Clinical Implications of the MINT Trial:  \( p=0.07 \)

Jeffrey L Carson, MD
Study Chair and Principal Investigator
Rutgers Robert Wood Johnson Medical School
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
<table>
<thead>
<tr>
<th>Outcome, No. of participants (No. of RCTs)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effects, %</th>
<th>Difference (95% CI)</th>
<th>Certainty</th>
<th>Plain language summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-d Mortality, N = 16092 (30)</td>
<td>RR, 1.00 (0.86-1.16)</td>
<td>8.3</td>
<td>8.3</td>
<td>0.0 Fewer (1.2 fewer to 1.3 more)</td>
<td>High</td>
</tr>
<tr>
<td>MI, N = 14370 (23)</td>
<td>RR, 1.04 (0.87-1.24)</td>
<td>3.3</td>
<td>3.2</td>
<td>0.1 More (0.4 fewer to 0.8 more)</td>
<td>High</td>
</tr>
<tr>
<td>CHF, N = 6610 (15)</td>
<td>RR, 0.86 (0.56-1.33)</td>
<td>3.2</td>
<td>3.7</td>
<td>0.5 Fewer (1.6 fewer to 1.2 more)</td>
<td>Low</td>
</tr>
<tr>
<td>CVA, N = 13985 (19)</td>
<td>RR, 0.84 (0.64-1.09)</td>
<td>1.4</td>
<td>1.7</td>
<td>0.3 Fewer (0.6 fewer to 0.2 more)</td>
<td>High</td>
</tr>
<tr>
<td>Rebleeding, N = 3412 (8)</td>
<td>RR, 0.80 (0.59-1.09)</td>
<td>12.6</td>
<td>15.8</td>
<td>3.2 Fewer (6.5 fewer to 1.4 more)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Infection, N = 16466 (24)</td>
<td>RR, 0.98 (0.89-1.09)</td>
<td>13.6</td>
<td>13.9</td>
<td>0.3 Fewer (1.5 fewer to 1.2 more)</td>
<td>High</td>
</tr>
<tr>
<td>Thromboembolism, N = 4201 (13)</td>
<td>OR, 1.11 (0.65-1.88)</td>
<td>1.7</td>
<td>1.5</td>
<td>0.2 More (0.5 fewer to 1.3 more)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Delirium, N = 6442 (9)</td>
<td>RR, 1.11 (0.88-1.40)</td>
<td>11.9</td>
<td>10.7</td>
<td>1.2 More (1.3 fewer to 4.3 more)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Transfusion, N = 19419 (41)</td>
<td>RR, 0.60 (0.54-0.66)</td>
<td>48.6</td>
<td>81.0</td>
<td>32.4 Fewer (37.3 to 27.5 fewer)</td>
<td>High</td>
</tr>
</tbody>
</table>

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.
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

<table>
<thead>
<tr>
<th>Patient group (No. of RCTs)</th>
<th>30-d Mortality relative effect (95% CI)</th>
<th>Absolute effects, %</th>
<th>Certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Restrictive</td>
<td>Liberal</td>
</tr>
<tr>
<td>Hematologic malignancies, N = 149 (2)</td>
<td>RR, 0.37 (0.07-1.95)</td>
<td>2.4</td>
<td>6.6</td>
</tr>
<tr>
<td>Myocardial infarction, N = 820 (3)</td>
<td>RR, 0.99 (0.59-1.65)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6.7</td>
<td>6.8</td>
</tr>
</tbody>
</table>

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

<sup>a</sup> Two downgrades for very serious imprecision.
<sup>b</sup> 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).
<sup>c</sup> Imprecision.
<sup>d</sup> Inconsistency: 95% CIs calculated with Review Manager version 5.4 (Cochrane Collaboration).<sup>27</sup>
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
Restrictive Blood Transfusion

7 g/dL for Everyone
OR
Different thresholds by clinical subgroup
• 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.
Restrictive or Liberal Transfusion Strategy in Myocardial Infarction and Anemia

