Disclosures

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

Outline of Presentation

- AABB Transfusion Guidelines
- MINT Trial methods and results


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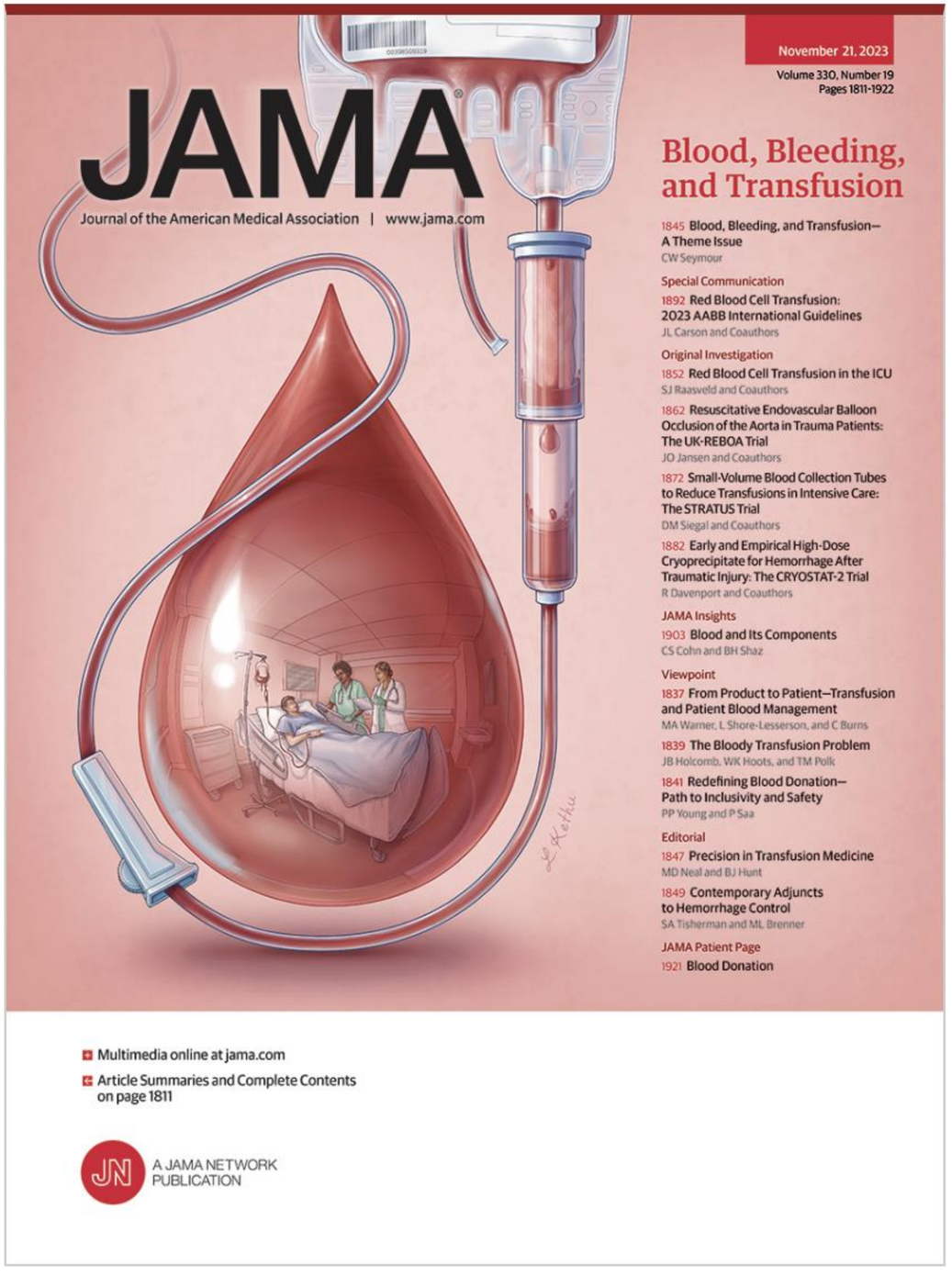


Theme Issue:
Blood, Bleeding, and Transfusion

Editorial

Blood, Bleeding, and Transfusion—A Theme Issue

Christopher W. Seymour, MD, MSc

Special Communication

Red Blood Cell Transfusion: 2023 AABB International Guidelines

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

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

Deborah M. Siegal; et al

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 (No. of RCTs)	Relative effect (95% CI)	Absolute effects, %				
		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
[illegible]	[illegible]	[illegible]	[illegible]	more)	[illegible]	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[a,b]	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[a]	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[b]	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[b]	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, relative risk.

[a] Downgraded for inconsistency.

[b] Downgraded for imprecision. 95% CIs were calculated with Review Manager version 5.4 (Cochrane).[27] See eFigures 1 through 9 in the Supplement for details.

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

Patient group (No. of RCTs)	30-d Mortality relative effect (95% CI)	Absolute effects, %			Certainty
		Restrictive	Liberal	Difference (95% CI)	
Hematologic malignancies, N = 149 (2)	RR, 0.37 (0.07-1.95)	2.4	6.6	4.1 fewer (6.1 fewer to 6.2 more)	Low[a]
Myocardial infarction, N = 820 (3)	RR, 0.99 (0.59-1.65)[b]	6.7	6.8	0.1 fewer (2.8 fewer to 4.4 more)	Low[c,d]

Abbreviations: RCT, randomized controlled trial; RR, relative risk.

[a] Two downgrades for very serious imprecision.

