)	2475 (41·0%)	3656 (55·1%)
Africa	2490 (33·4%)	1437 (23·8%)	872 (13·1%)
Central and South America	2453 (32·9%)	1456 (24·1%)	1355 (20·4%)
North America, Europe, and Oceania	1295 (17·4 %)	665 (11·0%)	751 (11·3%)

CRASH-2 Collaborators Lancet 2011;377:1096-101

Trauma

- Externally generalizable?
  - > 20,000 patients randomized
  - **Number of patients from developed countries → 382**
  - **Number of patients from Canada → 2**
  - **Number of patients from UK → 135**
  - **Number randomized by central telephone system → 95**
    - "Hospitals with telephone access used a telephone randomisation service"

CRASH-2 Collaborators Lancet 2010;376:23-32

Cardiac Surgery

Tranexamic Acid in Patients Undergoing Coronary-Artery Surgery

Paul S. Myles, M.P.H., M.D., Julian A. Smith, F.R.A.C.S., Andrew Forbes, Ph.D., Brendan Silbert, M.B., B.S., Mohandas Jayarajah, M.B., B.S.,

- N = 4631
- **Dose: 100 mg/kg → seizures → 50 mg/kg**
- Primary outcome: 30-day mortality + thromboembolic events

Myles et al. NEJM 2017;376:136-48

Cardiac Surgery

Outcome	TA (n = 2311)	Placebo (n = 2320)	Risk Ratio
Death or TE	16.7%	18.1%	0.92 (0.81 – 1.05)
Reoperation	1.4%	2.8%	0.49 (0.32 – 0.75)
Blood Product Tx	37.9%	54.7%	0.69 (P < 0.001)
Blood Product (Units)	3 (2-6)	4 (2-8)	P < 0.001
Seizures	0.7%	0.1%	7.62 (1.77 – 68.7)

Myles et al. NEJM 2017;376:136-48

PPH

Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial

*WOMAN Trial Collaborators**

- N = 20,060
- Dose: 1 g; repeated x1 if needed
- Primary outcome: 42-day all-cause mortality

WOMAN Trial Collaborators Lancet 2017;389:2105-2116

PPH

Outcome	TA (n = 10,036)	Placebo (n = 9,985)	Risk Ratio
Death or Hysterectomy	534 (5.3%)	546 (5.6%)	0.98 (0.87 – 1.10); P = 0.75
Death (Any cause)	227 (2.3%)	256 (2.6%)	0.88 (0.74 – 1.05); P = 0.16
Death (Bleeding)	155 (1.5%)	191 (1.9%)	0.81 (0.65 – 1.00); P = 0.045
Laparotomy (Bleeding)	82 (0.8%)	127 (1.3%)	0.64 (0.49 – 0.85); P = 0.002
Blood Product Tx	5461 (54%)	5426 (54%)	

