Critical Review Form
Therapy

HYPERLINK "http://pmid.us/33560322"[Ducrocq G, Gonzalez-Juanatey JR, Puymirat E; REALITY Investigators. Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Major Cardiovascular Events Among Patients With Acute Myocardial Infarction and Anemia: The REALITY Randomized Clinical Trial. JAMA. 2021 Feb 9;325(6):552-560.](http://pmid.us/33560322)

Objectives: "to determine whether a restrictive transfusion strategy was clinically noninferior to a liberal transfusion strategy." (p. 553)

Methods: This international, multicenter, non-inferiority, randomized controlled trials was conducted at 26 centers in France and 9 centers in Spain between March 2016 and September 2019. Patients aged 18 years and older with symptoms of myocardial ischemia within the 48 hours before admission, with elevated cardiac biomarkers and a hemoglobin between 7 and 10 g/dL, were eligible for inclusion. Exclusion criteria were shock (SBP < 90 mmHg with signs of low output or the need for inotropic drugs), myocardial infarction after percutaneous intervention or coronary artery bypass grafting, life-threatening or massive ongoing bleeding, blood transfusion in the previous 30 days, and malignant hematologic disease.

Patients were assigned in a 1:1 fashion to restrictive or liberal transfusion strategies. Patients in the restrictive strategy group were not to receive a transfusion unless their hemoglobin dropped to 8 g/dL or less, with a post-transfusion target of 8-10 g/dL. Patients in the liberal strategy group were to receive transfusions for a hemoglobin of 10 g/dL or less, with a post-transfusion target of 11 g/dL or higher. These strategies were to be maintained until hospital discharge (or up to 30 days of hospitalization).

Follow-up was obtained at around 30 days after discharge by visit, phone call, or mail. The primary outcome was a composite of major adverse cardiovascular events (MACE) at 30 days, including all-cause death, nonfatal stroke, nonfatal recurrent myocardial infarction, or emergency revascularization. Secondary outcomes included individual components of MACE at 30 days and 1 year (to be reported separately) and adverse events (including transfusion reactions) during the hospital stay.

A total of 666 patients with AMI and anemia were enrolled and randomized, with 342 randomized to a restrictive transfusion strategy and 324 to a liberal transfusion strategy. The median age was 77 years and 57.8% were male.

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 undergo a restrictive or a liberal transfusion strategy. A web-based randomization system was used, with a centralized block randomization list with blocks of varying size (range, 2-6), stratified by center." (p. 553)
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 use of a web-based randomization system and varying-sized blocks should be adequate to maintain allocation concealment and prevent subversion of the randomization process.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "All secondary analyses were performed on the as-randomized population with available data." (p. 556) This was an intention to treat analysis. Fifteen patients in the restrictive group and 2 in the liberal group were not treated according to protocol but were still analyzed based on group assignment. A secondary "as-treated" analysis was also performed.
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, BMI, baseline hemoglobin concentration, medical comorbidities, cardiac history, and nature of AMI (STEMI vs. NSTEMI).
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	Yes. Given the intervention it would have been very difficult to blind patients to group allocation.
2.	Were clinicians aware of group allocation?	Yes. Again, given the interventions it would have been difficult to blinding clinicians (and other staff) to group allocation. It is possible that performance bias on the part of those caring for the patient could have affected outcomes.
3.	Were outcome assessors aware of group allocation?	No. While the authors report that "Group assignment was not blinded for data collection," (p. 553) "All components of the primary efficacy clinical outcome as well as acute heart failure were adjudicated by a critical event committee blinded to treatment

		assignment and hemoglobin levels." (p. 554)
		This study is at low risk of observer bias.
4.	Was follow-up complete?	Yes. "Follow-up data for 30-day MACE were complete for all 666 patients who consented and were randomized." (p. 557)
II.	**What are the results ?**	
1.	How large was the treatment effect?	122 patients in the restrictive group (35.7%) and 323 in the liberal group (99.7%) received at least one transfusion. - Median hospital length of stay was 7.0 days in both groups. In the as-randomized analysis, 30-day MACE occurred with similar frequency in the restrictive (11.1%) and liberal (14.2%) groups: RR 0.78, 1-sided 97.5% CI 0.00 to 1.17. - These results fulfill the criteria for noninferiority. - The restrictive strategy did NOT meet criteria for superiority when compared to the liberal strategy (upper bound of 1-sided 97.5% CI > 1.00). - All-cause death occurred in 5.6% of the restrictive group and 7.7% of the liberal group. - Nonfatal recurrent MI occurred in 2.1% of the restrictive group and 3.1% of the liberal group. - Emergency revascularization occurred in 1.5% of the restrictive group and 1.9% of the liberal group. - Nonfatal stroke occurred in 0.6% of patients in both groups. - There were higher incidences of acute lung injury/ARDS (2.2% vs. 0.3%), multiorgan system dysfunction (0.9% vs. 0.3%), and infection (1.5% vs. 0%) in the liberal transfusion group.
2.	How precise was the estimate of the treatment effect?	See above. This was a relatively large study with resulting 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 study was conducted at multiple centers in France and Spain, given the nature of the intervention—which would not be changed by location—and the fact that all patients enrolled had an

		acute MI, I suspect these results would be generalizable to our patient population.
2.	Were all clinically important outcomes considered?	Yes. The patients evaluated multiple outcomes, including death, myocardial infarction, unscheduled revascularization, stroke, development of CHF. and the incidence of potential adverse transfusion reactions.
3.	Are the likely treatment benefits worth the potential harm and costs?	Yes. This study demonstrated that a restrictive blood transfusion strategy for patients with anemia in the setting of acute myocardial infarction was not inferior to a liberal transfusion strategy. There was a statistically nonsignificant trend towards a decrease in the composite outcome with a restrictive strategy (RR 0.78, 1-sided 97.5% CI 0.00 to 1.17) and fewer adverse transfusion reactions

Limitations:

1. **The chose to include a <u>composite outcome</u>, the components of which are not equal in terms of their impact.**

2. **Due to the nature of the intervention, <u>blinding</u> of patients and clinicians would have been extremely difficult. There is a very real risk of <u>performance bias</u> influencing the results.**

3. **The authors report that the components of the 30-day outcome were assessed by visit, phone call, or mail. They do not specify how many patients in each group were followed by each modality. It is unclear how accurate each modality would be for the outcomes (aside from death).**

Bottom Line:

This large, multicenter trial conducted in France and Spain comparing a restrictive blood transfusion strategy to a more liberal strategy among anemic patients with acute myocardial infarction found the restrictive strategy to be noninferior to the liberal strategy (RR 0.78, 1-sided 97.5% CI 0.00 to 1.17) with regards to a composite outcome of death, stroke, recurrent MI, or need for emergent revascularization at 30 days.