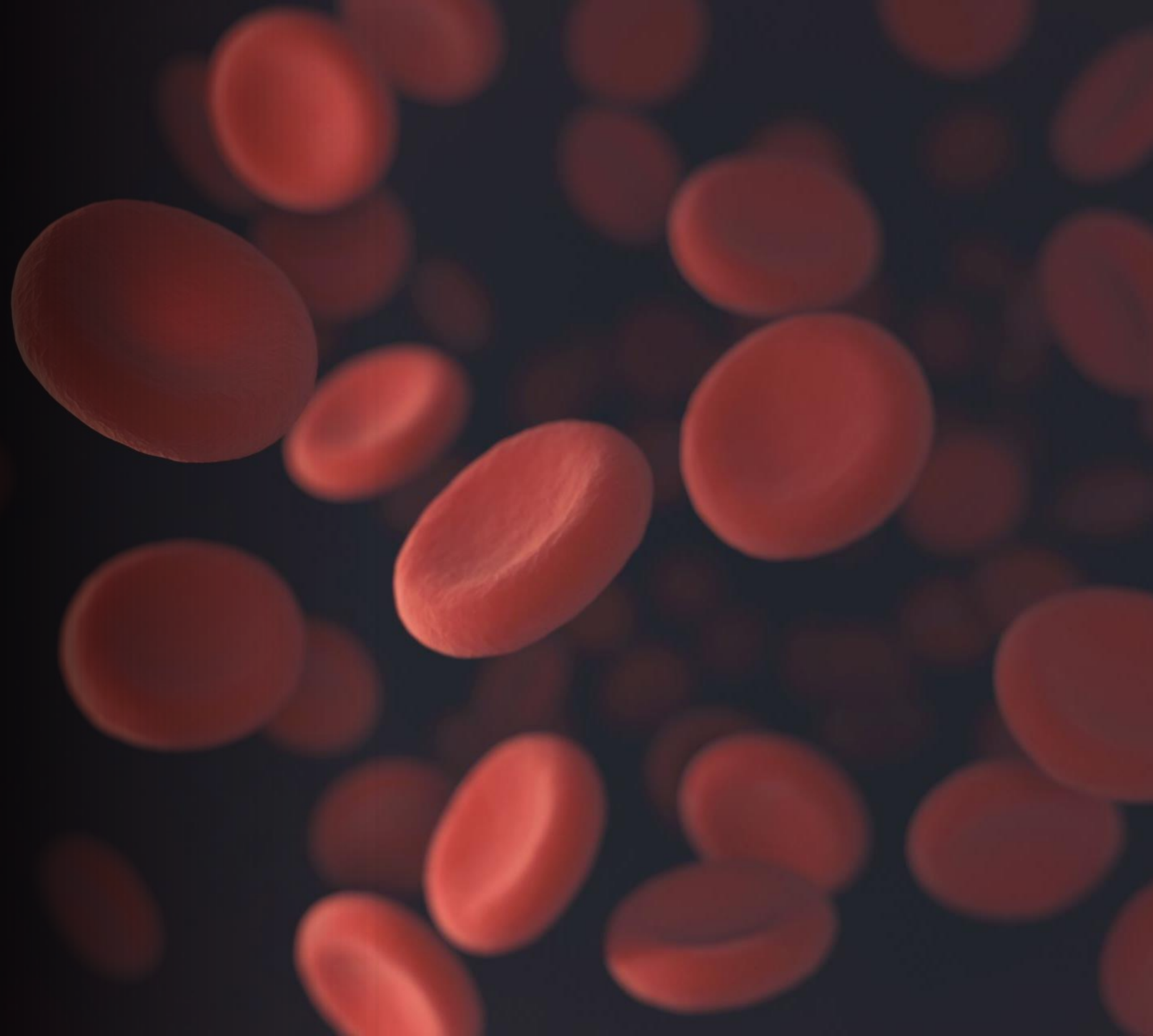
[b] Note that in consultation with a methodologist (GG), a fixed effect model has been presented for this outcome due to low event rate. Random effects model absolute difference = 4.1% more (4.2 fewer and 39.7 more).

[c] Imprecision.

[d] Inconsistency. 95% CIs calculated with Review Manager version 5.4 (Cochrane Collaboration).[27]

JAMA. 2023;330(19):1892-1902.

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.

Good Practice Statement

We consider it good clinical practice in deciding when to transfuse a particular patient to consider not only the hemoglobin level, but also symptoms, signs, other laboratory results, and the overall clinical context.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Restrictive or Liberal Transfusion Strategy in Myocardial Infarction and Anemia

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MINT
Myocardial Ischemia and Transfusion

Jeffrey L Carson, MD
Study Chair and Principal Investigator
Rutgers Robert Wood Johnson Medical School

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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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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


Canada 885
United States 2157
France 323
Brazil 105
Australia 9
New Zealand 25
ARCTIC OCEAN
Greenland
(Denmark)
Svalbard
(Norway)
Iceland
United States
Russia
Canada
Mexico
Caribbean
Central America
Colombia
Venez.
Ecuador
Peru
Bolivia
Paraguay
Chile
Argentina
Uruguay
PACIFIC OCEAN
ATLANTIC OCEAN
INDIAN OCEAN
Norway
Sweden
Finland
Estonia
Latvia
Lithuania
U.K.
Ireland
Belar.
Poland
Ukraine
Mol.
Rom.
Bul.
Armenia
Georg.
Az.
Kazakhstan
Mongolia
Uzbek.
Turkm.
Kyrgyzstan
Tajikistan
China
N.Korea
S.Korea
Japan
Portugal
Spain
France
Italy
Turkey
Cyprus
Greece
Syr.
Lebanon
Iraq
Iran
Afghan.
Pakistan
Nepal
Bhutan
India
Laos
Vietnam
Taiwan
Bur.
Bangl.
Thai.
Cambodia
Philippines
Sri Lanka
Malaysia
Indonesia
Papua New Guinea
Solomon Islands
Fiji
New Caledonia
New Zealand
Morocco
Tunisia
Algeria
Libya
Egypt
Israel
Jordan
Kuwait
Qatar
Saudi Arabia
U.A.E.
Oman
Yemen
Djibouti
Western Sahara
Senegal
Maurit.
Mali
Niger
Chad
Eritrea
Sudan
The Gambia
Guinea-Bissau
Guinea
Sierra Leone
Liberia
B.Faso
Ghana
Togo
Benin
Nigeria
Cam.
C.A.R.
South Sudan
Ethiopia
Somalia
Ken.
Uganda
Rwanda
Burundi
Tanz.
Equatorial Guinea
Gabon
Congo
Dem. Rep. of Congo
Angola
Zambia
Zim.
Bots.
Namibia
South Africa
Lesotho
eSwatini
Mozambique
Malawi
Madagascar