WOMAN Trial Collaborators Lancet 2017;389:2105-2116

PPH

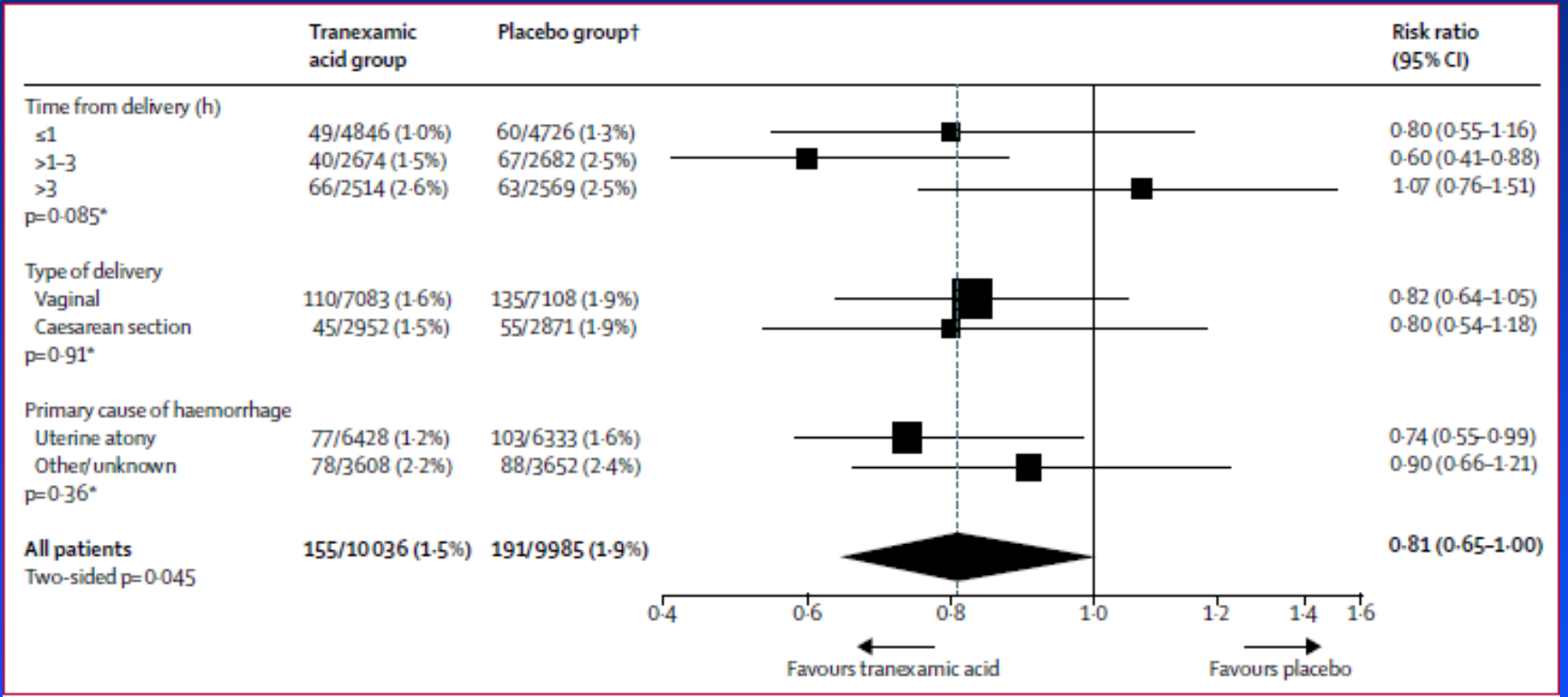


Figure 3: **Death from bleeding by subgroup**

*Heterogeneity p value. †One patient excluded from subgroup analysis because of missing baseline data.

WOMAN Trial Collaborators Lancet 2017;389:2105-2116

PPH

	Tranexamic acid group	Placebo group	RR (95% CI)	p value
Thromboembolic events*	10 033	9985	..	
Any event	30 (0·3%)	34 (0·3%)	0·88 (0·54–1·43)	0·603
Venous events	20 (0·2%)	25 (0·3%)	0·80 (0·44–1·43)	0·446
Deep vein thrombosis	3 (0·03%)	7 (0·07%)	0·43 (0·11–1·65)	0·203
Pulmonary embolism	17 (0·2%)	20 (0·2%)	0·85 (0·44–1·61)	0·611
Arterial events	10 (0·1%)	9 (0·09%)	1·11 (0·45–2·72)	0·827
Myocardial infarction	2 (0·02%)	3 (0·03%)	0·66 (0·11–3·97)	0·651
Stroke	8 (0·08%)	6 (0·06%)	1·33 (0·46–3·82)	0·599
Complications*	10 033	9985	..	..
Renal failure	129 (1·3%)	118 (1·2%)	1·09 (0·85–1·39)	0·505
Cardiac failure	110 (1·1%)	115 (1·2%)	0·95 (0·73–1·23)	0·710
Respiratory failure	108 (1·1%)	124 (1·2%)	0·87 (0·67–1·12)	0·274
Hepatic failure	29 (0·3%)	30 (0·3%)	0·96 (0·58–1·60)	0·882
Sepsis	180 (1·8%)	185 (1·9%)	0·97 (0·79–1·19)	0·756
Seizure	33 (0·3%)	43 (0·4%)	0·76 (0·49–1·20)	0·242

