ORIGINAL ARTICLE

Restrictive or Liberal Transfusion Strategy in Myocardial Infarction and Anemia

J.L. Carson, M.M. Brooks, P.C. Hébert, S.G. Goodman, M. Bertolet, S.A. Glynn, B.R. Chaitman, T. Simon, R.D. Lopes, A.M. Goldsweig, A.P. DeFilippis, J.D. Abbott, B.J. Potter, F.M. Carrier, S.V. Rao, H.A. Cooper, S. Ghafghazi, D.A. Fergusson, W.J. Kostis, H. Noveck, S. Kim, M. Tessalee, G. Ducrocq, P. Gabriel Melo de Barros e Silva, D.J. Triulzi, C. Alsweiler, M.A. Menegus, J.D. Neary, L. Uhl, J.B. Strom, C.B. Fordyce, E. Ferrari, J. Silvain, F.O. Wood, B. Daneault, T.S. Polonsky, M. Senaratne, E. Puymirat, C. Bouleti, B. Lattuca, H.D. White, S.F. Kelsey, P.G. Steg, and J.H. Alexander, for the MINT Investigators*

ABSTRACT

BACKGROUND

A strategy of administering a transfusion only when the hemoglobin level falls below 7 or 8 g per deciliter has been widely adopted. However, patients with acute myocardial infarction may benefit from a higher hemoglobin level.

METHODS

In this phase 3, interventional trial, we randomly assigned patients with myocardial infarction and a hemoglobin level of less than 10 g per deciliter to a restrictive transfusion strategy (hemoglobin cutoff for transfusion, 7 or 8 g per deciliter) or a liberal transfusion strategy (hemoglobin cutoff, <10 g per deciliter). The primary outcome was a composite of myocardial infarction or death at 30 days.

RESULTS

A total of 3504 patients were included in the primary analysis. The mean (±SD) number of red-cell units that were transfused was 0.7±1.6 in the restrictive-strategy group and 2.5±2.3 in the liberal-strategy group. The mean hemoglobin level was 1.3 to 1.6 g per deciliter lower in the restrictive-strategy group than in the liberal-strategy group on days 1 to 3 after randomization. A primary-outcome event occurred in 295 of 1749 patients (16.9%) in the restrictive-strategy group and in 255 of 1755 patients (14.5%) in the liberal-strategy group (risk ratio modeled with multiple imputation for incomplete follow-up, 1.15; 95% confidence interval [CI], 0.99 to 1.34; P=0.07). Death occurred in 9.9% of the patients with the restrictive strategy and in 8.3% of the patients with the liberal strategy (risk ratio, 1.19; 95% CI, 0.96 to 1.47); myocardial infarction occurred in 8.5% and 7.2% of the patients, respectively (risk ratio, 1.19; 95% CI, 0.94 to 1.49).

CONCLUSIONS

In patients with acute myocardial infarction and anemia, a liberal transfusion strategy did not significantly reduce the risk of recurrent myocardial infarction or death at 30 days. However, potential harms of a restrictive transfusion strategy cannot be excluded. (Funded by the National Heart, Lung, and Blood Institute and others; MINT ClinicalTrials.gov number, NCT02981407.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Carson can be contacted at jeffrey.carson@rutgers.edu or at the Department of Medicine, Rutgers Robert Wood Johnson Medical School, Clinical Academic Bldg., 125 Paterson St., New Brunswick, NJ 08901.

*A complete list of the investigators in the MINT trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Carson and Brooks contributed equally to this article.

This article was published on November 11, 2023, at NEJM.org.

This is the *New England Journal of Medicine* version of record, which includes all *Journal* editing and enhancements. The Author Accepted Manuscript, which is the author's version after external peer review and before publication in the *Journal*, is available at PubMed Central.

N Engl J Med 2023;389:2446-56.
DOI: 10.1056/NEJMoa2307983

Anemia is common in patients with acute myocardial infarction.[1,2] Indications for red-cell transfusion remain controversial in such patients, given the paucity of evidence. Three small randomized trials that have compared transfusion thresholds in a total of 820 patients with myocardial infarction have shown inconsistent results. The largest trial showed the noninferiority of a restrictive strategy as compared with a liberal strategy for preventing major adverse cardiac events at 30 days.[3-5] From a mechanistic perspective, blood transfusion may decrease ischemic injury by improving oxygen delivery to myocardial tissues and reduce the risk of reinfarction or death. Alternatively, administering more blood could result in more frequent heart failure from fluid overload, infection from immunosuppression, thrombosis from higher viscosity, and inflammation.

Randomized trials that have compared a restrictive transfusion strategy with a liberal strategy in more than 21,433 patients have shown a decrease of 50% in blood use without differences in morbidity or mortality.[6] Guidelines for red-cell transfusion have identified patients with myocardial infarction as a population in which more clinical trial data are needed.[7,8]

The primary objective of the Myocardial Ischemia and Transfusion (MINT) trial was to determine 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.

Methods

Trial Design and Oversight

We conducted this open-label, randomized trial at 144 sites in the United States, Canada, France, Brazil, New Zealand, and Australia. The trial rationale and design have been reported previously.[9] The trial protocol (available with the full text of this article at NEJM.org) was approved by the institutional review board or ethics committee at each trial site. Patients or their surrogates provided written informed consent.

The trial was designed and led by executive and steering committees that included representatives of the clinical coordinating center, data coordinating center, trial sites, and the National Heart, Lung, and Blood Institute (NHLBI). The first two authors wrote the first draft of the manuscript and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. An independent data and safety monitoring committee reporting to the NHLBI reviewed unmasked data every 6 months to ensure patient safety and reviewed protocol-specified formal interim efficacy analyses annually.

