Restrictive or liberal transfusion strategy in myocardial infarction and anemia Webinar Q&A

This Q&A was developed to support implementation of the *MINT Trial*.

Trial Design and Interpretation

Q: Would you apply the interpretation of this data differently for type 1 versus type 2 myocardial infarction (MI)?

> A: The trial showed consistent effects across MI types but suggested potential benefit for the liberal strategy in type 1 MI in subgroup analysis.

Q: How was a liberal threshold of 10 g/dL vs 9 g/dL chosen?

> A: The cutoffs chosen are administrative and easier to apply in trials. Historically, 10 g/dL threshold has been used. Also, data in Jehovah Witness cohort study suggests that mortality starts to rise around 10 g/dL. A key design issue is to create two groups that have clinically meaningful differences in hemoglobin levels and frequency of transfusions.

Q: Although the trial protocol is an administrative threshold, the actual hemoglobin levels in the trial differ and range across patients. Does this affect the results?

> A: Trial design aims for clinically significant differences between the liberal and restrictive groups. It is possible that the range in actual levels in the patients during the trial might not significantly affect the outcomes.

Q: The supplemental materials show differences in the most serious transfusion reactions between the arms. Should we determine the risk ratio and its clinical significance?

> A: It is correct and not surprising that serious transfusion reactions occurred more frequently in the liberal transfusion strategy than the restrictive transfusion strategy since these patients received more blood transfusions. However, what is most important is that the rate of these reactions was very low. Further, the most important outcomes such as death and MI were more common in the restrictive transfusion strategy.

Q: How might prior transfusion in 1/3 of the patients before study enrollment have affected the results?

> A: Prior transfusions might reflect unique patient populations but could potentially influence trial outcomes, but likely biasing the trial towards the null hypothesis.

Q: Can you comment on the differences in protocol violation between the two arms (e.g., discontinuation and adherence differences)?

A: There were meaningful differences in adherence to transfusion protocol between the restrictive and liberal transfusion strategies. Discontinuation of the protocol in the restrictive-strategy group occurred in 46 patients (2.6%); 24 of these discontinuations were for clinical reasons, including surgery and bleeding. Discontinuation of the protocol in the liberal-strategy group occurred in 241 patients (13.7%); clinical reasons were provided for 89 of these patients and included adverse effects, fluid overload, dialysis, and transfusion reactions. Other reasons for discontinuation were patient preference (in 68), provider preference (in 53), and other reasons (in 31), including blood-supply shortages and staffing issues.

It is likely that adherence led to smaller differences in hemoglobin levels and transfusions between the two arms of the trial. This would make it more difficult to show differences in clinical outcomes. Further this reflects actual clinical decisions made by physicians and might be attributed to various factors, including adverse reactions and fluid overload in the liberal arm.

Q: Cardiac death was not adjudicated. How might this have affected the results?

A: Lack of adjudication for cardiac death highlights a limitation in the certainty for this outcome; future research should consider its impact on the study outcomes.

Data Analysis and Future Research

Q: Has the data been added to the previous systematic review to find out what the updated evidence is across all trials on acute MI?

A: Meta-analyses including MINT trial data are in progress, expecting completion and publication in the coming months.

Q: Is the research being expanded beyond 30 days post-transfusion?

A: Long-term follow-up data beyond 30 days isn't available yet, however we did collect outcomes at 6 months and there will be additional publications once this analysis is complete. However, in other trials like REALITY, liberal transfusion had better outcomes at 1-year.

Q: Couched within the existing literature which shows no differences, could the findings from this study be due to chance?

A: The trial design, pilot study results, and basic science literature support that liberal transfusion may improve outcome. The published protocol of the MINT trial specified the hypothesis that liberal transfusion would be superior to restrictive transfusion strategy.

Clinical Implications and Safety

Q: What kind of surveillance data would it be prudent to collect in cardiac patients in whom we adopt liberal thresholds?

> A: Long-term data on outcomes and potential risks associated with liberal transfusion in cardiac patients could provide more insight into its implications.

Q: Although it goes against intention-to-treat methodology, what were the outcomes in the patients who didn't get a transfusion at all?

> A: Exploring outcomes in non-transfused patients helps understand natural disease progression. It provides context but wasn't the focus of this trial.

Q: Maybe MI with anemia is a physiological trigger (symptom) for transfusion. Thoughts?

> A: Hemoglobin isn't an ideal measure for transfusion triggers. We lack precise physiological markers but future research should explore developing other transfusion triggers than hemoglobin level. Anemia may signal an underlying issue, but our trial enrolled individuals three days post-MI (on average), some post-stabilization, yet we observed effects persisting.

Public Health Impact and Future Directions

Q: To what extent might liberal transfusion strategies impact blood management and supply?

> A: Liberal strategy might increase demand but remains relatively small in the context of overall blood units – estimated to be an additional 30,000 units required in Canada (300,000 in the US).

Q: Any thoughts on the next steps or how to utilize the study results?

> A: Focus on replication studies specific to type 1 MI, adjudicating cardiac death, and examining patients with pre-existing cardiovascular disease could guide future research.