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Inclusions

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

Exclusions

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

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

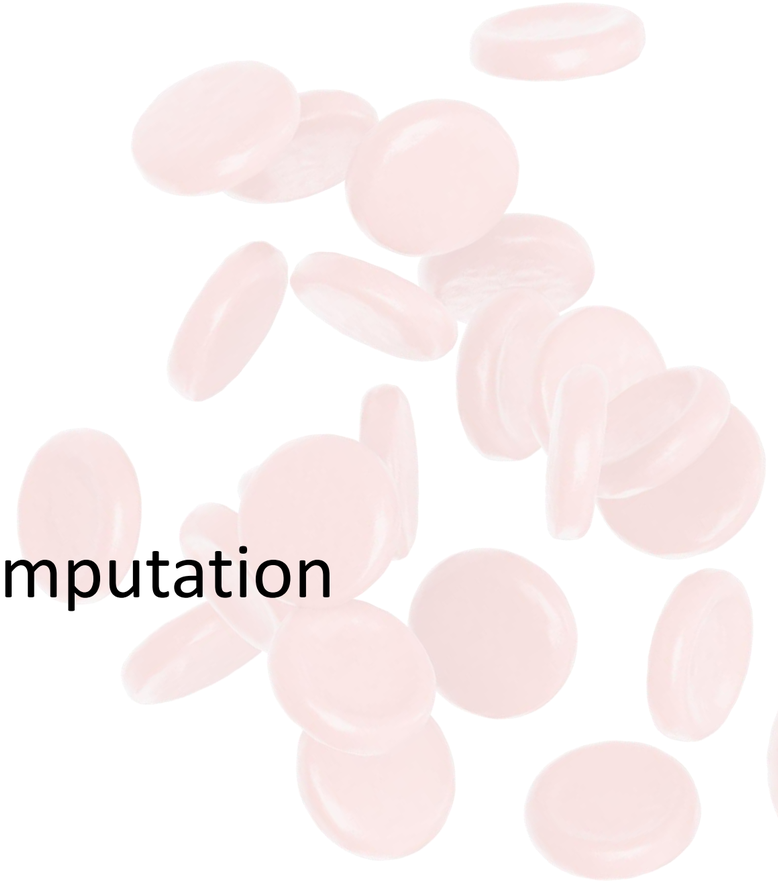
Liberal strategy: 1 unit of packed red blood cells administered following randomization and red blood cells transfused to maintain hemoglobin concentration ≥ 10 g/dL through hospital discharge or 30 days

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

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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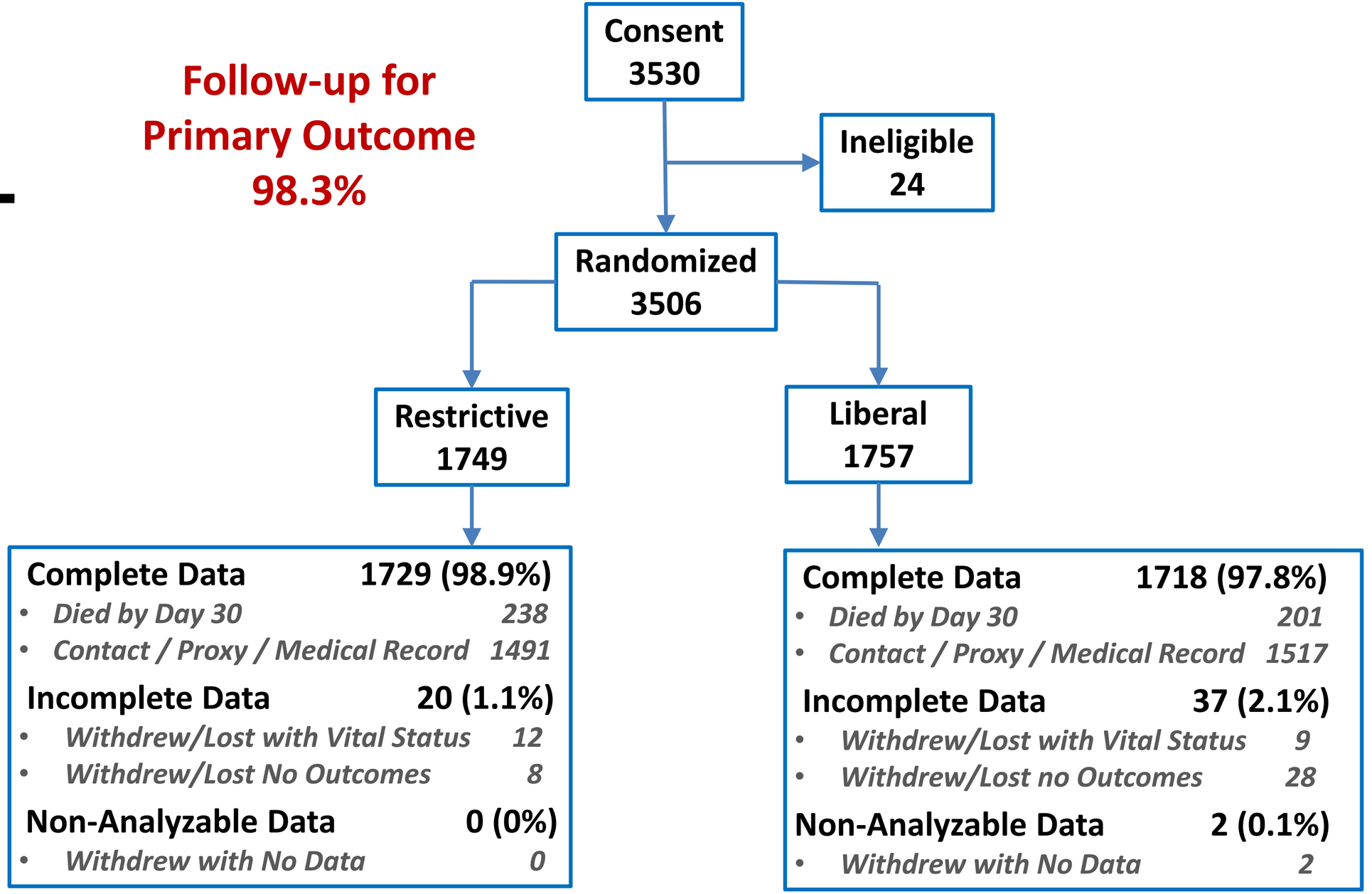
CONSORT Diagram

