Mitigating the Risk of Anemia-
the integrative roles of Blood Management and Red Blood Cell Transfusion

St. Michael's
Inspired Care.
Inspiring Science.

Professors Rounds, UofT, September 11, 2023

Vision
Safe anesthesia and perioperative care globally

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VISION STATEMENT
Transformative patient care.

Mitigating the Risk of Anemia-
The integrative roles of Blood Management and Red Blood Cell Transfusion

Aims:

1) to review the risk of perioperative anemia

2) to review effective strategies in perioperative patient blood management

3) to explore the evidence for “liberal” red blood cell transfusion.

Review of the Physiology of Oxygen Delivery to Tissue

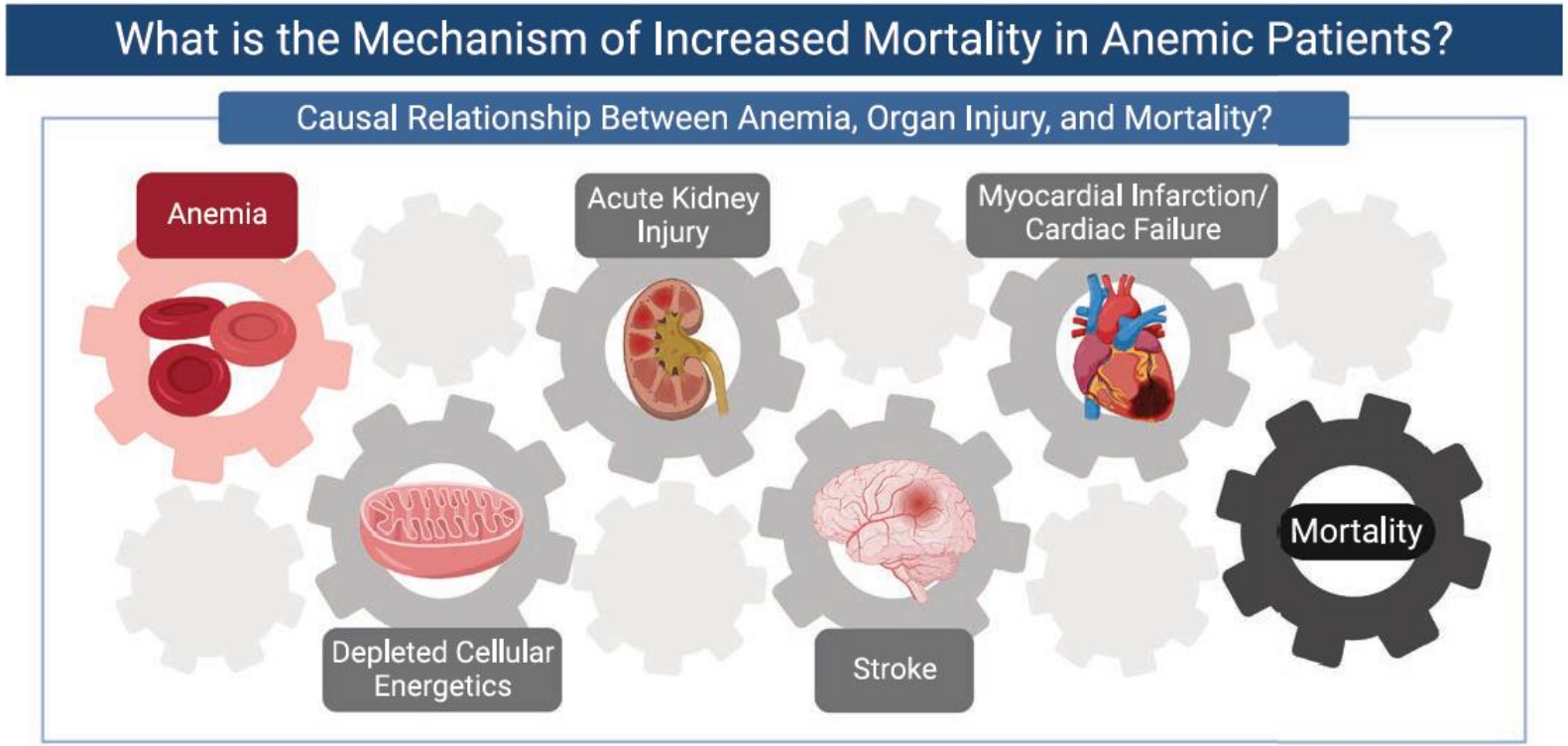
The Primary Function of The Red Blood Cell is to Deliver Oxygen to Tissue

CLINICAL FOCUS REVIEW

Jerrold H. Levy, M.D., F.A.H.A., F.C.C.M., Editor

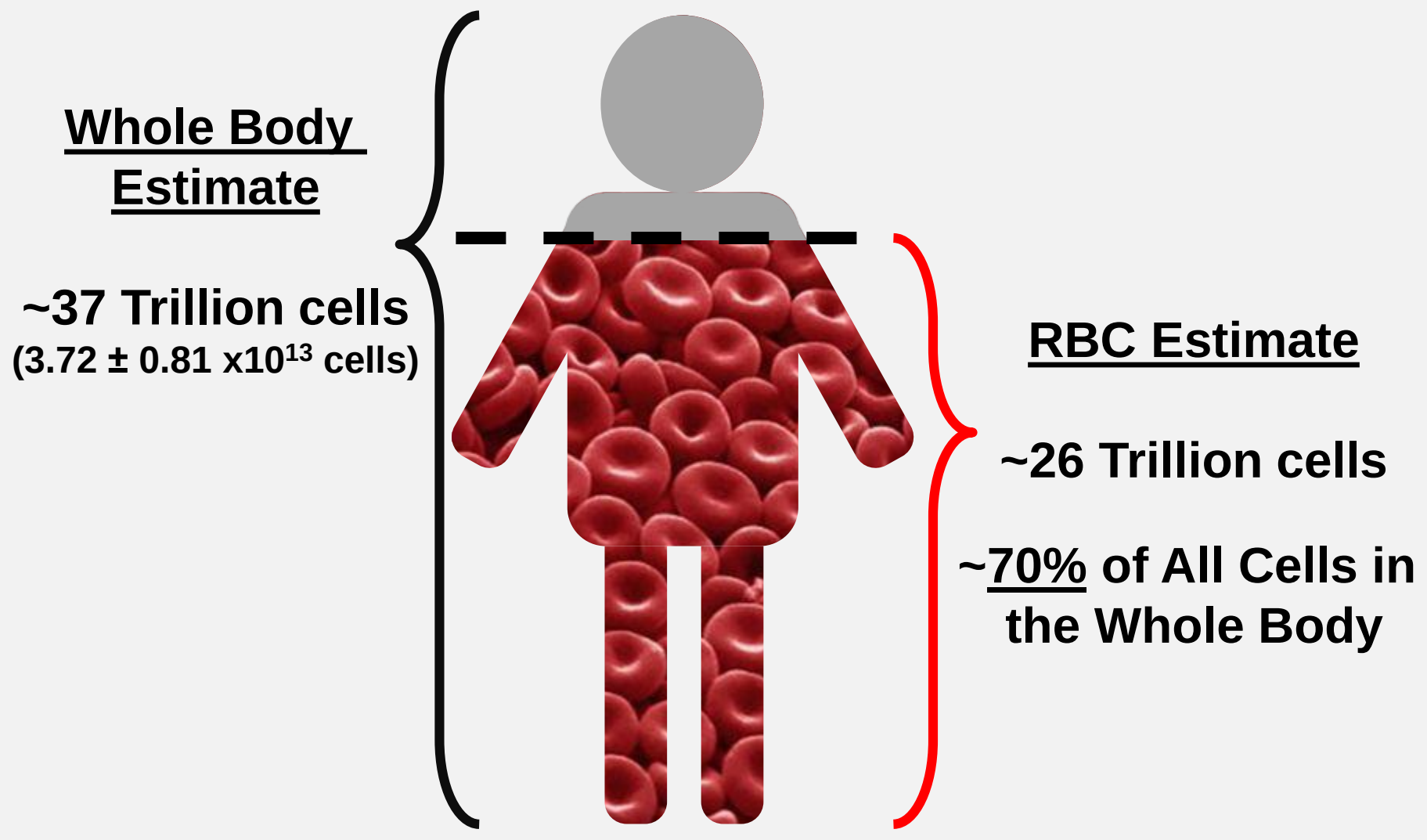
Anemia: Perioperative Risk and Treatment Opportunity

Gregory M. T. Hare, M.D., Ph.D., C. David Mazer, M.D.



Hare GMT, Mazer CD, Anesthesiology 2021

Red Blood Cells are Estimated To Be the Most Numerous Cell in the Human Body



Bianconi Ann Hum Biol. 2013

Primary Function of the Red Blood Cell (RBC): To Supply Oxygen (O_2) to Tissue

The tissue's demand for O_2 governs cardiac output

"The single factor most responsible for the…linkage between metabolic rate and cardiac output is the tissue need for O_2"- **Guyton AC *Am J Physiol* 1973**.

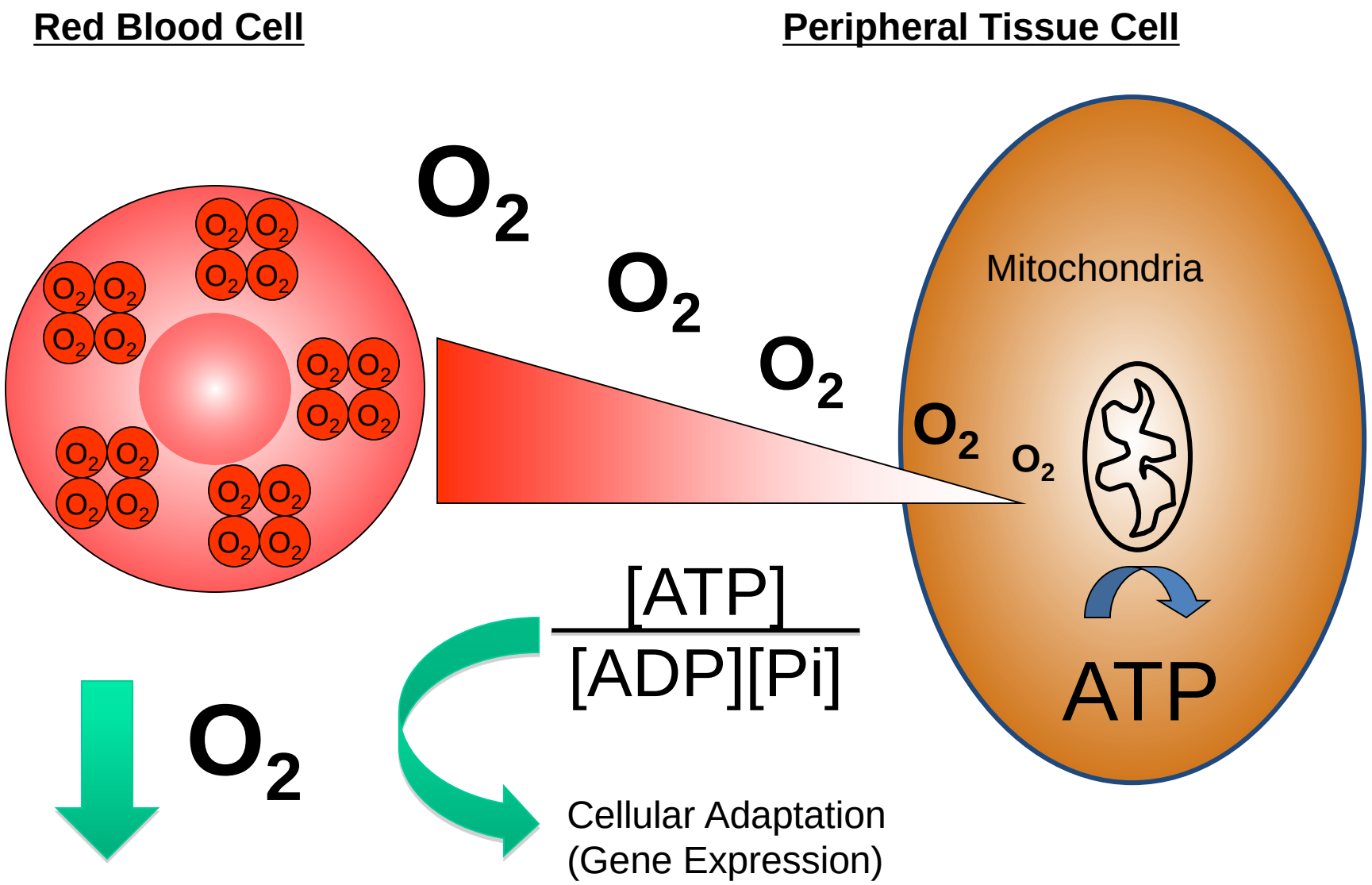
The tissue's demand for O_2 governs tissue blood flow

"O_2 dependence of mitochondrial oxidative phosphorylation is such that mitochondria could function as…tissue oxygen sensors for regulation of …local blood flow"- **Wilson DF. J *Biol Chem* 1988**.

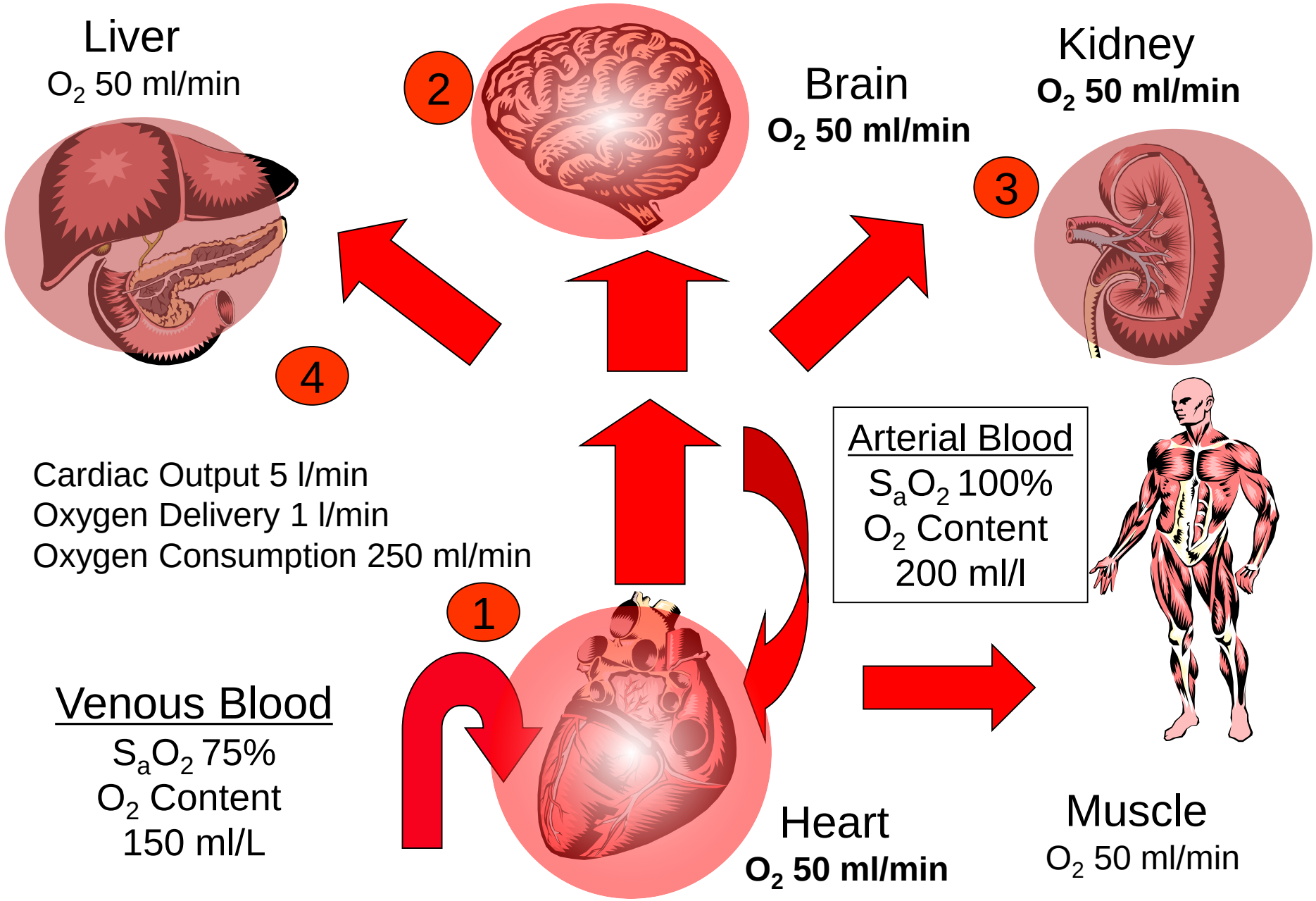
The function of the RBC is to supply O_2 to Tissue

"A general principle of physiology holds that cells precisely regulate their primary function. For Red Blood Cells (RBCs) this primary function is delivery of O_2 to tissues"-**Stamler JS *Ann Rev Physiol* 2005.**

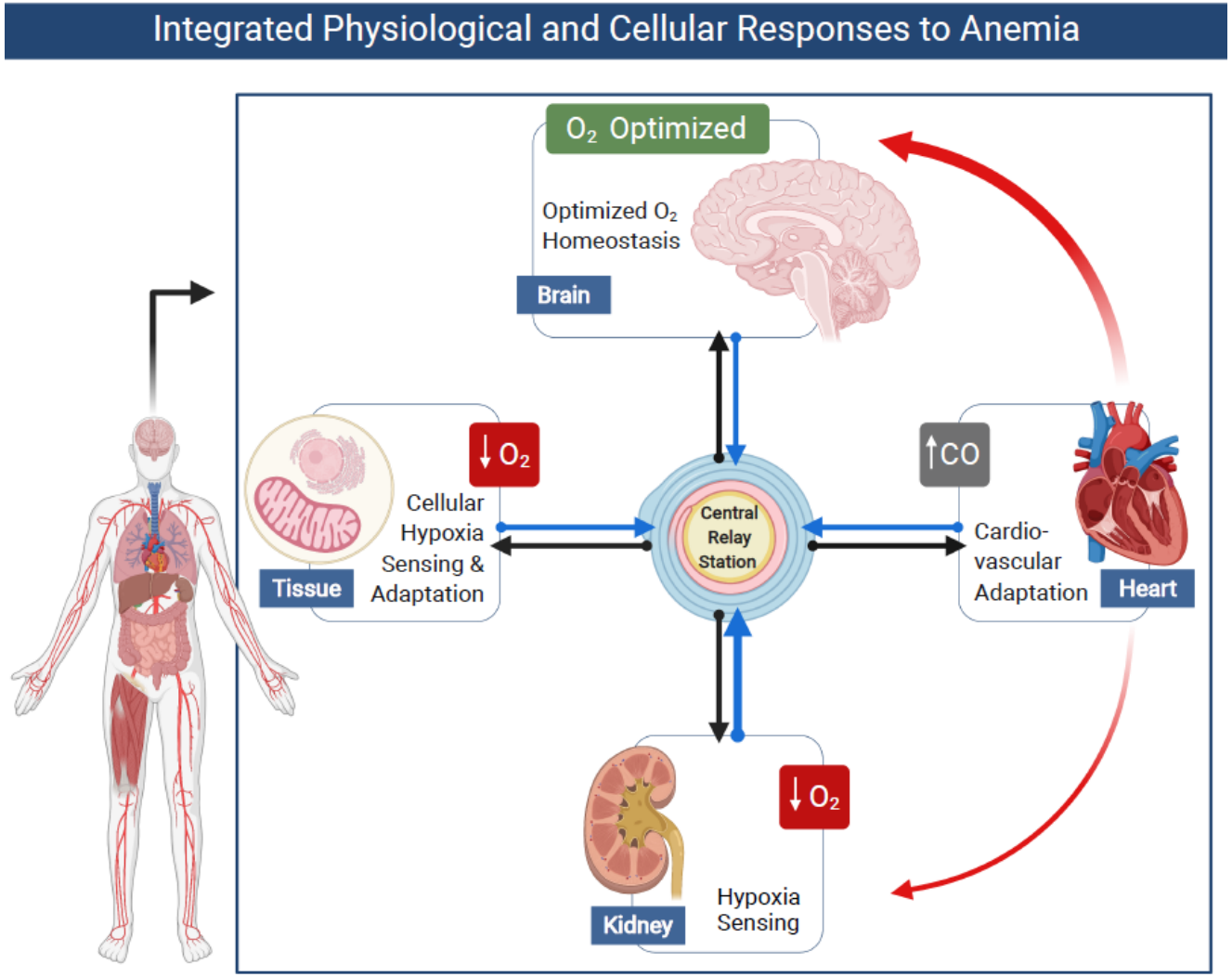
During Anemia O_2 Homeostasis is Jeopardized



Adaptive Cardiovascular Responses During Anemia



Integrative Physiological Responses to Anemia Support Survival



Hare GMT, Mazer CD, Anesthesiology 2021

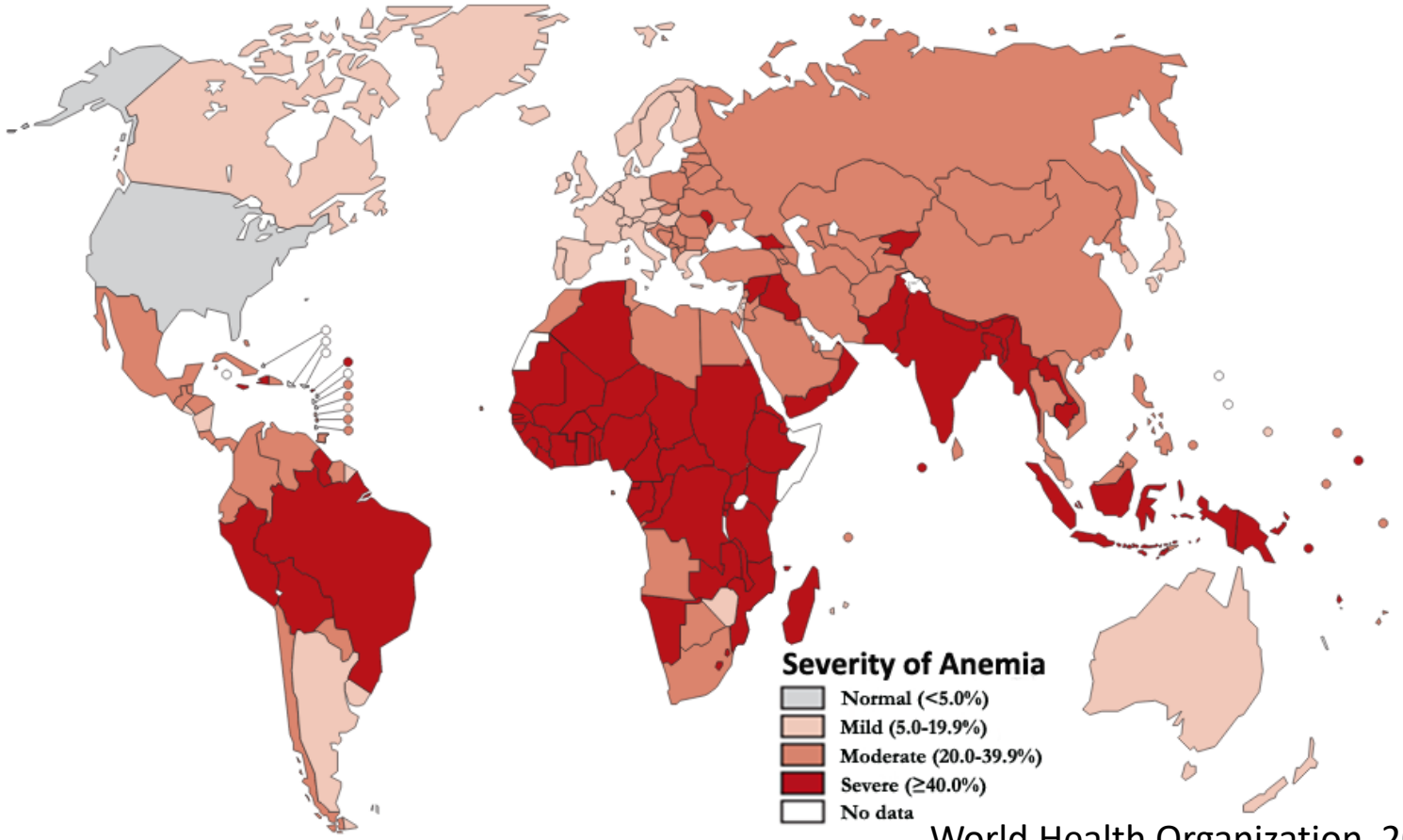
What is the Problem with Anemia?