Trial Population

We enrolled adults (≥18 years of age) with ST-segment elevation or non–ST-segment elevation myocardial infarction, defined in accordance with the Third Universal Definition of Myocardial Infarction,[10] along with anemia (hemoglobin level, <10 g per deciliter within 24 hours before randomization). Patients with type 1, 2, 4b, or 4c myocardial infarction were eligible for enrollment; diagnosis and categorization of myocardial infarction were performed by site investigators. Patients were ineligible for enrollment if they had uncontrolled bleeding, were receiving palliative treatment, were scheduled for cardiac surgery during the current admission, or had declined to receive blood transfusion.[9] Trial staff members identified potential patients with acute myocardial infarction and low hemoglobin levels during the index hospitalization, confirmed eligibility criteria, and confirmed that the patient's attending physician approved enrollment.

Randomization Procedures

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. The randomization sequence was created at the data coordinating center by an independent statistician.

Transfusion Strategies

In the restrictive-strategy group, transfusion was permitted but not required when the hemoglobin level was less than 8 g per deciliter and was strongly recommended when the level was less than 7 g per deciliter or when anginal symptoms were not controlled with medications. In the liberal-strategy group, one unit of packed red cells was administered after randomization and red cells were transfused to maintain the hemoglobin level

at or above 10 g per deciliter until the time of hospital discharge or 30 days. With both strategies, transfusion was administered one unit at a time, followed by measurement of the hemoglobin level. The transfusion protocol was paused if the clinician judged that active bleeding required immediate transfusion. Transfusion could be delayed in patients with volume overload until adequate diuresis or on the day of dialysis in patients with end-stage renal disease. After randomization, the transfusion strategy was not masked to site investigators or patients.

MEASUREMENTS AND ASSESSMENTS

Assessment by means of electrocardiography and measurements of hemoglobin and troponin levels were required within 24 hours before randomization and daily for 3 days after randomization (with two troponin measures required on day 1). Patients were contacted by telephone 30 days after randomization to assess vital status, quality of life, and readmission to the hospital or emergency department; patients were also contacted at 6 months to assess vital status. Trial staff members reviewed the medical records of the patients who had been readmitted to the hospital or emergency department within 30 days after randomization to identify and report the occurrence of clinical events and to record all available troponin levels.

OUTCOMES

The primary outcome was a composite of myocardial infarction or death from any cause up to 30 days after randomization. Death was ascertained from medical records during the index hospitalization and by telephone follow-up at 30 days after randomization, with subsequent review of medical records. 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. The committee reviewed hospital records and adjudicated recurrent myocardial infarction using the Third Universal Definition of Myocardial Infarction.[10] The only trial outcome that was centrally adjudicated was myocardial infarction.

The prespecified secondary outcomes were the individual components of the primary outcome (myocardial infarction or death at 30 days) and the composite outcome of death, myocardial infarction, ischemia-driven unscheduled coronary revascularization, or readmission to the hospital for an ischemic cardiac condition within 30 days. Other clinically relevant 30-day outcomes were recorded as defined in the protocol and the Supplementary Appendix, available at NEJM.org. The cause of death was classified as cardiac, noncardiac, or undetermined.

PRESPECIFIED SUBGROUPS

Prespecified baseline subgroups included the type of myocardial infarction (type 1 [occlusion of a coronary artery because of atherosclerotic plaque disruption] or type 2 [supply–demand mismatch without atherothrombotic plaque disruption]), myocardial infarction presentation (ST-segment elevation or non–ST-segment elevation), revascularization for the index myocardial infarction (yes or no), heart failure (a composite of a history of heart failure, left ventricular ejection fraction of <45%, or acute heart failure) or no heart failure, prerandomization hemoglobin level (<8, 8 to <9, or 9 to <10 g per deciliter), type of anemia (chronic or acute), renal function (undergoing dialysis or an estimated glomerular filtration rate of <30, 30 to 59, or ≥60 ml per minute per 1.73 m^2 of body-surface area), a history of diabetes therapy (yes or no), sex, and age (<60, 60 to 69, 70 to 79, or ≥80 years). Subgroups that were defined according to race and Hispanic ethnic group were evaluated among the patients from the United States, Canada, New Zealand, and Australia.

STATISTICAL ANALYSIS

We determined that the enrollment of 3500 patients would provide the trial with 80% power to detect a 20% relative between-group difference in the incidence of the primary outcome, assuming an overall incidence of myocardial infarction or death of 16.4% and using a two-sided test with an alpha level of 0.05. All the analyses were conducted in the intention-to-treat population with two-sided hypothesis tests for superiority. Risk ratios were used to assess the risk with the restrictive strategy as compared with the liberal strategy (with values of >1 favoring the liberal strategy), in accordance with the methods described in transfusion literature.[6]

For the primary analysis, we used a log-binomial regression model that included a fixed effect for the assigned transfusion strategy and a random

effect for clinical sites. Multiple imputation by chained equations (MICE) was used to impute missing outcome data for patients who withdrew or were lost to follow-up before 30 days without a primary-outcome event after adjustment for all measured variables potentially associated with missing data (see the Supplementary Appendix for details).

For all trial outcomes, we report crude 30-day risk according to the assigned group, without multiple imputation, and risk ratios with 95% confidence intervals. All available data from randomization through 30 days were used to identify trial outcomes, and we assumed that no event occurred after the final day of data collection for patients with incomplete follow-up when computing these estimates.

As a secondary analysis, we used Kaplan–Meier methods to assess the cumulative risk of a primary-outcome event according to the assigned group and used log-rank statistics with data censoring at the time of the patient's withdrawal and at 30 days to compare the two cumulative risk curves. The crude risk ratios and 95% confidence intervals for the primary outcome are reported within prespecified subgroups. A post hoc analysis was conducted by creating a log-binomial regression model for the primary outcome according to the assigned group after adjustment for baseline prognostic factors that were prespecified as subgroup variables. We did not adjust for multiple comparisons for any secondary outcome or subgroup, so 95% confidence intervals should not be used for hypothesis testing.