Follow-up for Primary Outcome 98.3%



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Baseline Characteristics

Characteristic	Restrictive (N=1749)	Liberal (N=1755)
Age in years, mean (SD)	72	72
Female (identity), n (%)	44%	47%
White or Caucasian	78%	78%
Black or African-American	14%	14%
Multivessel CAD >50%	66%	65%
NSTEMI	82%	81%

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Baseline Characteristics

Characteristic	Restrictive (N=1749)	Liberal (N=1755)
Type 1 MI	42%	42%
Type 2 MI	55%	56%
Revascularization prior to randomization	29%	28%
Heart failure in-hospital	22%	23%
LV ejection fraction (%)	47%	48%
Intubated on ventilator	14%	13%
Renal dialysis	12%	12%

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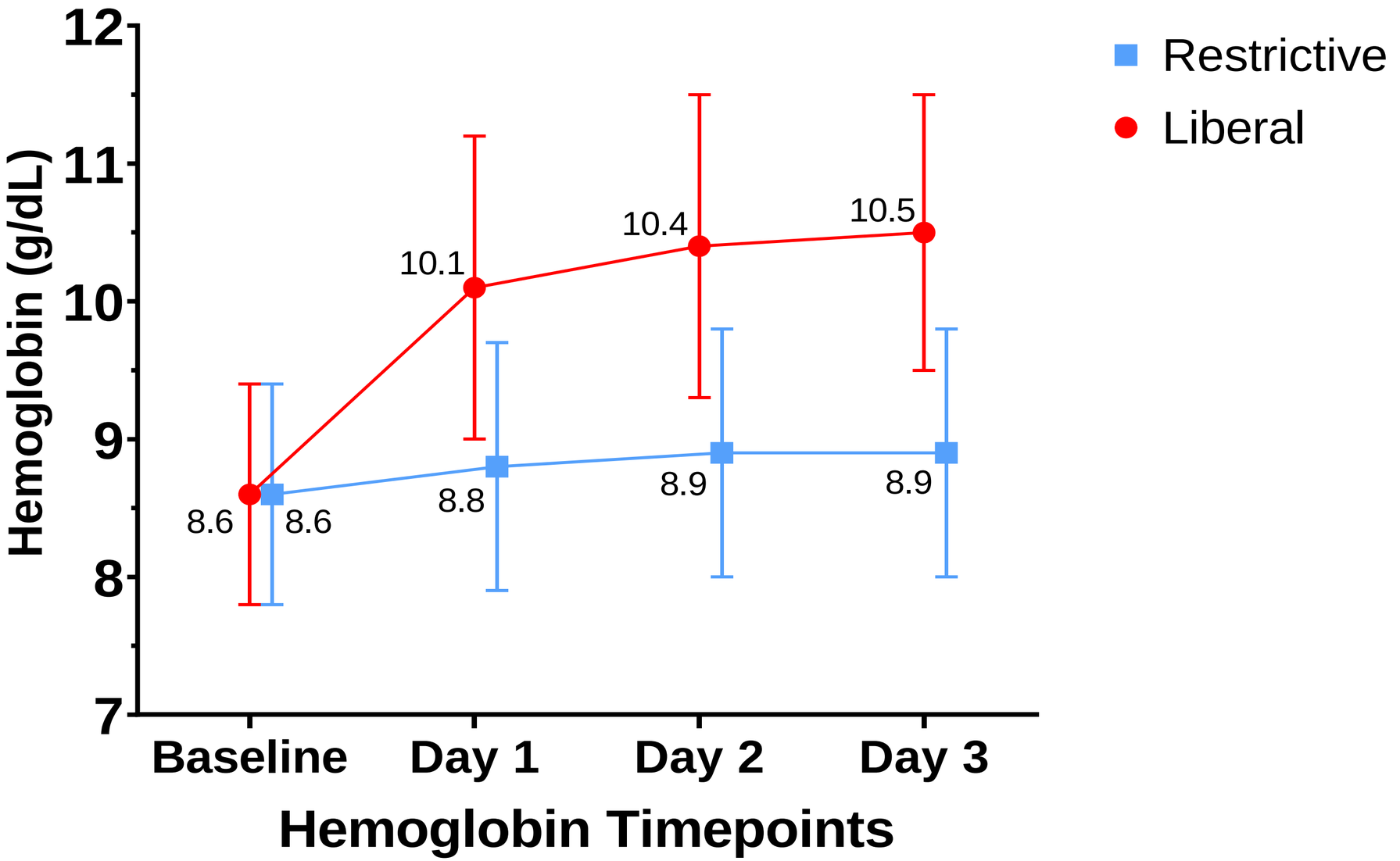
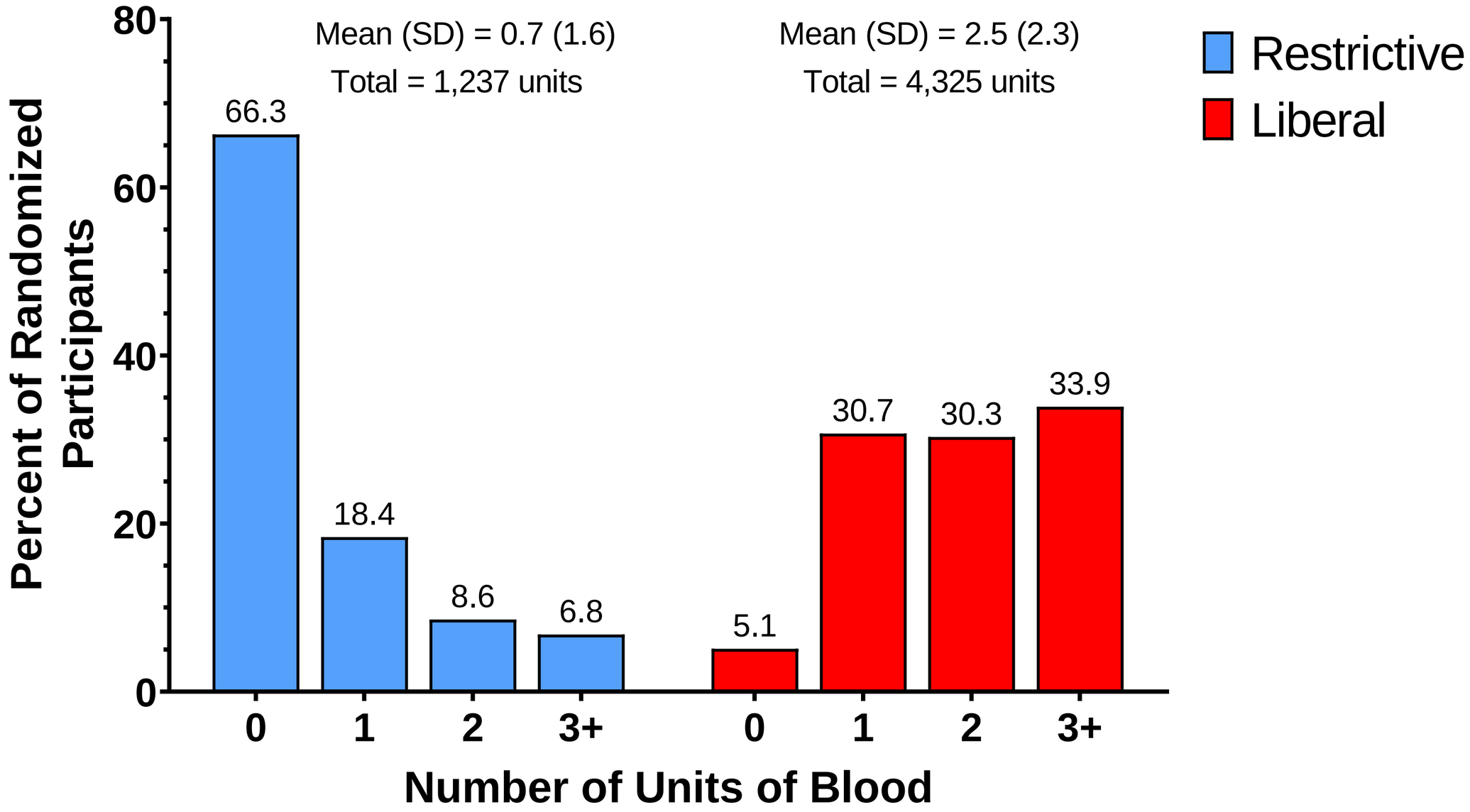
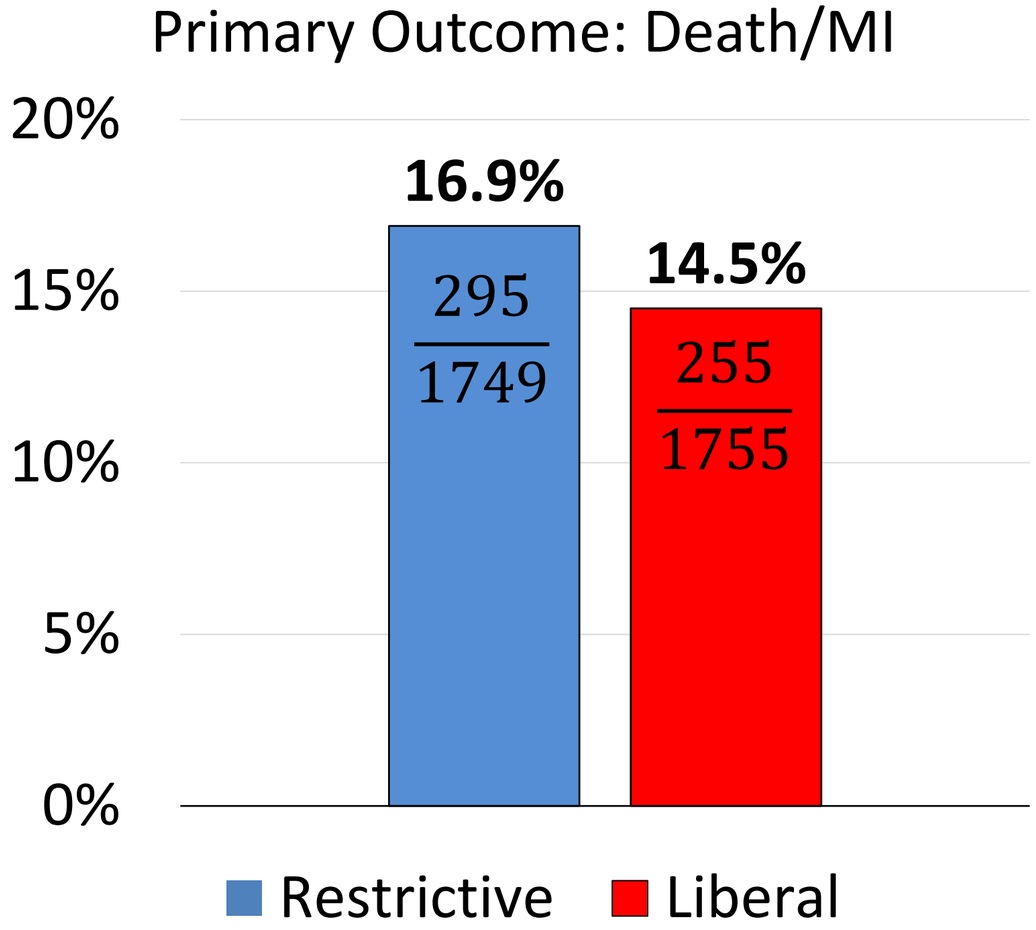
Post-Randomization Hemoglobin by Assigned Strategy