Anemia is a Critical Global Health Issue

Anemia is a Worldwide Health Problem

- **It is estimated that one third of the global population is affected by anemia (Kassebaum N *et al.*, Blood 2014)**

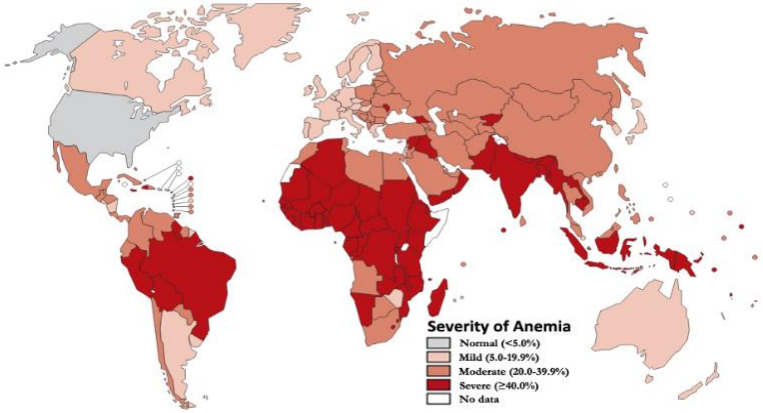
- **Anemia leading cause of disability in children and adolescents. (Global Burden of Disease Pediatrics Collaboration, JAMA 2016)**



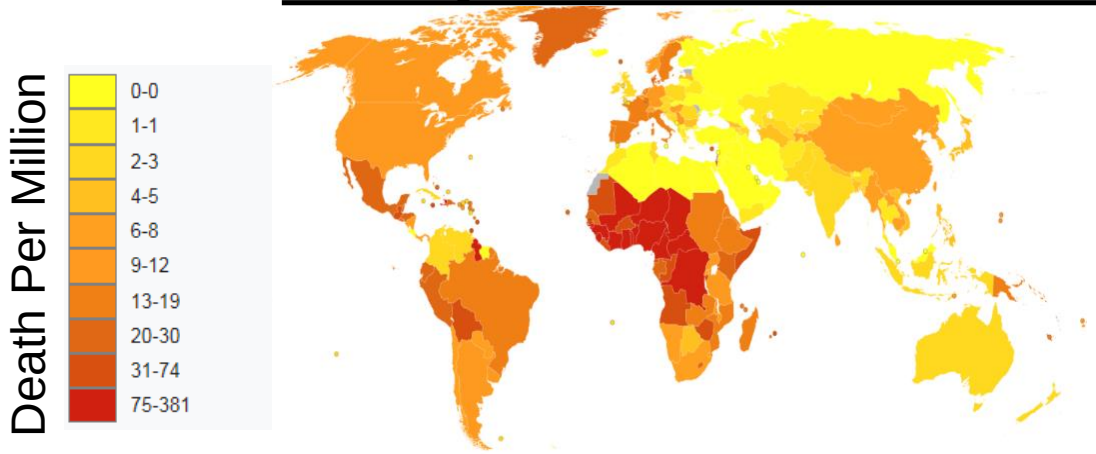
World Health Organization, 2008

Anemia is a Worldwide Health Problem

Prevalence of Anemia, by Severity

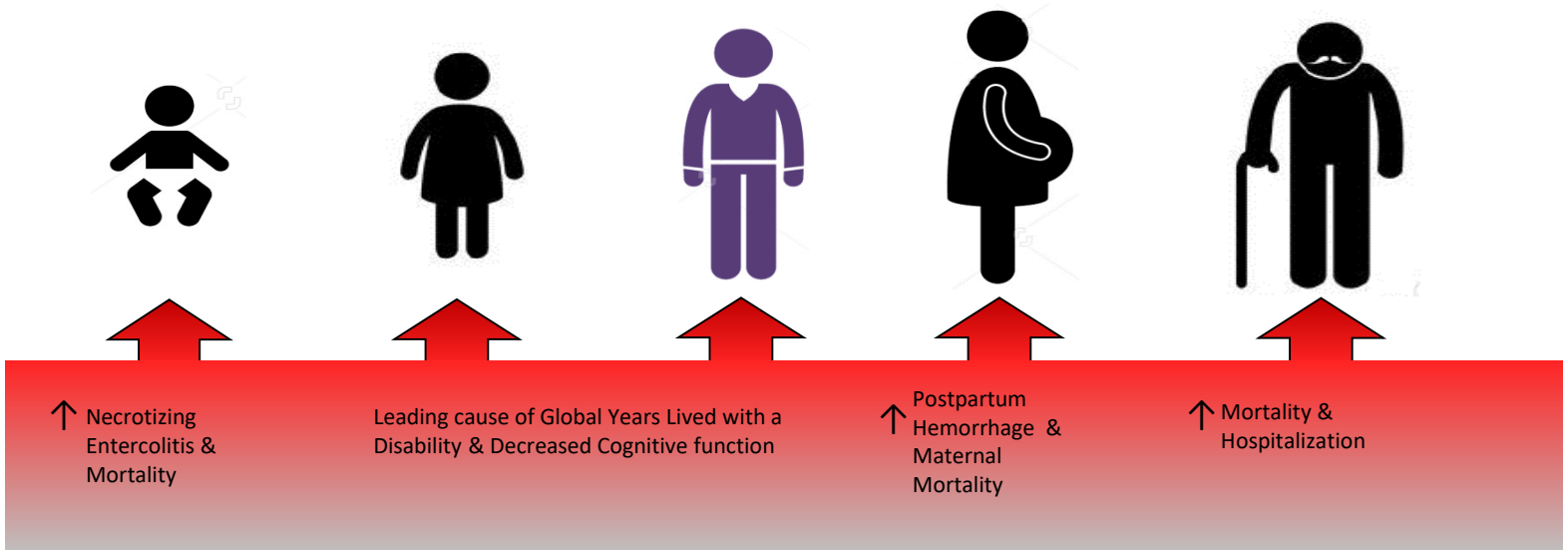


Mortality Attributed to Iron-Deficiency



World Health Organization, 2008, 2012, Kassebaum N, Blood 2014

Anemia Impacts Patients of All Ages



Anemia Is Associated With Serious Adverse Events

1. Patel et al. JAMA *2016.* 2. Global Burden of Disease Pediatrics Collaboration, JAMA *2016*. 3.Sungthong et al., Asia Pacific J Clin Nutr *2002*.
4. Tort et al., BMC Pregnancy & Childbirth, *2015* 5. Penninx et al., Gerontology *2006*. 6. Zakai et al., Arch Internal Med *2005.*

What is the Problem with Anemia?

Perioperative Anemia is Associated with Organ Injury and Increased Mortality

Preoperative Anemia is Associated With Increased Adverse Outcomes after Cardiac Surgery

Systematic review and meta-analysis of 22 studies assessing postoperative outcomes between anemic and non-anemic patients undergoing cardiac surgery

Prevalence of Preoperative Anemia: 20.6% (23,62 4 of 114,277 patients)

Outcome	Odds Ratio (95% CI)	I^2	*P* value
Mortality	2.74 (2.32, 3.24)	69.6%	<0.001
AKI	3.13 (2.37, 4.12)	71.1%	<0.001
Stroke	1.66 (1.29, 2.15)	21.6%	<0.001
Infection	2.65 (1.98, 3.55)	46.7%	<0.001
Blood Transfusion	1.35 (0.92, 1.98)	83.7%	0.12

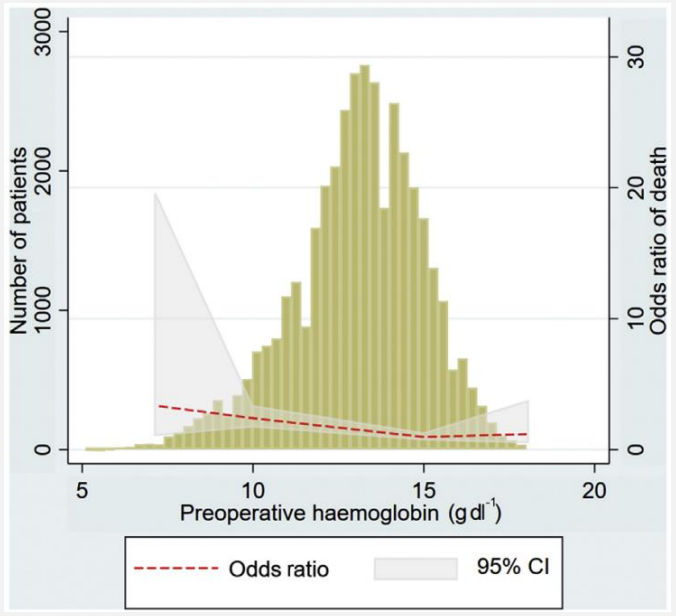
Pandamanabhan H, Ann Thorac Surg 2019

Association of Preoperative Anaemia with Postoperative Morbidity and Mortality

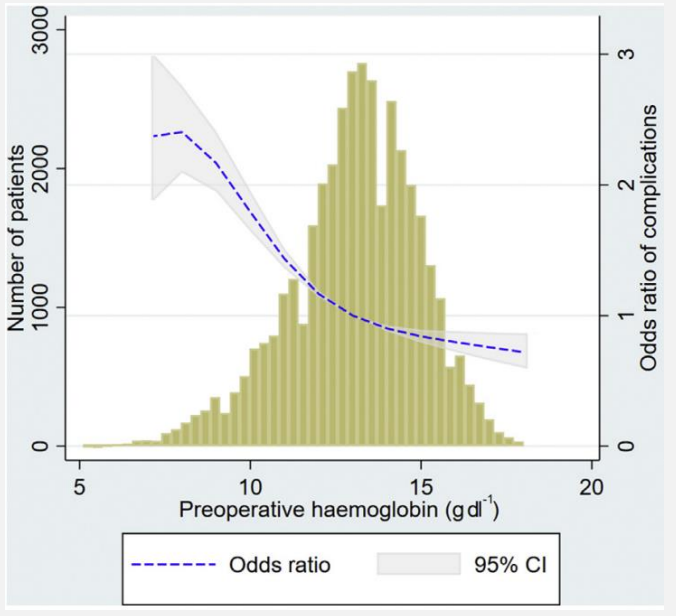
Retrospective analysis of 38,770 patients from 474 hospitals in 27 countries undergoing elective inpatient surgery assessing the impact of anemia on in-hospital (30-day) death and complications

Prevalence of Preoperative Anemia: 30.1% (11,675/38,770 patients)

Relationship Between Preop Hb and 30-day Death



Relationship Between Preop Hb and 30-day Complications



Fowler Br J Anaesth 2018

Anemia Risk In Patients with Acute Hip Fracture

JB&JS OPEN ACCESS

Anemia at Presentation Predicts Acute Mortality and Need for Readmission Following Geriatric Hip Fracture

Gareth Ryan, BSc(Hons), Lauren Nowak, PhD, Luana Melo, PhD, Sarah Ward, MD, MSc, FRCSC, Amit Atrey, MD, MSc, FRCSC, Emil H. Schemitsch, MD, FRCSC, Aaron Nauth, MD, MSc, FRCSC, and Amir Khoshbin, MD, MSc, FRCSC

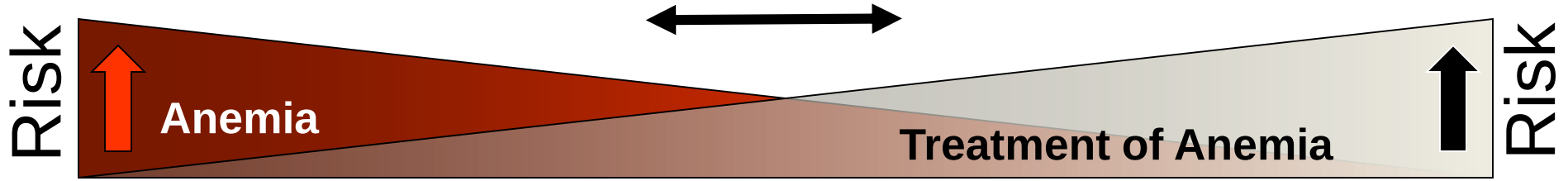
TABLE III Unadjusted Rates of 30-Day Postoperative Complications: Comparison of Non-Anemic and Anemic Groups*

Complication	No. (%) of Total Cohort (N = 34,805)	No. (%) with Normal HCT (N = 12,336)	No. (%) with Low HCT (N = 22,469)	P Value†
Death	1,432 (4.1)	313 (2.5)	1,119 (5.0)	**<0.001**
Readmission	2,989 (8.6)	829 (6.7)	2,160 (9.6)	**<0.001**
MI	570 (1.6)	139 (1.1)	431 (1.9)	**<0.001**
CVA	246 (0.7)	83 (0.7)	163 (0.7)	0.6

*HCT = hematocrit, MI = myocardial infarction, and CVA = cerebrovascular accident. The values are given as the number, with the percentage in parentheses. The percentages in the Complication column are of the total cohort (n = 34,805). †Bold indicates a significant difference between the Normal HCT and Low HCT groups.

JBJS Open 2020

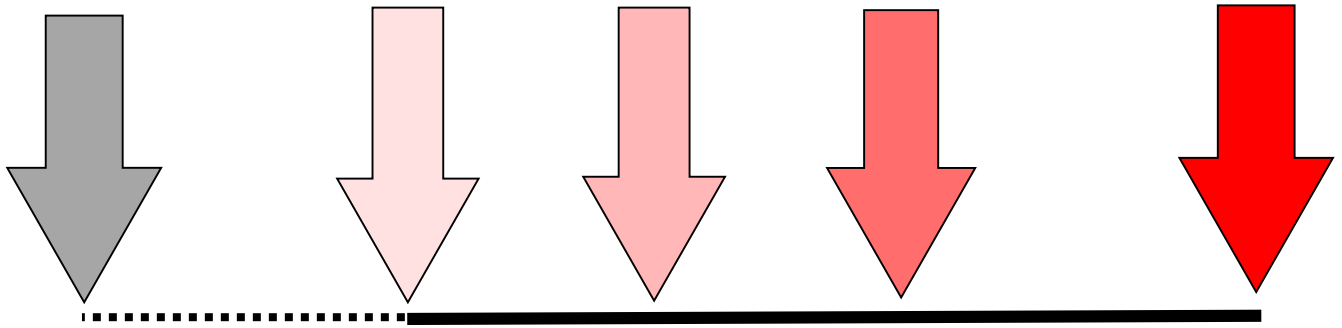
Balancing the Risk of Anemia and Its Treatments



Severe Tissue Hypoxia (~50% mortality)

Anemia Induced Tissue Hypoxia (~Anemic Organ Injury?)

Adequate Hb (~Maintained Tissue Perfusion)



30 $g \cdot L^{-1}$ 50 $g \cdot L^{-1}$ 70 $g \cdot L^{-1}$ 90 $g \cdot L^{-1}$ 100 $g \cdot L^{-1}$

Hemoglobin Concentration

Death ⇐ Organ Injury ⇐ Dysfunction ⇐ Function

Hare GMT, Can J Anesth 2020

“An update on Patient Blood Management in 2023”

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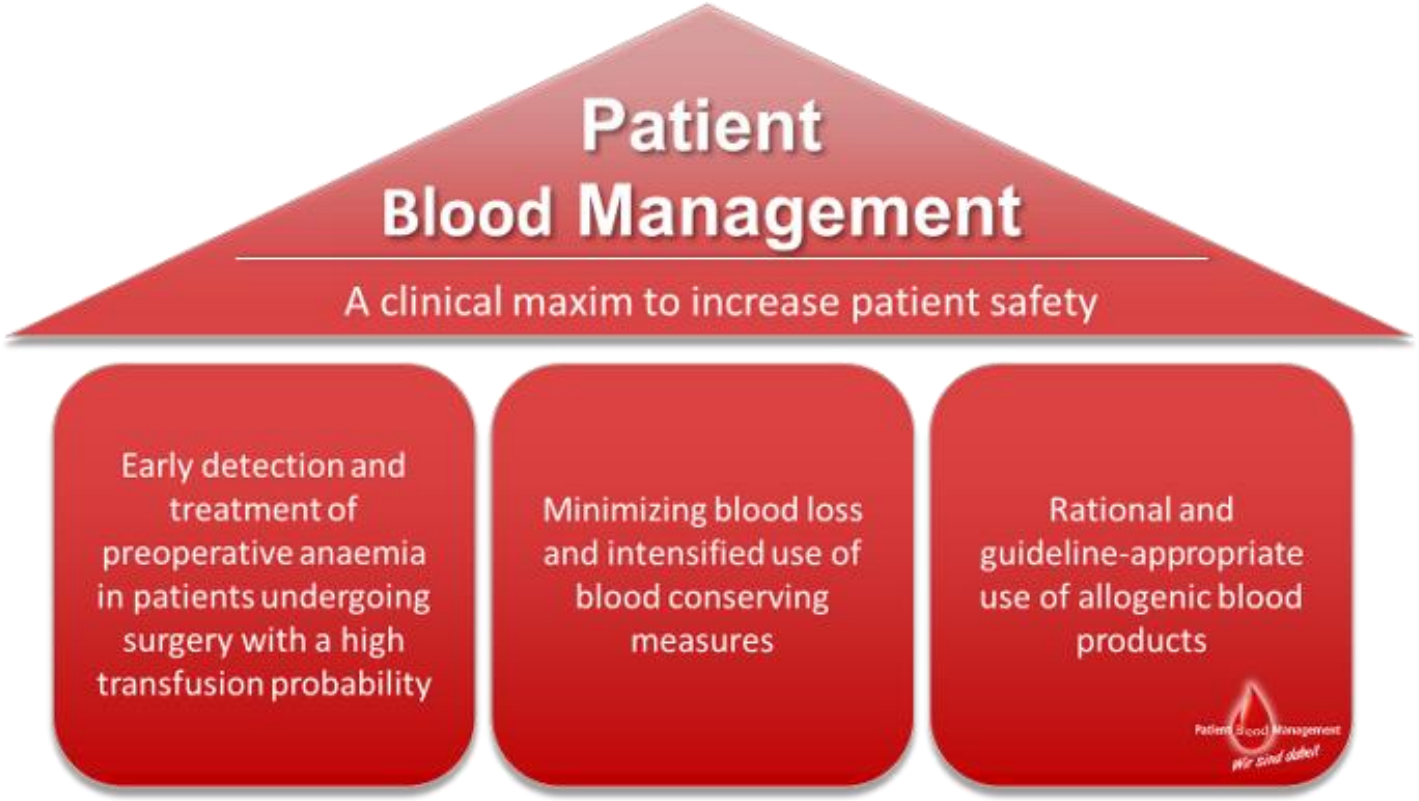
Inspired Care.
Inspiring Science.



