Rationale and design for the myocardial ischemia and transfusion (MINT) randomized clinical trial

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ABSTRACT

Background Accumulating evidence from clinical trials suggests that a lower (restrictive) hemoglobin threshold (<8 g/dL) for red blood cell (RBC) transfusion, compared with a higher (liberal) threshold (≥10 g/dL) is safe. However, in anemic patients with acute myocardial infarction (MI), maintaining a higher hemoglobin level may increase oxygen delivery to vulnerable myocardium resulting in improved clinical outcomes. Conversely, RBC transfusion may result in increased blood viscosity, vascular inflammation, and reduction in available nitric oxide resulting in worse clinical outcomes. We hypothesize that a liberal transfusion strategy would improve clinical outcomes as compared to a more restrictive strategy.

Methods We will enroll 3500 patients with acute MI (type 1, 2, 4b or 4c) as defined by the Third Universal Definition of MI and a hemoglobin <10 g/dL at 144 centers in the United States, Canada, France, Brazil, New Zealand, and Australia. We randomly assign trial participants to a liberal or restrictive transfusion strategy. Participants assigned to the liberal strategy receive transfusion of RBCs sufficient to raise their hemoglobin to at least 10 g/dL. Participants assigned to the restrictive strategy are permitted to receive transfusion of RBCs if the hemoglobin falls below 8 g/dL or for persistent angina despite medical therapy. We will contact each participant at 30 days to assess clinical outcomes and at 180 days to ascertain vital status. The primary end point is a composite of all-cause death or recurrent MI through 30 days following randomization. Secondary end points include all-cause mortality at 30 days, recurrent adjudicated MI, and the composite outcome of all-cause mortality, nonfatal recurrent MI, ischemia driven unscheduled coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), or readmission to the hospital for ischemic cardiac diagnosis within 30 days. The trial will assess multiple tertiary end points.

Conclusions The MINT trial will inform RBC transfusion practice in patients with acute MI. (Am Heart J 2023;257:120–129.)

Background

Blood transfusion is a common medical intervention, with 118.5 million units of blood collected worldwide each year.[1] Physicians often transfuse patients based on

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a specific hemoglobin threshold, although it is unclear at what threshold the benefits of increasing hemoglobin outweighs the risks of transfusion.

In most clinical settings, trials have demonstrated that a restrictive transfusion strategy using a hemoglobin threshold of 7 to 8 g/dL is as effective as a liberal transfusion strategy using a hemoglobin threshold of 9 to 10 g/dL.[2] A recent systematic review published in the Cochrane database identified 48 trials involving 21,433 participants that evaluated transfusion triggers in a variety of populations.[2] This meta-analysis documented that a restrictive strategy is associated with 41% fewer transfusions (risk ratio 0.59, 95% confidence interval 0.53- 0.66) and no difference in 30-day mortality (risk ratio 0.99, 95% confidence interval 0.86-1.15) as compared with a liberal transfusion strategy. Prior to initiating MINT, only 2 small randomized controlled trials comparing liberal and restrictive transfusion strategies in the setting of acute coronary events had been published. The first was a pilot trial with 45 patients,[3] and the second was the MINT pilot with 110 patients.[4] Both small studies noted a trend toward increased mortality in the restrictive group; however, the number of patients and events were inadequate to guide transfusion practice in the population of patients with acute MI. Indeed, all transfusion practice guidelines clearly stated that there were too few patients with MI enrolled in clinical trials to provide clinical guidance.[5,6] Anemia in this setting is not only common but has been shown to be associated with adverse outcomes such as mortality rates.[7,8] It is also biologically plausible that patients with acute coronary events may require greater blood supply to the myocardium. With such justification and limited high quality studies, we designed and undertook the MINT trial to fill existing knowledge gaps.[9,10]

Methods

Trial aims and objectives

The MINT trial was designed to determine whether a liberal transfusion strategy with a threshold of 10 g/dL reduces the composite outcome of all-cause mortality or nonfatal recurrent MI through 30 days, compared with a restrictive transfusion strategy with a threshold of 7 to 8 g/dL among patients with an acute MI and a hemoglobin concentration less than 10 g/dL.