WOMAN Trial Collaborators Lancet 2017;389:2105-2116

GI Bleed

Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial

*The HALT-IT Trial Collaborators**

- N = 12,009
- Dose: 1 g + 3g/24 hours
- Primary outcome: 5-day bleeding mortality

HALT-IT Trial Collaborators Lancet 2020;395:1927-1936

GI Bleed

Outcome	TXA N=5994	Placebo N=6015	RR (95% CI)
Death due to bleeding within 5 d	3.7%	3.8%	0.99 (0.82-1.18)
Arterial TE (MI/CVA)	0.7%	0.8%	0.92 (0.60-1.39)
Venous TE* Seizures	0.8% 0.6%	0.4% 0.4%	1.85 (1.15-2.98) 1.73 (1.03-2.93)
Transfusion	68.5%	69.1%	0.99 (0.97-1.02)

*higher in variceal bleed or liver disease

HALT-IT Trial Collaborators Lancet 2020;395:1927-1936

Tranexamic Acid

1. Has to be effective ✓
2. Has to be at least as safe as transfusion ✓
3. Costs should be reasonable ✓

Tranexamic Acid – Summary

Excessive bleeding

↓

Consider Administering

↓

10 mg/kg bolus + 1 mg/kg/hour

Restrictive Transfusion Threshold

JAMA | Special Communication

Patient Blood Management Recommendations From the 2018 Frankfurt Consensus Conference

Markus M. Mueller, MD; Hans Van Remoortel, PhD; Patrick Meybohm, MD, PhD; Kari Aranko, MD, PhD; Cécile Aubron, MD, PhD; Reinhard Burger, PhD; Jeffrey L. Carson, MD, PhD; Klaus Cichutek, PhD; Emmy De Buck, PhD; Dana Devine, PhD; Dean Fergusson, PhD; Gilles Folléa, MD, PhD; Craig French, MB, BS; Kathrine P. Frey, MD; Richard Gammon, MD; Jerrold H. Levy, MD; Michael F. Murphy, MD, MBBS; Yves Ozier, MD; Katerina Pavenski, MD; Cynthia So-Osman, MD, PhD; Pierre Tiberghien, MD, PhD; Jimmy Volmink, DPhil; Jonathan H. Waters, MD; Erica M. Wood, MB, BS; Erhard Seifried, MD, PhD; for the ICC PBM Frankfurt 2018 Group

Mueller et al. JAMA 2019;321:983-997

Restrictive Transfusion Threshold

Table 2. Clinical Recommendations: Red Blood Cell Transfusion Thresholds

Clinical Recommendation	Level of Evidence
CR5—Restrictive RBC transfusion threshold (hemoglobin concentration <7 g/dL) in critically ill but clinically stable intensive care patients	Strong recommendation, moderate certainty in the evidence of effects
CR6—Restrictive RBC transfusion threshold (hemoglobin concentration <7.5 g/dL) in patients undergoing cardiac surgery	Strong recommendation, moderate certainty in the evidence of effects
CR7—Restrictive transfusion threshold (hemoglobin concentration <8 g/dL) in patients with hip fracture and cardiovascular disease or other risk factors	Conditional recommendation, moderate certainty in the evidence of effects
CR8—Restrictive transfusion threshold (hemoglobin concentration 7-8 g/dL) in hemodynamically stable patients with acute gastrointestinal bleeding	Conditional recommendation, low certainty in the evidence of effects

Abbreviations: CR, clinical recommendation; RBC, red blood cell.