Treat Anemia

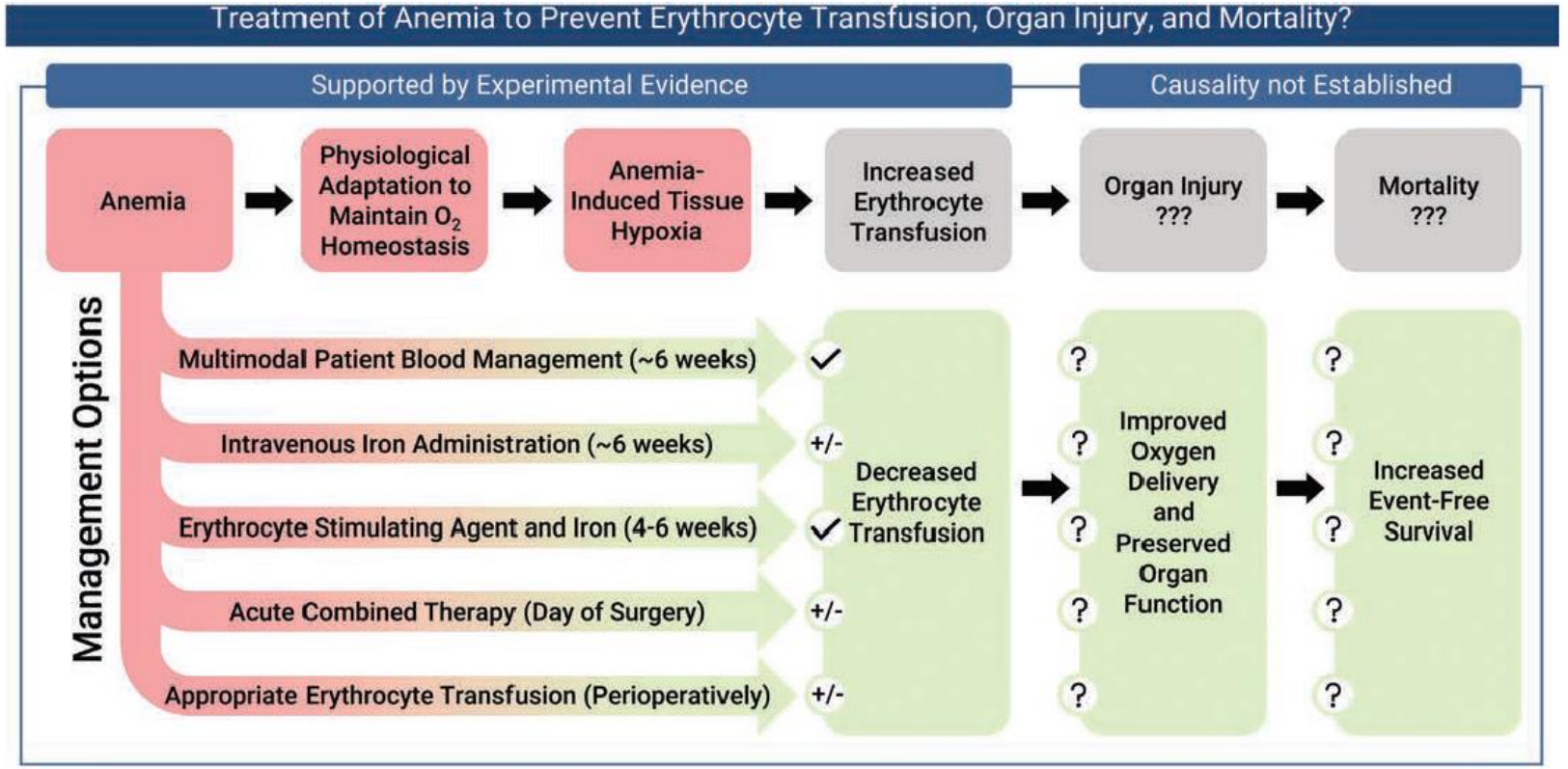
Surgical Technique
Utilize TXA

Appropriate
REstrictive
RBC
Transfusion

VELUT ARBOR ÆVO

Anemia: Perioperative Risk and Treatment Opportunity

Gregory M. T. Hare, M.D., Ph.D., C. David Mazer, M.D.



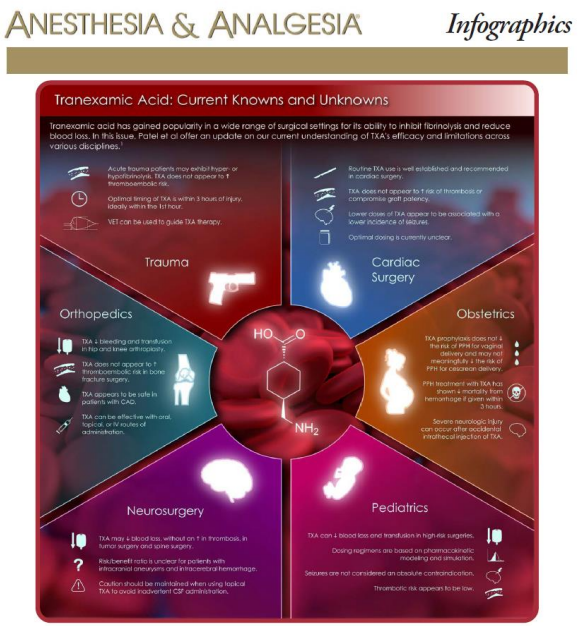
Hare GMT, Mazer CD Anesthesiology 2021

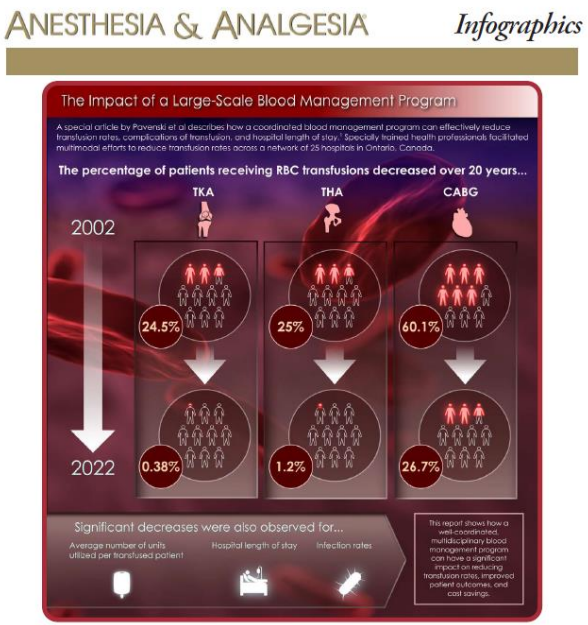
SPECIAL ARTICLE

ONTraC: A 20-Year History of a Successfully Coordinated Provincewide Patient Blood Management Program: Lessons Learned and Goals Achieved

Katerina Pavenski, MD,*†‡ Alanna Howell, RN,*§ C. David Mazer, MD,‖¶#
Gregory M. T. Hare, MD, PhD,‡‖¶# and John Freedman, MD*§‖

Anesthesia & Analgesia Themed Issue Webinar – Patient Blood Management





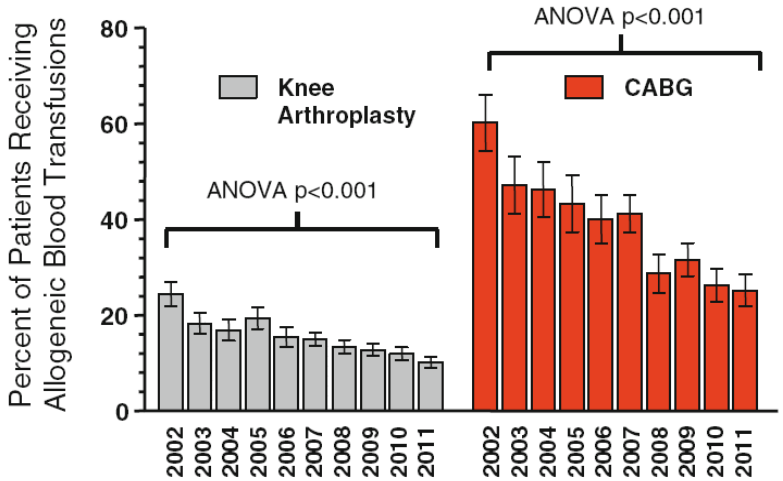
Blood Transfusion- An Expensive and Potentially Hazardous Alternative to Patient Blood Management

A Network of Health Care Practitioners
Coordinators in 25 Hospitals in Ontario

John Freedman

**Professor Emeritus, Medicine &
Laboratory Medicine & Pathobiology
SMH, University of Toronto**

ONTraC Medical Director



Ontario is the ONLY province in Canada to fully fund a Blood Conservation Program.

ONTraC
ontario transfusion coordinators

Freedman J. Transfusion 2008.

ONTraC and Patient Blood Management Team

A Network of Health Care Practitioners
Coordinators in 25 Hospitals in Ontario

Alanna Howell, RN

Manager, Laboratory Medicine

ONTraC Program Manager

Farnoosh Yazdanpanah, RN

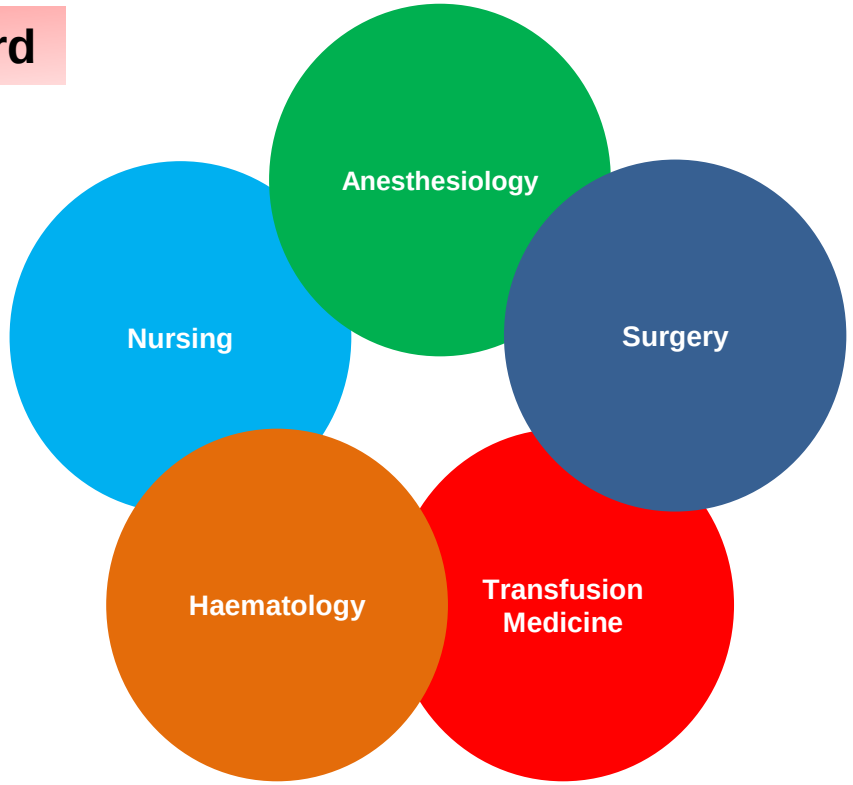
ONTraC Coordinator

Anna Nassis, RN

ONTraC Coordinator

Patient Blood Management at SMH-
A Collaborative Program

Recipient of the 2021 CSTM Ortho Award



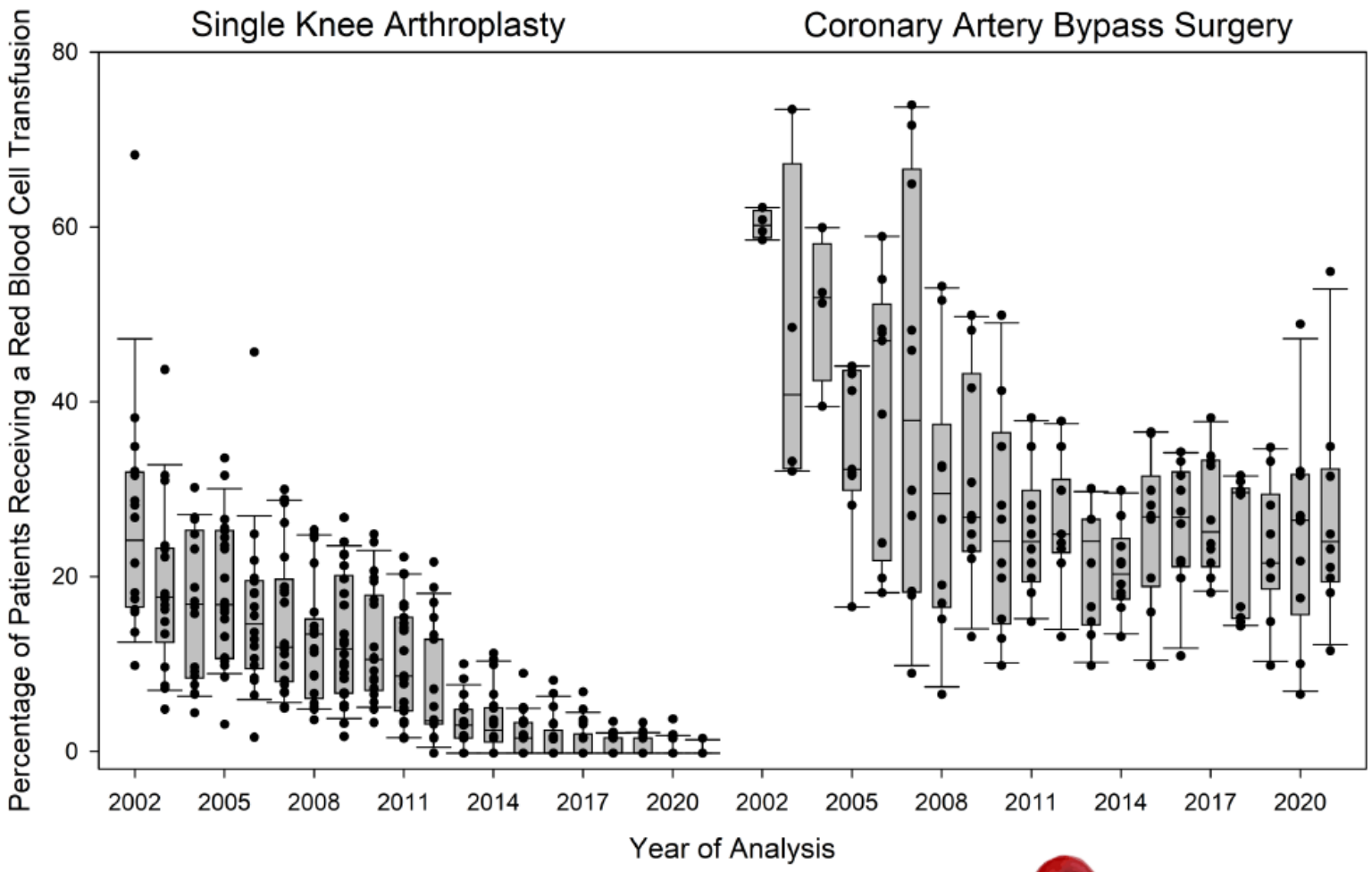
Katerina Pavenski

Associate Professor, Laboratory Medicine & Pathobiology
Director of Transfusion Medicine
SMH, University of Toronto

Ontario Transfusion Coordinator (ONTraC) Program

Pavenski K. Anesth & Analg 2022

RBC Transfusion Rates for TKA and CABG



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The Hemoglobin Threshold for Increased RBC Transfusion is High

Major Joint Arthroplasty
Hb<110 g/L

Cardiovascular Surgery
Hb<130 g/L

Gynecological Surgery
Hb>130 g/L

Table. Relationship Between Preoperative Hemoglobin Concentration (Hb) and RBC Transfusion Rate.

	Percentage of patients transfused during the 2021 data collection period				
	Knee arthroplasty	CABG surgery	Valve surgery	CABG + valve surgery	Gynecological surgery
Preoperative Hb	Transfusion rate, % (n)	Transfusion rate, % (n)	Transfusion rate, % (n)	Transfusion rate, % (n)	Transfusion rate, % (n)
Hb < 100 g/L	100 (3)	100 (9)	75.0 (8)	100 (4)	41.7 (24)
Hb < 110 g/L	5.0 (20)	100 (13)	70.6 (17)	100 (11)	28.8 (59)
Hb < 120 g/L	1.3 (76)	68.2 (44)	70.6 (34)	84.0 (25)	20.0 (115)
Hb < 130 g/L	0.8 (256)	61.2 (113)	67.8 (90)	78.4 (51)	11.8 (228)
Hb > 130 g/L	0.1 (884)	17.5 (456)	20.2 (273)	37.3 (153)	0.9 (216)
Hb > 140 g/L	0 (516)	15.4 (318)	13.1 (176)	30.3 (109)	0 (100)

Abbreviations: CABG, coronary artery bypass graft; Hb, hemoglobin.

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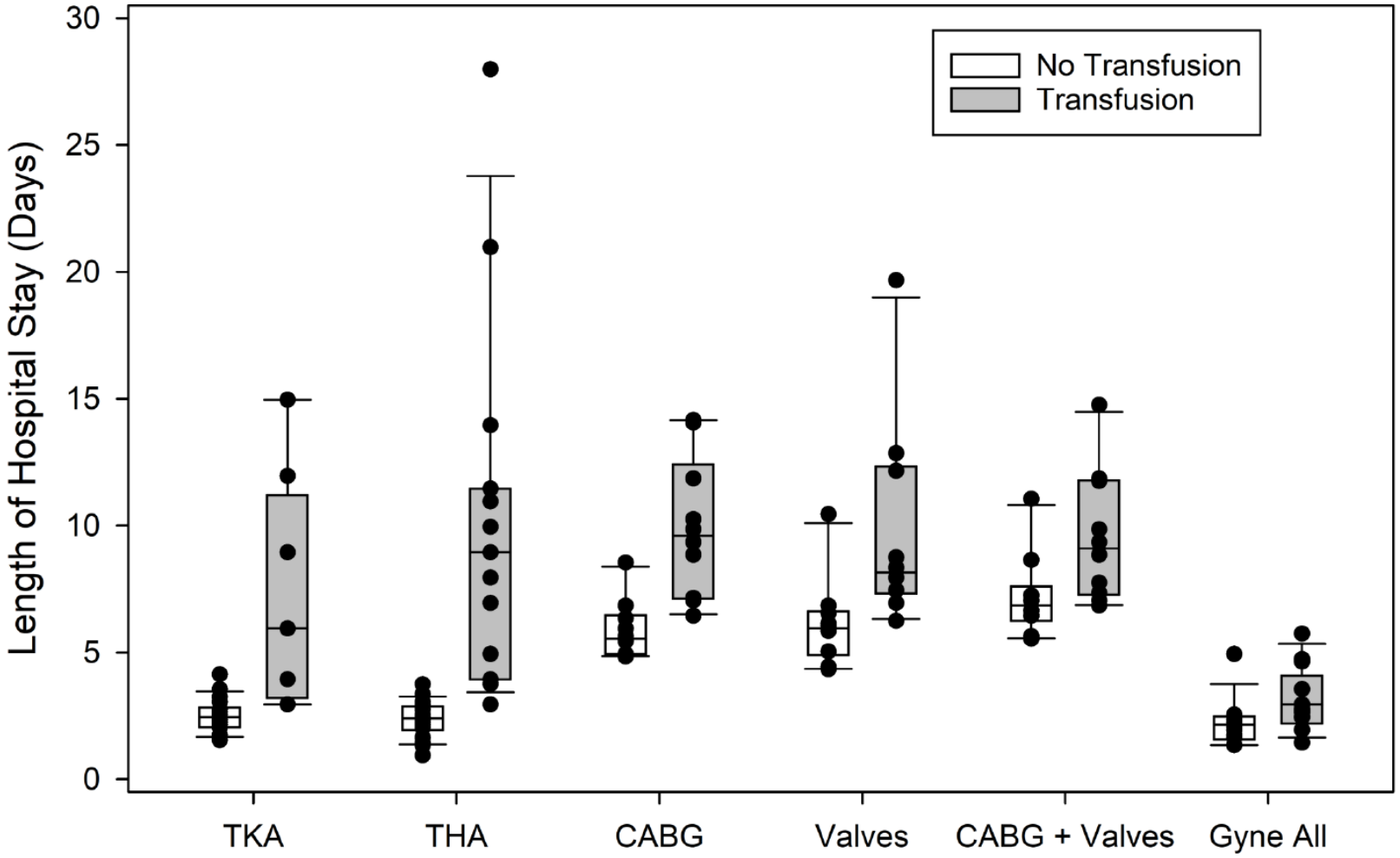
Evidence of Reduced Length of Hospital Stay when RBC Transfusion is Avoided



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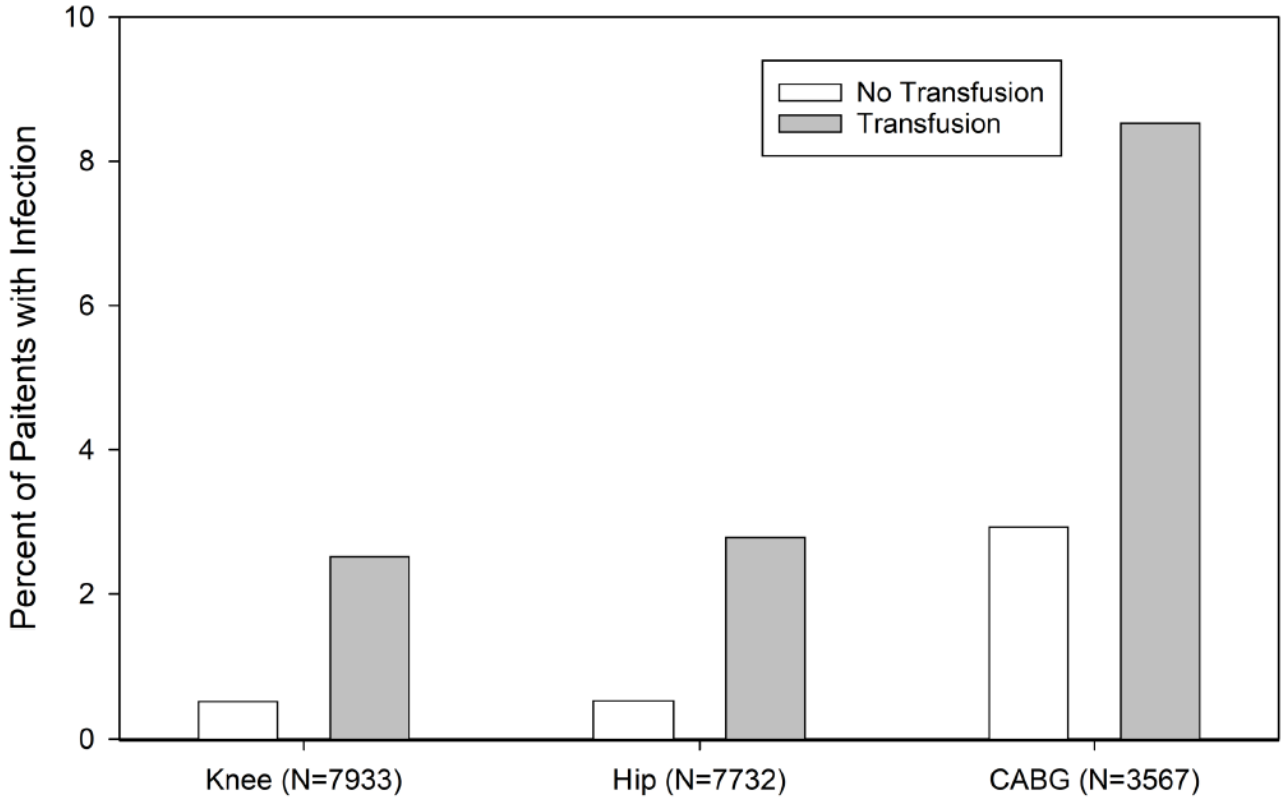
Evidence of Reduced Infection Rates when RBC Transfusion is Avoided



