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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

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IMPORTANCE The optimal transfusion strategy in patients with acute myocardial infarction and anemia is unclear.

OBJECTIVE To determine whether a restrictive transfusion strategy would be clinically noninferior to a liberal strategy.

DESIGN, SETTING, AND PARTICIPANTS Open-label, noninferiority, randomized trial conducted in 35 hospitals in France and Spain including 668 patients with myocardial infarction and hemoglobin level between 7 and 10 g/dL. Enrollment could be considered at any time during the index admission for myocardial infarction. The first participant was enrolled in March 2016 and the last was enrolled in September 2019. The final 30-day follow-up was accrued in November 2019.

INTERVENTIONS Patients were randomly assigned to undergo a restrictive (transfusion triggered by hemoglobin ≤8; n = 342) or a liberal (transfusion triggered by hemoglobin ≤10 g/dL; n = 324) transfusion strategy.

MAIN OUTCOMES AND MEASURES The primary clinical outcome was major adverse cardiovascular events (MACE; composite of all-cause death, stroke, recurrent myocardial infarction, or emergency revascularization prompted by ischemia) at 30 days. Noninferiority required that the upper bound of the 1-sided 97.5% CI for the relative risk of the primary outcome be less than 1.25. The secondary outcomes included the individual components of the primary outcome.

RESULTS Among 668 patients who were randomized, 666 patients (median [interquartile range] age, 77 [69-84] years; 281 [42.2%] women) completed the 30-day follow-up, including 342 in the restrictive transfusion group (122 [35.7%] received transfusion; 342 total units of packed red blood cells transfused) and 324 in the liberal transfusion group (323 [99.7%] received transfusion; 758 total units transfused). At 30 days, MACE occurred in 36 patients (11.0% [95% CI, 7.5%-14.6%]) in the restrictive group and in 45 patients (14.0% [95% CI, 10.0%-17.9%]) in the liberal group (difference, −3.0% [95% CI, −8.4% to 2.4%]). The relative risk of the primary outcome was 0.79 (1-sided 97.5% CI, 0.00-1.19), meeting the prespecified noninferiority criterion. In the restrictive vs liberal group, all-cause death occurred in 5.6% vs 7.7% of patients, recurrent myocardial infarction occurred in 2.1% vs 3.1%, emergency revascularization prompted by ischemia occurred in 1.5% vs 1.9%, and nonfatal ischemic stroke occurred in 0.6% of patients in both groups.

CONCLUSIONS AND RELEVANCE Among patients with acute myocardial infarction and anemia, a restrictive compared with a liberal transfusion strategy resulted in a noninferior rate of MACE after 30 days. However, the CI included what may be a clinically important harm.

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+ **Visual Abstract**

+ **Supplemental content**

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Anemia, with or without overt bleeding, is common in patients with acute myocardial infarction (AMI) and affects prognosis. Even moderate levels of anemia (hemoglobin level of 10-12 g/dL) are associated with increased cardiovascular mortality compared with normal hemoglobin values in the context of acute coronary syndromes.[1] Transfusion is often considered to be indicated when the hemoglobin level falls below 10 g/dL, with large variations in clinical practice due to lack of robust data. Observational studies have yielded conflicting results[2-4] and only 2 small randomized trials (including 45 and 110 patients) have compared restrictive with liberal transfusion strategies in this setting.[5,6] Large randomized trials have compared transfusion strategies in patients with gastrointestinal bleeding[7] and those undergoing surgical procedures[8-10] and generally found benefit from a restrictive strategy, but these trials excluded patients with AMI.[11]

In addition to uncertain benefit in patients with AMI, transfusion has potential adverse effects, logistical implications (particularly for blood supply), and cost. The objective of this study, the Restrictive and Liberal Transfusion Strategies in Patients With Acute Myocardial Infarction (REALITY) randomized trial, was to determine whether a restrictive transfusion strategy was clinically noninferior to a liberal transfusion strategy.

Methods

The protocol and statistical analysis plan are presented in Supplement 1. The trial was approved by the Comité de Protection des Personnes, Ile de France-I, France, and the ethics committee at the Hospital Clinic, Barcelona, Spain. Patients provided written informed consent.