- Editorial (Zeller, Kaufman)
  - Thresholds are ‘particularly specific’
  - If sole consideration for transfusion is the Hb level, then a restrictive threshold should be used

Mueller et al. JAMA 2019;321:983-997

Restrictive Transfusion Threshold

Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery

C.D. Mazer, R.P. Whitlock, D.A. Fergusson, J. Hall, E. Belley-Cote, K. Connolly, B. Khanykin, A.J. Gregory, É. de Médicis, S. McGuinness, A. Royse, F.M. Carrier, P.J. Young, J.C. Villar, H.P. Grocott, M.D. Seeberger, S. Fremes, F. Lellouche, S. Syed, K. Byrne, S.M. Bagshaw, N.C. Hwang, C. Mehta, T.W. Painter, C. Royse, S. Verma, G.M.T. Hare, A. Cohen, K.E. Thorpe, P. Jüni, and N. Shehata, for the TRICS Investigators and Perioperative Anesthesia Clinical Trials Group*

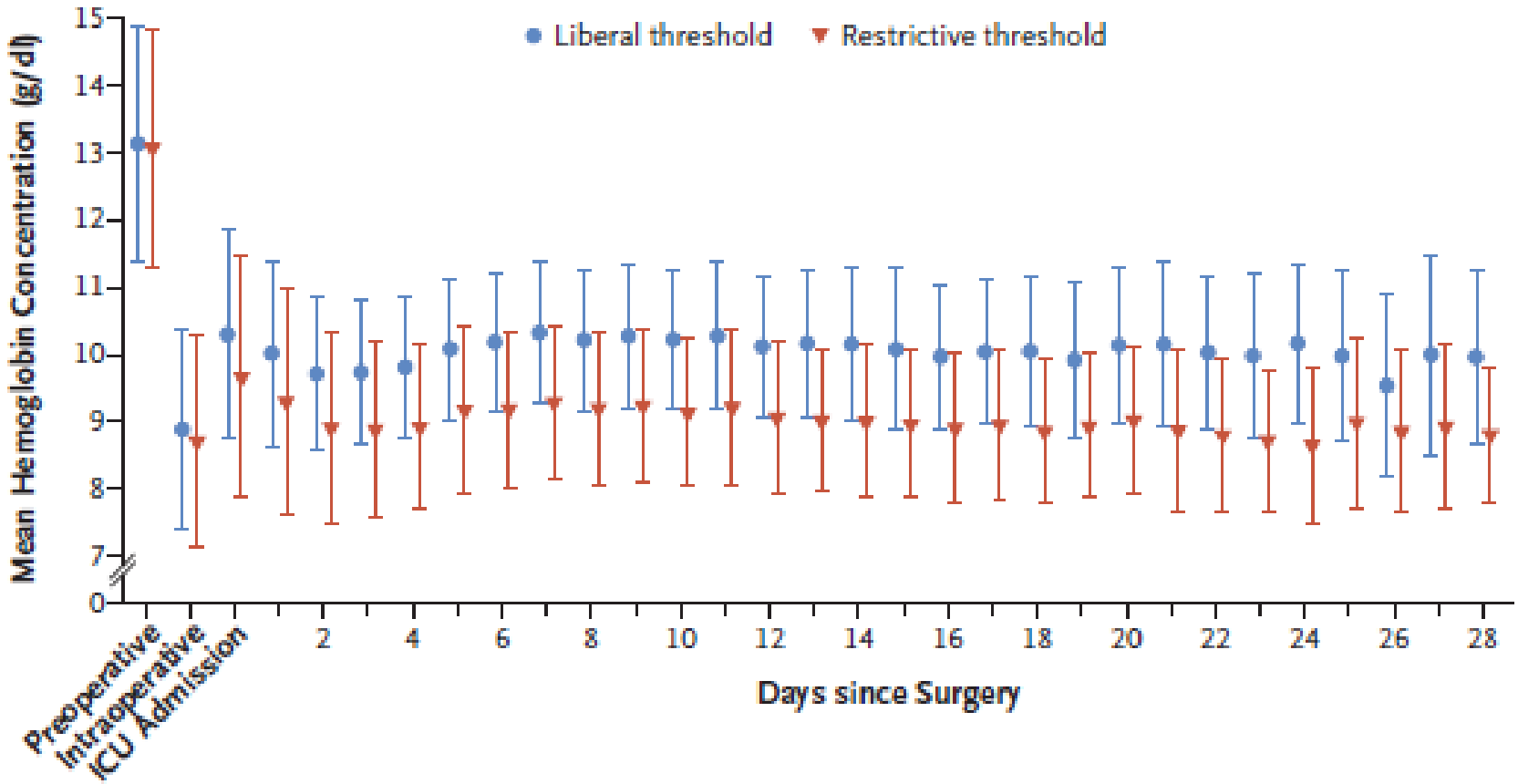
Mazer et al. NEJM 2017;377:2133-44

Restrictive Transfusion Threshold

- Higher-risk cardiac surgery
- Randomized before surgery
- Restrictive group:
  - Transfuse if Hb < 75 g/L
- Liberal group:
  - Transfuse if Hb < 95 g/L during surgery/ICU stay
  - Transfuse if Hb < 85 g/L on ward
- Protocol suspended if rapid bleeding or hemodynamic instability due to bleeding