RESULTS

PATIENTS

A total of 3506 patients were enrolled from April 2017 through April 2023, and 3504 were included in the analyses after 2 patients did not approve the use of their data (Fig. S1 in the Supplementary Appendix). The mean age of the patients was 72.1 years, and 45.5% of the patients were women (Table 1 and Table S1). The patients had frequent coexisting illnesses; approximately a third had a history of myocardial infarction, percutaneous coronary intervention, or heart failure, and nearly half had renal insufficiency. Among the patients who were undergoing coronary angiography and assessment of left ventricular function before randomization, the presence of multivessel disease and reduced left ventricular systolic function was common.

A majority of the patients (55.8%) had type 2 myocardial infarction; the second most common form (in 41.7%) was type 1. The prerandomization mean hemoglobin level was 8.6 g per deciliter, and the median creatinine level was 1.4 mg per deciliter (124 μmol per liter). Follow-up at 30 days was complete for 3447 patients (98.3%) who had undergone randomization (Fig. S1).

IMPLEMENTATION OF ASSIGNED INTERVENTIONS

The mean hemoglobin level was lower in the restrictive-strategy group than in the liberal-strategy group by 1.3 g per deciliter (95% confidence interval [CI], 1.2 to 1.4) on day 1 and lower by 1.6 g per deciliter (95% CI, 1.5 to 1.7) on day 3 (Fig. 1). The total number of units of red cells that were transfused in the liberal-strategy group was 3.5 times the number that were transfused in the restrictive-strategy group (4325 units vs. 1237 units). The mean (±SD) number of red-cell units that were transfused in the liberal-strategy group was 2.5±2.3, as compared with 0.7±1.6 in the restrictive-strategy group. The median duration of hospitalization from randomization until discharge, withdrawal, or death was 5 days (interquartile range, 2 to 10) in the two groups.

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.

TRIAL OUTCOMES

Myocardial infarction or death from any cause at 30 days (the primary outcome) occurred in 295 of 1749 patients (16.9%) in restrictive-strategy group and in 255 of 1755 patients (14.5%) in the liberal-strategy group. The crude risk ratio (restrictive vs. liberal) was 1.16 (95% CI, 1.00 to 1.35) (Fig. 2). According to a log-binomial model after adjustment for site and incomplete follow-up in 57 patients (20 with the restrictive strategy and 37 with

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	All Patients (N=3504)	Restrictive Strategy (N=1749)	Liberal Strategy (N=1755)
Age — yr	72.1±11.6	72.2±11.5	72.1±11.6
Female sex — no. (%)	1593 (45.5)	774 (44.3)	819 (46.7)
Race or ethnic group — no. (%)†			
White	2474 (70.6)	1229 (70.3)	1245 (70.9)
Black	440 (12.6)	217 (12.4)	223 (12.7)
Other	244 (7.0)	129 (7.4)	115 (6.6)
Missing	346 (9.9)	174 (9.9)	172 (9.8)
Medical history — no./total no. (%)			
Myocardial infarction	1138/3504 (32.5)	589/1749 (33.7)	549/1755 (31.3)
Percutaneous coronary intervention	1200/3503 (34.3)	623/1749 (35.6)	577/1754 (32.9)
Coronary-artery bypass grafting	762/3504 (21.7)	372/1749 (21.3)	390/1755 (22.2)
Heart failure	1066/3504 (30.4)	527/1749 (30.1)	539/1755 (30.7)
Angiography — no./total no. (%)			
Results available before randomization	1738/3504 (49.6)	885/1749 (50.6)	853/1755 (48.6)
Multivessel coronary artery disease: >50% obstruction	1103/1679 (65.7)	565/856 (66.0)	538/823 (65.4)
Left ventricular ejection fraction			
Quantitative assessment available — no. (%)	2558 (73.0)	1282 (73.3)	1276 (72.7)
Most recent result in past year — %	47.4±13.5	47.3±13.4	47.5±13.7
Categorical assessment available — no./total no. (%)			
30 to <45%: moderate	807/2929 (27.6)	397/1460 (27.2)	410/1469 (27.9)
<30%: severe	292/2929 (10.0)	145/1460 (9.9)	147/1469 (10.0)
Index myocardial infarction — no. (%)			
NSTEMI	2848 (81.3)	1430 (81.8)	1418 (80.8)
Type 1	1460 (41.7)	730 (41.7)	730 (41.6)
Type 2	1955 (55.8)	967 (55.3)	988 (56.3)
Medical finding or therapy before randomization			
Revascularization for treatment of index myocardial infarction — no. (%)	1002 (28.6)	509 (29.1)	493 (28.1)
In-hospital heart failure — no. (%)	780 (22.3)	377 (21.6)	403 (23.0)
Mechanical ventilation — no. (%)	481 (13.7)	250 (14.3)	231 (13.2)
Active bleeding — no. (%)	459 (13.1)	246 (14.1)	213 (12.1)
Red-cell transfusion — no. (%)	1237 (35.3)	599 (34.2)	638 (36.4)
Hemoglobin — g/dl	8.6±0.8	8.6±0.8	8.6±0.8
Median creatinine (IQR) — mg/dl	1.4 (0.9–2.5)	1.4 (0.9–2.6)	1.4 (0.9–2.5)
Renal dialysis — no./total no. (%)	415/3503 (11.8)	203/1748 (11.6)	212/1755 (12.1)

* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. IQR denotes interquartile range, and NSTEMI non–ST-segment elevation myocardial infarction.
† Race or ethnic group was reported by the patients. The "other" category included patients who identified as Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, First Nations Inuit or Metis, or multiracial. Data were missing for 323 patients in France (where racial data are not reported) and for 23 patients in other countries.

the liberal strategy) with multiple imputation, the estimated risk ratio for the primary outcome was 1.15 (95% CI, 0.99 to 1.34; P=0.07). The estimate for the primary outcome from the model after adjustment for baseline prognostic factors (risk ratio, 1.16; 95% CI, 1.00 to 1.36) was consistent with the previous two calculations.