Trial Population

To be eligible for inclusion, patients had to be aged at least 18 years and have AMI (with or without ST-segment elevation with a combination of ischemic symptoms occurring in the 48 hours before admission and elevation of biomarkers of myocardial injury) and a hemoglobin level between 7 and 10 g/dL. Enrollment could be considered at any time during the index admission for myocardial infarction. Exclusion criteria were shock at the time of randomization (systolic blood pressure <90 mm Hg with clinical signs of low output or requiring inotropic drugs), myocardial infarction occurring after percutaneous coronary intervention or coronary artery bypass graft, life-threatening or massive ongoing bleeding (judged by the investigator), blood transfusion in the past 30 days, and malignant hematologic disease. Given the higher prevalence of chronic anemia in certain ethnic groups, race/ethnicity was recorded (self-reported using fixed categories).

Randomization and Interventions

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. In the restrictive strategy group, no transfusion was to be performed unless hemoglobin level decreased to less than

Key Points

Question Is a restrictive strategy of blood transfusion noninferior to a liberal strategy among patients with acute myocardial infarction and anemia?

Findings In this randomized clinical trial that included 668 patients with acute myocardial infarction and hemoglobin level between 7 and 10 g/dL who were treated with a restrictive transfusion strategy (triggered by hemoglobin ≤8 g/dL) vs a liberal strategy (triggered by hemoglobin ≤10 g/dL), the composite outcome (all-cause death, stroke, recurrent myocardial infarction, or emergency revascularization) at 30 days occurred in 11% vs 14% of patients, a difference that met the noninferiority criterion of relative risk less than 1.25.

Meaning A restrictive transfusion strategy compared with a liberal strategy resulted in a noninferior rate of major cardiovascular events among patients with acute myocardial infarction and anemia, but the CI included what may be a clinically important harm.

or equal to 8 g/dL, with a target range for posttransfusion hemoglobin of 8 to 10 g/dL (the initial protocol used a threshold of 7 g/dL but this was changed to 8 g/dL to maximize investigator adherence to the protocol before inclusion of the first patient). In the liberal strategy group, transfusion was to be performed after randomization on all patients with a hemoglobin level less than or equal to 10 g/dL, with a target posttransfusion hemoglobin level of at least 11 g/dL. Homologous leukoreduced packed red blood cells were used for transfusion.

Both strategies were to be maintained until patient discharge or 30 days after randomization, whichever occurred first. The protocol allowed transfusion to be administered at any time in the following documented instances: massive overt active bleeding, presumed important decrease in hemoglobin level and no time to wait for hemoglobin measurement (indicating suspected massive bleeding), and shock presumably due to blood loss occurring after randomization.

After discharge, patient follow-up was scheduled at day 30 (±5 days) and follow-up data were collected by the investigator, either by direct contact (if the patient was still hospitalized) or by a visit, phone call, or mail. Group assignment was not blinded for data collection.

Outcome Measures and Definitions

The primary clinical efficacy outcome was a composite of major adverse cardiovascular events (MACE) at 30 days, defined as all-cause death, nonfatal stroke, nonfatal recurrent myocardial infarction, or emergency revascularization prompted by ischemia. Secondary outcomes included the individual components of the composite MACE outcome at 30 days and 1 year. Descriptive end points included the baseline characteristics of patients, use of transfusion, hemoglobin values, and bleeding episodes in each group. The current analysis reports 30-day clinical outcomes. The 1-year outcomes and the cost-effectiveness analyses will be reported separately. Adverse events were monitored during hospital stay and included the following potential adverse effects of transfusion: hemolysis, documented bacteremia acquired after transfusion, multiorgan system dysfunction, acute respiratory distress syndrome, acute heart failure, acute kidney