Mazer et al. NEJM 2017;377:2133-44

Restrictive Transfusion Threshold

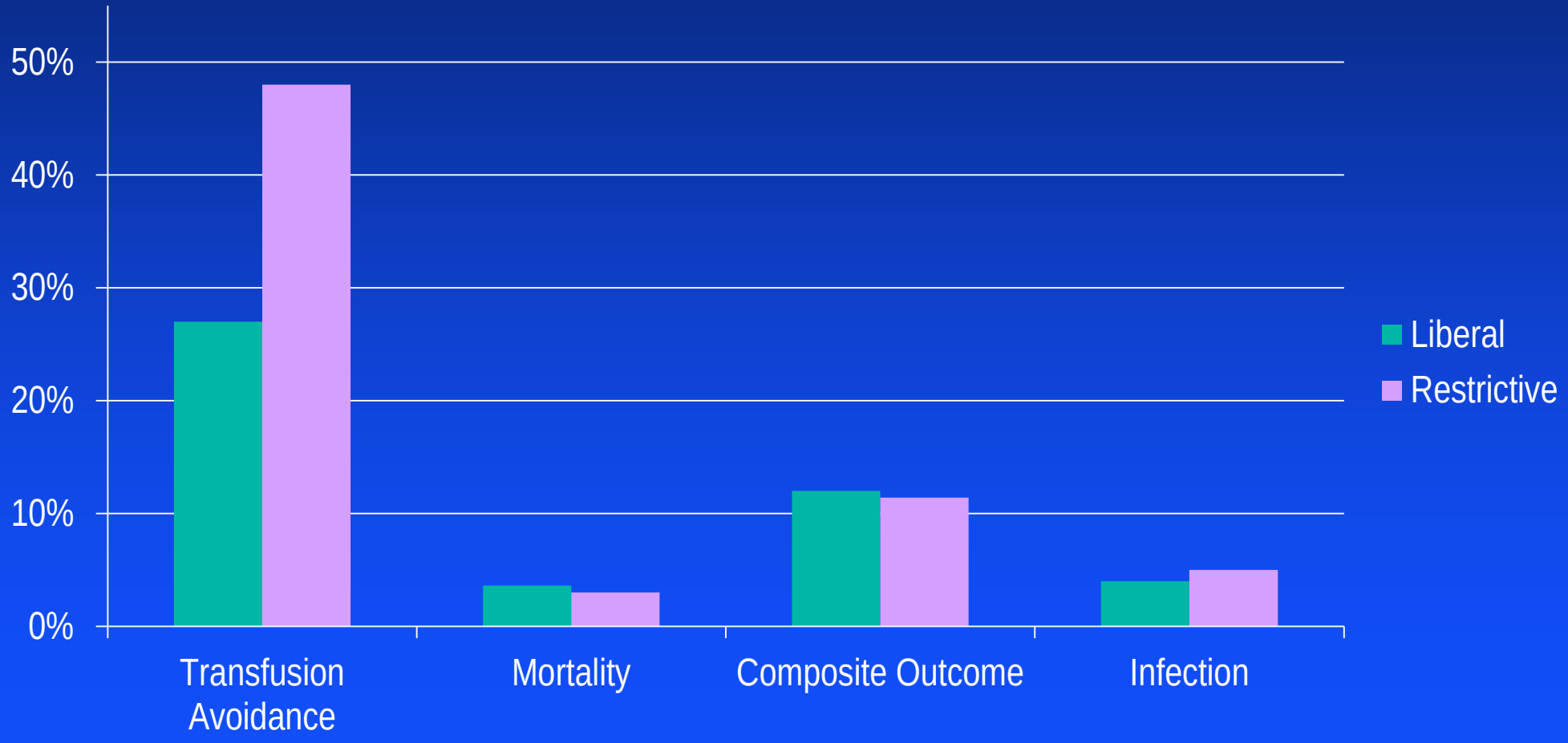


No. at Risk

Liberal threshold	2428	2435	2015	1354	731	443	327	233	153	122	112	76	69	57	51
Restrictive threshold	2429	2454	2007	1431	841	527	376	305	215	165	131	117	91	77	76

Mazer et al. NEJM 2017;377:2133-44

Restrictive Transfusion Threshold



Mazer et al. NEJM 2017;377:2133-44

Restrictive Transfusion Threshold

1. Has to be effective ✓
2. Has to be at least as safe as transfusion ✓
3. Costs should be reasonable ✓

Restrictive Transfusion Threshold

- Caveat