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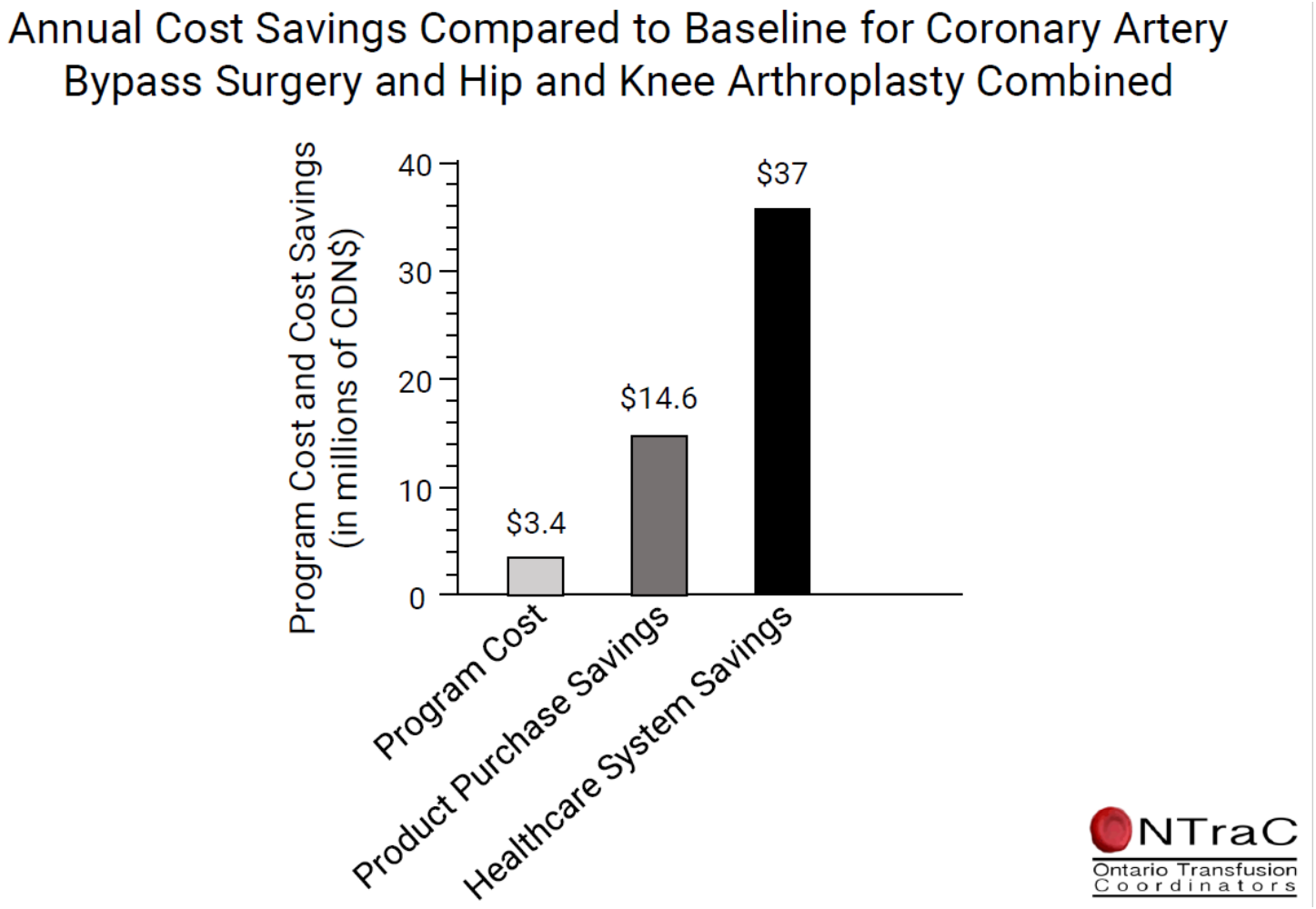
Evidence that PBM Improves Healthcare Efficiency



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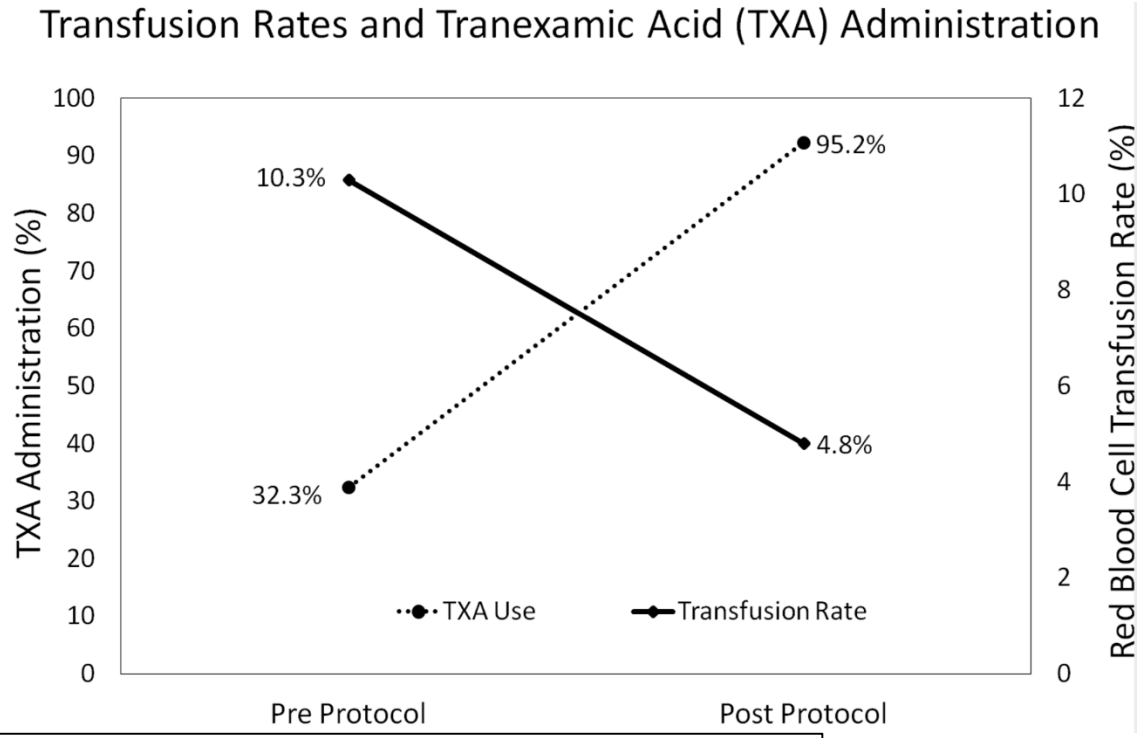
Impact of Implementing TXA Protocol on RBC Transfusion at SMH (2012)

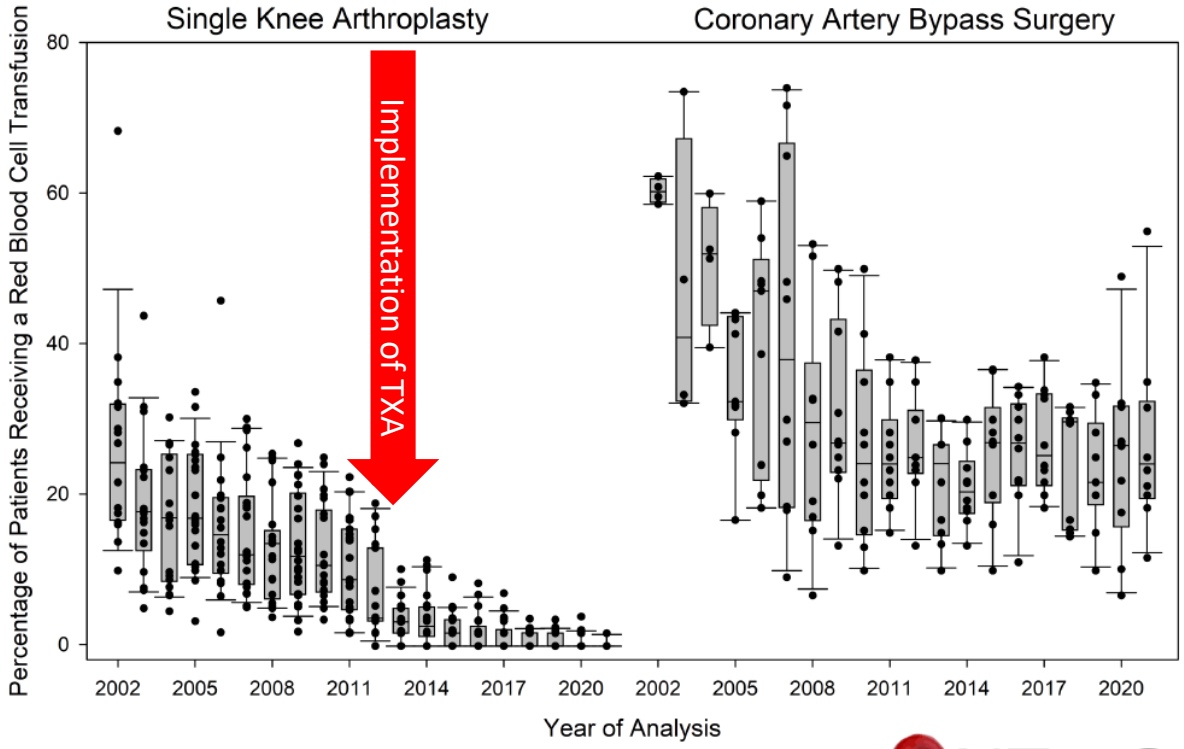
St. Michael's Hospital



Protocol:
TXA was administered (20 mg/kg IV, to a maximum dose of 2 g) to all eligible patients undergoing primary or revision THA or TKA.

Pavenski K et al. Transfusion 2019

RBC Transfusion Rates for TKA and CABG



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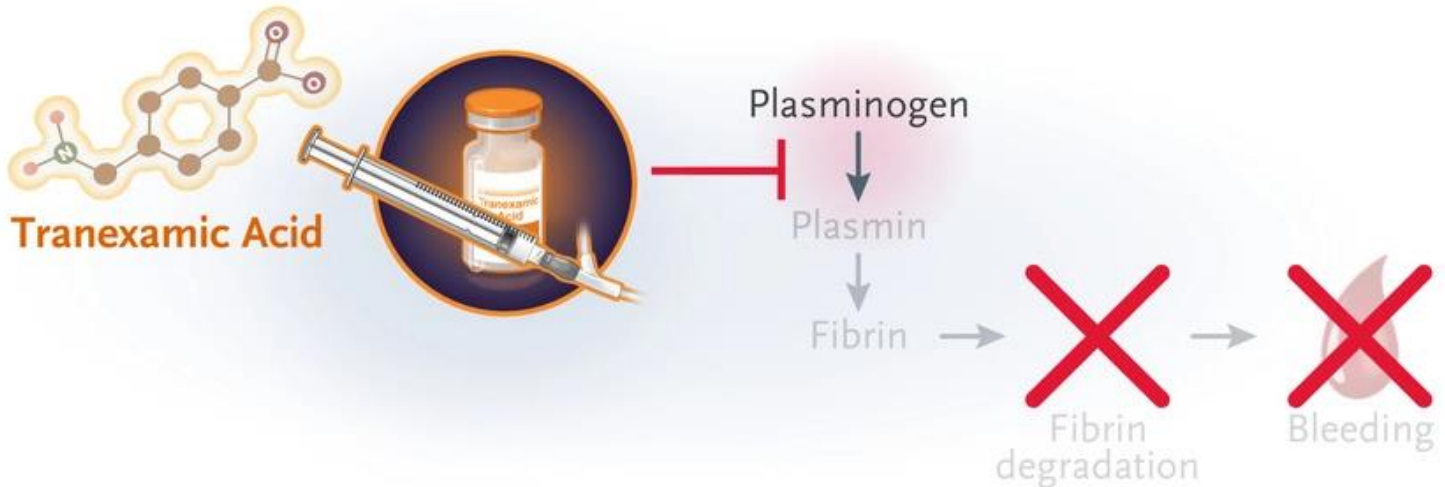
The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

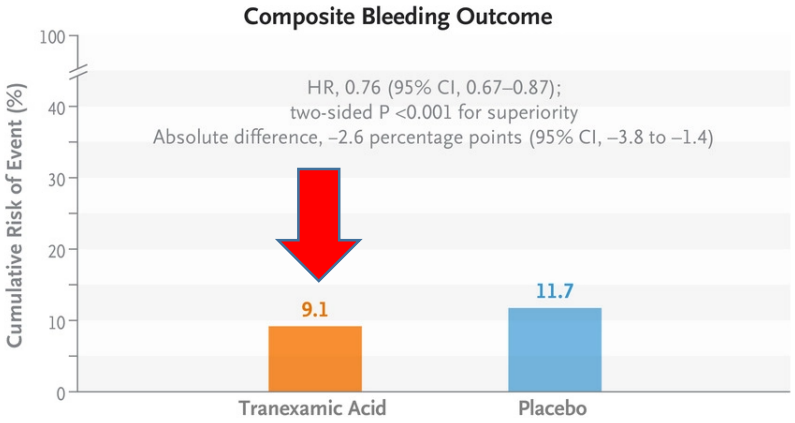
Tranexamic Acid in Patients Undergoing Noncardiac Surgery

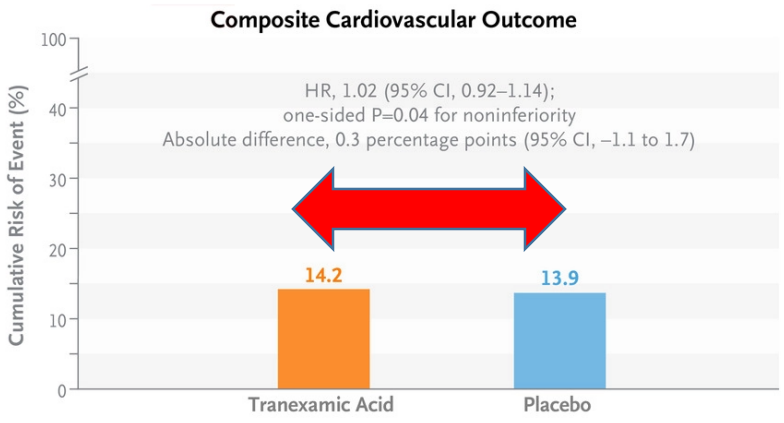
Devereaux PJ et al. DOI: 10.1056/NEJMoa2201171

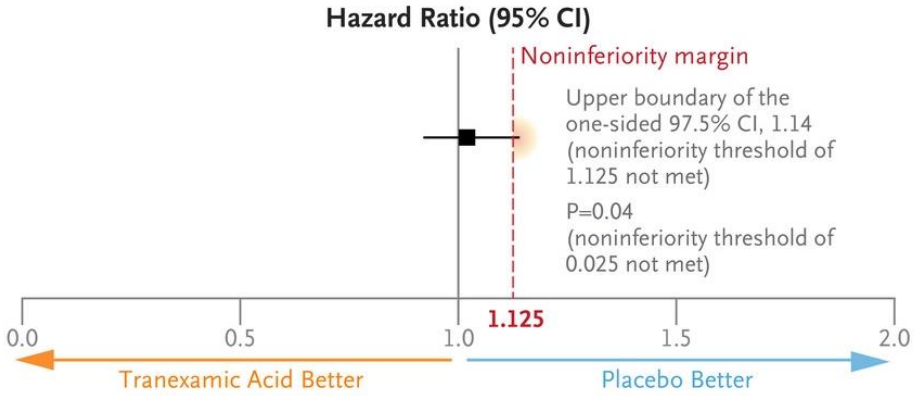


Devereaux PJ NEJM 2022

TXA in Patients Undergoing Non-Cardiac Surgery







Devereaux PJ NEJM 2022

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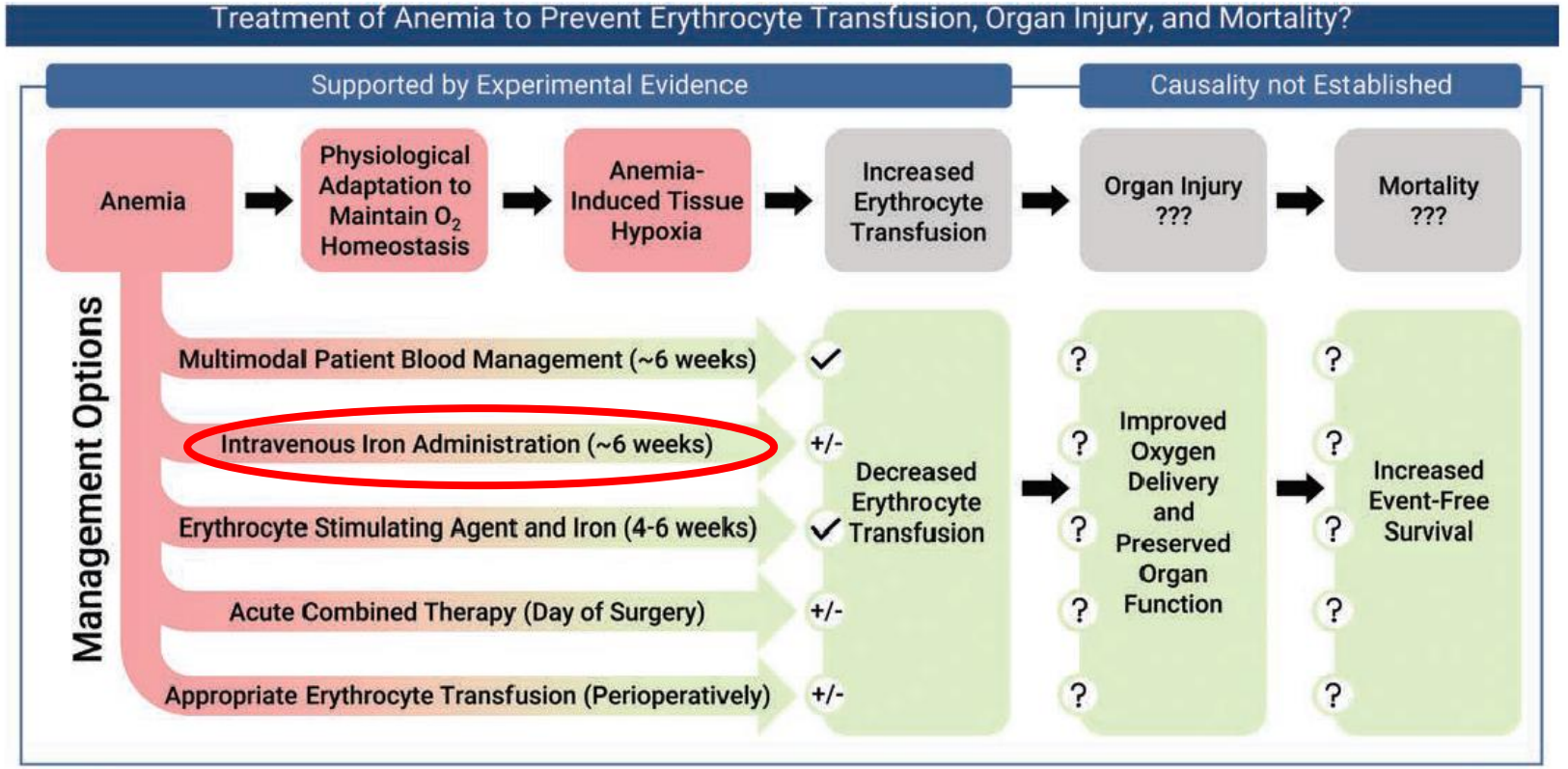
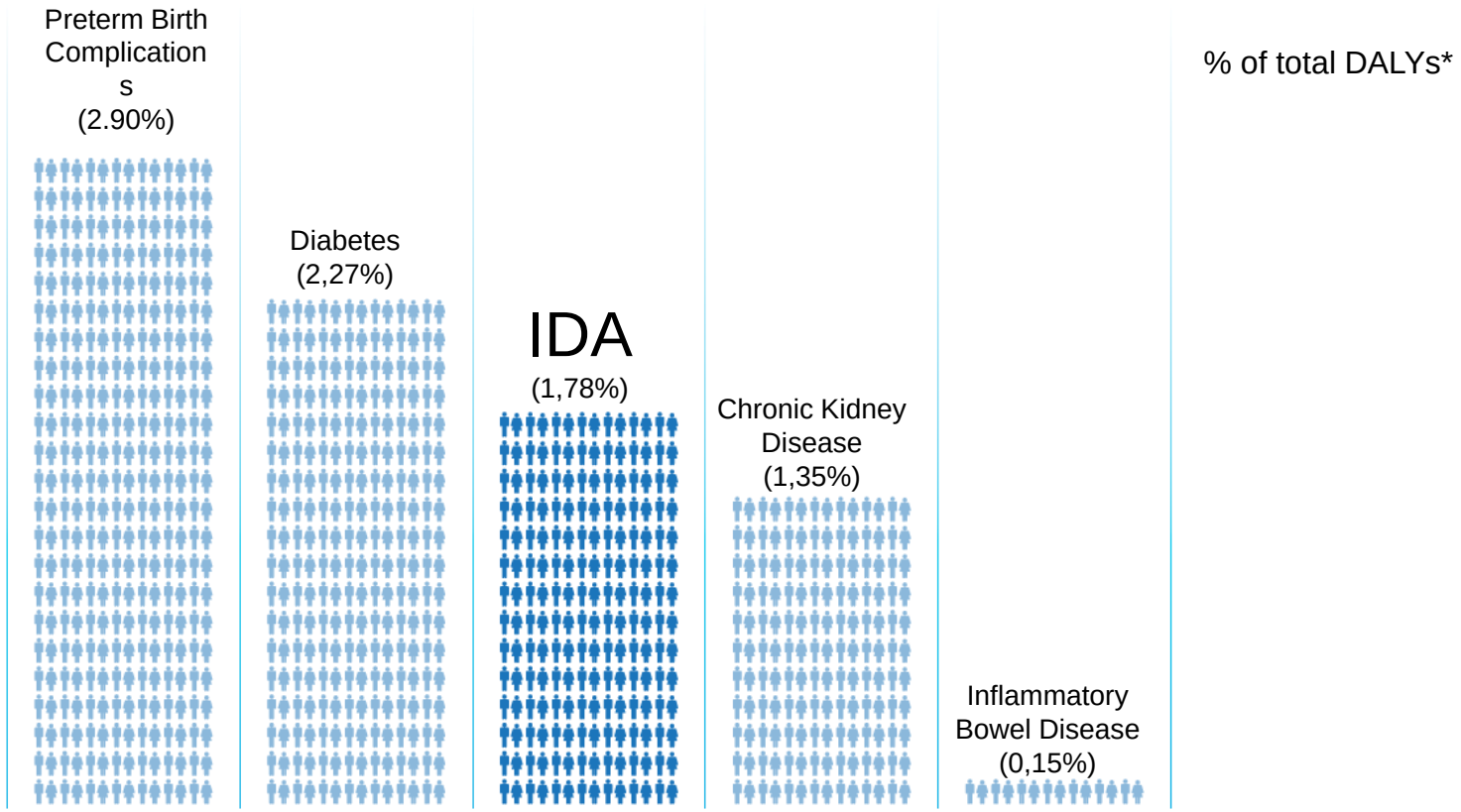


Hare GMT, Mazer CD Anesthesiology 2021

Iron Deficiency Anemia (IDA)
A Major Global Health Concern



Source: Institute of Health Metrics & Evaluation, University of Washington, 2013: http://vizhub.healthdata.org/gbd-compare/

* **Disability-Adjusted Life Year (DALY).** One DALY can be thought of as one lost year of "healthy" life.