Figure 1. Flow of Patients in a Study of the Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Major Cardiovascular Events Among Patients With Acute Myocardial Infarction and Anemia
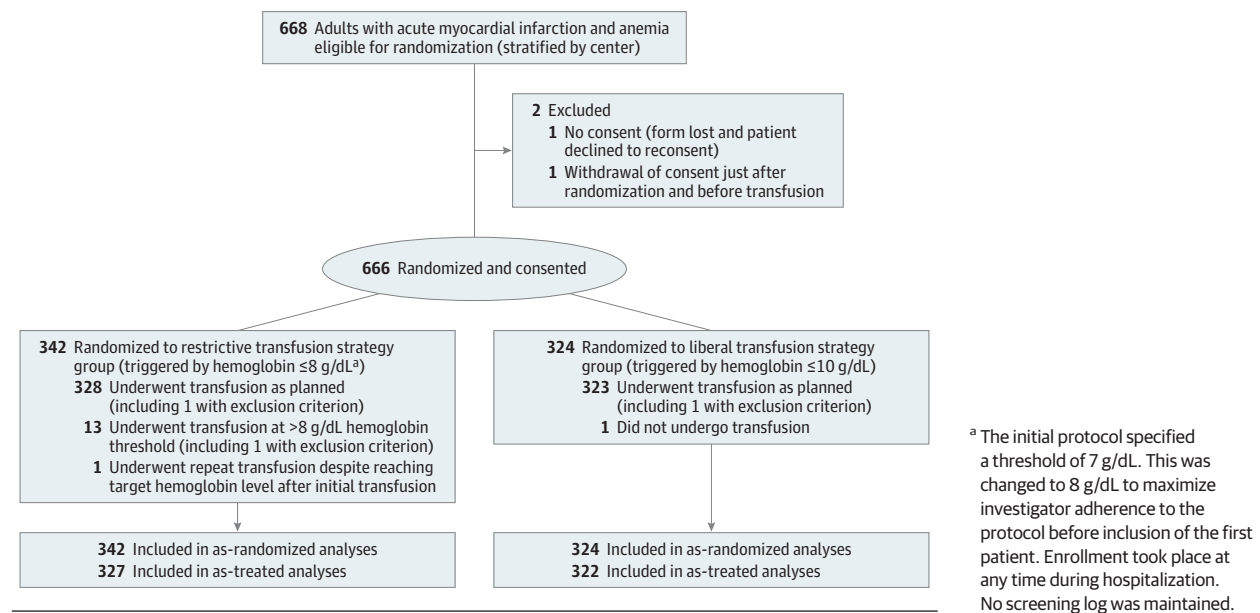
failure, and severe allergic reactions. All components of the primary efficacy clinical outcome as well as acute heart failure were adjudicated by a critical event committee blinded to treatment assignment and hemoglobin levels. The third universal definition of myocardial infarction was used.[12] All other safety outcomes were investigator-reported. Outcome definitions are detailed in eAppendix 1 in Supplement 2.

Statistical Analysis

Based on unpublished observations from the French nationwide FAST-MI registry of AMI,[13,14] we assumed the percentages of patients with MACE at 30 days of approximately 11% in the restrictive transfusion group and 15% in the liberal transfusion group. Noninferiority was assessed using a CI method with a 1-sided 97.5% CI and without any other statistical tests, as recommended by the International Conference on Harmonization.[15] The noninferiority margin was set using a relative, rather than absolute, risk margin to minimize the risk of overestimating event rates when planning the trial, because this can make it easy to achieve noninferiority if the overall event rate is lower than expected.[16,17] With these assumptions, a sample size of 300 patients per group would provide 80% power to demonstrate noninferiority of the restrictive group, with a margin corresponding to a relative risk equal to 1.25. With a conservative hypothesis of 5% of patients with major protocol violations, 630 patients (315 per group) were required for the trial to be adequately powered for the noninferiority analysis. Because there was no established clinical superiority of either transfusion strategy and no randomized trial of transfusion vs no transfusion, the choice of a noninferiority margin was based on clinical judgment based on what clinicians would be prepared to accept as potential loss of efficacy of a restrictive transfusion strategy compared with a liberal strategy given the expected theoretical benefits of the for-

mer of sparing scarce blood resources,[18] reducing transfusion adverse effects, and reducing logistical burden and costs. A relative margin of 1.25 appeared an acceptable compromise, given that observational studies relating hemoglobin levels and outcomes after myocardial infarction have shown that the likelihood of MACE increased, with an adjusted odds ratio of 1.45 for each 1-g/dL decrement in hemoglobin below 11 g/dL,[1] and the expected difference in hemoglobin values between treatment groups would be expected to exceed 1 g/dL.

The analysis of the primary efficacy outcome used relative risk, defined as p_1/p_2, with $p_1 = n_{11}/n_1$ and $p_1 = n_{21}/n_2$, where n_{11} is the event number and n_1 is the total number of patients in the restrictive group and n_{21} is the event number and n_2 is the total number of patients in the liberal group. Ninety-five percent CIs were estimated using the Wald method. The analysis was performed among both the as-treated population, which included all patients without a major protocol violation (including eligibility criteria not fulfilled), and the as-randomized population, which included all randomized patients with the exception of 2 patients (1 without a consent form and 1 who withdrew consent immediately after randomization). Concordance in the noninferiority analysis between the as-randomized and the as-treated populations was required to establish noninferiority. The use of multiple imputation methods was planned in the statistical analysis plan in the case of missing data for the primary clinical outcome. Given the absence of missing data at day 30, imputation was not needed. Because the trial was conducted at multiple sites, site effect was accounted for in a post hoc sensitivity analysis using a generalized linear regression mixed model with binary distribution and a log link function with strategy as a fixed effect and center as a random effect. If clinical noninferiority of the restrictive strategy was established, a test of superiority of the restrictive strategy was planned.