Jeffrey L. Carson, MD, Maria Mori Brooks, PhD, Paul C. Hébert MD MHSc, Shaun G. Goodman, MD, MSc, Marnie Bertolet, PhD, Simone A. Glynn, MD, MPH, Bernard R. Chaitman, MD, Tabassome Simon, MD, PhD, Renato D. Lopes MD, PhD, Andrew M. Goldsweig, MD, Andrew P. DeFilippis, MD, MSc, J Dawn Abbott, MD, Brian J. Potter, MDCM SM, Francois Martin Carrier, MD, Sunil V. Rao, MD, Howard A Cooper, MD, Shahab Ghafghazi, MD, Dean A. Fergusson, PhD, William J Kostis, PhD, MD, Helaine Noveck, MPH, Sarang Kim, MD, Meechai Tessalee, MD, Gregory Ducrocq MD, PhD, Pedro Gabriel Melo de Barros e Silva, MD, Darrell J. Triulzi MD, Caroline Alsweiler, MHSc, Mark A Menegus, MD, John D. Neary MD, Lynn Uhl, MD, Jordan B. Strom, MD, MSc, Christopher B. Fordyce, M.D., M.H.S., M.Sc., Emile Ferrari, MD, Johanne Silvain, MD PhD, Frances O. Wood, MD, Benoit Daneault, MD, Tamar S Polonsky, MD, Manohara Senaratne, MD, Etienne Puymirat, MD, Claire Bouleti, MD, Benoit Lattuca, MD, Harvey D White, MD, Sheryl F Kelsey, PhD, Philippe Gabriel Steg, MD, John H. Alexander, MD, MHS, for the MINT Investigators
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
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
Enrollment
Completed
April 17, 2023
CONSORT Diagram

Follow-up for Primary Outcome 98.3%

Consent 3530
  -> Ineligible 24

Randomized 3506
  -> Restrictive 1749
  -> Liberal 1757

Complete Data 1729 (98.9%)
  - Died by Day 30 238
  - Contact / Proxy / Medical Record 1491

Incomplete Data 20 (1.1%)
  - Withdrew/Lost with Vital Status 12
  - Withdrew/Lost No Outcomes 8

Non-Analyzable Data 0 (0%)
  - Withdrew with No Data 0

Complete Data 1718 (97.8%)
  - Died by Day 30 201
  - Contact / Proxy / Medical Record 1517

Incomplete Data 37 (2.1%)
  - Withdrew/Lost with Vital Status 9
  - Withdrew/Lost no Outcomes 28

Non-Analyzable Data 2 (0.1%)
  - Withdrew with No Data 2
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Restrictive (N=1749)</th>
<th>Liberal (N=1755)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>Female (identity), n (%)</td>
<td>44%</td>
<td>47%</td>
</tr>
<tr>
<td>White or Caucasian</td>
<td>78%</td>
<td>78%</td>
</tr>
<tr>
<td>Black or African-American</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Multivessel CAD &gt;50%</td>
<td>66%</td>
<td>65%</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>82%</td>
<td>81%</td>
</tr>
</tbody>
</table>
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Restrictive (N=1749)</th>
<th>Liberal (N=1755)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 MI</td>
<td>42%</td>
<td>42%</td>
</tr>
<tr>
<td>Type 2 MI</td>
<td>55%</td>
<td>56%</td>
</tr>
<tr>
<td>Revascularization prior to randomization</td>
<td>29%</td>
<td>28%</td>
</tr>
<tr>
<td>Heart failure in-hospital</td>
<td>22%</td>
<td>23%</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>47%</td>
<td>48%</td>
</tr>
<tr>
<td>Intubated on ventilator</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>Renal dialysis</td>
<td>12%</td>
<td>12%</td>
</tr>
</tbody>
</table>
## Implementation of Transfusion Protocol

<table>
<thead>
<tr>
<th>Reason</th>
<th>Restrictive 46 of 1749 2.6%</th>
<th>Liberal 241 of 1755 13.7%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical reason (e.g. surgery, bleeding)</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>Adverse risks of transfusion (e.g., fluid overload, dialysis, transfusion reactions)</td>
<td>-</td>
<td>89</td>
</tr>
<tr>
<td>Participant preference</td>
<td>4</td>
<td>68</td>
</tr>
<tr>
<td>Provider preference</td>
<td>11</td>
<td>53</td>
</tr>
<tr>
<td>Other reasons (e.g., blood supply and staffing shortages)</td>
<td>7</td>
<td>31</td>
</tr>
</tbody>
</table>
Post-Randomization Hemoglobin by Assigned Strategy

<table>
<thead>
<tr>
<th>Hemoglobin Timepoints</th>
<th>Liberal</th>
<th>Restrictive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.6</td>
<td>8.6</td>
</tr>
<tr>
<td>Day 1</td>
<td>10.1</td>
<td>8.8</td>
</tr>
<tr>
<td>Day 2</td>
<td>10.4</td>
<td>8.9</td>
</tr>
<tr>
<td>Day 3</td>
<td>10.5</td>
<td>8.9</td>
</tr>
</tbody>
</table>

**Graph:**
- **Restrictive** line starts at 8.6 and increases to 8.8, then 8.9, and finally 8.9 over the days.
- **Liberal** line starts at 8.6 and increases to 10.1, then 10.4, and finally 10.5 over the days.
Units of Blood by Assigned Strategy