At 30 days, death had occurred in 173 of 1749 patients (9.9%) in the restrictive-strategy group and in 146 of 1755 patients (8.3%) in the liberal-strategy group (risk ratio, 1.19; 95% CI, 0.96 to 1.47), and myocardial infarction had occurred in 8.5% and 7.2% of the patients, respectively (risk ratio, 1.19; 95% CI, 0.94 to 1.49) (Fig. 2). Death, myocardial infarction, ischemia-driven unscheduled coronary revascularization, or readmission to the hospital for an ischemic cardiac condition within 30 days occurred in 19.6% of the patients in the restrictive-strategy group and in 17.4% of those in the liberal-strategy group (risk ratio, 1.13; 95% CI, 0.98 to 1.29). Figure 3 shows Kaplan–Meier estimates of the 30-day cumulative incidence of myocardial infarction or death from any cause (the primary outcome) and of death from any cause with censoring of data for patients at the time of withdrawal or loss to follow-up.

Cardiac death was more common in the restrictive-strategy group than in the liberal-strategy group (5.5% and 3.2%, respectively; risk ratio, 1.74; 95% CI, 1.26 to 2.40); the risk of other clinical-outcome events did not differ significantly between the two groups (Fig. 2 and Table S2). The risk of heart failure at 30 days was similar in the restrictive-strategy group and the liberal-strategy group (5.8% and 6.3%, respectively; risk ratio, 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 (0.5% and 1.3%, respectively; risk ratio, 0.35; 95% CI, 0.16 to 0.78). Pulmonary embolism or deep venous thrombosis was infrequent in both the restrictive-strategy group and the liberal-strategy group (1.5% vs. 1.9%; risk ratio, 0.77; 95% CI, 0.46 to 1.27). Transfusion reactions were uncommon, and the absolute differences in the incidence between the two groups were small (Table S2).

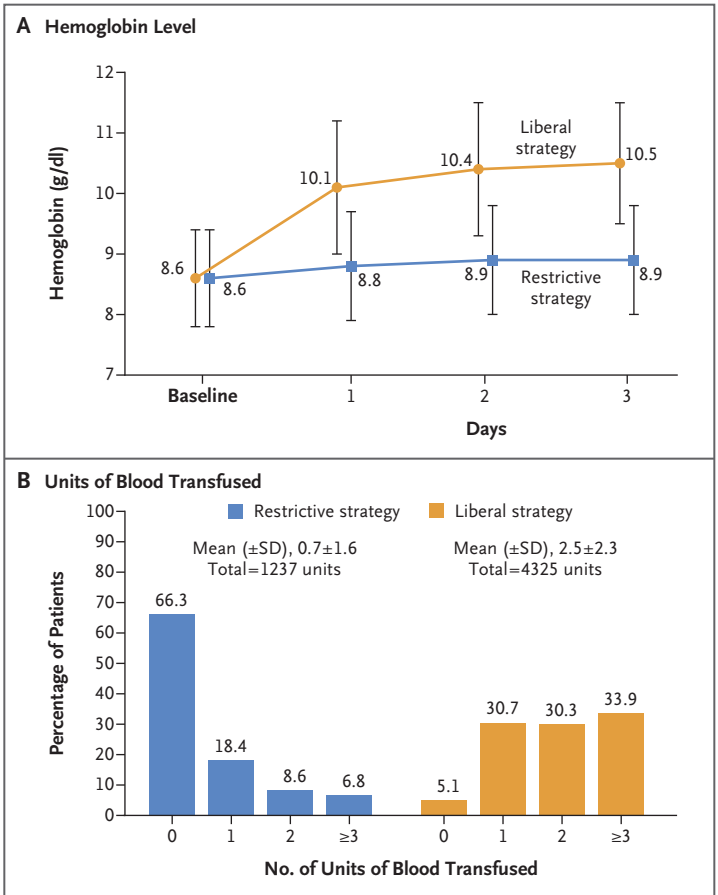

Figure 1. Hemoglobin Level and Number of Units of Red-Cell Transfusions.
Panel A shows the mean (±SD) hemoglobin level at baseline, day 1, day 2, and day 3 in the restrictive-strategy group and the liberal-strategy group. I bars indicate 95% confidence intervals. Panel B shows the number of units of red cells transfused in the two groups.

SUBGROUP ANALYSES

The effect of the restrictive as compared with the liberal transfusion strategy on the primary outcome was consistent across all prespecified subgroups (Fig. 4 and Table S3). Among the patients with type 1 myocardial infarction, the restrictive strategy led to more primary-outcome events than the liberal strategy (risk ratio, 1.32; 95% CI, 1.04 to 1.67), with no apparent effect among the patients with type 2 myocardial infarction (risk ratio, 1.05; 95% CI, 0.85 to 1.29).

DISCUSSION

In the MINT trial, we did not find a significant difference in the incidence of recurrent myocardial infarction or death at 30 days between patients with acute myocardial infarction and anemia who were assigned to a restrictive transfusion strategy

and those who were assigned to a liberal transfusion strategy. However, the liberal transfusion strategy was consistently favored in point estimates for the primary outcome and for death, cardiac death, recurrent myocardial infarction, and the composite of death, myocardial infarction, ischemia-driven unscheduled coronary revascularization, or readmission to the hospital for an ischemic cardiac condition. The frequency of heart failure, a more comprehensive measure of volume overload than TACO, and other safety-outcome events was similar in the two transfusion groups.