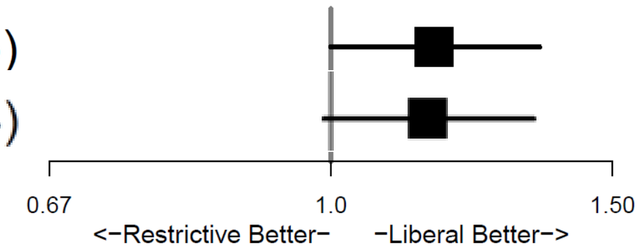
Units of Blood by Assigned Strategy



Primary Outcome

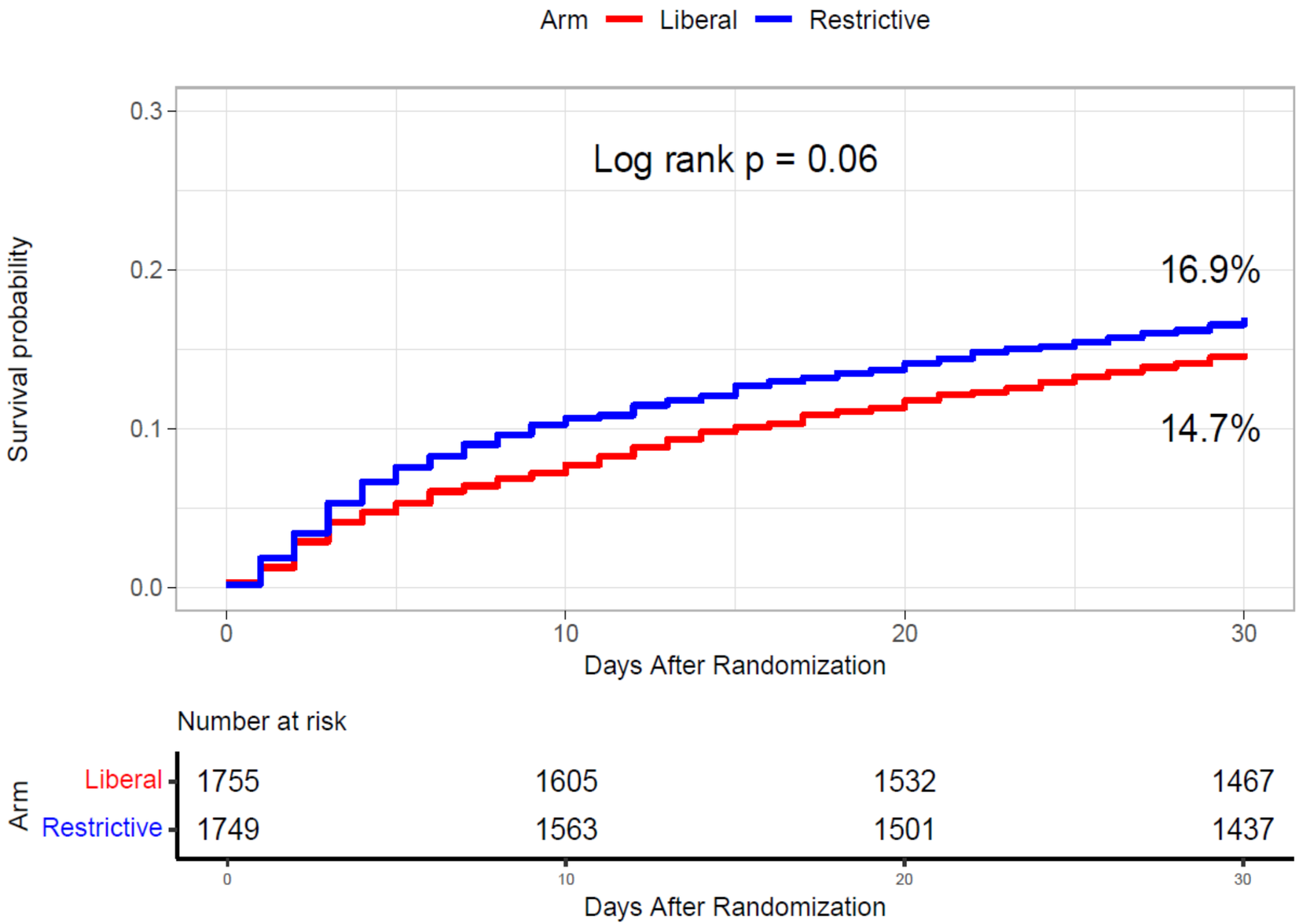


Primary Outcome	RR (95% CI)
Death/MI	1.16 (1.00, 1.35)
Death/MI: Imputed	1.15 (0.99, 1.34)