<table>
<thead>
<tr>
<th>Number of Units of Blood</th>
<th>Restrictive Mean (SD)</th>
<th>Liberal Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.7 (1.6)</td>
<td>2.5 (2.3)</td>
</tr>
<tr>
<td>1</td>
<td>Total = 1,237 units</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>66.3</td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>18.4</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6.8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>30.7</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>30.3</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>33.9</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total = 4,325 units
Primary Outcome

Primary Outcome: Death/MI

- **Restrictive**: 16.9% (295/1749)
- **Liberal**: 14.5% (255/1755)

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

Log rank $p = 0.06$

Survival probability

Days After Randomization

Number at risk

<table>
<thead>
<tr>
<th>Arm</th>
<th>Liberal</th>
<th>Restrictive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1755</td>
<td>1749</td>
</tr>
<tr>
<td></td>
<td>1605</td>
<td>1563</td>
</tr>
<tr>
<td></td>
<td>1532</td>
<td>1501</td>
</tr>
<tr>
<td></td>
<td>1467</td>
<td>1437</td>
</tr>
</tbody>
</table>
### Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Restrictive %</th>
<th>Liberal %</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>9.9%</td>
<td>8.3%</td>
<td>1.19 (0.96, 1.47)</td>
</tr>
<tr>
<td>MI</td>
<td>8.5%</td>
<td>7.2%</td>
<td>1.19 (0.94, 1.49)</td>
</tr>
<tr>
<td>Death/MI/Rev/Readmit</td>
<td>19.6%</td>
<td>17.4%</td>
<td>1.13 (0.98, 1.29)</td>
</tr>
</tbody>
</table>

### Other Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Restrictive %</th>
<th>Liberal %</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure</td>
<td>5.8%</td>
<td>6.3%</td>
<td>0.92 (0.71, 1.20)</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>5.5%</td>
<td>3.2%</td>
<td>1.74 (1.26, 2.40)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.7%</td>
<td>1.5%</td>
<td>1.16 (0.69, 1.95)</td>
</tr>
<tr>
<td>Pneumonia/Bacteremia</td>
<td>9.5%</td>
<td>8.7%</td>
<td>1.09 (0.88, 1.34)</td>
</tr>
</tbody>
</table>

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<----Restrictive Better----> 1.0 <----Liberal Better---->
# 30-day Death or MI by Baseline Pre-specified Subgroups

## Entire Study
- RR (95% CI): 1.16 (1.00, 1.35)

## Index MI Type
- **Type 1**: RR (95% CI): 1.32 (1.04, 1.67)
- **Type 2**: RR (95% CI): 1.05 (0.85, 1.29)

## STEMI or NSTEMI
- **STEMI**: RR (95% CI): 1.04 (0.72, 1.49)
- **NSTEMI**: RR (95% CI): 1.19 (1.00, 1.41)

## Revasc. Pre-Rand
- **No**: RR (95% CI): 1.17 (0.98, 1.40)
- **Yes**: RR (95% CI): 1.15 (0.84, 1.56)

## Hx CHF/Acute CHF/Low LVEF
- **No**: RR (95% CI): 1.06 (0.83, 1.35)
- **Yes**: RR (95% CI): 1.25 (1.02, 1.52)

## Hemoglobin category
- **<8**: RR (95% CI): 0.97 (0.72, 1.30)
- **8 – <9**: RR (95% CI): 1.23 (0.95, 1.59)
- **9 – <10**: RR (95% CI): 1.23 (0.96, 1.59)

## Type of Anemia
- **Chronic anemia**: RR (95% CI): 1.26 (1.00, 1.58)
- **Acute anemia**: RR (95% CI): 1.12 (0.87, 1.44)

## Sex
- **Male**: RR (95% CI): 1.21 (0.98, 1.49)
- **Female**: RR (95% CI): 1.11 (0.88, 1.39)

## Age
- **<60**: RR (95% CI): 1.18 (0.70, 1.99)
- **60–69**: RR (95% CI): 1.27 (0.91, 1.78)
- **70–79**: RR (95% CI): 1.13 (0.89, 1.42)
- **>=80**: RR (95% CI): 1.08 (0.81, 1.45)
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
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
The primary outcome RR confidence interval for restrictive versus liberal strategy is (0.99, 1.34).

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%.
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.
Other Challenges
NCDR

- The National Cardiovascular Data Registry (NCDR®) 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.
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 well-powered 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 non-inferiority of the restrictive strategy.
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.
Thanks to the MINT Investigator team and to all of the MINT trial participants!