Study design

The MINT trial is a randomized, open-label, 2 group multicenter clinical trial. The trial is being conducted in approximately 144 clinical sites in the United States, Canada, France, Brazil, New Zealand, and Australia (see Supplementary Appendix 5 for list of trial sites). Eligible consenting patients who have had an acute MI and have a hemoglobin < 10 g/dL are randomized to receive either the liberal or the restrictive transfusion strategy using a centralized web-based system. Treatment is allocated with a 1:1 ratio using a permuted block design, with random variable block sizes, stratified by clinical site. The trial intervention is delivered during the index hospitalization, and primary and secondary outcomes are collected through 30 days postrandomization. Follow-up continues for 6 months. An overview of the trial enrollment, treatment and follow-up processes is shown in Figure 1.

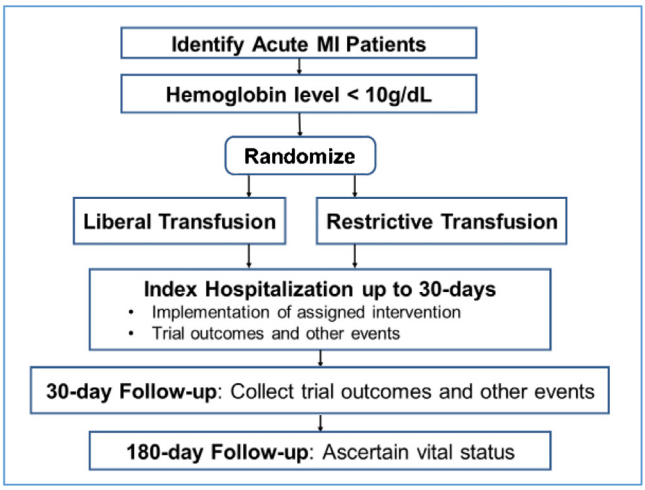
MINT was designed as a pragmatic trial.[11] The trial uses broad eligibility criteria based on standard clinical criteria for diagnosing MI and anemia, tests 2 transfusion strategies that are routinely used in current medical practice, and assesses trial outcomes that are clinically meaningful and objectively measured. Further, assessment of adherence to the transfusion protocol is based on routinely drawn hemoglobin measures, an abbreviated follow-up schedule and streamlined data collection, and the analysis strategy includes all available outcome data and utilizes the intention to treat principle. A description of the MINT design using the domains from the PRECIS-2 wheel[12] is shown in Supplementary Appendix A.

Population

The eligible study population includes adult patients with ST-segment elevation MI or non-ST-segment elevation MI consistent with the Third Universal Definition of Myocardial Infarction criteria[13] that occurs on admission or during the index hospitalization, and anemia defined as a hemoglobin concentration less than 10 g/dL at the time of randomization. Patients with type 1 (spontaneous), type 2 (oxygen supply/demand mismatch), type 4b (stent thrombosis at angiography), and type 4c (in-stent restenosis without evidence of thrombus) are eligible for the trial, and MI type is determined by the enrollment site team (Table I). Patients scheduled for cardiac surgery during the current admission are excluded.

Given the pragmatic nature of MINT, several approaches to screening study patients are used. Study staff are encouraged to review results of troponin tests performed in hospitalized patients daily. Medical records for patients with values meeting study enrollment criteria are reviewed and assessed for eligibility. Staff may also screen admissions to the cardiac intensive care unit, cardiac service, and patients scheduled for cardiac catheterization. Study staff contact the physician of each eligible patient to confirm clinical equipoise between transfusion strategies and to obtain permission to approach the patient about trial enrollment. Once physician approval has been obtained, the patient is approached to seek informed consent to participate in the trial. Surrogate consent, in accordance with local ethics rules, can be sought for each patient who is not able to grant consent. Enrollment of patients with COVID-19 infection is

Figure 1



Patient flow for the MINT trial. MINT, Myocardial Ischemia and Transfusion.