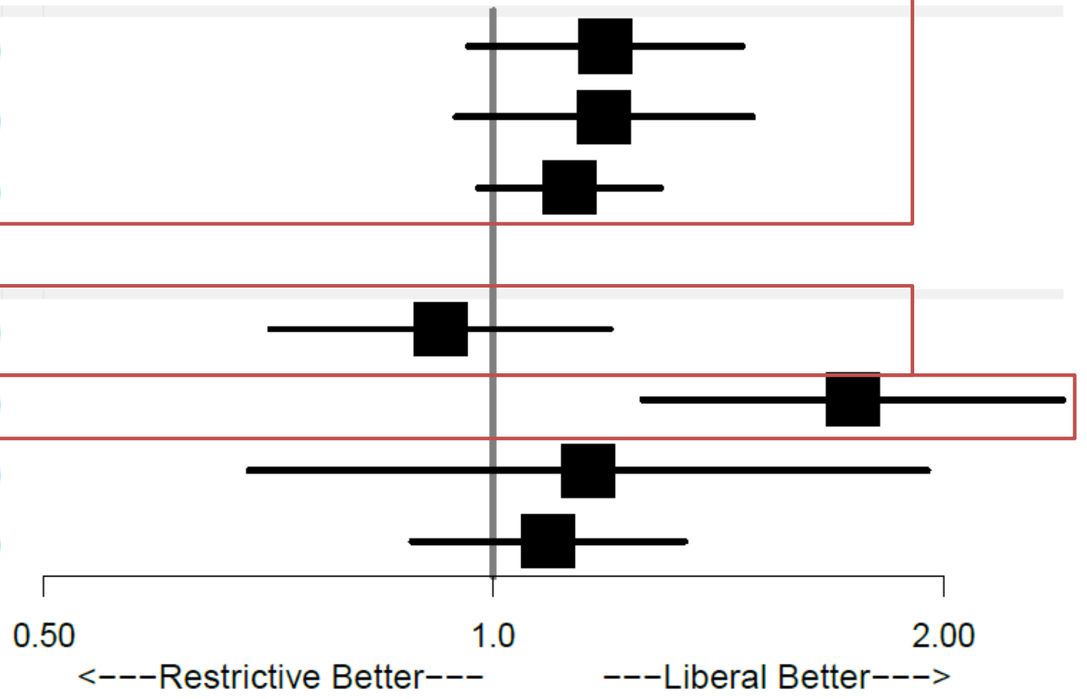
P = 0.07

Primary Outcome Over 30-days

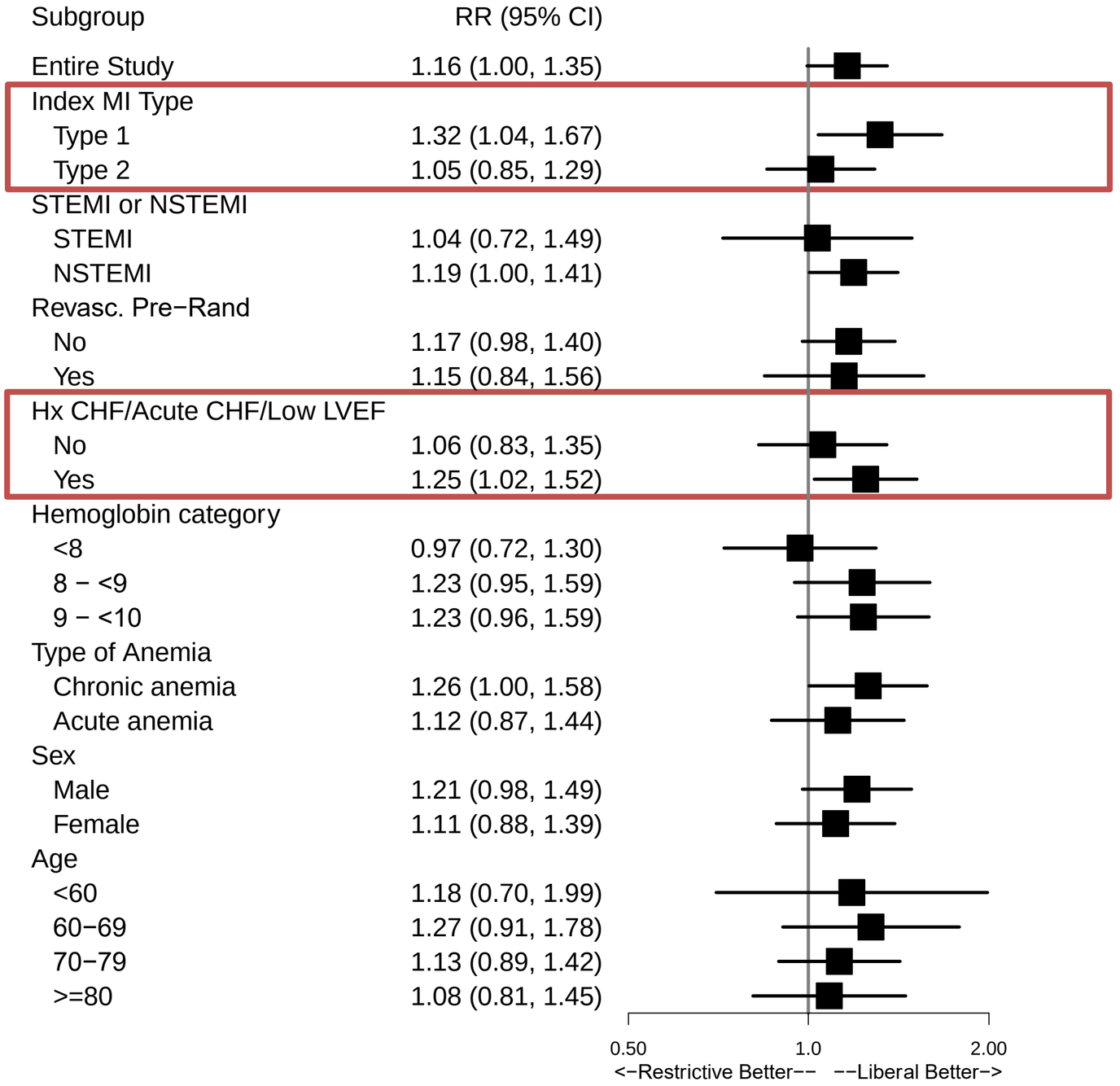


Secondary and Other Outcomes

	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)