The findings in our trial contrast with the results from previous transfusion trials conducted across a wide range of patient populations and treatments (including cardiac surgery) in our Cochrane meta-analysis.[6] In the other clinical situations involving patients without acute myocardial infarction, a restrictive strategy decreased blood use by 50% without adversely affecting clinical outcomes.[11,12]

Of three transfusion trials involving patients with acute myocardial infarction, a cost-effectiveness study that enrolled 668 patients showed that a restrictive transfusion strategy was less costly and was clinically noninferior to a liberal strategy with respect to the risk of major adverse cardiac events (including death, reinfarction, stroke, and emergency revascularization) at 30 days.[3] One-year outcomes were similar in the two groups, and the restrictive strategy did not meet the prespecified noninferiority threshold.[13] In the MINT pilot study involving 110 patients, there were 7 deaths in the restrictive-strategy group and 1 death in the liberal-strategy group.[4] In the CRIT trial, which involved 45 patients, point estimates favored the restrictive group.[5] In our trial, the enrollment was four times as large as the enrollment in all three of the other studies combined.

Although the between-group difference in the primary outcome in our trial did not reach the prespecified level of significance, it was not because of poor implementation of the transfusion strategy, given the large difference (by a factor of three) in blood use, the hemoglobin differences between the trial groups, or the occurrence of the estimated primary-outcome events overall. The trial was designed to detect a 20% relative between-group difference, and the observed effect was a relative difference of approximately 15%. The smaller-than-expected difference may have occurred as a result of introducing more hetero-

Outcome	Restrictive Strategy	Liberal Strategy	Risk Ratio (95% CI)
	no. of patients/total no. (%)		
Primary outcome			
Myocardial infarction or death	295/1749 (16.9)	255/1755 (14.5)	1.16 (1.00–1.35)
Secondary outcomes			
Death	173/1749 (9.9)	146/1755 (8.3)	1.19 (0.96–1.47)
Myocardial infarction	149/1749 (8.5)	126/1755 (7.2)	1.19 (0.94–1.49)
Death, myocardial infarction, revascularization, or rehospitalization	342/1749 (19.6)	305/1755 (17.4)	1.13 (0.98–1.29)
Other outcomes			
Heart failure	102/1749 (5.8)	111/1755 (6.3)	0.92 (0.71–1.20)
Death, myocardial infarction, or unstable angina	338/1749 (19.3)	300/1755 (17.1)	1.13 (0.98–1.30)
Unscheduled revascularization	43/1749 (2.5)	39/1755 (2.2)	1.11 (0.72–1.70)
Cardiac death	97/1749 (5.5)	56/1755 (3.2)	1.74 (1.26–2.40)
Stroke	30/1749 (1.7)	26/1755 (1.5)	1.16 (0.69–1.95)
Pulmonary embolism or deep venous thrombosis	26/1749 (1.5)	34/1755 (1.9)	0.77 (0.46–1.27)
Pneumonia or bacteremia	166/1749 (9.5)	153/1755 (8.7)	1.09 (0.88–1.34)

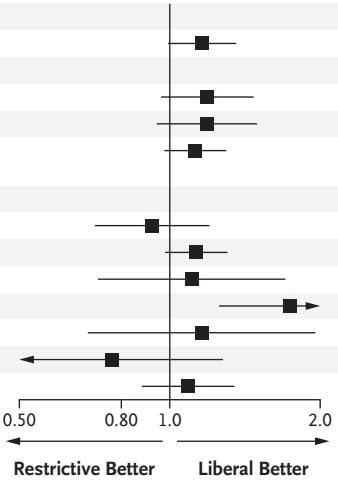

Figure 2. Trial Outcomes at 30 Days.

Shown are the unadjusted risk ratios for the primary, secondary, and other outcomes in patients assigned to a restrictive transfusion strategy as compared with those assigned to a liberal transfusion strategy. The estimate for the primary model with imputed missing data was a risk ratio of 1.15 (95% CI, 0.99 to 1.34; P=0.07).

geneity of the treatment effect than anticipated with the enrollment of a broad group of patients with acute myocardial infarction, including a large percentage of patients with demand ischemia (type 2 myocardial infarction).

Our trial has several strengths. It was pragmatic, since it was designed to maximize the generalizability of the results. With few exclusions, the enrollment of 3504 patients included a wide variety of older patients who had a variety of myocardial infarction diagnoses, including both ST-segment elevation and non–ST-segment elevation and both type 1 and type 2 myocardial infarctions. In addition, the patients had many coexisting illnesses and were generally representative of patients in clinical practice with acute myocardial infarction and anemia. In making these inclusion decisions, we may have included patients who had an increased severity of illness, who had an increased number of coexisting illnesses, and who were less likely to benefit from a liberal transfusion strategy. Transfusion protocols were also straightforward and easy to manage and closely approximated clinical practice in a variety of settings and health systems. The transfusion protocol made accommodations for patients with heart failure and for transfusing during dialysis. The protocol also advised transfusion in patients with ongoing ischemic symptoms who did not have a response to intensification of medical therapy or who had hemorrhage. The trial transfusion protocol led to large differences in the number of blood transfusions and clinically meaningful differences in hemoglobin levels between the two groups. The trial outcomes were clinically relevant, and other interventions were applied according to standard clinical practice. Follow-up for the 30-day primary outcome was complete for 98.3% of the patients. The myocardial infarction component of the primary outcome was centrally adjudicated in a blinded fashion by an expert committee that examined all available troponin levels and clinical information over the 30-day follow-up period.

