Critical Review Form
Therapy

PGY-2

HYPERLINK "http://pmid.us/37952133"Carson JL, Brooks MM, Hébert PC, et al; MINT Investigators. Restrictive or Liberal Transfusion Strategy in Myocardial Infarction and Anemia. N Engl J Med. 2023 Dec 28;389(26):2446-2456.

Objectives: **"to deter- mine whether the risk of death or myocardial infarction through 30 days differed between a restrictive transfusion strategy (hemoglobin threshold, 7 to 8 g per deciliter) and a liberal transfusion strategy (hemoglobin threshold, <10 g per deciliter) among patients with an acute myocardial infarction and anemia." (p. 2447)**

Methods: **This open label, randomized controlled trial was conducted at 144 sites in the US, Canada, France, Brazil, New Zealand, and Australia between April 2017 and April 2023. Adult patients ≥ 18 years of age with STEMI or NSTEMI along with anemia (defined as hemoglobin < 10 g/dL within 24 hours prior to randomization) were eligible or enrollment. Exclusion criteria were uncontrolled bleeding, palliative treatment, cardiac surgery during the admission, or refusal to receive blood products.**

Patients were randomized in a 1:1 fashion to either a restrictive or liberal transfusion strategy. In the restrictive group, transfusion was permitted (not required) for hemoglobin < 8 g/dL and strongly recommended for hemoglobin < 7 g/dL. In the liberal group, one unit of PRBCs was administered after randomization, and red cells were transfused to maintain the hemoglobin level at or above 10 g/dL until hospital discharge or 30 days. Patients were contacted by telephone at 30 days after randomization to assess vital status, quality of life, and need for repeat ED visit or readmission; patients were also contacted at 6 months to assess vital status.

The primary outcome was a composite of myocardial infarction or death at 30 days. Secondary outcomes included MI at 30 days; death at 30 days; and a composite of death, MI, ischemia-driven unscheduled coronary revascularization, or readmission for an ischemic cardiac condition within 30 days.

A total of 3506 patients were enrolled and included in the analysis during the study period. The mean age was 72.1 years and 45.5% were women. A type 2 MI was seen in 55.8% of patients and type 1 MI was seen in 41.7% of patients. The mean baseline hemoglobin was 8.6 g/dL in both groups.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	Yes. "Patients were randomly assigned in a 1:1 ratio to a restrictive or liberal transfusion strategy by means of a Web-based system and a permuted-block design with random block sizes of 4 and 6, stratified according to clinical site." (p. 2447)
2.	Was allocation concealed? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Yes. "The randomization sequence was created at the data coordinating center by an independent statistician." (p. 2447) This should be sufficient to maintain allocation concealment.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "All the analyses were conducted in the intention-to-treat population with two-sided hypothesis tests for superiority." (p. 2448) There were 46 patients in the restrictive group (2.6%) and 241 patients in the liberal group (13.7%) for whom the protocol was discontinued; these patients were analyzed in the group to which they were assigned.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, gender, race, medical history, presence of multivessel CAD, left ventricular ejection fraction, NSTEMI type, baseline hemoglobin, and need for dialysis or mechanical ventilation prior to randomization.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	Yes. "After randomization, the transfusion strategy was not masked to site investigators or patients." (p. 2448) While blinding would have been difficulty given the interventions, it is possible that performance bias contributed to outcomes.
2.	Were clinicians aware of group allocation?	Yes. See above.
3.	Were outcome assessors aware of group allocation?	Some were. "The clinical events committee, whose members were unaware of treatment assignments, systematically screened for suspected recurrent myocardial infarction by examining all recorded troponin values, and clinical sites reported suspected

		myocardial infarction." (p. 2448) There is no mention of blinding of outcome assessors to other outcomes.
4.	Was follow-up complete?	Yes for 98% of patients.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• The mean hemoglobin level on days 1 and 3 were lower in the restrictive group than the liberal group by 1.3 g/dL (95% CI 1.2 to 1.4) and 1.6 g/dL (95% CI 1.5 to 1.7), respectively. • Patients in the liberal group received 3.5 times the mean number of units of RBCs during hospitalization than the restrictive group (2.5 vs. 0.7 units). • The primary outcome occurred with slightly higher frequency in the restrictive group compared to the liberal group: 16.9% vs. 14.5%, unadjusted risk ratio 1.16 (95% CI 1.00 to 1.35). ○ Following adjustment for site and loss to follow-up the risk ratio was 1.15 (95% CI 0.99 to 1.34). • There was no statistically significant difference in the rates of death (RR 1.19, 95% CI 0.96 to 1.47) or MI (RR 1.19, 95% CI 0.94 to 1.49) at 30 days. • The composite of death, MI, ischemic-driven unscheduled revascularization, or hospital readmission for an ischemic cardiac condition occurred with similar frequency in the two group (RR 1.13, 95% CI 0.98 to 1.29). • Cardiac death was more common in the restrictive-strategy group than in the liberal-strategy group (5.5% and 3.2; RR 1.74; 95% CI, 1.26 to 2.40). • The risk of heart failure at 30 days was similar in the restrictive-strategy group and the liberal-strategy group (RR 0.92; 95% CI, 0.71 to 1.20), although there were fewer transfusion-associated cardiac overload (TACO) events in the restrictive-strategy group than in the liberal-strategy group (RR 0.35; 95% CI, 0.16 to 0.78).
2.	How precise was the estimate of the treatment effect?	See above. This was a large study with relatively narrow confidence intervals.
III.	**How can I apply the results to patient care?**	

1.	Were the study patients similar to my patient?	Likely yes. While this was an international trial conducted at centers in the US, Canada, France, Brazil, New Zealand, and Australia, and while the authors do not specify how many participants were recruited from each country, it is likely that patients, providers, and clinical care was similar enough to those in our institution for us to apply the results (external validity).
2.	Were all clinically important outcomes considered?	Yes. The authors considered a very wide array of outcomes, including mortality, MI, unscheduled coronary revascularization, readmission, heart failure, stroke, and transfusion-associated cardiac overload (TACO).
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. While there was no statistically significant difference in the primary composite outcome, there was a very clear trend toward better outcomes in the liberal strategy group compared to the restrictive strategy group, both for the primary outcome, mortality alone, and MI alone. These results unfortunately make it less clear what threshold should be used for transfusion in patients with anemia and active myocardial infarction.

Limitations:

1. **This was, understandably, an open-label trial with no blinding of participants or clinicians; it is possible that some degree of performance bias may have influenced outcomes.**

2. **The myocardial infarction requirement for enrollment was not centrally adjudicated and was not strictly defined by the authors.**

3. **Adherence to the hemoglobin threshold of less than 10 g per deciliter in the liberal-strategy group was moderate (86.3% at hospital discharge).**

4. **The study was designed to detect a 20% difference in the primary outcome between groups, and hence the 15% difference observed did not achieve statistical significance, while being potentially clinically significant (study power).**

Bottom Line:

This large, international, multicenter trial comparing a liberal versus restrictive transfusion strategy for patients with anemia and myocardial infarction found no statistically significant difference in the primary composite outcome of myocardial infarction or death at 30 days (risk ratio 1.16 95% CI 1.00 to 1.35), but a trend towards improved outcome with the liberal strategy.