Table I. MINT eligibility criteria

Inclusion criteria:

1) 18 y of age or older;
2) with either ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction consistent with the Third Universal Definition of Myocardial Infarction and type 1 (spontaneous), type 2 (oxygen supply/demand mismatch), type 4b (stent thrombosis at angiography), or type 4c (in-stent restenosis)[13] that occurs on admission or during the index hospitalization,
3) with a hemoglobin concentration less than 10 g/dL at the time of random allocation, and
4) the patient's attending physician, with expertise in cardiovascular care, believes that both of the transfusion strategies are consistent with good medical care for the patient as determined by his/her clinical judgement.

Exclusion criteria:

1) uncontrolled acute bleeding at the time of randomization defined as the need for uncrossed or nontype specific blood;
2) decline blood transfusion;
3) scheduled for cardiac surgery during the current admission;
4) are receiving only palliative treatment;
5) if known that follow-up will not be possible at 30 d;
6) if previously participated in MINT
7) if currently enrolled in a competing study that interferes with the intervention or follow-up of MINT or enrolled in a competing study that has not been approved by the local IRB; or
8) if the attending physician does not believe the patient is an appropriate candidate for the trial for any reason.

not encouraged but is permitted at the discretion of the individual study sites.

Transfusion strategies

The trial compares 2 common approaches to transfusion therapy: a restrictive and a liberal approach.

Restrictive transfusion strategy: Patients randomized to the restrictive transfusion strategy are to receive a transfusion if the hemoglobin concentration falls below 8 g/dL and are strongly recommended to receive transfusion if the hemoglobin concentration is below 7 g/dL. Transfusion is also allowed when anginal symptoms (ie, retrosternal chest discomfort, chest discomfort described as pressure or heaviness) are determined by the patient's treating physician to be related to anemia and are not controlled with antianginal medications. Enough blood is given to increase the hemoglobin concentration to above 7 to 8 g/dL or to relieve anginal symptoms.

Liberal transfusion strategy: Patients randomly allocated to the liberal transfusion strategy receive one unit of packed RBCs following randomization and receive enough blood to raise the hemoglobin concentration to 10 g/dL or above any time during the index hospitalization that the hemoglobin concentration is detected to be below 10 g/dL. A posttransfusion hemoglobin measurement showing a hemoglobin level of at least 10 g/dL must be obtained.

Table II. Information collected at various time points

	Screening	Baseline	Randomization	12h post randomization	D 1	D 2	D 3	Daily up to 30 ds	Hospital discharge/30 d	30 d follow-up	6 Mofollow-up
Confirm Eligibility	X										
Informed Consent	X										
Hemoglobin Level*		X†,‡			X†	X[b]	X†	X			
Troponin Level*		X†,‡		X[b]	X†	X[b]	X†	X			
ECG*		X†,‡			X†	X†	X†	X			
Demographics	X										
Medical History		X									
Medications		X									
Implement Transfusion Strategy			XX								
RBC Transfusions[§]			XX								
Study Outcomes									X	X	X[‖]
Quality of Life (EQ-5D)										X	
Vital Status									X	X	X
Assessment of AEs and Ups Safety Monitoring		XX									

* in addition to required time points, all performed for clinical reasons are collected.
† required, if still in hospital.
‡ within the 24 hours prior to randomization.
§ including unit information (eg, leukoreduction) mortality outcome only.
‖ mortality outcome only.

For both strategies, blood is administered 1 unit at a time followed by a hemoglobin measurement. The transfusion strategy is followed throughout the index hospitalization up to 30 days, discharge, or death. A patient in either group may be transfused at any time without a measured hemoglobin level if the patient is actively bleeding (eg, brisk gastrointestinal bleeding) and the treating physician believes an emergency transfusion is needed. A patient in either group with a history of congestive heart failure or low ejection fraction may receive diuretics prior to or after transfusion, and transfusion may be delayed until the patient can safely tolerate the additional volume. Patients with end stage renal disease may receive transfusion during dialysis if requested by treating physician. The transfusion protocol may be suspended for 24 hours if the patient undergoes a surgical procedure. The trial centrally monitors transfusions and hemoglobin levels on an ongoing basis.