Our trial also has several limitations. As in all transfusion-threshold trials, the assigned intervention was not masked from health professionals caring for the patients. This factor may have influenced the use of revascularization or other interventions or the classification of cause of death. Death from cardiac causes was a prespecified outcome,[9] but it was not designated as a primary, secondary, or tertiary outcome and was not adjudicated, and fewer than half the deaths were classified as cardiac. The qualifying myocardial infarction and the outcomes, other than myocardial infarction, were not centrally adjudicated. Adherence to the hemoglobin threshold of less than 10 g per deciliter in the liberal-strategy group was moderate (86.3% at hospital discharge); this lapse was frequently due to clinical discretion, such as concern about fluid overload, and

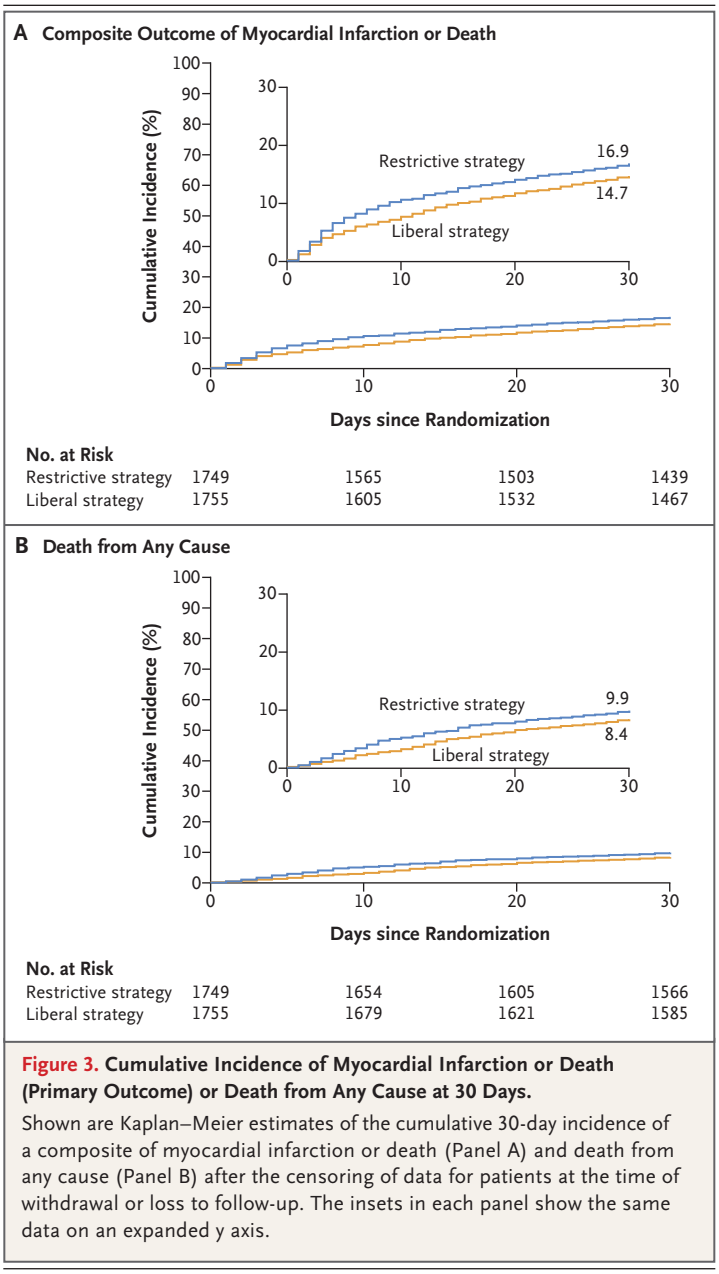

Figure 3. Cumulative Incidence of Myocardial Infarction or Death (Primary Outcome) or Death from Any Cause at 30 Days.

Shown are Kaplan–Meier estimates of the cumulative 30-day incidence of a composite of myocardial infarction or death (Panel A) and death from any cause (Panel B) after the censoring of data for patients at the time of withdrawal or loss to follow-up. The insets in each panel show the same data on an expanded y axis.

Subgroup	Restrictive Strategy	Liberal Strategy	Risk Ratio (95% CI)
	no. of patients/total no. (%)		
All patients	295/1749 (16.9)	255/1755 (14.5)	1.16 (1.00–1.35)
Type of index myocardial infarction			
Type 1	133/730 (18.2)	101/730 (13.8)	1.32 (1.04–1.67)
Type 2	153/967 (15.8)	149/988 (15.1)	1.05 (0.85–1.29)
STEMI or NSTEMI			
STEMI	49/319 (15.4)	50/337 (14.8)	1.04 (0.72–1.49)
NSTEMI	246/1430 (17.2)	205/1418 (14.5)	1.19 (1.00–1.41)
Revascularization before randomization			
No	218/1240 (17.6)	190/1262 (15.1)	1.17 (0.98–1.40)
Yes	77/509 (15.1)	65/493 (13.2)	1.15 (0.84–1.56)
CHF, acute HF, or low LVEF			
No	115/831 (13.8)	105/802 (13.1)	1.06 (0.83–1.35)
Yes	180/918 (19.6)	150/953 (15.7)	1.25 (1.02–1.52)
Hemoglobin category			
<8 g/dl	74/404 (18.3)	73/386 (18.9)	0.97 (0.72–1.30)
8 to <9 g/dl	107/662 (16.2)	89/677 (13.1)	1.23 (0.95–1.59)
9 to <10 g/dl	114/681 (16.7)	93/686 (13.6)	1.23 (0.96–1.59)
Type of anemia			
Chronic	144/902 (16.0)	116/914 (12.7)	1.26 (1.00–1.58)
Acute	103/539 (19.1)	92/539 (17.1)	1.12 (0.87–1.44)
Renal function			
Renal dialysis at baseline	34/203 (16.7)	41/212 (19.3)	0.87 (0.57–1.31)
eGFR <30 ml/min/1.73 m^2	88/406 (21.7)	63/396 (15.9)	1.36 (1.02–1.83)
eGFR 30 to 59 ml/min/1.73 m^2	89/505 (17.6)	69/493 (14.0)	1.26 (0.94–1.68)
eGFR ≥60 ml/min/1.73 m^2	84/633 (13.3)	80/646 (12.4)	1.07 (0.81–1.43)
History of diabetes therapy			
No	132/801 (16.5)	117/807 (14.5)	1.14 (0.90–1.43)
Yes	163/948 (17.2)	138/948 (14.6)	1.18 (0.96–1.45)
Sex			
Male	167/975 (17.1)	133/936 (14.2)	1.21 (0.98–1.49)
Female	128/774 (16.5)	122/819 (14.9)	1.11 (0.88–1.39)
Age			
<60 yr	27/238 (11.3)	24/250 (9.6)	1.18 (0.70–1.99)
60–69 yr	63/421 (15.0)	54/459 (11.8)	1.27 (0.91–1.78)
70–79 yr	126/631 (20.0)	106/598 (17.7)	1.13 (0.89–1.42)
≥80 yr	79/459 (17.2)	71/447 (15.9)	1.08 (0.81–1.45)