Treatment of Iron Deficiency Anemia with IV Iron

A randomized trial of iron isomaltoside versus iron sucrose in patients with iron deficiency anemia

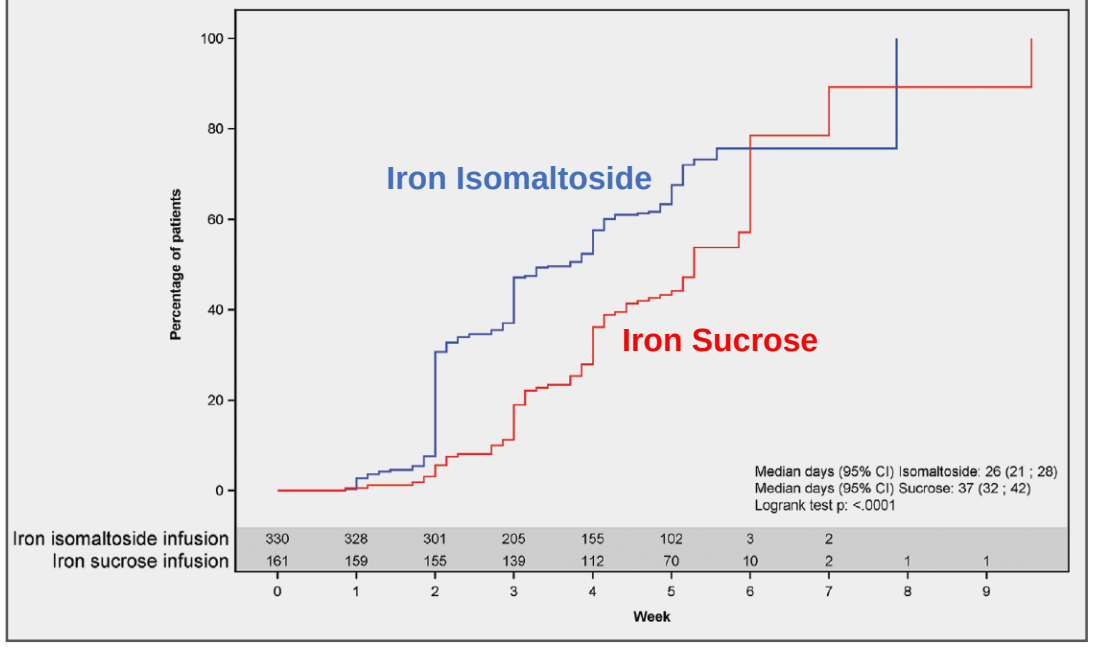
AJH

Patients with iron deficiency anemia → Randomized (2:1)

- **Iron Isomaltoside; N = 330** *(1000 mg, 1500 mg or 2000 mg, depending on body weight and Hb)*
- **Iron Sucrose; N = 161** *(Dose calculated using the Ganzoni formula; max. cumulative dose of 2000mg)*

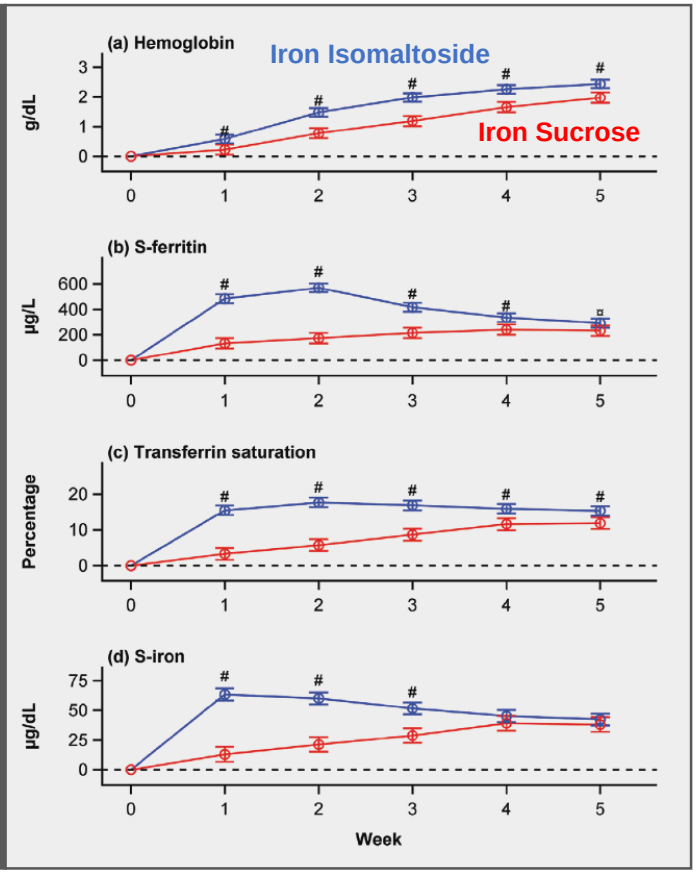
→ Primary Outcome: Proportion of patients with a Hb increase of ≥2g/dL from baseline to any time between 1-5 weeks

Time to Increased Hemoglobin by 20 g/L



Derman R. Am J Hematol 2017; 92: 286-291

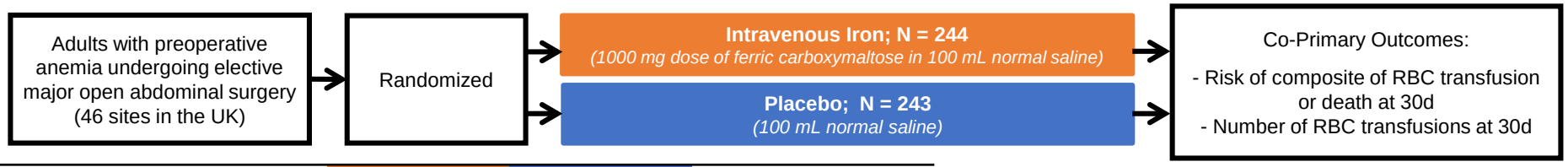
IV Iron Restores Iron Stores and Increase Hb



IV Iron Safely Increased Post-Operative Hemoglobin Concentration and Reduced Hospital Readmission

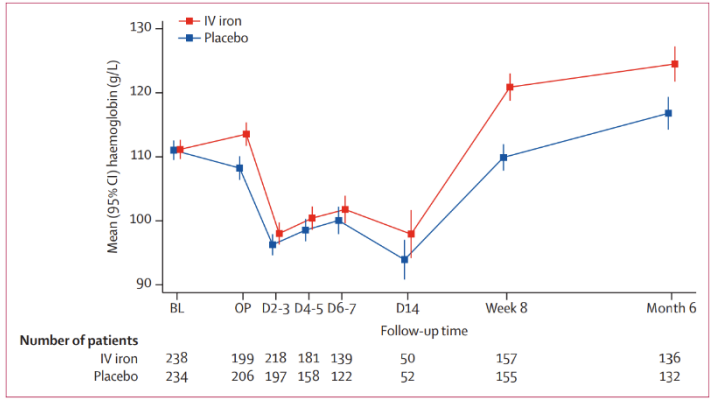
Preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT): a randomized, double-blind, controlled trial

THE LANCET



	IV Iron (n = 244)	Placebo (n = 243)	Iron vs. Placebo (OR, 95% CI)
Blood Transfusion or Death (30d)			1.03 (0.78–1.37)
Composite	69/237 (29%)	67/237 (28%)	
Transfusion	68/237 (29%)	67/237 (28%)	
Death	2/237 (1%)	2/237 (1%)	
ICU Length of Stay	2 (0–3)	1 (0–3)	--
Hospital Length of Stay	9 (7–14)	9 (5–14)	--
Mortality at 6 months	12/238 (5%)	10/236 (4%)	1.19 (0.52 to 2.70)
Readmission			
Discharge to 8 weeks	31/234 (13%)	51/234 (22%)	0.61 (0.40 to 0.91)
Discharge to 6 months	58/227 (26%)	73/223 (32%)	0.78 (0.58 to 1.04)

IV Iron Increased Post-Operative Hb



Richards T. Lancet 2020; 396: 1353-61

Impact of Treating Iron Deficiency…on Outcomes After Prolonged ICU Stay

Treatment: 1 g ferric carboxymaltose when hepcidin <20 ug/L)
Background: Hepcidin is low when Hypoxia Inducible Factor (HIF) is stabilized

Probability of Survival

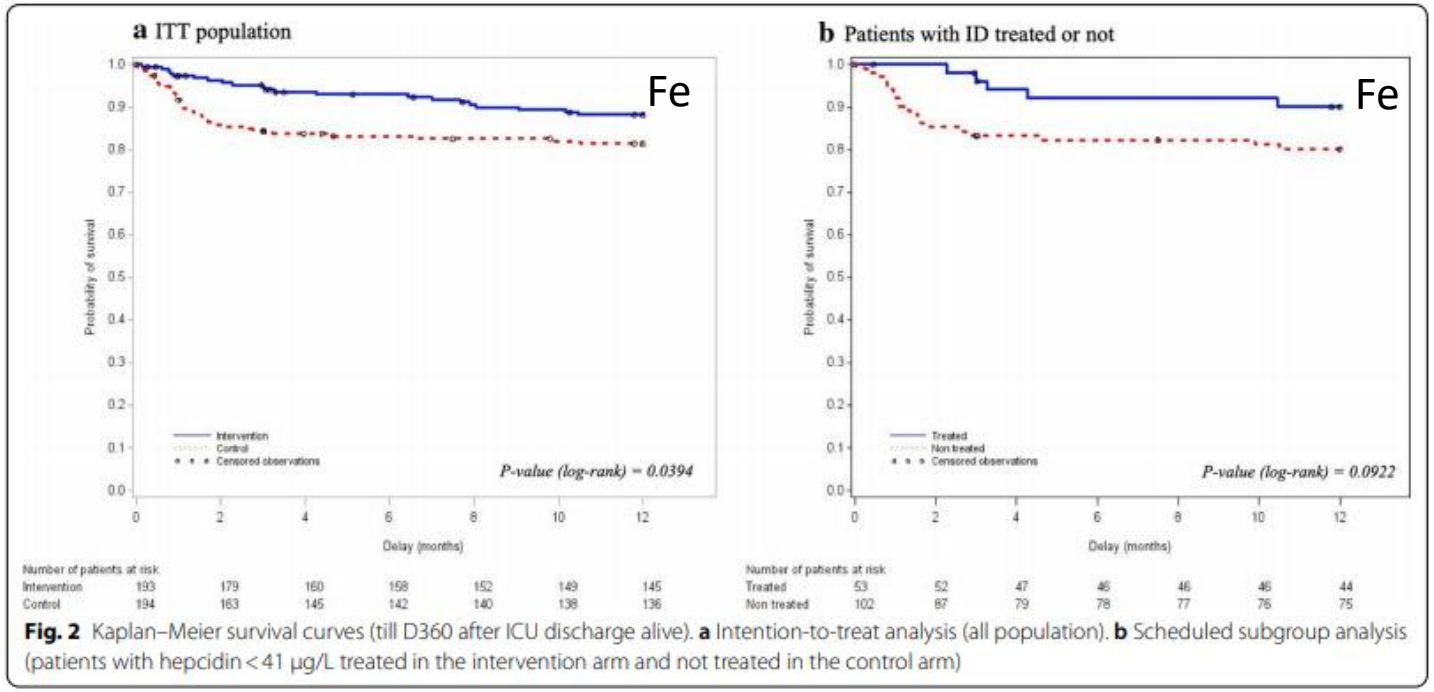
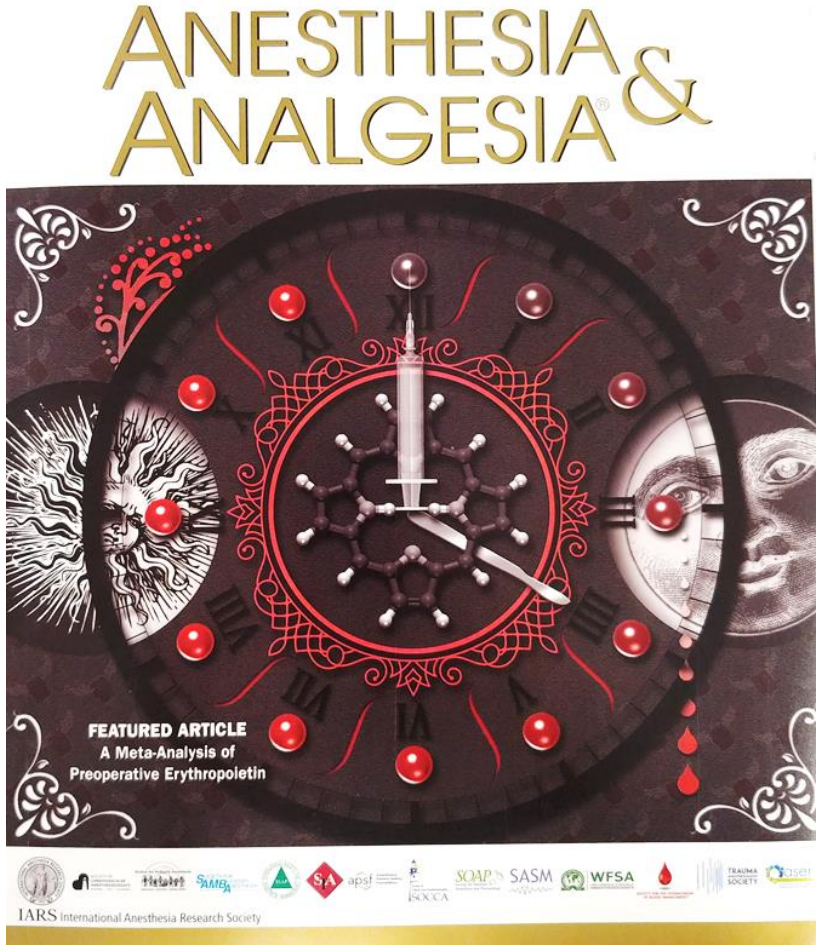


Fig. 2 Kaplan–Meier survival curves (till D360 after ICU discharge alive). **a** Intention-to-treat analysis (all population). **b** Scheduled subgroup analysis (patients with hepcidin < 41 µg/L treated in the intervention arm and not treated in the control arm)

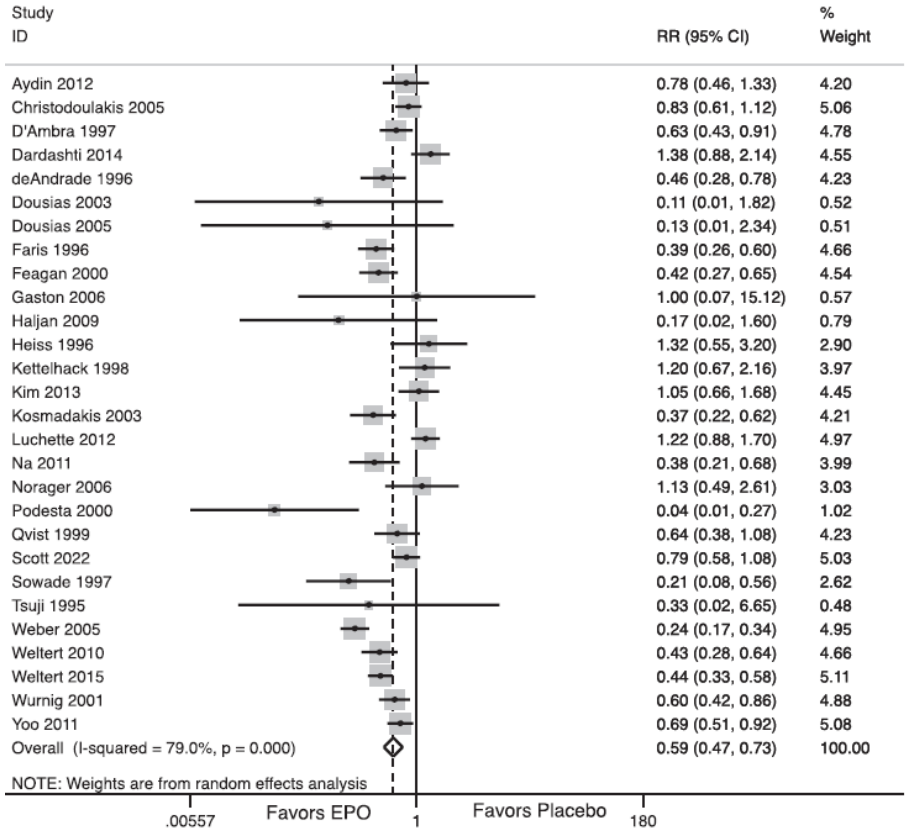
Death at 90 Days:
Treated 16/201 (8.0) vs. Untreated 33/198 (16.7), p< 0.008

Lasocki et al Crit Care 2021

EPO as a Strategy to Reduce Perioperative RBC Transfusion



Red Blood Cell Transfusion



OR (95% CI) = 0.59 (0.47, 0.73)

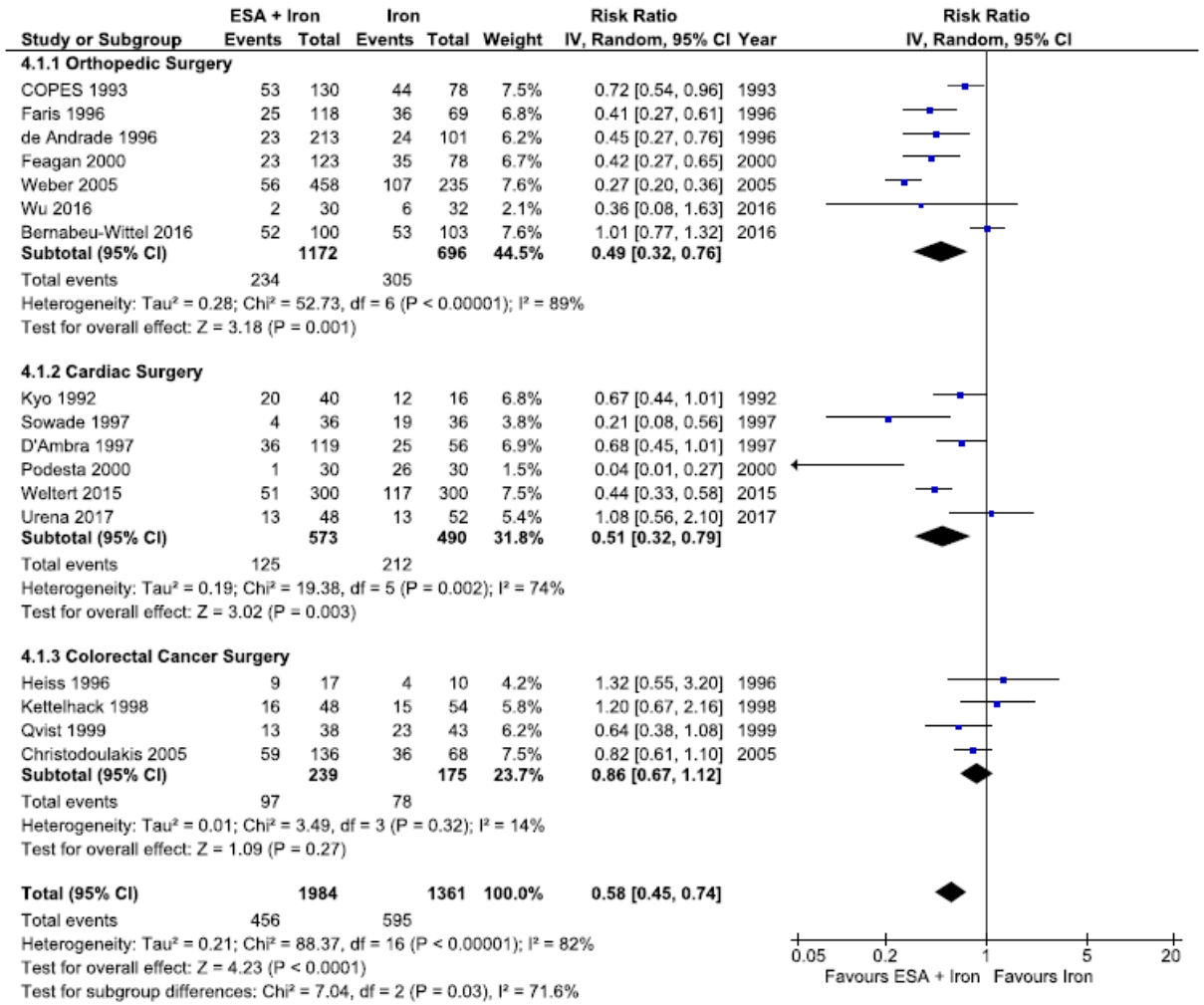
Cho Anesth Analg 2019

Efficacy and safety of erythropoietin and iron therapy to reduce red blood cell transfusion in surgical patients: a systematic review and meta-analysis

Orthopedic Surgery
RR: 0.49 [0.32, 0.76]

Cardiac Surgery
RR: 0.51 [0.32, 0.79]

Colorectal Cancer Surgery
RR: 0.86 [0.67, 1.12]



Kei T. Can J Anesth 2019

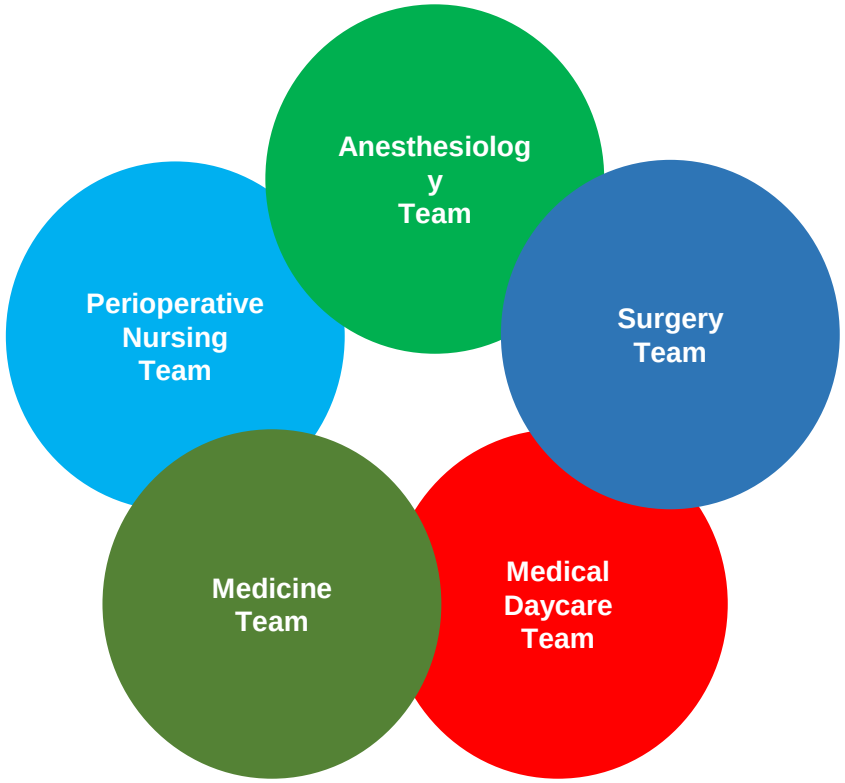
Teamwork to Build a New Infusion Clinic

Skilled Healthcare Professionals

Francis + Balraj + Many Others

+

Resources



20 months-40 Clinics – ~500 Patients Treated

Perioperative Blood Management-
Center of Excellence at SMH

Surgical Referral

Pre-Admission Assessment

Diagnosis of Anemia

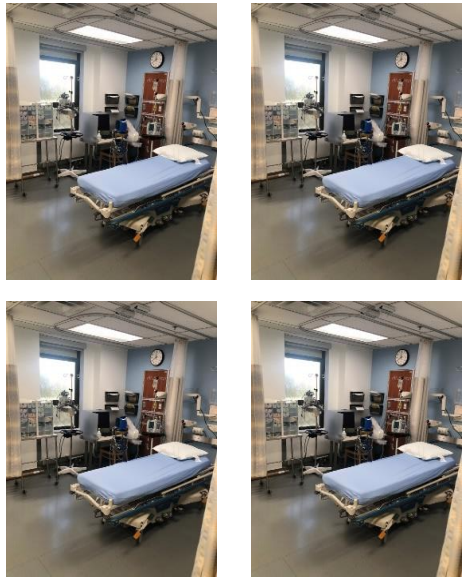
Medical Referral

Treatment of Anemia

Diagnosis and Treatment of Depression

Diagnosis and Treatment of Acute and Chronic Pain

Diagnosis and Treatment of Respiratory Outcomes



Improved Patient Outcomes and Experience

What is the Problem with RBC Transfusion?