Table 1. Baseline Characteristics of the As-Randomized Population in a Study of the Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Patients With Acute Myocardial Infarction and Anemia

Characteristic	No. (%)[a]	
	Restrictive (n = 342)	Liberal (n = 324)
Age, median (IQR), y	78 (69-85)	76 (69-84)
Sex		
Men	201 (58.8)	184 (56.8)
Women	141 (41.2)	140 (43.2)
Race (self-reported)	n = 336	n = 322
White	298 (88.7)	266 (82.6)
North African	29 (8.6)	36 (11.2)
African/Caribbean	7 (2.1)	9 (2.8)
Indian	2 (0.6)	5 (1.6)
Other Asian	0	6 (1.9)
BMI, mean (SD)	26.9 (5.3) [n = 334]	26.4 (5.0) [n = 317]
Risk factor[b]		
Hypertension	272 (79.5)	256 (79.0)
Dyslipidemia	189 (55.3)	201 (62.0)
Diabetes	176 (51.5)	158 (48.8)
Tobacco smoking status	n = 316	n = 293
Never	149 (47.2)	141 (48.1)
Former	116 (36.7)	111 (37.9)
Current	51 (16.1)	41 (14.0)
Family history of premature coronary artery disease	46 (13.6) [n = 337]	43 (13.4) [n = 321]
Cardiac history before index event[b]		
Acute coronary syndrome	121 (35.4)	119 (36.7)
Percutaneous coronary intervention	114 (33.3)	111 (34.3)
Angina	55 (16.1)	44 (13.6)
Atrial fibrillation	54 (15.8)	65 (20.1)
CABG	44 (12.9)	42 (13.0)
Congestive heart failure	44 (12.9)	38 (11.7)
Internal cardiac defibrillator	14 (4.1)	8 (2.5)
Noncardiac medical history[b]		
Chronic anemia[c]	61 (17.8)	62 (19.1)
Cancer		
Previously treated	42 (12.3)	44 (13.6)
Receiving treatment	25 (7.3)	18 (5.6)
COPD	34 (9.9)	40 (12.3)
Dialysis	25 (7.3)	30 (9.3)
History of bleeding requiring hospitalization and transfusion	23 (6.7)	20 (6.2)
Index hospitalization		
Myocardial infarction type		
Non–ST-segment elevation	234 (68.4)	231 (71.3)
ST-segment elevation	108 (31.6)	93 (28.7)
Killip class at admission[d]	n = 336	n = 321
I	189 (56.3)	183 (57.0)
II	87 (25.9)	88 (27.4)
III	54 (16.1)	39 (12.1)
IV	6 (1.8)	11 (3.4)
Delay between admission and randomization, median (IQR), d	1.6 (0.8-3.6)	1.9 (0.8-3.6)
Active bleeding[e]	36 (10.5)	49 (15.1)
1 active bleed	29 (80.6)	42 (85.7)
2 active bleeds	6 (16.7)	6 (12.2)
3 active bleeds	1 (2.8)	1 (2.0)
Creatinine clearance at randomization,[f] median (IQR), mL/min/1.73 m^2	45.1 (27.2-73.2) [n = 338]	46.6 (24.9-73.2) [n = 321]

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; IQR, interquartile range.

[a] Percentages may not add to 100 due to rounding.

[b] Collected through chart review.

[c] Preexisting anemia not caused by acute bleeding.

[d] Killip class was determined by the investigator according to clinical examination. Class I indicates no sign of congestion; class II, basal rales on auscultation; class III, acute pulmonary edema; and class IV, cardiogenic shock.

[e] Active bleeding identified and documented during the index admission prior to randomization.

[f] According to the Chronic Kidney Disease Epidemiology Collaboration formula.