Assessments of laboratory markers

Information collected as part of the trial includes hemoglobin and troponin levels and electrocardiogram (ECG) readings at specified time points while the patient is in the hospital (Table II). The blood samples are normally drawn with daily morning phlebotomy. The required collection time points for hemoglobin levels and ECGs are within 24 hours prior to randomization (eligibility hemoglobin level), and on days 1, 2, and 3 following randomization. The required time points for the troponin levels are within 24 hours prior to randomization and at 12 hours after randomization, and on days 1, 2 and 3 following randomization. All hemoglobin and troponin levels performed for clinical purposes during the index hospitalization are collected by the trial.

Participant follow-up

Study staff review medical records and follow participants during the index hospitalization for up to 30 days following randomization. At hospital discharge or 30 days following randomization, whichever comes first, the site submits data related to the hospitalization including health status, laboratory results, electrocardiograms performed, and postrandomization clinical events.

Study staff at the clinical sites contact the patient at 30 days to ascertain vital status, administer the quality-of-life questionnaire, and determine if there has been a subsequent hospital admission or emergency room visit (Table II). Staff obtain and review the medical records for each readmission and record all relevant data and identify the study outcomes. If there is a suspected acute coronary syndrome event, the site submits de-identified copies of the documentation from the index admission or the readmission for review. Study staff perform a final follow-up contact at 6 months following randomization to ascertain the patient's vital status.

Outcome definitions

The prespecified trial end points are presented in Table III. The primary end point is the composite outcome of all-cause mortality and recurrent MI at 30 days

Table III. MINT trial end points

Primary end point: Composite of all-cause mortality and recurrent MI through 30 d.

Secondary end points:

1) all-cause mortality through 30 d,
2) recurrent MI through 30 d,
3) the composite outcome of all-cause mortality, nonfatal recurrent MI, ischemia driven unscheduled coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting), or readmission to the hospital for ischemic cardiac diagnosis within 30 d.

Tertiary end points:

1) all-cause mortality, nonfatal recurrent MI, or unstable angina (ie, acute coronary syndrome) within 30 d;
2) ischemia driven unscheduled coronary revascularization within 30 d;
3) unscheduled readmission to hospital for ischemic cardiac diagnosis within 30 d;
4) congestive heart failure within 30 d;
5) unscheduled readmission to hospital for any reason within 30 d;
6) individual thrombotic/hemorrhagic outcomes of stroke, pulmonary embolism or deep venous thrombosis, and bleeding within 30 d;
7) individual infectious outcomes of pneumonia, and blood stream infection within 30 d;
8) individual in-hospital outcomes of length of hospital stay following randomization and number of days in intensive care unit;
9) patient reported quality of life using the EuroQol questionnaire (EQ-5D) at 30 d;
10) all-cause mortality at 6-months following randomization.

following randomization. Recurrent MI in the 30-day window is classified by the Clinical Events Classification committee (CEC) using the Third Universal Definition of Myocardial Infarction.[11] The diagnosis of recurrent MI requires a rise in the troponin value of at least 20% from the trough with additional evidence of myocardial ischemia (new ECG changes, imaging evidence, clinical history). (See Supplementary Appendix B). The definitions of secondary and tertiary outcomes are included in Supplementary Appendix C. Clinical outcomes other than MI are not centrally adjudicated.

Recurrent MI is diagnosed when a suspected myocardial ischemic event is reported by the investigators at the clinical sites and confirmed by the CEC masked to assignment. In addition, all cardiac troponin values from all randomized participants are reviewed by the CEC to detect abnormal biomarker patterns that meet the protocol biomarker definition of a 20% rise from trough values or an increase above the 99th percentile upper reference limit for patients that have an initial normal cardiac troponin value. When surveillance criteria for a suspected MI are met, the CEC requests the medical records and ECGs that are temporally related to the abnormal values. The CEC adjudicates occurrences of MI masked to assignment. Recurrent MI is diagnosed when biomarker and clinical or ECG criteria of myocardial ischemia meet the Third Universal Definition of MI definition. MI is classified according to MI type as specified in the Third Universal Definition of Myocardial Infarction and whether MI type was ST segment elevation MI (STEMI) non-ST segment elevation MI (NSTEMI), or cannot be determined. The definition of recurrent MI will include all MI types. A sensitivity analysis is planned that will exclude procedural MIs (types 4a and 5). The cause of death is classified by the site personnel into 1 of 3 categories: cardiovascular death (eg, congestive heart failure, arrhythmia), noncardiovascular death (eg, infection, cancer), or undetermined cause of death. Information about the specific cause of death will also be collected and compared by treatment groups.