Transfusion is “Life Saving” but has been Associated with Adverse Outcomes and Death?

Military History of RBC Transfusion for Wound Shock
Liberal (WWI) vs. Restrictive (Early WWII)

THE TRANSFUSION OF WHOLE BLOOD:
A SUGGESTION FOR ITS MORE FREQUENT EMPLOYMENT IN WAR SURGERY.
BY
L. BRUCE ROBERTSON, B.A., M.B. TORONTO,
CAPTAIN C.A.M.C.,
JUNIOR ASSISTANT SURGEON, HOSPITAL FOR SICK CHILDREN, TORONTO, CANADA.

Battle of the Somme

~60,000 casualties on the first day

"treatment (with) …intravenous …normal saline …was found most disappointing."

"One week after the Somme battle began , Bruce Robertson's article on blood transfusion appeared in the *BMJ"*

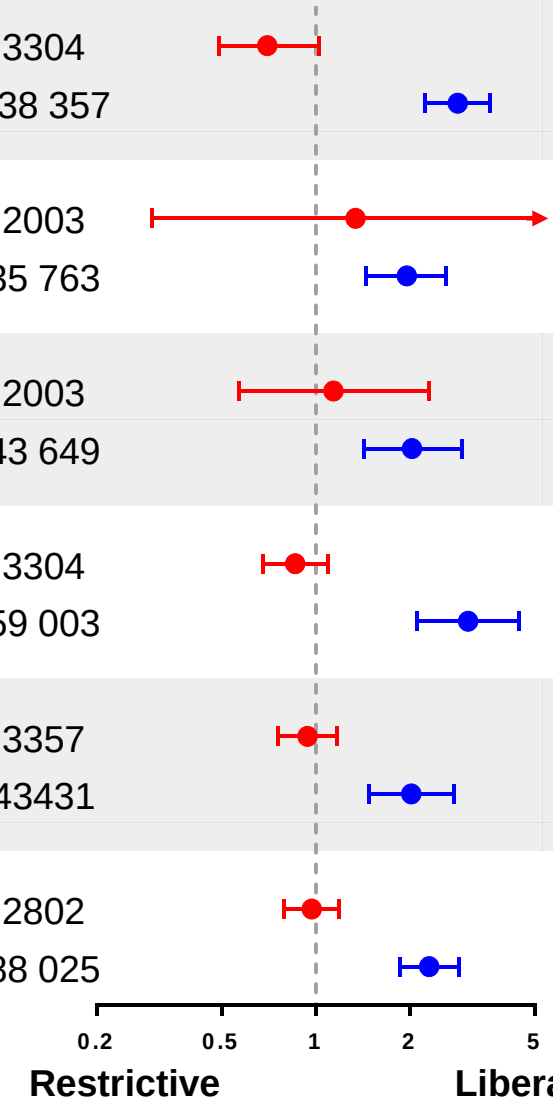
"Blood transfusion came to play a key role in saving soldiers suffering from wound shock."

"World War I experiences led to the universal adoption of blood typing to select blood donors"

1) L Bruce Robertson, BMJ 1916; 2) Pelis K, J Hist Med Al Sci 2001
3) Pinkerton PH, Transf Med Rev 2008.

Discrepancy Between Observational study and RCT Evidence for Transfusion Trials

Outcome	Study	*N*	Participants	Odds Ratio (95% CI)	*P* Value
Mortality	Cardiac RCT	5	3304	0.70 (0.49–1.02)	0.06
	Observational	19	138 357	2.84 (2.23–3.61)	<0.0001
Myocardial Infarction	Cardiac RCT	1	2003	1.34 (0.30– 6.02)	0.7
	Observational	8	35 763	1.95 (1.45–2.61)	<0.0001
Stroke	Cardiac RCT	1	2003	1.14 (0.57- 2.30)	0.71
	Observational	7	43 649	2.03 (1.42–2.92)	<0.0001
AKI	Cardiac RCT	5	3304	0.86 (0.68–1.09)	0.22
	Observational	14	59 003	3.06 (2.10–4.46)	<0.0001
Pulmonary	Cardiac RCT	6	3357	0.94 (0.76–1.17)	0.58
	Observational	7	43431	2.02 (1.48–2.75)	<0.0001
Infection	Cardiac RCT	4	2802	0.97 (0.79–1.19)	0.75
	Observational	11	88 025	2.30 (1.85–2.86)	<0.0001



Patel NN Lancet Haematol 2015

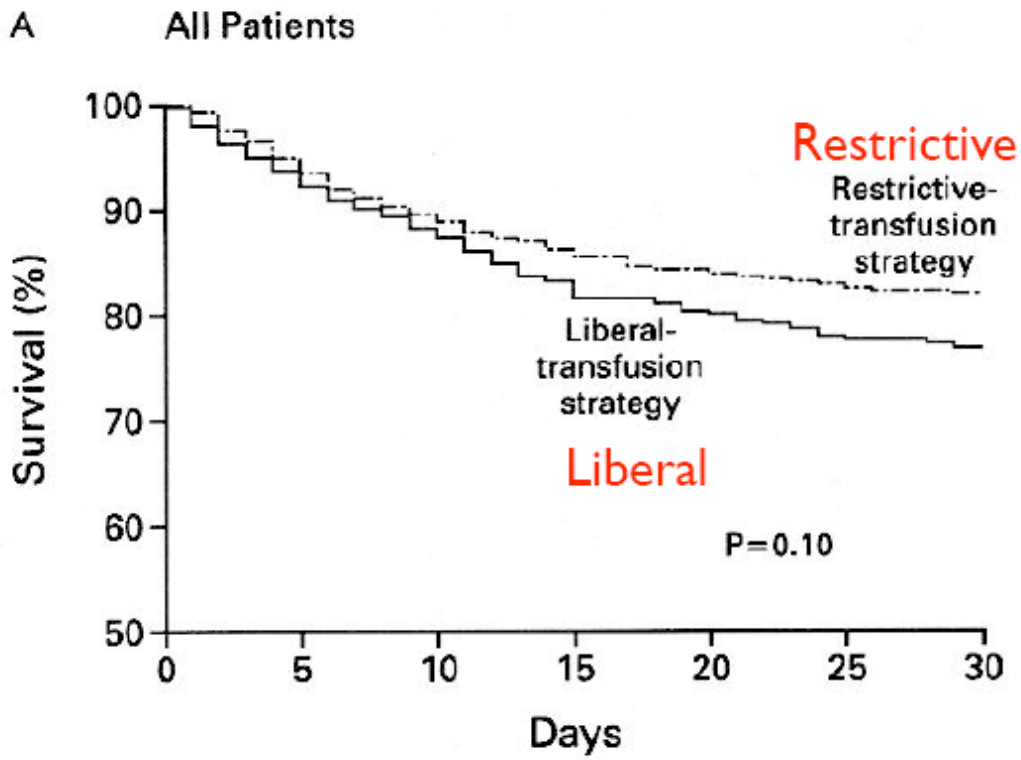
TRICC Trial Demonstrated That it May be Safe To Reduce the Transfusion Threshold

The New England
Journal of Medicine

VOLUME 340 FEBRUARY 11, 1999 NUMBER 6

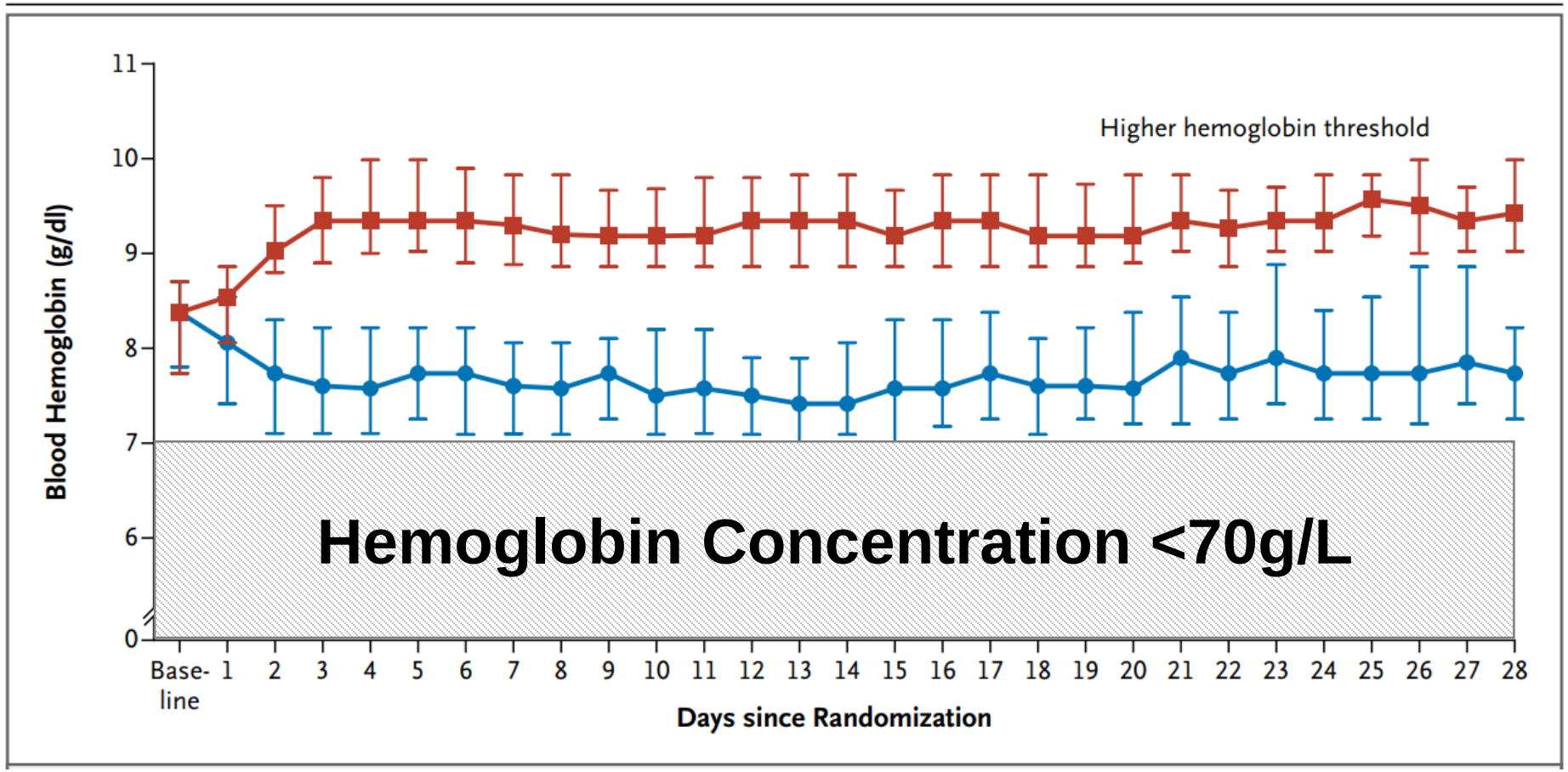
A MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL OF TRANSFUSION REQUIREMENTS IN CRITICAL CARE

PAUL C. HÉBERT, M.D., GEORGE WELLS, PH.D., MORRIS A. BLAJCHMAN, M.D., JOHN MARSHALL, M.D., CLAUDIO MARTIN, M.D., GIUSEPPE PAGLIARELLO, M.D., MARTIN TWEEDDALE, M.D., PH.D., IRWIN SCHWEITZER, M.SC., ELIZABETH YETISIR, M.SC., AND THE TRANSFUSION REQUIREMENTS IN CRITICAL CARE INVESTIGATORS FOR THE CANADIAN CRITICAL CARE TRIALS GROUP*



Paul Hebert, MD, FRCPC, MHSc,
Chief, Department of Medicine, CHUM, Montreal, Quebec; Scientist CRCHUM, Montreal, Quebec.

Median Nadir Hemoglobin Concentrations Do Not Meet Recommended Threshold for Transfusion



Holst N Engl J Med. 2014

Transfusion Threshold of 7 g per Deciliter — The New Normal

Paul C. Hébert, M.D., and Jeffrey L. Carson, M.D.

"We believe it has become abundantly clear that a transfusion threshold of 7 g per dL should become the new normal, recommended in all critically ill patients, including those with severe sepsis and septic shock…."

"It is time to adopt a threshold of 7 g/dL as the standard of care… "

"We endorse upgrading the evidence base…to 1A (strong recommendation and evidence)…"

Evidence remains weak in patients with acute coronary syndrome…(who) benefit from higher Hb concentrations (9 or 10 g per deciliter)."

The NEW ENGLAND JOURNAL of MEDICINE

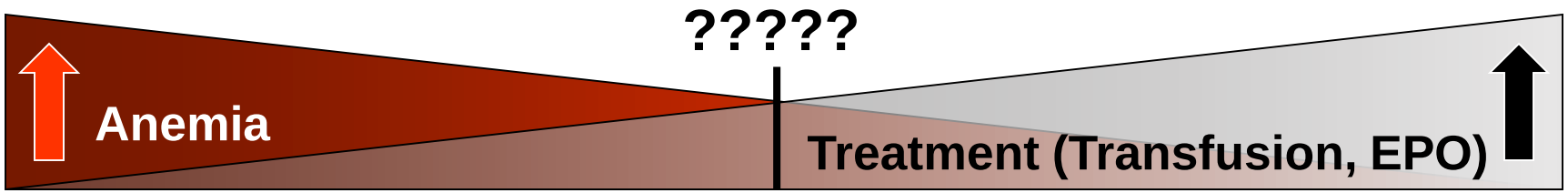
Hebert PC Carson JL NEJM 2014

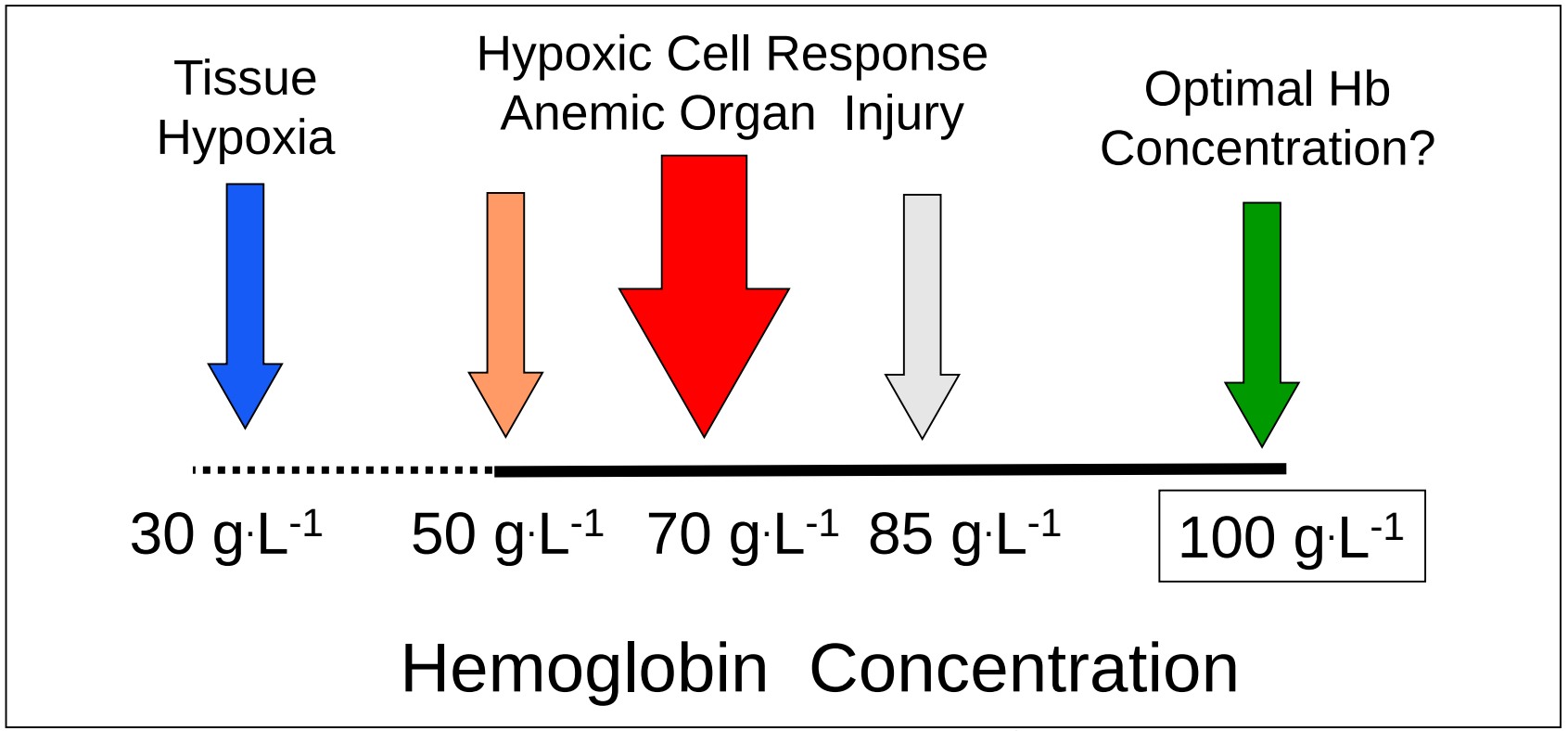
The Current Clinical Issue

We Don’t Transfuse Until The Hemoglobin Concentration Reaches 70 g/L

Balancing the Risk of Anemia and Its Treatments

What is Really Dangerous: Anemia or Transfusion?

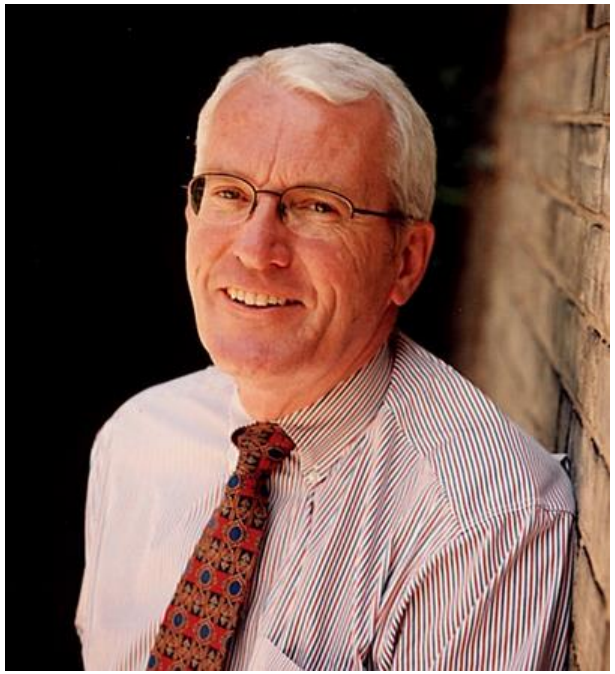




Organ Injury ⇐ Dysfunction ⇐ Function

Shander A BJA 2011

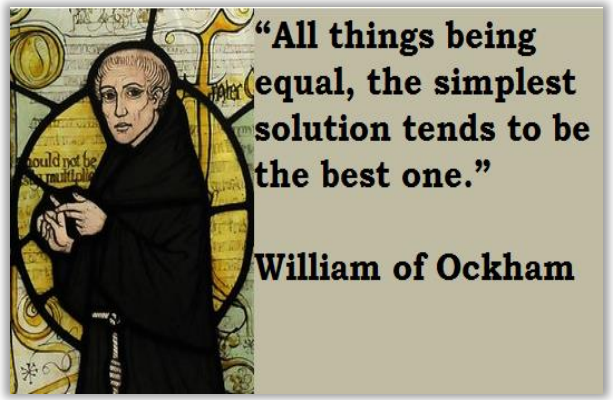
Surgical Strategy to Determining Transfusion Thresholds

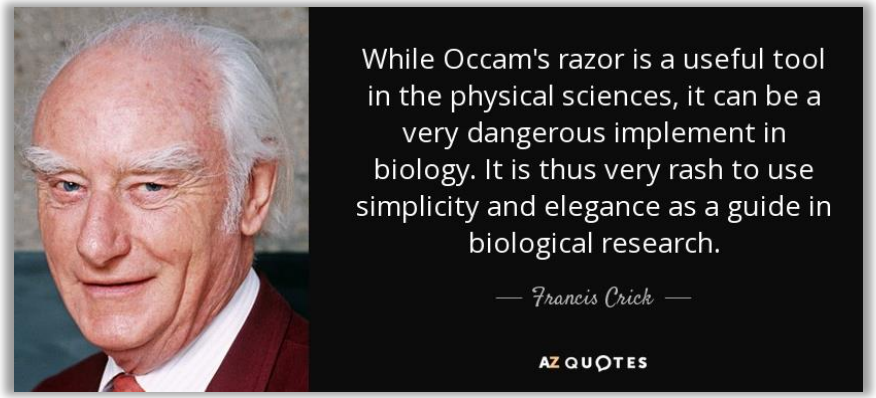


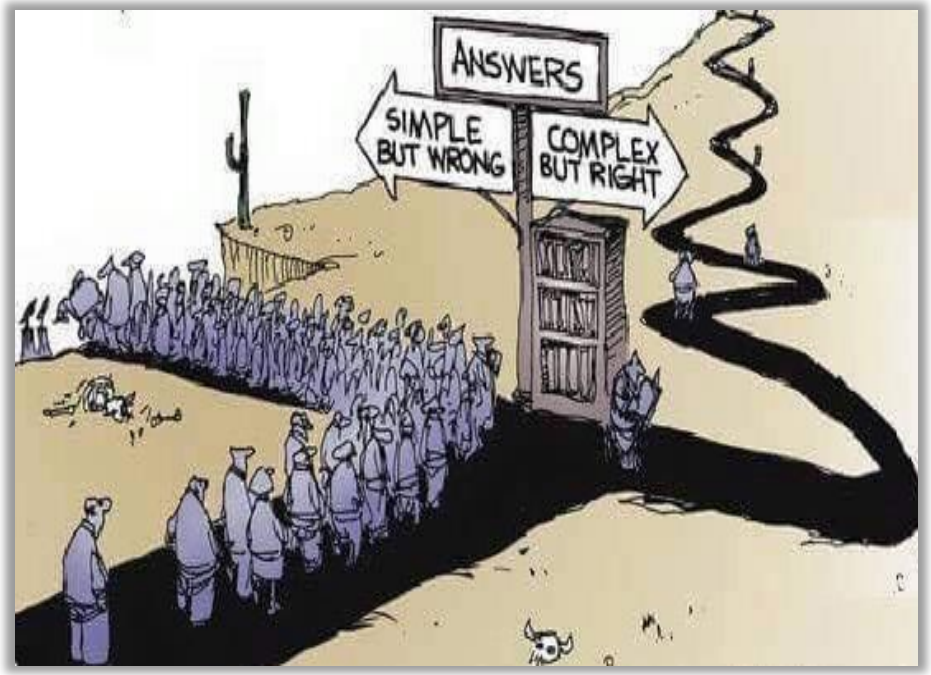
“If the Patient’s Age is Higher than the Hemoglobin You Should Probably Transfuse.”