Table 2. Hemoglobin Levels and Transfusions Among the As-Randomized Population in a Study of the Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Patients With Acute Myocardial Infarction and Anemia

Variable	No. (%)	
	Restrictive (n = 342)	Liberal (n = 324)
Hemoglobin level, mean (SD), g/dL		
At admission	10.0 (1.7)	10.1 (1.6) [n = 322]
Most recent prior to randomization	9.0 (0.8)	9.1 (0.8) [n = 323]
Lowest value during hospital stay	8.3 (0.9)	8.8 (0.9) [n = 323]
At discharge	9.7 (1.0) [n = 337]	11.1 (1.4) [n = 320]
Red blood cell transfusion		
Patients who received ≥1 unit of packed red blood cells	122 (35.7)	323 (99.7)[a]
Units transfused, No.	342	758
Per patient transfused, mean (SD)	2.9 (3.7)	2.8 (2.7)
Per patient transfused, median (IQR)	2.0 (2.0-3.0)	2.0 (2.0-3.0)
Units transfused		
0	220 (64.3)	1 (0.3)
1	25 (7.3)	43 (13.3)
2	62 (18.1)	128 (39.5)
3	12 (3.5)	47 (14.5)
≥4	19 (5.6)	54 (16.7)
≥1 (exact No. not available)	4 (1.2)	51 (15.7)
Duration of red blood cell storage, median (IQR), d	20.0 (17.0-25.0)	21.0 (15.0-30.0)
No. of units for which data were available	90	299
Transfusion		
Fresh frozen plasma	3 (0.9)	7 (2.2)
Platelet	4 (1.2)	6 (1.9)

Abbreviation: IQR, interquartile range.

[a] One patient had been transferred to a non–study site where local physicians declined to implement transfusion.

All secondary analyses were performed on the as-randomized population with available data. In a secondary analysis of the main outcome, survival was estimated using the Kaplan-Meier method and groups were compared using a log-rank test. A stratified Cox proportional hazards model was used to estimate the hazard ratios and 95% CIs for the effect of transfusion strategy on MACE-free survival and each component of the MACE outcome. Data for patients with no evidence of MACE were censored at 30 days. The risk proportionality hypothesis was verified by testing the interaction between interest variable and time.

Differences and 95% CIs between strategies were estimated using the Wald method, with continuity correction for binary variables. No adjustment was planned for multiplicity and there was no prespecified hierarchy for secondary efficacy outcomes. Because of the potential for type I error due to multiple comparisons, analyses of secondary end points should be interpreted as exploratory. The effect of transfusion strategy on the primary composite outcome was explored in subgroups of clinical interest (age, sex, body weight, presence or absence of diabetes, smoking status, presence or absence of hypertension, presence or absence of dyslipidemia, Killip class, kid-

ney function [creatinine clearance], presence or absence of active bleeding, hemoglobin levels at the time of randomization, ST- vs non–ST-segment elevation myocardial infarction, and revascularization by percutaneous coronary intervention for the index event before or after randomization); the interaction between subgroup and transfusion strategy was tested using logistic regression. For safety adverse events, only point estimates of treatment effects with 2-sided 95% CIs are provided. All superiority tests and 95% CI were 2-sided, and P values <.05 were considered significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) and R version 3.6.3 (R Foundation for Statistical Computing).

Results

Descriptive Findings

From March 2016 to September 2019, a total of 668 patients with AMI and anemia were consecutively enrolled in the trial (in 26 centers in France and 9 centers in Spain; Figure 1). Baseline characteristics of the as-randomized population were similar between the groups (Table 1). The median age of patients was 77 years, 385 (57.8%) were men, and 334 (50.2%) had diabetes. In most patients, the cause of anemia was unknown; 43 patients (6.5%) had a history of bleeding requiring hospitalization and transfusion. The qualifying myocardial infarction was non–ST-elevation myocardial infarction in approximately two-thirds of the patients. A minority of patients had an identified active bleeding site (Table 1; eTable 1 in Supplement 2).

In-hospital management is detailed in eTable 2 in Supplement 2. Most patients underwent coronary angiography (81.9% in the restrictive group and 79.3% in the liberal group) and approximately two-thirds underwent myocardial revascularization. Treatments before hospitalization and during the first 24 hours of admission are shown in eTable 3 in Supplement 2. Most patients received dual antiplatelet therapy for the qualifying myocardial infarction. Baseline characteristics and treatment of the as-treated population are shown in eTable 4 in Supplement 2 and were consistent with the as-randomized population.