  - For the most part, studies have included non-bleeding, euvolemic, stable patients without heart disease, and have studied fixed transfusion thresholds
- Surgical patients, however, may be:
  - Bleeding and coagulopathic
  - Unstable and hypovolemic
  - Critically ill with limited organ reserve
- Transfusion decision more complicated than just measuring Hb level

Optimizing Coagulation

- Point-of-care guided coagulation management algorithms
  - Whole-blood based assays
    - Viscoelastic
      - ROTEM, TEG
    - Platelet function
      - Multiple assays available

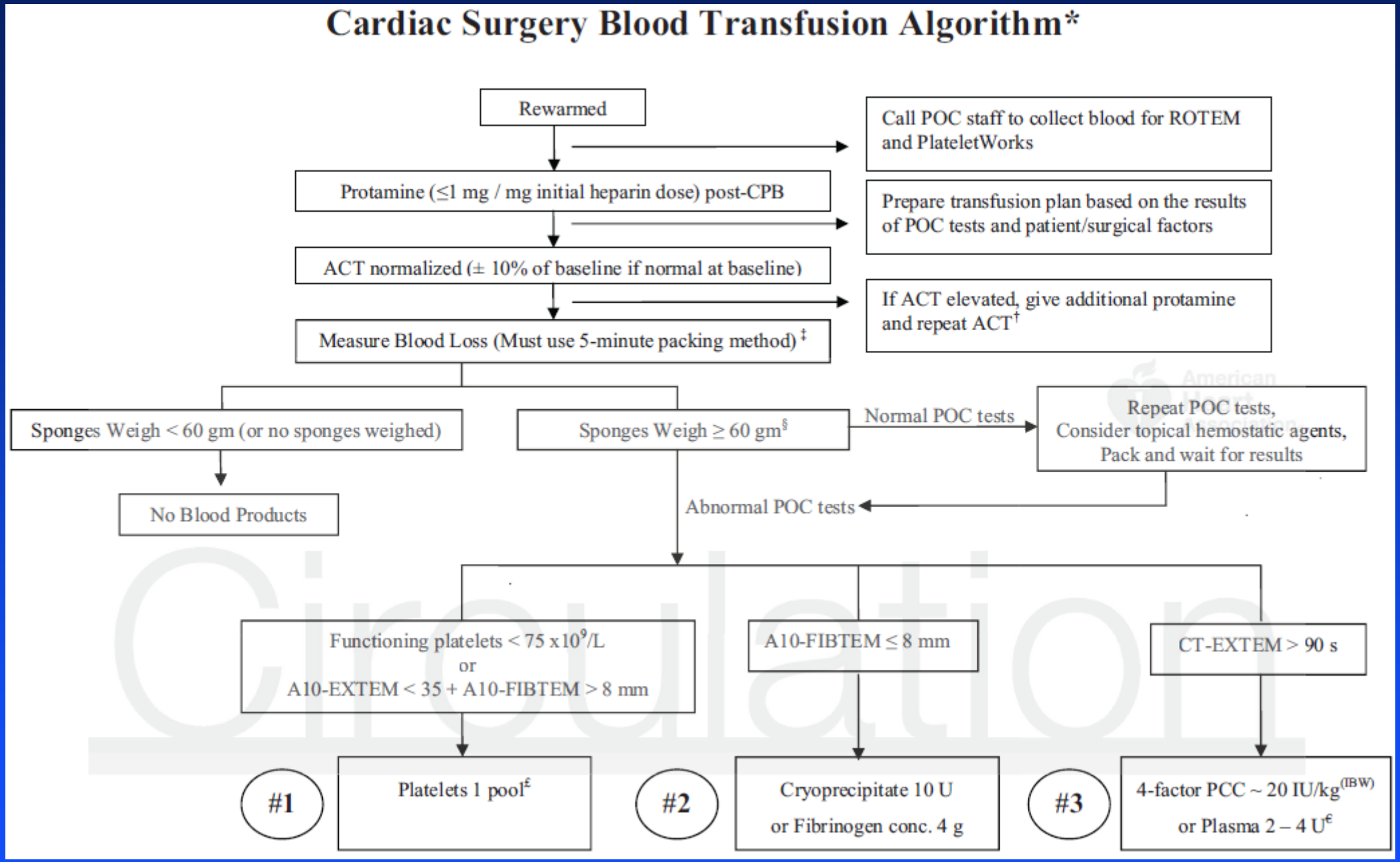
Point-of-Care Hemostatic Testing in Cardiac Surgery