James Waddell M.D., F.R.C.S.C
Professor, Department of Surgery
Order of Canada

Does the Concept of Occam's Razor Apply to Biological Medical Research?

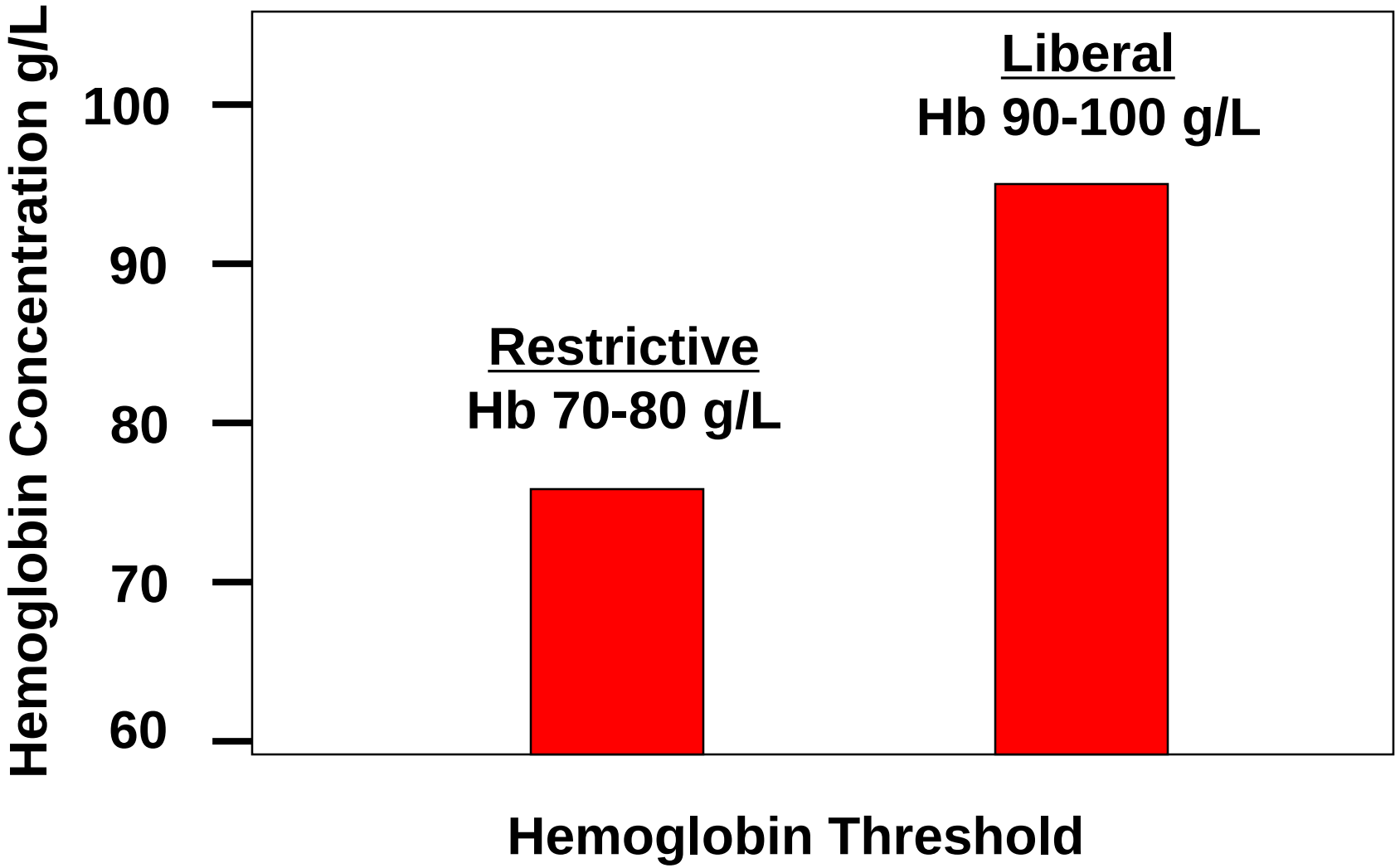






What Do The Current Trials Say About Liberal vs. Restrictive Transfusion?

Restrictive vs. Liberal Transfusion Strategy



Restrictive Transfusion Threshold is Non-Inferior

Cochrane Library — Trusted evidence. Informed decisions. Better health.

Transfusion thresholds for guiding red blood cell transfusion (Review)

Cochrane Database of Systematic Reviews

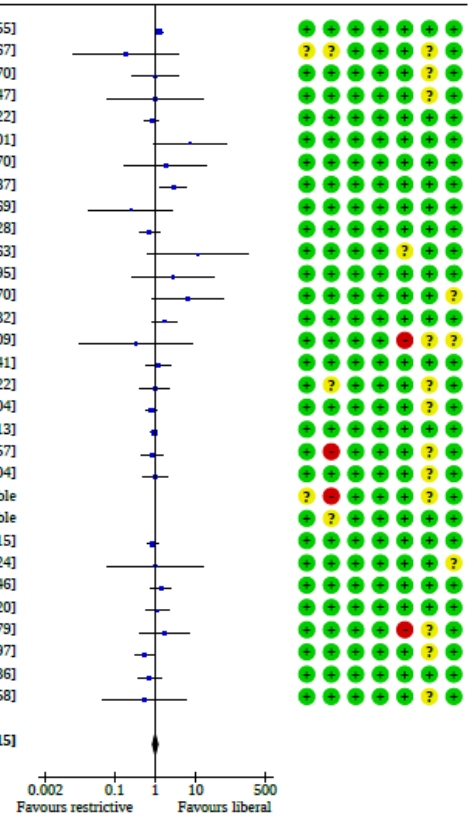
Analysis 1.1. Comparison 1: Mortality at 30 days, Outcome 1: 30-Day mortality

Study or Subgroup	Restrictive Events	Restrictive Total	Liberal Events	Liberal Total	Weight	Risk Ratio M-H, Random, 95% CI
Bergamin 2017	84	151	67	149	11.8%	1.24 [0.99 , 1.55]
Blair 1986	0	26	2	24	0.2%	0.19 [0.01 , 3.67]
Bush 1997	4	50	4	49	1.1%	0.98 [0.26 , 3.70]
Carson 1998	1	42	1	42	0.3%	1.00 [0.06 , 15.47]
Carson 2011	43	1009	52	1007	7.4%	0.83 [0.56 , 1.22]
Carson 2013	7	55	1	55	0.5%	7.00 [0.89 , 55.01]
Cooper 2011	2	23	1	21	0.4%	1.83 [0.18 , 18.70]
de Almeida 2015	23	101	8	97	3.0%	2.76 [1.30 , 5.87]
DeZern 2016	1	59	2	30	0.4%	0.25 [0.02 , 2.69]
Ducrocq 2021	19	342	25	324	4.6%	0.72 [0.40 , 1.28]
Foss 2009	5	60	0	60	0.2%	11.00 [0.62 , 194.63]
Gillies 2020	2	26	1	36	0.4%	2.77 [0.26 , 28.95]
Gobatto 2019	7	23	1	21	0.5%	6.39 [0.86 , 47.70]
Gregersen 2015	21	144	12	140	3.6%	1.70 [0.87 , 3.32]
Grover 2006	0	109	1	109	0.2%	0.33 [0.01 , 8.09]
Hajjar 2010	15	249	13	253	3.2%	1.17 [0.57 , 2.41]
Hébert 1995	8	33	9	36	2.6%	0.97 [0.42 , 2.22]
Hébert 1999	78	418	98	420	10.7%	0.80 [0.61 , 1.04]
Holst 2014	168	502	175	496	13.5%	0.95 [0.80 , 1.13]
Jairath 2015	14	257	25	382	4.0%	0.83 [0.44 , 1.57]
Lacroix 2007	14	320	14	317	3.2%	0.99 [0.48 , 2.04]
Laine 2018	0	40	0	40		Not estimable
Lotke 1999	0	62	0	65		Not estimable
Mazer 2017	74	2427	87	2429	9.6%	0.85 [0.63 , 1.15]
Møller 2019	1	29	1	29	0.3%	1.00 [0.07 , 15.24]
Murphy 2015	26	1000	19	1003	4.5%	1.37 [0.76 , 2.46]
Palmieri 2017	16	168	15	177	3.6%	1.12 [0.57 , 2.20]
Parker 2013	5	100	3	100	1.0%	1.67 [0.41 , 6.79]
Villanueva 2013	19	416	34	417	5.0%	0.56 [0.32 , 0.97]
Walsh 2013	12	51	16	49	3.9%	0.72 [0.38 , 1.36]
Webert 2008	1	29	2	31	0.4%	0.53 [0.05 , 5.58]
Total (95% CI)		**8321**		**8408**	**100.0%**	**0.99 [0.86 , 1.15]**
Total events:	670		689			

Heterogeneity: Tau² = 0.03; Chi² = 40.06, df = 28 (P = 0.07); I² = 30%

Test for overall effect: Z = 0.07 (P = 0.94)

Test for subgroup differences: Not applicable

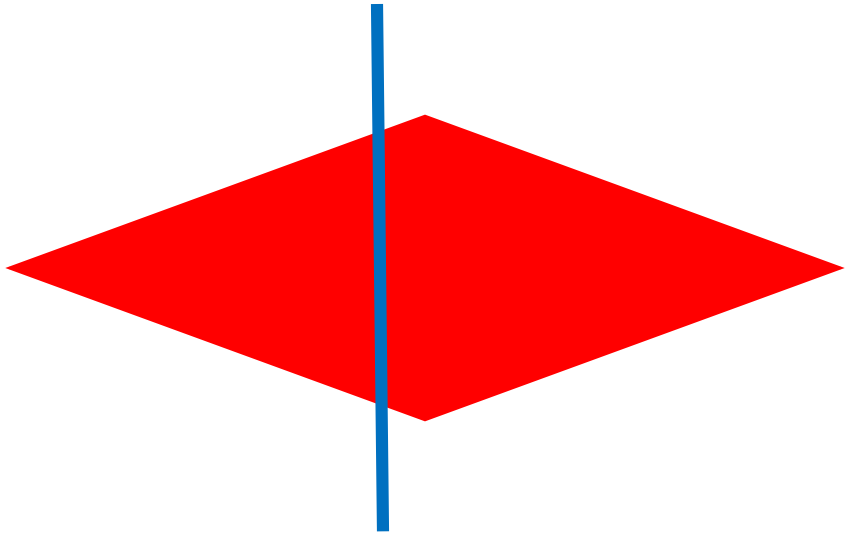


Carson JL. Cochrane Database Syst Rev. 2021

Restrictive vs. Liberal Transfusion Threshold: Does Equipoise Still Exist?

Mortality

OR 1.15 (0.88 to 1.50)



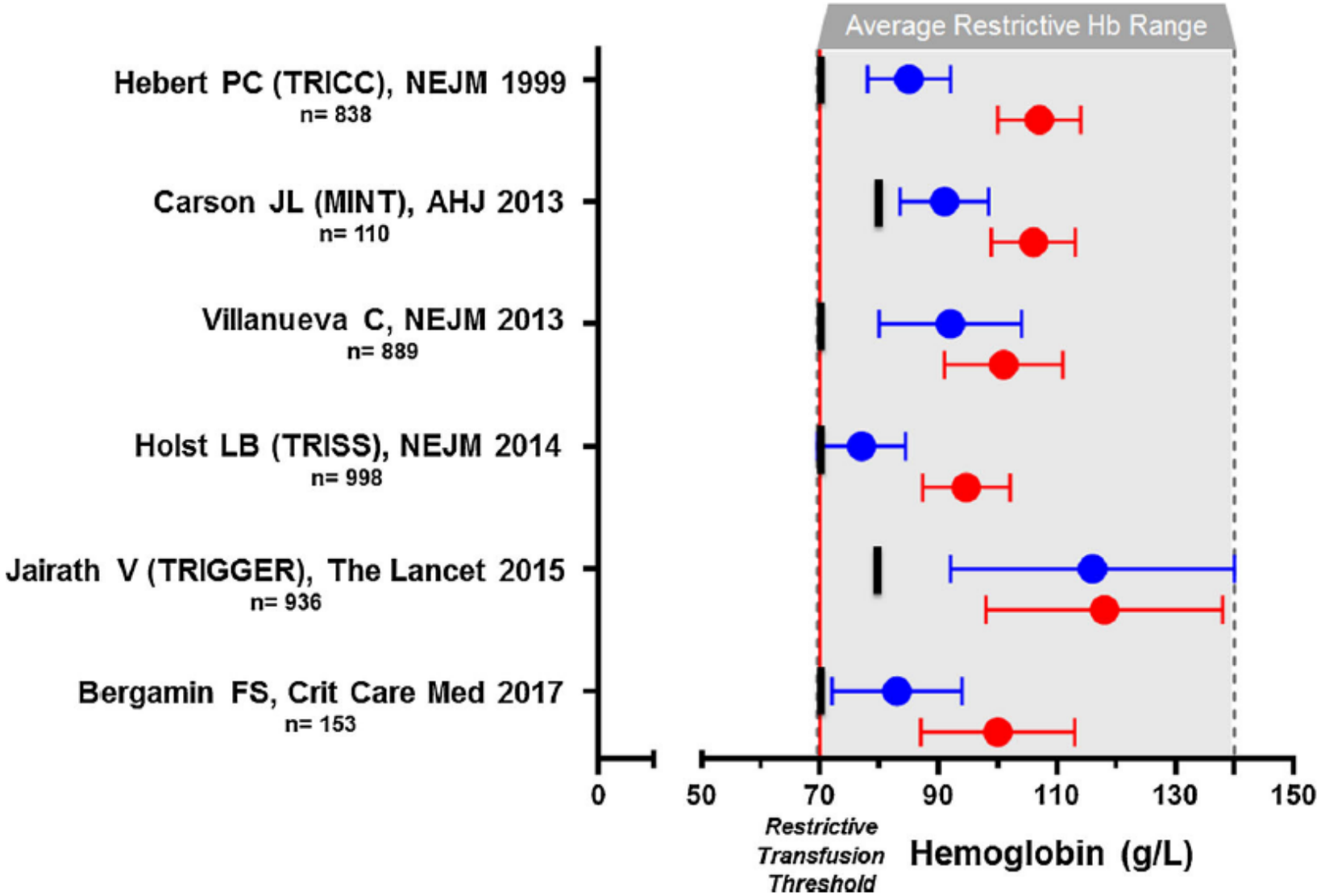
Restrictive Transfusion Strategy is Safe?

Liberal Transfusion Strategy is Not Harmful?

Favours Restrictive **Favours Liberal**

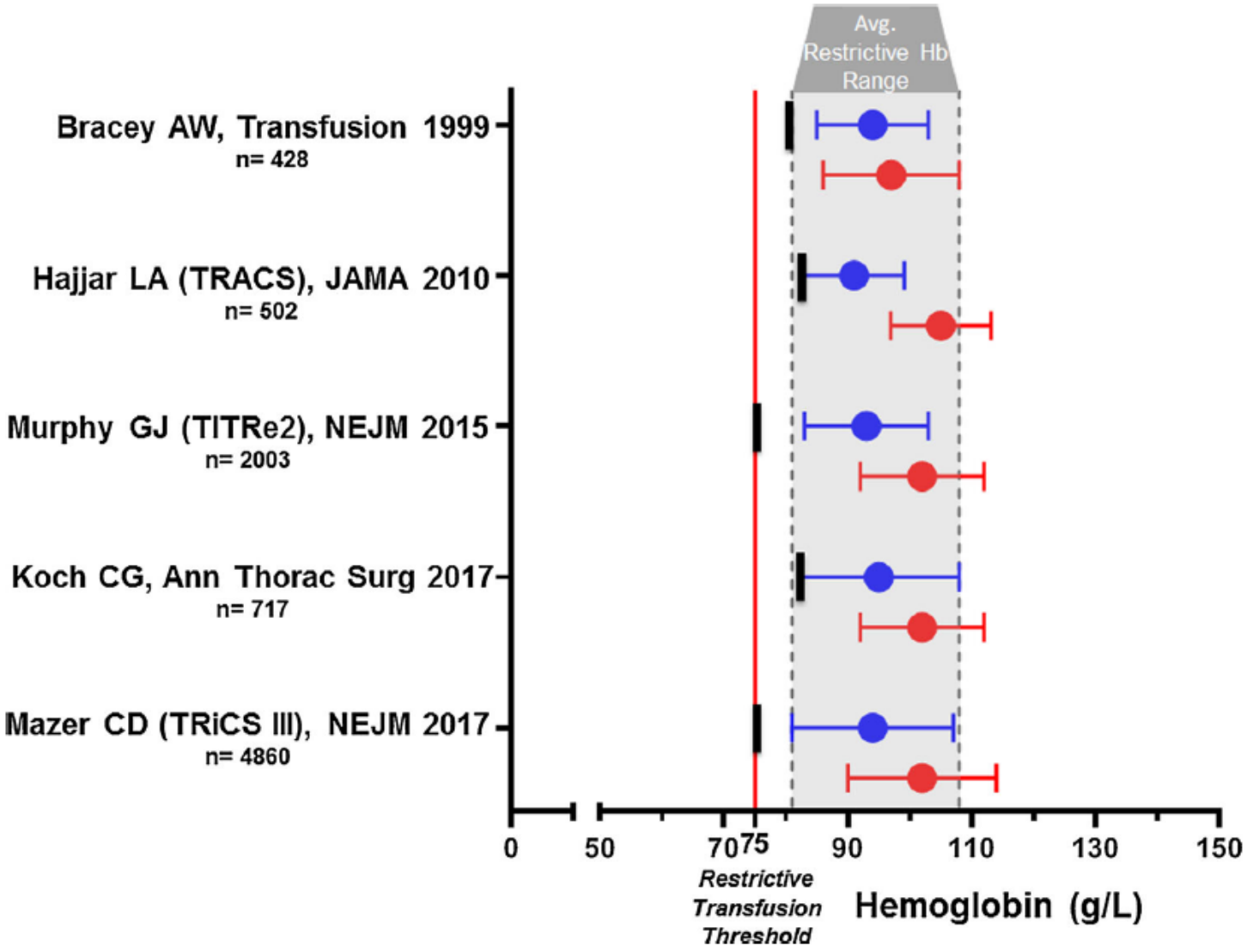
Docherty AB BMJ 2016

Restrictive Transfusion Thresholds and Restrictive Hemoglobin Range in Critically Ill Patients



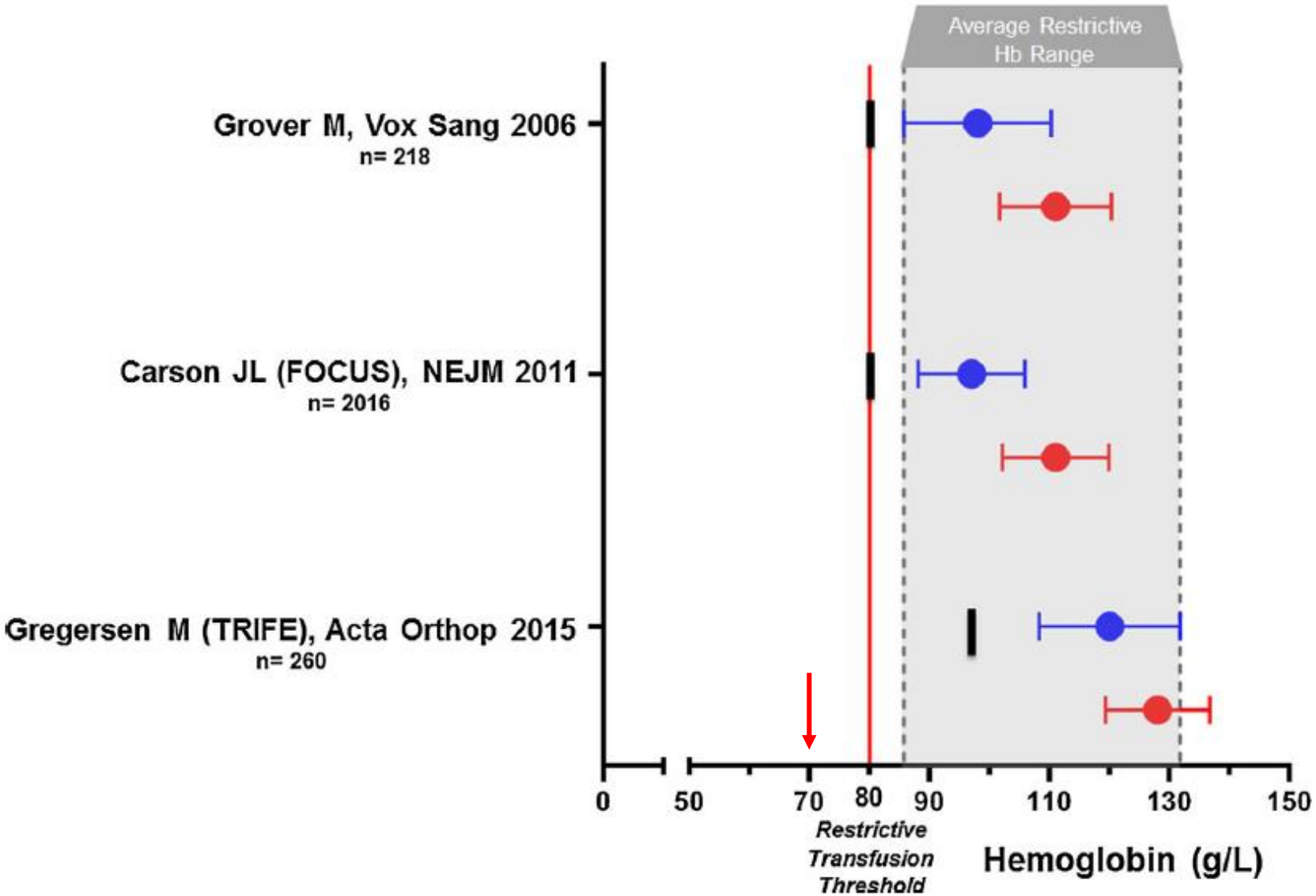
Hare GMT et al. Can J Anesth 2020

Restrictive Transfusion Thresholds and Restrictive Hemoglobin Range in Cardiac Surgery



Hare GMT et al. Can J Anesth 2020

Restrictive Transfusion Thresholds and Restrictive Hemoglobin Range in Orthopedic Surgery



Hare GMT et al. Can J Anesth 2020

TRiCS·III
Transfusion Requirements in Cardiac Surgery

Restrictive versus liberal red blood cell transfusion in cardiac surgery:

C. David Mazer and Nadine Shehata

On behalf of TRICS investigators and Perioperative Anesthesia Clinical Trials Group

Australian Government
National Health and Medical Research Council

AHRC
APPLIED HEALTH RESEARCH CENTRE

St. Michael's
Inspired Care. Inspiring Science.