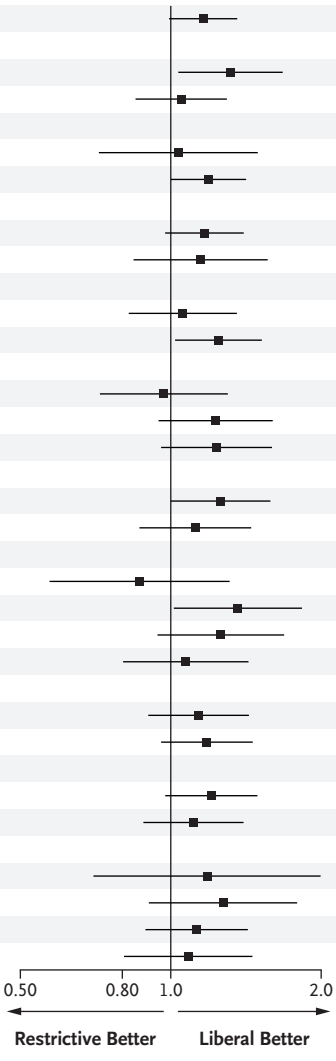

Figure 4. Subgroup Analysis of Myocardial Infarction or Death.

Shown is the unadjusted risk ratio for myocardial infarction or death (primary outcome) in the restrictive-strategy group as compared with the liberal-strategy group, according to prespecified subgroup. CHF denotes chronic heart failure, eGFR estimated glomerular filtration rate, LVEF left ventricular ejection fraction, NSTEMI non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.

to the timing of hospital discharge. The trial analyses were not adjusted for multiplicity, so caution must be used in interpreting the results beyond the primary outcome.

Whether to transfuse is an everyday decision faced by clinicians caring for patients with acute myocardial infarction. We observed that the 95% confidence interval contains values that suggest a clinical benefit for the liberal transfusion strategy and does not include values that suggest a benefit for the more restrictive transfusion strategy. At 30 days, the risk of myocardial infarction or death was 2.4 percentage points lower in the liberal-strategy group than in the restrictive-strategy group, and the risk of death was 1.6 percentage points lower. Furthermore, the

safety profile of the liberal transfusion strategy indicated low risk.

Our results show that in patients with acute myocardial infarction and anemia, a liberal transfusion strategy did not significantly reduce the risk of recurrent myocardial infarction or death at 30 days. Trial end points suggest some benefit of a liberal strategy over a restrictive strategy, but additional studies would be needed to confirm that conclusion.

The views expressed in this article are those of the authors and do not necessarily reflect the official policies of the National Institutes of Health.

Supported by grants (U01 HL133817 and U01HL132853) from the National Heart, Lung, and Blood Institute and by the Canadian Blood Services and Canadian Institutes of Health Research Institute of Circulatory and Respiratory Health.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

The authors' full names and academic degrees are as follows: Jeffrey L. Carson, M.D., Maria Mori Brooks, Ph.D., Paul C. Hébert, M.D., M.H.Sc., Shaun G. Goodman, M.D., Marnie Bertolet, Ph.D., Simone A. Glynn, M.D., M.P.H., Bernard R. Chaitman, M.D., Tabassome Simon, M.D., Ph.D., Renato D. Lopes, M.D., Ph.D., Andrew M. Goldsweig, M.D., Andrew P. DeFilippis, M.D., J. Dawn Abbott, M.D., Brian J. Potter, M.D.C.M., Francois Martin Carrier, M.D., Sunil V. Rao, M.D., Howard A. Cooper, M.D., Shahab Ghafghazi, M.D., Dean A. Fergusson, Ph.D., William J. Kostis, Ph.D., M.D., Helaine Noveck, M.P.H., Sarang Kim, M.D., Meechai Tessalee, M.D., Gregory Ducrocq, M.D., Ph.D., Pedro Gabriel Melo de Barros e Silva, M.D., Darrell J. Triulzi, M.D., Caroline Alsweiler, M.H.Sc., Mark A. Menegus, M.D., John D. Neary, M.D., Lynn Uhl, M.D., Jordan B. Strom, M.D., Christopher B. Fordyce, M.D., M.H.S., Emile Ferrari, M.D., Johanne Silvain, M.D., Ph.D., Frances O. Wood, M.D., Benoit Daneault, M.D., Tamar S. Polonsky, M.D., Manohara Senaratne, M.D., Etienne Puymirat, M.D., Claire Bouleti, M.D., Benoit Lattuca, M.D., Harvey D. White, M.D., Sheryl F. Kelsey, Ph.D., P. Gabriel Steg, M.D., and John H. Alexander, M.D., M.H.S.