A Stepped-Wedge Clustered Randomized Controlled Trial

Keyvan Karkouti, MD
Jeannie Callum, MD
Duminda N. Wijeysundera, MD, PhD
Vivek Rao, MD, PhD
Mark Crowther, MD
Hilary P. Grocott, MD
Ruxandra Pinto, PhD
Damon C. Scales, MD, PhD
TACS Investigators

Karkouti et al. Circulation 2016;134:1152-1162

Cardiac Surgery Blood Transfusion Algorithm*



Karkouti et al. Circulation 2016;134:1152-1162

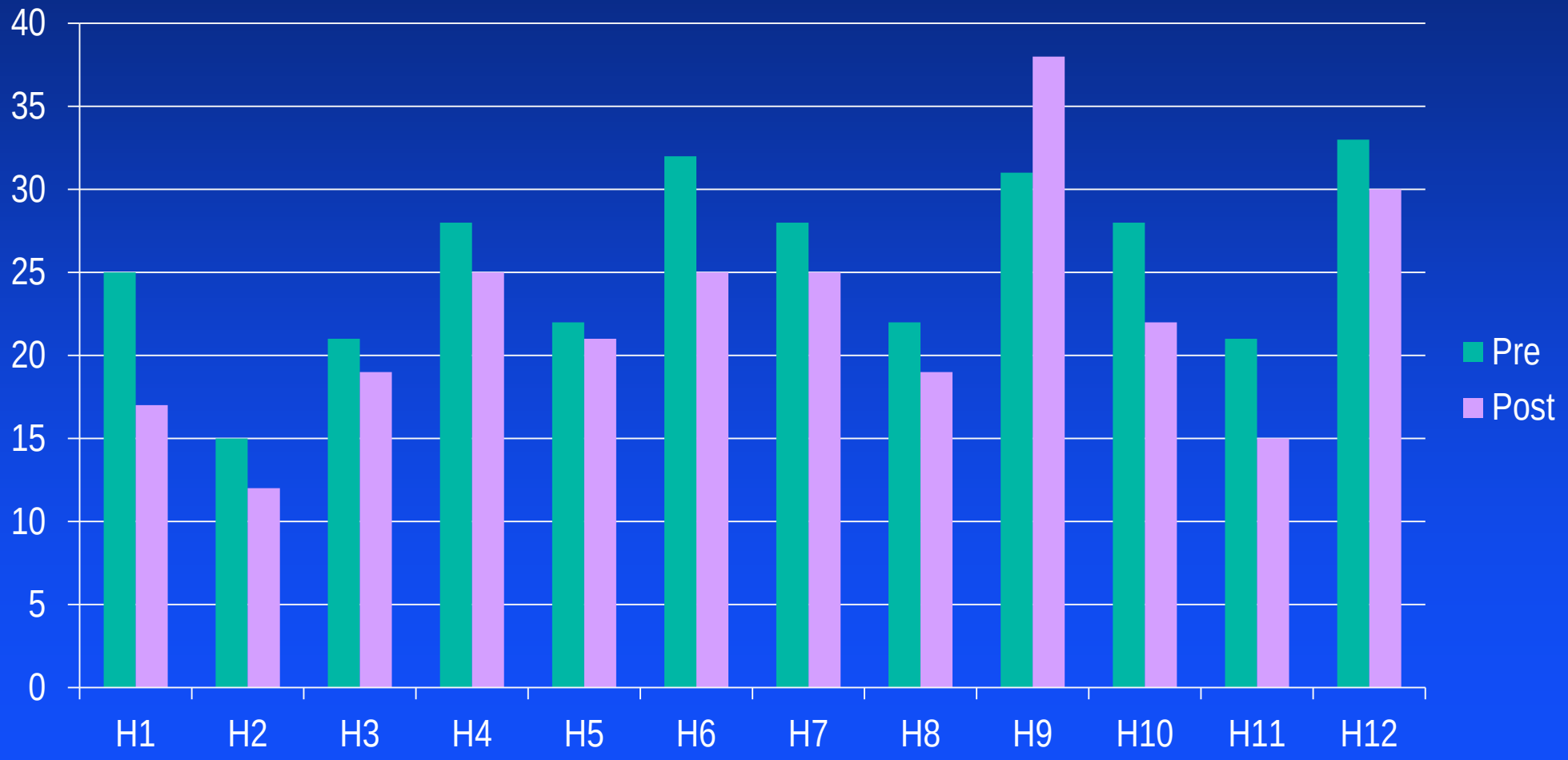
Results

- 7402 patients in the study
  - Control phase n = 3555; Intervention phase n = 3847

Outcome	Incidence
RBC	45%
Platelet	25%
Plasma	22%
Cryoprecipitate	5%
Major Bleeding	24%
Major Complications	10%

Karkouti et al. Circulation 2016;134:1152-1162

Major Bleeding



Karkouti et al. Circulation 2016;134:1152-1162

Results

Outcome	Relative Risk Reduction
RBC	0.91 (0.85 – 0.98); P = 0.02; NNT = 24.7
Platelet	0.77 (0.68 – 0.87); P < 0.001; NNT = 16.7
Plasma	NC
Cryoprecipitate	NC
Major Bleeding	0.83 (0.72 – 0.94); P = 0.004; NNT = 22.6
Adverse Outcomes	NC
Processes of Care	NC

Karkouti et al. Circulation 2016;134:1152-1162

Optimizing Coagulation

1. Has to be effective ✓
2. Has to be at least as safe as transfusion ✓
3. Costs should be reasonable ✓

Summary

The 3 Pillars of PBM – Intraoperative

- Optimize erythropoiesis
  - Schedule surgery with red cell mass in consideration PCC
  - Intravenous iron for acute alteration of risk ?

The 3 Pillars of PBM – Intraoperative

- Minimize blood loss
  - Anesthetic blood sparing techniques
  - Acute normovolemic hemodilution
  - Cell salvage
  - Pharmacological therapies (Tranexamic acid)
  - POC-based coagulation management algorithms

The 3 Pillars of PBM – Intraoperative

- Manage anemia
  - Improve tolerance of anemia
  - Evidence-based transfusion thresholds 

True or False

- Anesthetic blood sparing techniques are highly effective in reducing perioperative blood transfusions
- Salvaged blood is of higher quality than stored blood
- Tranexamic acid use should be considered for surgeries with moderate (>500 mL) blood loss
- Except for patients who are allergic, tranexamic acid can be offered to all patients
- Adhering to restrictive transfusion thresholds reduces transfusions and saves lives
- POC assays are effective because they allow for timely, targeted transfusion therapy

Questions?