Hemoglobin levels were similar in both groups at admission and at randomization (Table 2). A total of 122 patients (35.7%) in the restrictive group and 323 (99.7%) in the liberal group received at least 1 transfusion. The distribution of the number of red blood cell units transfused per patient is shown in Table 2. In the liberal group, the majority of patients received 2 or more units. The restrictive group used 342 red blood cell units and the liberal group used 758. Few patients received concomitant fresh frozen plasma or platelet transfusion. The in-hospital hemoglobin nadir was lower in the restrictive group than the liberal group.

The median (interquartile range) length of hospitalization was 7.0 (3.0-13.0) days in both groups; 56 patients in both the restrictive strategy (16.4%) and liberal strategy (17.3%) groups were hospitalized in an intensive care unit. At discharge, mean (SD) hemoglobin was 9.7 (1.0) g/dL in the restrictive group compared with 11.1 (1.4) g/dL in the liberal group (difference, −1.4 [95% CI, −1.6 to −1.2]; Table 2). Data for the as-treated population are provided in eTable 5 in Supplement 2.

Table 3. Primary and Secondary Outcomes at 30 Days Among the As-Randomized Population in a Study of the Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Patients With Acute Myocardial Infarction and Anemia

Outcome	No. (%) Restrictive	Liberal	Difference (95% CI), %	Relative risk (1-sided 97.5% CI)
Primary (major adverse cardiovascular events), No./total No. (%) [95% CI][a]				
As-treated population	36/327 (11.0) [7.5 to 14.6]	45/322 (14.0) [10.0 to 17.9]	−3.0 (−8.4 to 2.4)	0.79 (0.00 to 1.19)
As-randomized population	38/342 (11.1) [7.6 to 14.6]	46/324 (14.2) [10.2 to 18.2]	−3.1 (−8.4 to 2.3)	0.78 (0.00 to 1.17)
Secondary (individual outcomes in the as-randomized population)[b]	n = 342	n = 324		
All-cause death	19 (5.6)	25 (7.7)		
Cardiovascular	13 (68.4)	21 (84.0)		
Noncardiovascular	3 (15.8)	2 (8.0)		
Unknown	3 (15.8)	2 (8.0)		
Nonfatal recurrent myocardial infarction[c]	7 (2.1)	10 (3.1)		
ST-segment elevation recurrent myocardial infarction	0	3 (30.0)		
Non–ST-segment elevation recurrent myocardial infarction	7 (100.0)	7 (70.0)		
Type 1: spontaneous recurrent myocardial infarction	4 (57.1)	4 (40.0)		
Type 2: recurrent myocardial infarction secondary to an ischemic imbalance	2 (28.6)	5 (50.0)		
Type 4b: recurrent myocardial infarction related to stent thrombosis	1 (14.3)	1 (10.0)		
Emergency revascularization	5 (1.5)	6 (1.9)		
Nonfatal ischemic stroke	2 (0.6)	2 (0.6)		

[a] Composite of all-cause death, stroke, recurrent myocardial infarction, or emergency revascularization prompted by ischemia at 30 days.

[b] Given the potential for type I error due to multiple comparisons, no formal statistical comparisons were made for secondary outcomes.

[c] Type of myocardial infarction was adjudicated by a blinded event committee, according to the third universal definition of myocardial infarction.[12]

Primary Efficacy Outcome

Follow-up data for 30-day MACE were complete for all 666 patients who consented and were randomized. In the as-treated population, 30-day MACE occurred in 36 patients (11.0% [95% CI, 7.5%-14.6%]) in the restrictive group and in 45 patients (14.0% [95% CI, 10.0%-17.9%]) in the liberal group (relative risk, 0.79 [1-sided 97.5% CI, 0.00-1.19]), fulfilling the criterion for noninferiority (**Table 3**). Noninferiority of the restrictive strategy was also achieved in the as-randomized population (relative risk, 0.78 [1-sided 97.5% CI, 0.00-1.17]). Similar results were found in post hoc sensitivity analyses accounting for site effects (as-treated population: relative risk, 0.79 [1-sided 97.5% CI, 0.00-1.18]; as-randomized population: relative risk, 0.78 [1-sided 97.5% CI, 0.00-1.17]). In the planned sequential superiority analysis performed among the as-randomized population (**Figure 2**), the restrictive strategy did not meet criteria for superiority compared with the liberal strategy (upper bound of 1-sided 97.5% CI >1.00).[19] Subgroup analyses based on age; sex; body weight; smoking status; Killip class; kidney function (creatinine clearance); type of myocardial infarction (ST- vs non–ST-segment elevation myocardial infarction); presence or absence of diabetes, hypertension, dyslipidemia, and active bleeding; and hemoglobin levels at the time of randomization yielded results consistent with the main analysis, and results of the tests for interaction were not statistically significant (eFigure in Supplement 2).