We are collecting other events that are not designated primary, secondary, or tertiary outcomes including transfusion reactions (transfusion related acute lung injury, acute hemolytic transfusion reaction, transfusion associated sepsis, anaphylactic transfusion reaction, urticarial transfusion reaction, febrile nonhemolytic reaction) cardiac arrhythmias (ie, atrial fibrillation/flutter, ventricular tachycardia, ventricular fibrillation and others), thrombotic or ischemic events and complications of MI (chest pain or stable angina, mechanical complications of MI, pericarditis, pericardial effusion/tamponade, syncope, cardiomyopathy), other (acute respiratory failure, acute renal failure, urinary tract infection).

Safety and compliance monitoring

The trial centrally monitors key aspects of protocol compliance including enrollment, retention, adherence to assigned intervention, deviations from the protocol, missing data, and adherence to adverse event reporting requirements and event adjudication procedures. Sites submit a serious adverse event form for unexpected serious adverse events occurring within 30 days of randomization and for unexpected deaths occurring within 6 months of randomization. A designated Medical Safety Officer determines the severity, expectedness, and relatedness of the event to the study protocol masked to the transfusion strategy. An external Data and Safety Monitoring Board (DSMB) consisting of members appointed by the National Heart, Lung, and Blood Institute (NHLBI) monitors the trial. On a semiannual basis, the DSMB

reviews trial conduct, study end points, and adverse events. The DSMB annually reviews interim analyses of the primary end point by assigned treatment group using the Lan-DeMets approach and O'Brien Fleming monitoring boundaries. An interim analysis to assess sample size assumptions was conducted in January 2020 when 1028 participants were enrolled, and the DSMB recommended that the trial should continue with the planned sample size of 3500 patients.

Since MINT compares 2 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. As a result, the original Data Safety Monitoring Plan stated that no interim futility analyses would be conducted. Given the delay in enrollment due to COVID pandemic, a futility analysis was requested by NHLBI in February 2022. A plan to present the conditional power for detecting superiority of either transfusion strategy and the conditional power for detecting noninferiority of the restrictive strategy was submitted; conditional power is based on the observed trial data collected thus far, hypothesized treatment effect sizes, and the proposed trial sample size. The submitted futility analysis plan was approved by a blinded statistician at NHLBI in May 2022. The DSMB reviewed the futility analysis at July and August 2022 meetings and recommended that the trial complete enrollment to the target sample size of 3500 patients. The NHLBI accepted the DSMB's recommendation to complete enrollment.

Organization and participating centers

The Rutgers Robert Wood Johnson School of Medicine, Division of General Internal Medicine is responsible for overall clinical coordination of the trial (CCC). Each country has subsidiary coordinating center. The Canadian Coordinating Center is at the Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montréal Québec. The Brazilian Coordinating Center is at the Brazilian Clinical Research Institute (BCRI), Sao Paulo. The European Coordinating Center is at FACT (French Alliance for Cardiovascular clinical Trials), Paris. The New Zealand Coordinating Center is at Green Lane Coordinating Centre Ltd, Auckland and the Australian Coordinating Center is at Flinders University in Adelaide.

The Epidemiology Data Center at the University of Pittsburgh is responsible for the data coordination of the trial (DCC). FACT collects primary data for participants enrolled in Europe and transmits the data to the University of Pittsburgh.

The primary decision-making body of the MINT trial is the Executive Committee that includes the PIs of the CCC and DCC and the lead clinical investigators from the United States, Canada, Europe, Brazil, New Zealand and Australia. The Executive Committee identifies high-level study design and implementation issues and will serve as the Publications Committee. The Steering Committee is composed of a larger group of investigators and staff representing the sites, CCC, and DCC; they meet monthly to provide essential input on operational and scientific issues. A central and independent Clinical Events Classification committee is responsible for adjudication of recurrent MIs.

