

### Clinical Implications of the MINT Trial: p=0.07

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# Disclosures

- No relevant disclosures
- MINT funded by NHLBI
- MINT pilot funded by CIHR





# **Outline of Presentation**

- Brief clinical background
- AABB Transfusion Guidelines
- MINT Trial methods and results
- Statistical vs Clinical Significance
- Selected challenges





# Case

- 66 year old male presents with chest pain to ER and ECG shows STEMI
- Patient taken to cardiac catheterization lab, and stent inserted in LAD
- Admission Hgb 10.1.
- Following day Hgb 8.5, had a melanotic stool. Vitals normal
- Transfuse?



# Background

- Anemia is common in patients with acute MI
- Indications for red blood cell transfusion in MI patients are controversial given the paucity of evidence
- Three trials have compared transfusion thresholds in 820 patients with MI and found inconsistent results
- Trials in other clinical settings suggest use of restrictive transfusion strategy is safe



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Cochrane Database of Systematic Reviews Review - Intervention

### Transfusion thresholds for guiding red blood cell transfusion

✓ Jeffrey L Carson<sup>a</sup>, Simon J Stanworth<sup>a</sup>, Jane A Dennis<sup>a</sup>, Marialena Trivella, Nareg Roubinian, Dean A Fergusson, Darrell Triulzi, Carolyn Dorée, Paul C Hébert Authors' declarations of interest Version published: 21 December 2021 Version history https://doi.org/10.1002/14651858.CD002042.pub5 IS

### About 🔻 🛛 Help 🔻

Table 2. Summary of Findings in Trials Comparing Liberal vs Restrictive Transfusion Strategies on Mortality, Morbidity, and Blood Transfusion in Adults

Outcome No of participants	Relative effect (95%	Absolute effects, %				
(No. of RCTs)	CI)	Restrictive	Liberal	Difference (95% CI)	Certainty	Plain language summary
30-d Mortality, N = 16 092 (30)	RR, 1.00 (0.86-1.16)	8.3	8.3	0.0 Fewer (1.2 fewer to 1.3 more)	High	Transfusion threshold likely has little or no effect on mortality
MI, N = 14 370 (23)	RR, 1.04 (0.87-1.24)	3.3	3.2	0.1 More (0.4 fewer to 0.8 more)	High	Transfusion threshold has little or no effect on MI
CHF, N = 6610 (15)	RR, 0.86 (0.56-1.33)	3.2	3.7	0.5 Fewer (1.6 fewer to 1.2 more)	Low <sup>a,b</sup>	Transfusion threshold likely has little or no effect on CHF
CVA, N = 13 985 (19)	RR, 0.84 (0.64-1.09)	1.4	1.7	0.3 Fewer (0.6 fewer to 0.2 more)	High	Transfusion threshold likely has little or no effect on CVA
Rebleeding, N = 3412 (8)	RR, 0.80 (0.59-1.09)	12.6	15.8	3.2 Fewer (6.5 fewer to 1.4 to more)	Moderate <sup>a</sup>	Transfusion threshold likely has little or no effect on rebleeding
Infection, N = 16 466 (24)	RR, 0.98 (0.89-1.09)	13.6	13.9	0.3 Fewer (1.5 fewer to 1.2 more)	High	Transfusion threshold likely has little or no effect on infection
Thromboembolism, N = 4201 (13)	OR, 1.11 (0.65-1.88)	1.7	1.5	0.2 More (0.5 fewer to 1.3 more)	Moderate <sup>b</sup>	Transfusion threshold likely has little or no effect on thromboembolism
Delirium, N = 6442 (9)	RR, 1.11 (0.88-1.40)	11.9	10.7	1.2 More (1.3 fewer to 4.3 more)	Moderate <sup>b</sup>	Transfusion threshold likely has little or no effect on delirium
Transfusion, N = 19 419 (41)	RR, 0.60 (0.54-0.66)	48.6	81.0	32.4 Fewer (37.3 to 27.5 fewer)	High	Restrictive transfusion threshold results in large reduction in transfusion
Abbreviations: CHF, congestive heart failure; CVA, cerebrovascular accident; MI, myocardial infarction; OR, odds ratio; RCT, randomized controlled trial; RR, v relative risk.				<sup>b</sup> Downgraded for imprecisiversion 5.4 (Cochrane). <sup>27</sup> details.	sion. 95% Cls See eFigures	were calculated with Review Manager 1 through 9 in the Supplement for

<sup>a</sup> Downgraded for inconsistency.