Secondary Efficacy Outcomes

Components of 30-day MACE are detailed in Table 3. In the restrictive group vs the liberal group, all-cause death occurred

Figure 2. Rate of Major Adverse Cardiovascular Events in a Study of the Effect of a Restrictive vs Liberal Blood Transfusion Strategy Among Patients With Acute Myocardial Infarction and Anemia

No. of patients at risk
Liberal group	324	301	293	285	281	278	275
Restrictive group	342	326	319	314	307	305	305
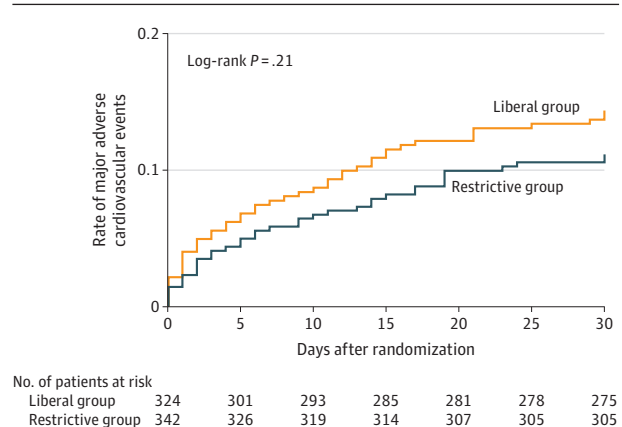
Results shown are of analyses including the as-randomized population. All patients were followed up to the first event or 30 days. Major adverse cardiovascular events are a composite of all-cause death, stroke, recurrent myocardial infarction, or emergency revascularization prompted by ischemia.

in 5.6% vs 7.7% of patients, recurrent myocardial infarction occurred in 2.1% vs 3.1% of patients, emergency revascularization prompted by ischemia occurred in 1.5% vs 1.9% of patients, and nonfatal ischemic stroke occurred in 0.6% of patients in both groups. Secondary outcomes in the as-treated population are provided in eTable 6 in Supplement 2.

Table 4. Adverse Events Among the As-Randomized Population in a Study of the Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Patients With Acute Myocardial Infarction and Anemia

Adverse event	No. (%)	
	Restrictive (n = 342)	Liberal (n = 324)
At least 1 adverse event	40 (11.7)	36 (11.1)
Acute kidney injury[a]	33 (9.7)	23 (7.1)
Acute heart failure[b]	11 (3.2)	12 (3.7)
Severe allergic reaction[a]	3 (0.9)	0
Acute lung injury/ARDS[a]	1 (0.3)	7 (2.2)
Multiorgan system dysfunction[a]	1 (0.3)	3 (0.9)
Infection[a,c]	0	5 (1.5)

Abbreviation: ARDS, acute respiratory distress syndrome.

[a] According to investigator judgment.

[b] Adjudicated according to the following criteria: new or worsening symptoms due to congestive heart failure, objective evidence of new congestive heart failure (physical examination, laboratory, imaging or hemodynamic evidence), and initiation or intensification of chronic heart failure treatment.

[c] Documented bacterial infection/bacteremia acquired at any time after the first transfusion.

Adverse Events

Adverse events are presented in **Table 4** for the as-randomized population and in eTable 6 in Supplement 2 for the as-treated population.

Discussion

Among patients with AMI and anemia, a restrictive compared with a liberal transfusion strategy resulted in a noninferior rate of MACE after 30 days. However, the CI included what may be a clinically important harm.