MINT initially included clinical sites in the U.S. and Canada. A small randomized study conducted in Montreal, Canada in 2016 (unpublished data) served as the "vanguard phase" of the trial, and this vanguard study contributed a total of 45 patients to the MINT trial. In 2020, the trial was expanded to include sites in Brazil, France, New Zealand, and Australia.

The MINT trial is funded by the National Heart Lung and Blood Institute (U01 HL133817, U01HL132853). The trial protocol is IRB approved through the CCC, and each clinical site has local IRB approval.

Statistical methods

Sample size and power

The composite 30-day rate of death and MI for the combined liberal and restrictive transfusion strategies was 16.4% in the MINT pilot trial.[4] Assuming a 16.4% event rate and that <5% of patients will have missing 30-day outcome data, a sample size of $N = 3500$ provides the MINT trial 80% power to detect a 20% relative risk reduction and 90% power to detect a 25% relative reduction for the trial primary end point with alpha = 0.05. Initial power calculations were performed using a 2-sided chi-square test, and we conducted simulations to confirm that a log binomial model with a random intercept for site had comparable power. The target relative risk reduction of 20% corresponds to an absolute risk reduction of 3.6% (ie, 18.2% vs 14.6%). The risk difference of 3.6% is small enough, such that, if a liberal transfusion threshold were not shown to be superior to a restrictive transfusion threshold, we would recommend that transfusion not be given.

Primary end point analysis

The intention-to-treat principle will be used for all analyses. The primary end point, 30-day death/MI, will be analyzed using a log-binomial regression model with a fixed effect variable for assigned treatment strategy and a random effect for clinical site. A two-sided test with alpha = 0.05 will be used for the assigned treatment variable. To address the primary aim, we will report the estimated relative risk and significance level accounting for interim monitoring and imputing missing primary outcome data. Markov Chain Monte Carlo (MCMC) multiple imputation methods will be used to impute the missing values for the primary end point.[14] A second log-binomial model with random effects for site will be created from patients with nonmissing 30-day primary end

point data (ie, no imputation). The proportion of events in each arm, the relative risk and absolute difference will be presented, and 95% confidence intervals will be calculated from the observed data. If superiority of one of the 2 transfusion strategies is not demonstrated through the primary hypothesis test, the noninferiority of the restrictive strategy compared to the liberal strategy will be evaluated setting the noninferiority margin to a 15% relative increase; that is, the restrictive arm will be considered noninferior to the liberal arm if the 95% confidence interval for the estimated relative risk is < 1.15. This noninferiority margin is consistent with other major cardiology trials.[9]

A per protocol analysis, including only patients who undergo transfusion according to their assignment and adjusting for baseline factors that are associated with adherence to the treatment protocol, will be conducted as a sensitivity analysis.

Analysis of secondary and tertiary end points

For dichotomous secondary and tertiary end points, we will present the relative and absolute risk differences with 95% confidence intervals. Length of hospital stay will be analyzed using Wilcoxon rank sum tests, and 6-month mortality will be analyzed with the log rank statistic. The median difference will be presented for length of stay and Kaplan-Meier methods will be used to estimate cumulative mortality at 180 days. We will use *t* tests or the Wilcoxon rank sum tests to compare the EQ-5D utility index and health today by assigned treatment. The alpha level will not be adjusted for the multiple secondary and tertiary analyses.