### **Red Blood Cell Transfusion: 2023 AABB International Guidelines**

Table 3. Summary of Findings in Trials of Patients With Hematologic Malignancies and Myocardial Infarction Comparing Liberal vs Restrictive Transfusion Strategies on 30-Day Mortality

	30-d Mortality relative effect	Absolute effects,	
Patient group (No. of RCTs)	(95% CI)	Restrictive	Li
Hematologic malignancies, N = 149 (2)	RR, 0.37 (0.07-1.95)	2.4	6.
Myocardial infarction, N = 820 (3)	RR, 0.99 (0.59-1.65) <sup>b</sup>	6.7	6.
Abbreviations: RCT, randomized controlled	<sup>c</sup> Imprecision.		
<sup>a</sup> Two downgrades for very serious imprec	<sup>d</sup> Inconsistency.	95%	
<sup>b</sup> Note that in consultation with a methodo been presented for this outcome due to l absolute difference = 4.1% more (4.2 few	Collaboration).	27	

%		Certainty
beral	Difference (95% CI)	
.6	4.1 fewer (6.1 fewer to 6.2 more)	Low <sup>a</sup>
.8	0.1 fewer (2.8 fewer to 4.4 more)	Low <sup>c,d</sup>

Cls calculated with Review Manager version 5.4 (Cochrane



November 21, 2023 Volume 330, Number 19 Pages 1811-1922

### Blood, Bleeding, and Transfusion

1845 Blood, Bleeding, and Transfusion-A Theme Issue CW Seymour

**Special Communication** 1892 Red Blood Cell Transfusion: 2023 AABB International Guidelines JL Carson and Coauthors

Original Investigation 1852 Red Blood Cell Transfusion in the ICU SJ Raasveld and Coauthors

1862 Resuscitative Endovascular Balloon Occlusion of the Aorta in Trauma Patients: The UK-REBOA Trial JO Jansen and Coauthors

1872 Small-Volume Blood Collection Tubes to Reduce Transfusions in Intensive Care: The STRATUS Trial DM Siegal and Coauthors

1882 Early and Empirical High-Dose Cryoprecipitate for Hemorrhage After Traumatic Injury: The CRYOSTAT-2 Trial R Davenport and Coauthors

JAMA Insights 1903 Blood and Its Components CS Cohn and BH Shaz

Viewpoint 1837 From Product to Patient-Transfusion and Patient Blood Management MA Warner, L Shore-Lesserson, and C Burns

1839 The Bloody Transfusion Problem JB Holcomb, WK Hoots, and TM Polk

1841 Redefining Blood Donation-Path to Inclusivity and Safety PP Young and P Saa

Editorial 1847 Precision in Transfusion Medicine MD Neal and BJ Hunt

1849 Contemporary Adjuncts to Hemorrhage Control SA Tisherman and ML Brenner

**JAMA** Patient Page 1921 Blood Donation Theme Issue:

Editorial

Christopher W. Seymour, MD, MSc

Special Communication

lines Jeffrey L. Carson, MD; et al

Original Investigation

### Red Blood Cell Transfusion in the Intensive Care Unit

Senta Jorinde Raasveld, MD; et al

Original Investigation Trial Deborah M. Siegal; et al

Multimedia online at jama.com

C Article Summaries and Complete Contents on page 1811



A JAMA NETWORK PUBLICATION

### **Blood**, **Bleeding**, and **Transfusion**

### Blood, Bleeding, and Transfusion—A Theme Issue

### Red Blood Cell Transfusion: 2023 AABB International Guide-

### Small-Volume Blood Collection Tubes to Reduce Transfusions in Intensive Care: The STRATUS Randomized Clinical

# Restrictive Blood Transfusion

7 g/dL for Everyone

OR

Different thresholds by clinical subgroup



### AABB Guideline Recommendations

 For hospitalized adult patients who are hemodynamically stable, the international panel recommends a restrictive transfusion strategy considering transfusion when the hemoglobin concentration < 7 g/dL, (strong recommendation, moderate certainty evidence).

• Based on the restrictive strategy threshold used in most trials, clinicians may choose a threshold of 7.5 g/dL for patients undergoing cardiac surgery and 8 g/dL for patients undergoing orthopedic surgery or those with pre-existing cardiovascular disease.

### **ORIGINAL ARTICLE**

### Restrictive or Liberal Transfusion Strategy in Myocardial Infarction and Anemia

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# Objective

To determine whether the risk of death or MI through 30 days differed with a restrictive transfusion strategy with a hemoglobin threshold of 7 to 8 g/dL as compared to a liberal transfusion strategy with a hemoglobin threshold of 10 g/dL among patients with an acute MI and a hemoglobin concentration < 10 g/dL





### Methods

- Randomized controlled trial
- Enrolled April 2017 to April 2023

### 144 sites in the United States, Canada, France, Brazil, New Zealand and Australia



![](_page_15_Picture_0.jpeg)

## Inclusions

- 18 years or older
- STEMI or NSTEMI
- Types 1, 2, 4b, and 4c MI
- Hemoglobin concentration < 10 g/dL within 24 hours</p>