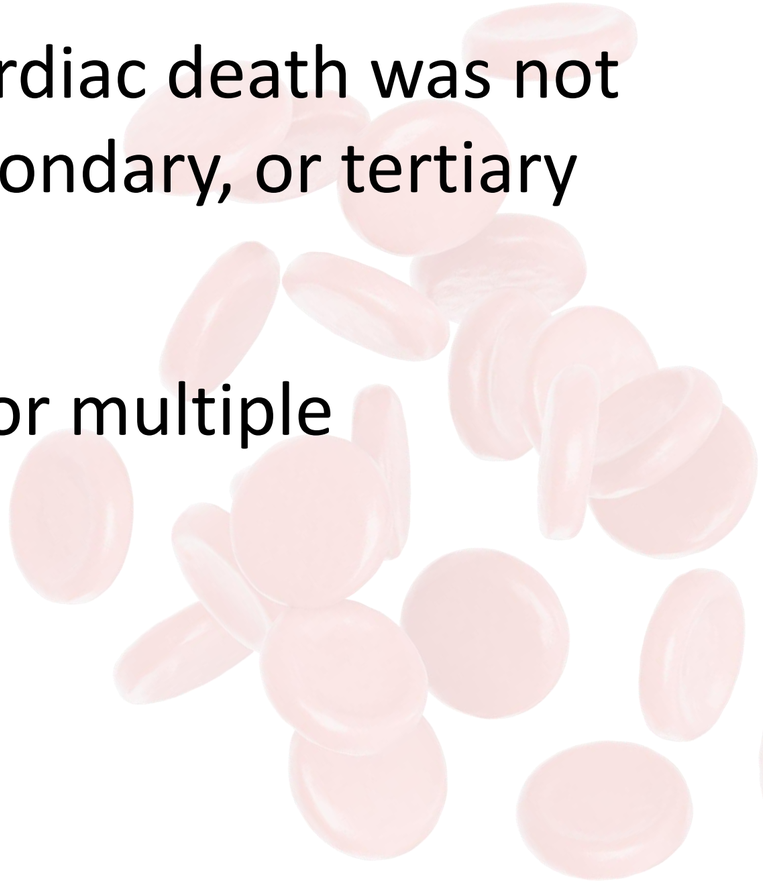


30-day Death or MI by Baseline Pre-specified Subgroups



Limitations

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



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Summary

- The MINT trial did not demonstrate a 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
- While not statistically significant, the point estimates for the primary outcome and secondary outcomes consistently favored a liberal transfusion strategy
- Heart failure and other safety outcomes were comparable in the two transfusion groups

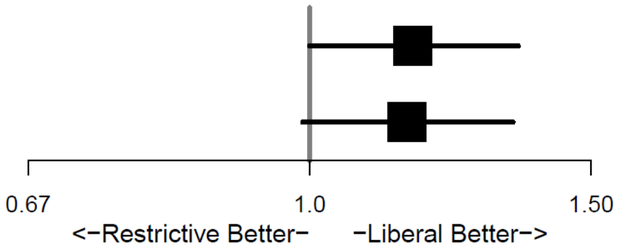
Clinical Implications

- 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 lower confidence interval of 0.99 means that if patient is transfused using the liberal threshold, there is a very small chance that the patient is not benefited.

Primary Outcome	RR (95% CI)
Death/MI	1.16 (1.00, 1.35)
Death/MI: Imputed	1.15 (0.99, 1.34)



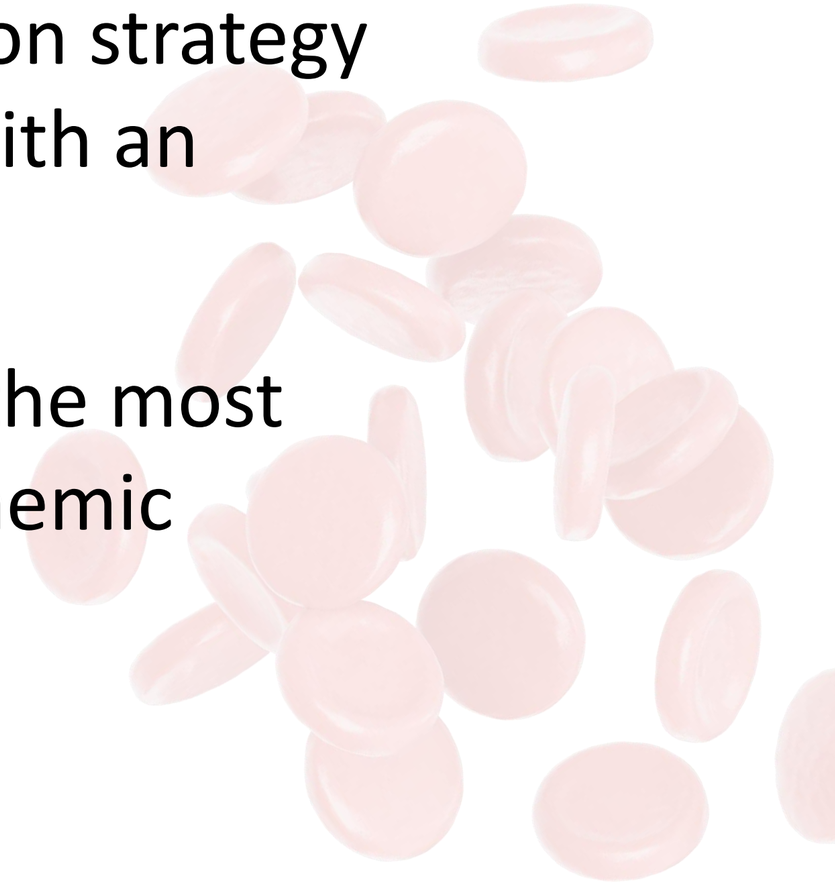
- The relative risk of 1.15 and upper confidence interval of 1.34 suggests that there is a clinically significant benefit; 15% to 34% relative odds that the patient will have less recurrent MI or die within 30 days.

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

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



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

MINT
MYOCARDIAL ISCHEMIA AND TRANSFUSION

NIH
National Heart, Lung, and Blood Institute

RUTGERS HEALTH

University of Pittsburgh
EPIDEMIOLOGY DATA CENTER

BCRI
Brazilian Clinical Research Institute

CIHR IRSC
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