Subgroup analyses

Subgroup analyses will be performed based on select baseline factors: ST segment elevation MI and non-ST segment elevation MI, MI types 1 or 2, baseline hemoglobin level (<8, 8-8.9, ≥9 g/dL), revascularization for treatment of index MI prior to randomization (yes/no), acute anemia (normal hemoglobin at admission, low hemoglobin at admission and no history of chronic anemia, and low hemoglobin at admission and history of chronic anemia), sex (male/female), age (<60, 60-69, 70-79, ≥80 years), heart failure (yes/no), renal function (renal dialysis, no dialysis and eGFR <30, 30-59, ≥60 mL/mi/1.73m^2), and diabetes status (yes/no). Among participants from sites in the U.S., Canada, New Zealand and Australia we will also examine subgroups defined by race (White, Black, Non-White and Non-Black Race) and Hispanic ethnicity (yes/no). The 30-day event rates by assigned transfusion strategy will be compared within each predefined subgroup. In addition, a log-binomial regression model including treatment assignment, subgroup variable, and the interaction between the subgroup variable and treatment assignment will be created, and the significance of the interaction will be presented. Cox proportional hazards regression models will be created with similar covariates to test whether prespecified subgroup variables modify the treatment effect on 6-month all-cause mortality.

MINT site survey

We created and administered a survey of MINT site investigators to document practice variation of transfusion practices and uncertainty about best transfusion strategies in patients with ischemic heart disease. Among the 81 physicians at 73 hospitals in U.S. and Canada, the response rate was 90.1%. We documented substantial heterogeneity in the preferred hemoglobin transfusion threshold among bedside clinicians for each of several specified clinical scenarios (Supplementary Appendix D). Investigators most frequently reported using transfusion thresholds of 7 to 8 g/dL in sample cases, but the threshold was somewhat higher in the case with active symptoms. For many of the investigators (>65%), the evidence to support the choice of a transfusion threshold was judged as uncertain or very uncertain. Another 20% to 25% of the investigators indicated that they were neutral about the strength of the evidence to transfuse at a particular threshold (neither certain nor uncertain). Only 4.1% to 8.5% of the investigators were certain or very certain about the evidence to support their decision to transfuse in any of the sample cases. When individual physicians were certain about a transfusion threshold for an acute MI case, the chosen thresholds varied among the site physicians and most often clustered close to 8 g/dL.

Discussion

The risks and benefits of a liberal vs a restrictive transfusion strategy remain unresolved in anemic patients presenting with acute MI. Observational data suggests an association between a liberal transfusion strategy and increased mortality.[15] Prior to the initiation of the MINT trial, 2 small trials comparing liberal to restrictive transfusion in patients with acute MI suggested that mortality may be higher in patients treated with restrictive transfusion.[3,4] The REALITY trial was completed after the MINT trial was initiated.[9,10] In 668 patients with acute MI and hemoglobin concentration less than 10 g/dL, the composite outcome of all cause 30-day mortality, recurrent myocardial infarction, stroke, or emergency revascularization for ischemia (or MACE) occurred in 36 (11.0%) in the restrictive transfusion strategy arm and 45 (14.0%) in the liberal transfusion strategy arm (relative risk = 0.79, one sided upper 95% confidence limit = 1.18, meeting the prespecified criteria for noninferiority). At 1 year, however, the restrictive strategy did not meet criteria for noninferiority.[10] When these 3 randomized trials were combined in a meta-analysis, the 30-day mortality risk was not significantly different between treatment strate-

gies owing to very wide confidence intervals given the limited sample size (relative risk 1.61, 95% CI, 0.38-6.88).[2]

At the start of MINT, we conducted an operational survey in 73 hospitals in U.S. and Canada to evaluate transfusion practice in patients with acute MI. The results from this survey documented variation in transfusion practice based on a high level of uncertainty regarding the best threshold for transfusion in patients with acute MI. Despite the recent publication of REALITY,[9] there remains a paucity of evidence helping clinicians decide what degree of anemia should trigger a transfusion in patients with acute MI.

The MINT trial outcomes were selected to assess the clinically important benefits and harms of transfusion and anemia in vulnerable individuals with compromised myocardium. The primary outcome in the MINT trial is the composite of all-cause mortality or recurrent MI within 30 days of randomization. Higher hemoglobin concentrations might decrease ischemic injury and improve myocardial performance by improving oxygen delivery to the myocardium in the acute MI patients, and additionally reduce other sequelae of decreased oxygen delivery to the myocardium: unscheduled coronary revascularization, hospital readmission for ischemic symptoms, unstable angina, arrhythmias, cardiogenic shock, and cardiovascular mortality. Higher hemoglobin levels may also be associated with a greater sense of well-being and a better perceived quality of life. On the other hand, if transfusion results in clinically important fluid overload, immunosuppression, increased viscosity, inflammation, microvascular vasoconstriction, and platelet activation, there may be an increase in congestive heart failure, infection, bleeding, stroke, venous thromboembolism, recurrent MI, or cardiovascular mortality, or a detrimental effect on the quality of life. Blood transfusion will likely have its maximum effect within a 30-day time period, but the MINT trial will also assess 6-month mortality to determine if early effects of blood transfusion persist over a longer period.