CIHR IRSC
Canadian Institutes of Health Research / Instituts de recherche en santé du Canada

Canadian Blood Services
Société canadienne du sang

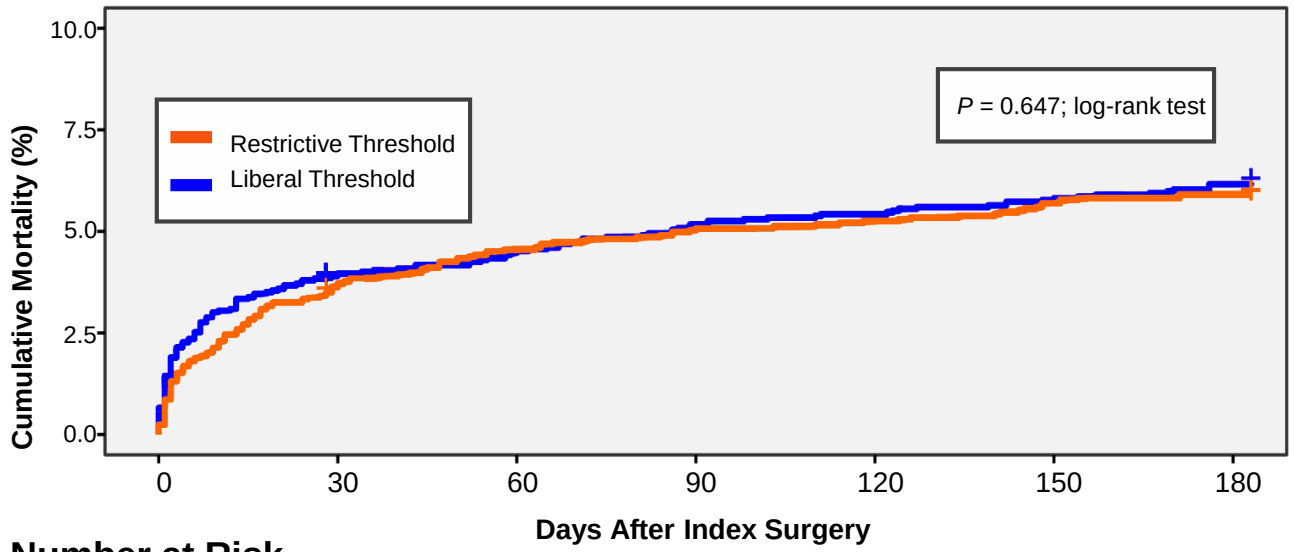
UNIVERSITY OF TORONTO

PACT
Perioperative Anesthesia Clinical Trials

hrc Health Research Council of New Zealand

Restrictive Versus Liberal Red Blood Cell Transfusion in Cardiac Surgery:

Cumulative Mortality at 6 Months



Number at Risk

Restrictive Threshold	2427	2202	2181	2170	2165	2155	2150
Liberal Threshold	2429	2222	2209	2193	2187	2179	2170

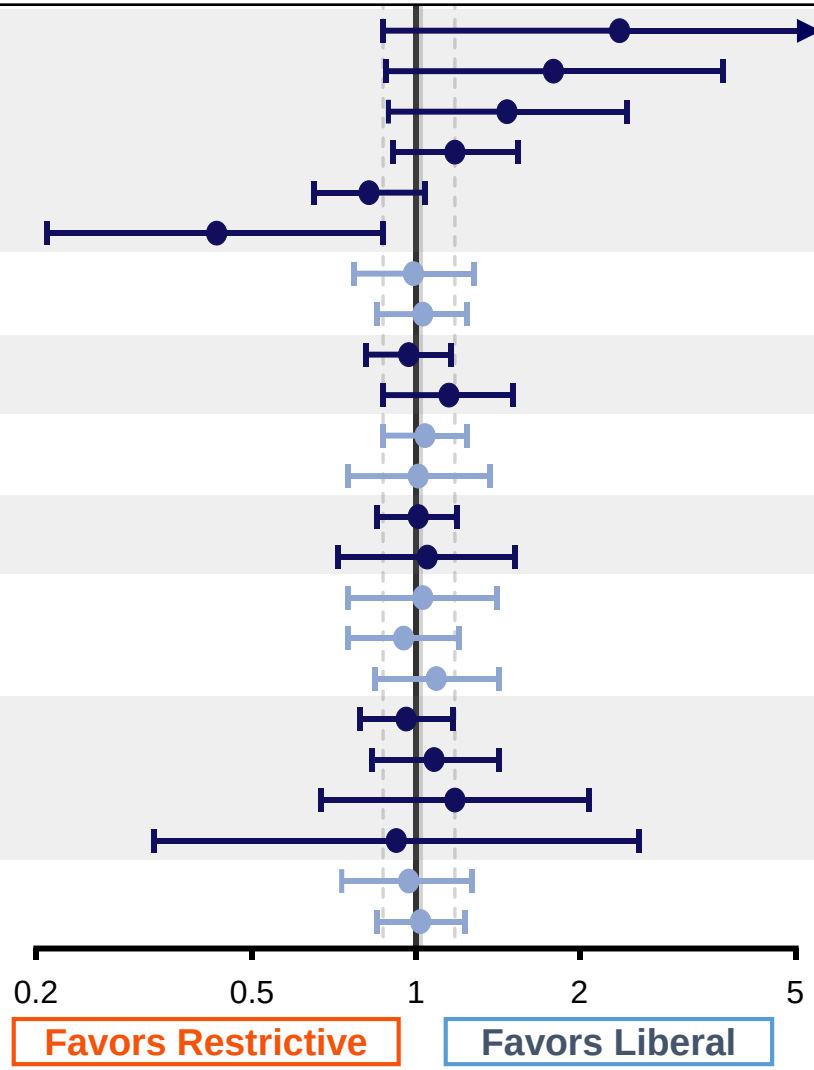
TRiCS·III
Transfusion Requirements in Cardiac Surgery

Mazer CD, NEJM 2017, 2018

Six-Month Outcomes after Restrictive or Liberal Transfusion for Cardiac Surgery

The NEW ENGLAND JOURNAL of MEDICINE

	Subgroup	*N*	P Value for Interaction
Age	<45 years	102	**0.004**
	45 – 54 years	172	
	55 – 64 years	507	
	65 – 74 years	1556	
	75 – 84 years	2108	
	85+ years	219	
Sex	Female	1631	**0.822**
	Male	3033	
Diabetes	No	3391	**0.307**
	Yes	1273	
Creat Clearance	≥ 50mL/min	3849	**0.907**
	< 50mL/min	813	
Pulm Disease	No	3888	**0.858**
	Yes	776	
Surgery	CABG Only	1218	**0.744**
	Non-CABG	2161	
	CABG+ Other	1285	
LV Function	Good	2887	**0.845**
	Moderate	1378	
	Poor	314	
	Very Poor	83	
Preop Hb	<120g/L	1083	**0.730**
	≥120g/L	3580	



Mazer NEJM 2015

Mazer CD, NEJM 2017, 2018

Is Liberal Red Blood Cell Transfusion Superior for Patients with Acute Coronary Syndrome?

Journal of the American Heart Association

RESEARCH LETTER

Transfusion Thresholds for Acute Coronary Syndromes—Insights From the TRICS-III Randomized Controlled Trial, Systematic Review, and Meta-Analysis

Nikhil Mistry, MSc; Gregory M. T. Hare, MD, PhD; Nadine Shehata, MD, MSc; Emilie Belley-Cote, MD, PhD; Fabio Papa, MD; Robert S. Kramer, MD; Tarit Saha, MD; Duminda N. Wijeysundera, MD, PhD; Dennis Ko, MD, MSc; Subodh Verma, MD, PhD; C. David Mazer, MD

A TRICS-AMI Cohort Characteristics

	Restrictive Strategy (n=89)	Liberal Strategy (n=105)
Age	67.4±9.8	67.5±8.9
Male sex	69/89 (77.5)	85/105 (81.0)
Body mass index	28.1±4.2	27.4±4.3
EuroSCORE I	9.2±2.0	9.5±2.3
Preserved left ventricular function (ejection fraction >50%)	32/89 (36.0)	29/104 (27.9)
Treated hypertension	73/89 (82.0)	84/105 (80.0)
Normal renal function (creatinine clearance >85 ml/min)	47/88 (53.4)	63/104 (60.6)
Preoperative use of aspirin	72/89 (80.9)	75/105 (71.4)
Preoperative anemia (male hemoglobin <13 g/L; female <12 g/dL)	46/89 (51.7)	48 /105 (45.7)
Duration of cardiopulmonary bypass, minutes	105±35	108±48
≥1 Red blood cell transfusion post-randomization	47/89 (52.8)	83/105 (79.0)
Number of units	1.82 ± 3.56	3.61 ± 4.61

B Meta-Analysis of Randomized Controlled Trials

Major Adverse Cardiovascular Events (all-cause death, myocardial infarction, and revascularization)

Trial	Restrictive, n (%)	Liberal, n (%)	Weight	Risk Difference (95% Confidence Interval)	Certainty of Evidence
CRIT	2/23 (9%)	2/19 (11%)	8.2%	-2% (-20% to 16%)	--
MINT Pilot	20/54 (37%)	15/55 (27%)	8.7%	10% (-8% to 27%)	--
REALITY	111/342 (32%)	92/324 (28%)	54.5%	4% (-3% to 11%)	--
TRICS-AMI	12/84 (14%)	11/101 (11%)	28.6%	3% (-6% to 13%)	--
Total	**145/503 (29%)**	**120/499 (24%)**	**100%**	**4% (-1% to 9%)**	⊕⊕⊕○ Moderate

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.84$, df = 3 (P = 0.84); $I^2 = 0\%$
Test for overall effect: Z = 1.48 (P = 0.14)

-30 -20 -10 0 10 20 30
Restrictive safer Liberal safer

Death

Trial	Restrictive, n (%)	Liberal, n (%)	Weight	Risk Difference (95% Confidence Interval)	Certainty of Evidence
CRIT	2/23 (9%)	1/19 (5%)	8.3%	3% (-12% to 19%)	--
MINT Pilot	10/54 (19%)	7/55 (13%)	10.5%	6% (-8% to 19%)	--
REALITY	79/342 (23%)	66/324 (20%)	49.7%	3% (-4% to 9%)	--
TRICS-AMI	7/85 (8%)	8/101 (8%)	31.5%	0% (-8% to 8%)	--
Total	**98/504 (19%)**	**82/499 (16%)**	**100%**	**2% (-2% to 7%)**	⊕⊕⊕○ Moderate

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.54$, df = 3 (P = 0.91); $I^2 = 0\%$
Test for overall effect: Z = 1.04 (P = 0.30)

-30 -20 -10 0 10 20 30
Restrictive safer Liberal safer

Myocardial Infarction

Trial	Restrictive, n (%)	Liberal, n (%)	Weight	Risk Difference (95% Confidence Interval)	Certainty of Evidence
MINT Pilot	7/54 (13%)	5/55 (9%)	8.2%	4% (-8% to 16%)	--
REALITY	33/342 (10%)	21/324 (6%)	66.7%	3% (-1% to 7%)	--
TRICS-AMI	5/79 (6%)	4/95 (4%)	25.1%	2% (-5% to 9%)	--
Total	**45/475 (9%)**	**30/474 (6%)**	**100%**	**3% (0% to 6%)**	⊕⊕⊕○ Moderate

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.09$, df = 2 (P = 0.95); $I^2 = 0\%$
Test for overall effect: Z = 1.73 (P = 0.08)

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Restrictive safer Liberal safer

Revascularization

Trial	Restrictive, n (%)	Liberal, n (%)	Weight	Risk Difference (95% Confidence Interval)	Certainty of Evidence
MINT Pilot	2/54 (4%)	0/55 (0%)	6.9%	4% (-2% to 10%)	--
REALITY	5/342 (1%)	6/324 (2%)	66.2%	0% (-2% to 2%)	--
TRICS-AMI	0/77 (0%)	1/95 (1%)	26.9%	-1% (-4% to 2%)	--
Total	**7/473 (1%)**	**7/474 (1%)**	**100%**	**0% (-2% to 1%)**	⊕⊕○○ Low

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.94$, df = 2 (P = 0.38); $I^2 = 0\%$
Test for overall effect: Z = 0.36 (P = 0.72)

-30 -20 -10 0 10 20 30
Restrictive safer Liberal safer

JAHA 2023

2018 Frankfurt Consensus Conference: Clinical Research Recommendations for RBC Transfusion Thresholds

Strong recommendation, moderate-quality evidence

Conditional recommendation, moderate-quality evidence

Conditional + research recommendation, low-quality evidence

Research recommendation, low-quality evidence

Research recommendation, very-low quality evidence

No evidence found

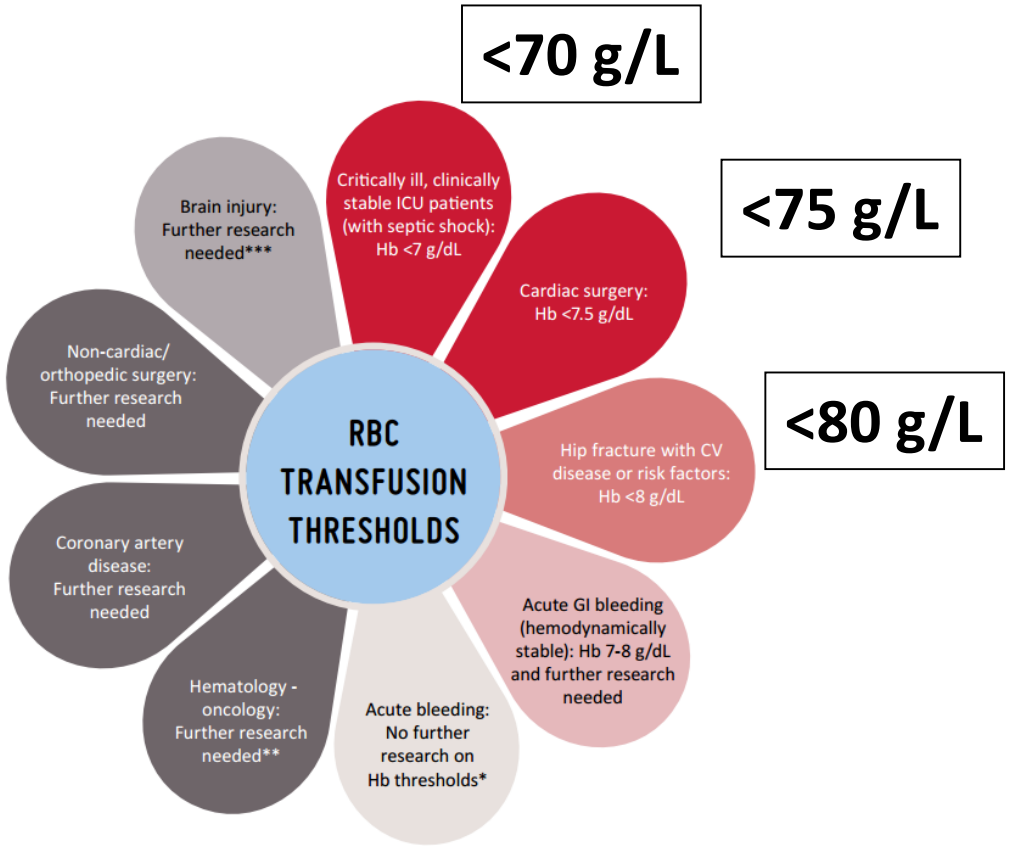
Abbreviation

CV	Cardiovascular
GI	Gastro-intestinal
Hb	Hemoglobin
ICU	Intensive Care Unit
RBC	(packed) Red Blood Cells

* For patients with critical bleeding (major blood loss), Hb level is not the most important, or deciding, factor in transfusion management. It is difficult to perform studies in exsanguinating patients, and they have been excluded from most trials. Stopping the bleeding is the priority – refer to published national/international guidelines on management of massive hemorrhage requiring transfusion support.

** Future research should focus on patients with non-malignant hematological disorders and patients undergoing chemotherapy, not surgery for solid tumors.

*** Patients with cerebral perfusion disorders or acute central nervous system injury (excluded: sickle cell disease)



Mueller JAMA 2019

Acknowledgments

CARF
Canadian Anesthesia Research Foundation
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PACT
Perioperative Anesthesia Clinical Trials

PSI
PSI FOUNDATION

St. Michael's
Inspired Care.
Inspiring Science.

CAS
CARF

University of Toronto

SMH-LKSKI

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Department of Anesthesia

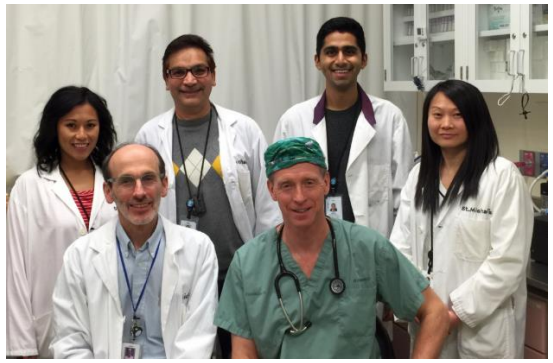
Canadian Anesthesiologists' Society
Société canadienne des anesthésiologistes

VELUT ARBOR ÆVO

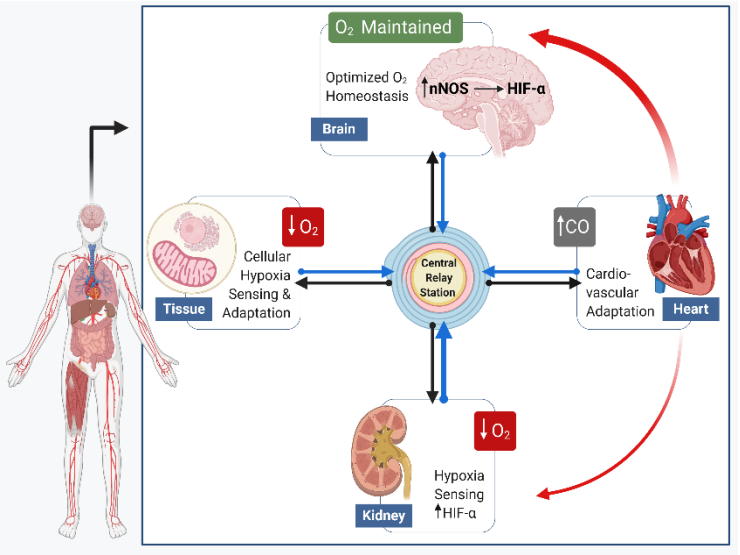
Thank You!

Acknowledgments-SMH Anesthesia Research Team

Translational Research Program and Future Directions



Directed by Translational Research



Translational Research Finding

- Demonstrated Anemia-induced organ hypoxia in Brain, heart and kidney
- Sickle cell anemia (SCA) Causes brain hypoxia and stroke
- Anemia causes low brain oxygen Increasing the amount of brain injury after trauma
- Muscle flaps have very low tissue oxygen levels despite reconnected vasculature
- Diabetic drugs -SGLT2 inhibitors- improve kidney function by regulating oxygen levels

Future Research Direction

- Develop continuous blood oxygen monitor for patients to reduce Myocardial Injury (MI) in patients undergoing surgery
- Develop Inexpensive Oxygen Based Therapies to Reduce Stroke In Children with Sickle Cell Anemia Worldwide
- Develop tissue oximeters to measure brain oxygen levels and assess treatments to reduce brain injury
- Measure muscle flap oxygen levels and improve success of tissue flaps for breast reconstruction
- Develop novel Strategies to Assess and reduce the risk of Kidney Injury (AKI) in patients with Diabetes

↓ MI

↓ Stroke

↓ Flap Failure

↓ AKI

Thank You for the Opportunity to Present!

Sunnywater Lake, Temagami, July 2020