### Exclusions

- Uncontrolled bleeding
- Receiving only palliative treatment
- Schedule during the
- Declined blood transfusion
- Scheduled for cardiac surgery
  - during the current admission

![](_page_16_Picture_0.jpeg)

# **Transfusion Strategies**

Restrictive strategy: transfusion permitted, but not required, when hemoglobin concentration < 8 g/dL and strongly recommended when < 7 g/dL or when anginal symptoms not controlled with medications

Liberal strategy: 1 unit of packed red blood cells administered following randomization and red blood cells transfused to maintain hemoglobin concentration  $\geq 10 \text{ g/dL}$  through hospital discharge or 30 days

![](_page_17_Picture_0.jpeg)

### **Outcomes**

- Primary outcome: composite of all-cause death or MI up to 30 days following randomization
  - MI adjudicated by masked committee
- Prespecified secondary outcomes
  - 30-day death
  - 30-day MI
  - Composite of death, MI, ischemia driven unscheduled coronary revascularization, or hospital readmission for ischemic cardiac diagnosis within 30 days

Cause of death was classified as cardiac, non-cardiac, or undetermined

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## **Analysis Plan and Power**

- 80% power to detect 20% relative difference in primary outcome assuming overall event rate of 16.4%
- Target sample size 3500 participants
- Intention-to-treat analysis
- Two-sided test with alpha=0.05
- Log-binomial regression model using multiple imputation

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![](_page_19_Picture_0.jpeg)

# Enrollment Completed April 17, 2023

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## CONSORT Diagram

![](_page_20_Figure_2.jpeg)

![](_page_21_Picture_0.jpeg)

### **Baseline Characteristics**

Characteristic	Restrictive (N=1749)
Age in years, mean (SD)	72
Female (identity), n (%)	44%
White or Caucasian	78%
Black or African-American	14%
Multivessel CAD >50%	66%
NSTEMI	82%

Liberal (N=1755)
72
47%
78%
14%
65%
81%

![](_page_22_Picture_0.jpeg)

### **Baseline Characteristics**

Characteristic	Restrictive (N=1749)
Type 1 MI	42%
Type 2 MI	55%
Revascularization prior to randomization	29%
Heart failure in-hospital	22%
LV ejection fraction (%)	47%
Intubated on ventilator	14%
Renal dialysis	12%

Liberal (N=1755)
42%
56%
28%
23%
48%
13%
12%

![](_page_23_Picture_0.jpeg)

	Restrictive 46 of 1749	Liberal 241 of 1755
Reason	2.6%	13.7%
Clinical reason (e.g. surgery, bleeding)	24	
Adverse risks of transfusion (e.g., fluid overload, dialysis, transfusion reactions)	_	89
Participant preference	4	68
Provider preference	11	53
Other reasons (e.g., blood supply and staffing shortages)	7	31

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### **Units of Blood by Assigned Strategy**

![](_page_25_Figure_2.jpeg)

### Restrictive Liberal

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### MINT Primary Outcome Over 30-days

![](_page_27_Figure_1.jpeg)

Days After Randomization

![](_page_27_Figure_3.jpeg)

![](_page_27_Figure_4.jpeg)

### **MINT Secondary and Other Outcomes**

	Restrictive %	Liberal %	RR (95% CI)
Secondary Outcomes			
Death	9.9%	8.3%	1.19 (0.96, 1.47)
MI	8.5%	7.2%	1.19 (0.94, 1.49)
Death/MI/Rev/Readmit	19.6%	17.4%	1.13 (0.98, 1.29)
Other Outcomes			
Heart Failure	5.8%	6.3%	0.92 (0.71, 1.20)
Cardiac Death	5.5%	3.2%	1.74 (1.26, 2.40)
Stroke	1.7%	1.5%	1.16 (0.69, 1.95)
Pneumonia/Bacteremia	9.5%	8.7%	1.09 (0.88, 1.34)

0.50

![](_page_28_Figure_4.jpeg)

![](_page_29_Picture_0.jpeg)

30-day Death or MI by Baseline Pre-specified Subgroups

Subgroup	RR (95% C
Entire Study	1.16 (1.00, 1.3
Index MI Type	
Type 1	1.32 (1.04, 1.67
Type 2	1.05 (0.85, 1.29
STEMI or NSTEMI	
STEMI	1.04 (0.72, 1.49
NSTEMI	1.19 (1.00, 1.4
Revasc. Pre-Rand	
No	1.17 (0.98, 1.40
Yes	1.15 (0.84, 1.56
Hx CHF/Acute CHF/Low LVEF	
No	1.06 (0.83, 1.3
Yes	1.25 (1.02, 1.52
Hemoglobin category	
<8	0.97 (0.72, 1.30
8 - <9	1.23 (0.95, 1.59
9 - <10	1.23 (0.96, 1.59
Type of Anemia	
Chronic anemia	1.26 (1.00, 1.58
Acute anemia	1.12 (0.87, 1.44
Sex	
Male	1.21 (0.98, 1.49
Female	1.11 (0.88, 1.39
Age	
<60	1.18 (0.70, 1.99
60-69	1.27 (0.91, 1.78
70–79	1.13 (0.89, 1.42
>=80	1.08 (0.81, 1.4