Anemia is common in patients with AMI and is associated with worse clinical outcomes.[1] In theory, transfusion should increase oxygen delivery, which would argue for a liberal transfusion strategy in patients with acute myocardial ischemia. However, data suggest that oxygen delivery is not necessarily increased in patients receiving transfusions, due to red blood cell depletion in nitric oxide and 2,3-diphosphoglyceric acid during storage, and that, conversely, transfusion may increase platelet activation and aggregation and produce vasoconstriction.[20,21] Observational studies have yielded uncertain results and are susceptible to unmeasured confounding,[22] highlighting the need for randomized trials.[23] To our knowledge, only 2 small randomized trials that examine transfusion in individuals with myocardial infarction are available, and they reported opposite conclusions. The first trial, which included 45 patients, found apparent benefit of a restrictive over a liberal transfusion strategy and the second pilot trial, which included 110 patients, found numerically fewer cardiac events and deaths with a liberal strategy, but no statistically significant difference, and led the authors to support the need for a definitive trial.[6,22] There is wide variation in clinical practice regarding the use of transfusion for patients with AMI.[24] Given the persistent equipoise in the clinical community regarding what transfusion strategy is optimal in the specific setting of AMI, there have been multiple calls for generating more evidence from randomized trials.[4,11,22,25]

Uncertainty exists on the optimal transfusion strategy and on what hemoglobin level should trigger transfusion in this population. In patients with AMI and anemia, the current trial showed statistical noninferiority of the restrictive strategy compared with the liberal strategy in both the as-randomized and as-treated populations, providing some confidence in the results.[26] However, determination of the margin used to declare noninferiority is critical to the interpretation of the result. This determination can be based on computation of preservation of at least a fraction of the benefit of an established treatment (often in the range of 50% preservation of the benefit). In the case of AMI, no trial to our knowledge has compared transfusion with no transfusion. However, a large observational analysis of the relationship between anemia and mortality after AMI showed that the risk of MACE increased, with an adjusted odds ratio of 1.45 (95% CI, 1.33-1.58) for each 1-g/dL decrement in hemoglobin below 11 g/dL.[1] A 25% relative noninferiority margin would preserve a substantial fraction of the expected benefit of transfusion, because the anticipated difference in hemoglobin value was expected to exceed 1 g/dL (as was actually observed). The noninferiority margin should also be justifiable on clinical grounds based on the estimate of what clinicians would find clinically acceptable as a potential loss of efficacy with an "experimental" strategy compared with an established strategy, given the benefits of the former. In the present setting, the theoretical advantages of the restrictive strategy would be reduced consumption of increasingly scarce blood resources,[18] reduced adverse effects from transfusion, potential cost savings, and logistical benefits related to the implementation of transfusion. The choice of a 25% relative increase as the margin for noninferiority was more conservative than the margin used in many recent large trials,[27-31] but did not eliminate inferiority. In any case, it is recommended that clinicians use their own judgment in interpreting noninferiority thresholds.[32] Although the 30-day primary clinical outcome was numerically lower with the restrictive strategy, this difference did not achieve statistical significance for superiority. Although the decision to initiate transfusion should not be based on hemoglobin level alone, the observed result suggests there may be merit to a restrictive strategy, which had no apparent downside in terms of logistics. Heart rate was not factored in the decision to initiate transfusion, particularly because most patients with AMI receive β-blockers.

Limitations

This study has several limitations. First, it was of moderate size and thus was not powered for evaluating the superiority of either strategy. A noninferiority margin of 1.25 includes potentially clinically important harm and may be considered too large. Even the observed confidence limit ranges up to an 18% increase in cardiac events, which would be clinically meaningful. A larger trial with a similar clinical design is ongoing in individuals with AMI (MINT trial; NCT02981407) and is powered for clinical superiority using the composite outcome of all-cause mortality and nonfatal recurrent AMI. Second, the

trial was open-label due to the logistical challenges of blinding transfusion in the setting of AMI. However, assessment of clinical efficacy relied on objective outcomes, which were blindly adjudicated. Third, because qualifying hemoglobin levels could be collected at any time during hospitalization, some patients may have qualified for enrollment due to shifts after catheterization, repeated blood draws during a long stay, or active bleeding from medications or procedures. Therefore, a mixture of individuals with anemia, bleeding, and dilution were included in the eligible population.[33] However, subgroup analyses based on the presence or absence of preexisting anemia or of active bleeding yielded results consistent with the main analysis. Fourth, this report was limited to analysis of 30-day outcomes. Longer follow-up to 1 year is being accrued and will allow evaluation of the potential long-term effects of the 2 transfusion strategies as well as assessment of potential quality of life and incremental cost-utility ratio differences between the groups.[34]

Conclusions

Among patients with AMI and anemia, a restrictive compared with liberal transfusion strategy resulted in a noninferior rate of major cardiovascular events after 30 days. However, the CI included what may be a clinically important harm.

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