The authors' affiliations are as follows: the Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ (J.L.C., W.J.K., H.N., S.K.); the Departments of Epidemiology and Biostatistics, School of Public Health, University of Pittsburgh (M.M.B., M.B., S.F.K.), and the Department of Pathology, Division of Transfusion Medicine, University of Pittsburgh School of Medicine (D.J.T.) — both in Pittsburgh; the Bruyere Research Institute, University of Ottawa (P.C.H.), and the Clinical Epidemiology Program, Ottawa Hospital Research Institute (D.A.F.), Ottawa, St. Michael's Hospital, University of Toronto, Toronto (S.G.G.), Canadian VIGOUR Centre, University of Alberta (S.G.G.), and the Department of Medicine, Grey Nuns Hospital (M.S.), Edmonton, CHUM Research Centre (B.J.P.), the Departments of Anesthesiology and Medicine, Division of Critical Care, Centre Hospitalier de l'Université de Montréal, Innovation and Evaluation Hub, Centre de Recherche du CHUM (F.M.C., P.C.H.), and the Department of Anesthesiology and Pain Medicine, Université de Montréal (F.M.C.), Montreal, the Department of Medicine, McMaster University, Hamilton, ON (J.D.N.), the Division of Cardiology and Centre for Cardiovascular Innovation, Vancouver General Hospital and University of British Columbia, Vancouver (C.B.F.), and Centre Hospitalier Universitaire (CHU) de Sherbrooke, Université de Sherbrooke, Sherbrooke, QC (B.D.) — all in Canada; the National Heart, Lung, and Blood Institute, Bethesda, MD (S.A.G.); St. Louis University School of Medicine, St. Louis (B.R.C.); FACT (French Alliance for Cardiovascular Trials) (T.S., G.D., P.G.S.), Service de Pharmacologie, Plateforme de Recherche Clinique de l'Est Parisien, Assistance Publique–Hôpitaux de Paris (AP-HP), Hôpital Saint Antoine, Sorbonne Université (T.S.), Université Paris-Cité, INSERM Unité 1148 and AP-HP, Hôpital Bichat (G.D., P.G.S.), Sorbonne Université, ACTION Study Group, INSERM UMRS1166, Hôpital Pitié–Salpêtrière AP-HP (J.S.), and AP-HP, Hôpital Européen Georges Pompidou, Department of Cardiology, Université de Paris (E.P.), Paris, Hôpital Pasteur, Service de Cardiologie, CHU Nice, Nice (E.F.), University Hospital of Poitiers, Clinical Investigation Center (INSERM 1204), Cardiology Department, Poitiers (C.B.), and Nimes University Hospital, Montpelier University, ACTION Group, Nimes (B.L.) — all in France; Duke Clinical Research Institute, Duke University, Durham (R.D.L., J.H.A.), and the Department of Medicine, WakeMed Health and Hospitals, Winston-Salem (F.O.W.) — both in North Carolina; Brazilian Clinical Research Institute, Sao Paulo (R.D.L., P.G.M.B.S.); the Department of Medicine, Baystate Medical Center, Springfield (A.M.G.), and the Department of Pathology (L.U.) and Richard A. and Susan F. Smith Center for Outcomes Research in Cardiology (J.B.S.), Beth Israel Deaconess Medical Center, Harvard Medical School, Boston — both in Massachusetts; the University of Nebraska Medical Center, Omaha (A.M.G.); the Department of Medicine, Vanderbilt University Medical Center, Nashville (A.P.D.); Lifespan Cardiovascular Institute and the Department of Medicine, Division of Cardiology, Alpert Medical School of Brown University, Providence, RI (J.D.A.); the Department of Medicine, NYU Langone Health System (S.V.R.), and the Department of Medicine, Montefiore Medical Center (M.A.M.), New York, and the Department of Cardiology, Westchester Medical Center, Valhalla (H.A.C.) — all in New York; the Department of Medicine, University of Louisville, Louiville, KY (S.G.); UChicago AdventHealth Heart and Vascular (M.T.) and the Department of Medicine, University of Chicago Medicine (T.S.P.) — both in Chicago; and Green Lane Coordinating Center, Auckland, New Zealand (C.A., H.D.W.).

REFERENCES

1. Sabatine MS, Morrow DA, Giugliano RP, et al. Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. Circulation 2005;111:2042-9.
2. Salisbury AC, Alexander KP, Reid KJ, et al. Incidence, correlates, and outcomes of acute, hospital-acquired anemia in patients with acute myocardial infarction. Circ Cardiovasc Qual Outcomes 2010;3:337-46.
3. Ducrocq G, Gonzalez-Juanatey JR, Puymirat E, et al. 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;325:552-60.
4. Carson JL, Brooks MM, Abbott JD, et al. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. Am Heart J 2013;165(6):964.e1-971.e1.

5. Cooper HA, Rao SV, Greenberg MD, et al. Conservative versus liberal red cell transfusion in acute myocardial infarction (the CRIT randomized pilot study). Am J Cardiol 2011;108:1108-11.
6. Carson JL, Stanworth SJ, Dennis JA, et al. Transfusion thresholds for guiding red blood cell transfusion. Cochrane Database Syst Rev 2021;12:CD002042.
7. Mueller MM, Van Remoortel H, Meybohm P, et al. Patient blood management: recommendations from the 2018 Frankfurt Consensus Conference. JAMA 2019;321:983-97.
8. Carson JL, Stanworth SJ, Guyatt G, et al. Red blood cell transfusion: 2023 AABB international guidelines. JAMA 2023 October 12 (Epub ahead of print).
9. Carson JL, Brooks MM, Chaitman BR, et al. Rationale and design for the myocardial ischemia and transfusion (MINT) randomized clinical trial. Am Heart J 2023;257:120-9.
10. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020-35.
11. Murphy GJ, Pike K, Rogers CA, et al. Liberal or restrictive transfusion after cardiac surgery. N Engl J Med 2015;372:997-1008.
12. Mazer CD, Whitlock RP, Fergusson DA, et al. Restrictive or liberal red-cell transfusion for cardiac surgery. N Engl J Med 2017;377:2133-44.
13. Gonzalez-Juanatey JR, Lemesle G, Puymirat E, et al. One-year major cardiovascular events after restrictive versus liberal blood transfusion strategy in patients with acute myocardial infarction and anemia: the REALITY randomized trial. Circulation 2022;145:486-8.