The trial compares 2 transfusion strategies routinely used in current medical practice. In the restrictive strategy, blood transfusion is not permitted unless the hemoglobin concentration is less than 8 g/dL (or there is clinical justification such as active bleeding/uncontrolled angina). A blood transfusion is not required if the hemoglobin concentration is less than 8 g/dL but is encouraged if the hemoglobin concentration is less than 7 g/dL. Prior trials performed in critical care patients established the safety of 7 g/dL threshold.[16,17] Discussions with many cardiologists suggested that many clinicians are not comfortable with a threshold as low as 7 g/dL (as used in other settings such as ICU patients); however, individual clinicians may choose to use a threshold of less than 7 g/dL to trigger transfusions. Patients may also be transfused for signs or symptoms when the clinician believes it is necessary, although this occurred infrequently in prior trials that incorporated symptoms into the restrictive transfusion protocol.[4,18]

In the liberal transfusion group, a threshold of less than 10 g/dL was chosen because oxygen delivery to the myocardium is flow dependent, and myocardial ischemia may be precipitated or worsened by low hemoglobin concentrations in patients with Type 1 MIs and plaque erosion or rupture as well as in type 2 MIs with oxygen supply/demand mismatch. Studies performed in canines and in patients who decline blood transfusion for religious reasons found that the odds of death rose as the hemoglobin fell below 10 g/dL.[19-22] The pragmatic transfusion protocol encourages administering transfusions more slowly or delaying transfusion in patients with congestive heart failure until fluid overload is adequately treated and administering transfusions on the days of dialysis in patients with end stage renal disease. If a patient is hemorrhaging, the transfusion protocol is paused (allowing emergency transfusion) until bleeding is controlled.

Recurrent MI is a component of the 30-day composite primary outcome along with all-cause mortality. Recurrent MI is detected by site study team evaluation of troponin levels and ECGs performed following randomization and by central surveillance of troponin levels. Abnormal postrandomization troponin profiles following the index MI event eg, a new rise in troponin greater than 20% or greater than the upper reference limit if initial values have returned to baseline triggers review of medical records for clinical signs, symptoms, and tests. These findings are used by clinical events committee blinded to transfusion group to adjudicate the diagnose recurrent MI.

The interventions in the MINT trial are not masked due to the logistical complexities for blinding a transfusion intervention. As a result, it is critical that the trial maintains good adherence to the assigned treatment protocol, the end points are objective, and the trial end point ascertainment is nearly complete. Recurrent MI is adjudicated blinded to assignment although other secondary outcomes are recorded by sites unblinded. Most outcomes are based on objective test results such as radiographic images.

The trial encountered enrollment challenges with the COVID-19 pandemic. To sustain recruitment, the trial was expanded from the U.S. and Canada to include sites in Brazil, France, New Zealand, and Australia. These additional sites have increased the recruitment capacity and generalizability of the trial as well as the complexity of conducting a trial with different healthcare systems, languages, and time zones.

Summary

In patients with acute MI, the risks and benefits of RBC transfusion may be different than in other patient pop-

ulations. Anemia, if untreated, may result in increased risks of further myocardial ischemia, injury, or infarction. Transfusions, on the other hand, may result in increased risks of volume overload and other adverse effects. Thus, it is unclear whether the benefits of immediate correction of anemia with transfusion are outweighed by the potential side effects of transfusion. Regardless of whether liberal transfusion strategy is proven to be superior or not, the MINT trial will inform clinical practice and RBC transfusion guidelines in patients with acute MI.

Author contribution

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2022.11.015.

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