![](_page_29_Figure_3.jpeg)

![](_page_29_Figure_4.jpeg)

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## Limitations

- Like all transfusion trianot masked
- Although pre-specified, cardiac death was not designated as primary, secondary, or tertiary outcome or adjudicated
- Trial results not adjusted for multiple comparisons

### Like all transfusion trials, assigned strategy was

![](_page_31_Picture_0.jpeg)

## Summary

- The MINT trial did not demonstrate a
- While not statistically significant, the point estimates for the primary outcome and secondary outcomes consistently favored a liberal transfusion strategy

statistically significant difference in the rate of 30-day death or recurrent MI in patients with acute MI and anemia assigned to a restrictive compared to a liberal transfusion strategy

Heart failure and other safety outcomes were comparable in the two transfusion groups

![](_page_32_Picture_0.jpeg)

## **Clinical Implications**

- Whether to transfuse is an every day decision faced by clinicians caring for patients with acute MI
- We cannot claim that a liberal transfusion strategy is definitively superior based on our primary outcome
- The interpretation of the MINT results requires consideration of the meaning of relative risk and confidence intervals in this trial

## **Statistical vs Clinical Significance**

The primary outcome RR confidence interval for restrictive versus liberal strategy is (0.99, 1.34).

> Primary Outcome RR (95% CI)

1.16 (1.00, 1.35) Death/MI Death/MI: Imputed 1.15 (0.99, 1.34)

> 0.67 <-Restrictive Better-

- At the lower end of this CI, the trial results are consistent with no difference between restrictive and liberal strategies.
- At the upper end, the trial results are consistent with clinically significant harm from restrictive strategy; restrictive strategy could increase risk of 30-day recurrent MI or death 15% to 34%.

![](_page_33_Figure_8.jpeg)

![](_page_34_Picture_0.jpeg)

## **Clinical Implications**

- The secondary outcomes consistently favored liberal transfusion and the risks associated with liberal transfusion were not elevated.
- Absolute risk difference
  - Primary outcome- 2.4%; Number needed to treat of 42
  - All cause mortality 1.6%; Number needed to treat 63
  - Conclusion: Clinically important effect

![](_page_35_Picture_0.jpeg)

## **Clinical Implications**

- In contrast to other clinical settings, the trial results suggest that a liberal transfusion strategy has the potential for clinical benefit with an acceptable risk of harm
- A liberal transfusion strategy may be the most prudent approach to transfusion in anemic patients with MI

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## **Other Challenges**

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### NCDR

- The National Cardiovascular Data Registry (NCDR<sup>®</sup>) is the ACC's suite of cardiovascular data registries helping hospitals and private practices measure and improve the quality of care they provide
- RBC transfusion after cardiac catheterization is a negative quality measure
- Some sites would not join trial and several very successful sites declined to continue to enroll patients
- We reached out but they were unwilling to adjust quality measures for hospitals enrolling in MINT

![](_page_38_Picture_0.jpeg)

# **Data Safety and Monitoring Plan**

- At trial initiation, all agreed futility analysis would not be conducted
  - Futility analyses are commonly applied in trials that compare a new treatment to placebo or an active standard-of-care comparator.
  - Since the MINT trial compares two established transfusion strategies with different resource and cost implications, a null result from a wellpowered trial would be important for establishing treatment guidelines and policy.
  - Goal was to ensure that the MINT trial has sufficient power to demonstrate superiority of either treatment as well as the noninferiority of the restrictive strategy.

![](_page_39_Picture_0.jpeg)

# **Funding-Futility Analysis**

- Because COVID slowed recruitment, we required additional funding to enroll the last 500 patients
- NHLBI required that we create a futility plan prior to approving funds needed to complete enrollment
- Blinded NHLBI statistician reviewed and approved the trial futility plan
- After reviewing the results of the futility analysis, the DSMB recommended to NHLBI that MINT continue enrollment • NHLBI provided supplemental funding to finish the trial

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### Thanks to the MINT Investigator team and to all of the MINT trial participants!

![](_page_40_Picture_2.jpeg)

### National Heart, Lung, and Blood Institute

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![](_page_40_Picture_5.jpeg)

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

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**RUTGERS HEALTH** 

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