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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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Visual Abstract

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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Supplemental content

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Anemia,withorwithoutovertbleeding,iscommoninpatients with acute myocardial infarction (AMI) and affects prognosis. Even moderate levels of anemia (hemoglobinlevelof10-12g/dL)areassociatedwithincreased 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 yieldedconflictingresults[2-4]andonly2smallrandomizedtrials (including45and110patients)havecomparedrestrictivewith liberal transfusion strategies in this setting.[5,6] Large randomizedtrialshavecomparedtransfusionstrategiesinpatientswith 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]

InadditiontouncertainbenefitinpatientswithAMI,transfusionhaspotentialadverseeffects,logisticalimplications(particularlyforbloodsupply),andcost.Theobjectiveofthisstudy, the Restrictive and Liberal Transfusion Strategies in Patients WithAcuteMyocardialInfarction(REALITY)randomizedtrial, wastodeterminewhetherarestrictivetransfusionstrategywas 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 committeeattheHospitalClinic,Barcelona,Spain.Patientsprovided written informed consent.

Trial Population

To be eligible for inclusion, patients had to be aged at least 18 yearsandhaveAMI(withorwithoutST-segmentelevationwith acombinationofischemicsymptomsoccurringinthe48hours before admission and elevation of biomarkers of myocardial injury)andahemoglobinlevelbetween7and10g/dL.Enrollmentcouldbeconsideredatanytimeduringtheindexadmission for myocardial infarction. Exclusion criteria were shock at the time of randomization (systolic blood pressure <90mmHgwithclinicalsignsoflowoutputorrequiringinotropic 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 chronicanemiaincertainethnicgroups,race/ethnicitywasrecorded (self-reported using fixed categories).

Randomization and Interventions

Patients were randomly assigned in a 1:1 ratio to undergo a restrictiveoraliberaltransfusionstrategy.Aweb-basedrandomization 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 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 investigatoradherencetotheprotocolbeforeinclusionofthefirstpatient). In the liberal strategy group, transfusion was to be performedafterrandomizationonallpatientswithahemoglobin level less than or equal to 10 g/dL, with a target posttransfusionhemoglobinlevelofatleast11g/dL.Homologousleukoreduced 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.

Afterdischarge,patientfollow-upwasscheduledatday30 (±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.

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.

Outcome Measures and Definitions

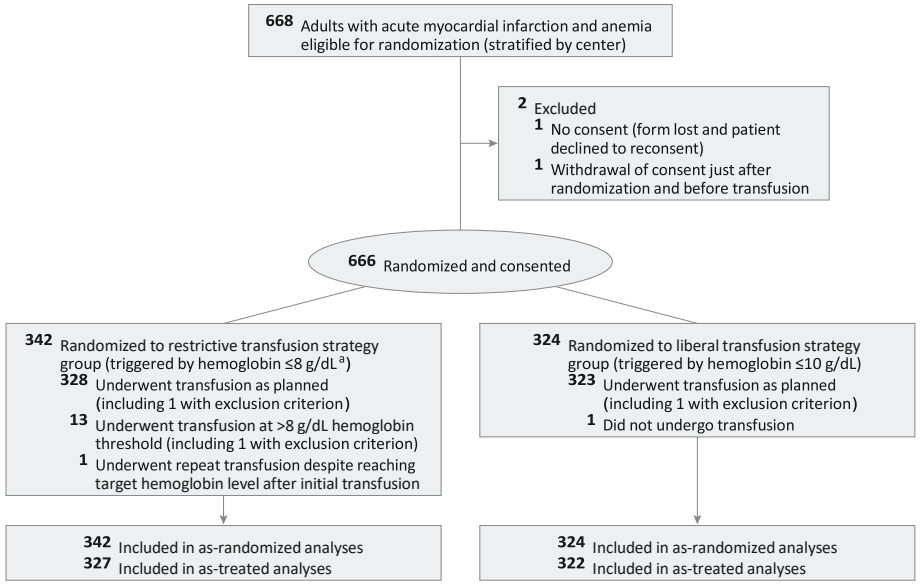
The primary clinical efficacy outcome was a composite of major adverse cardiovascular events (MACE) at 30 days, defined as all-cause death, nonfatal stroke, nonfatal recurrent myocardial infarction, or emergency revascularization prompted by ischemia. Secondary outcomes included the individual components of the composite MACE outcome at 30 days and 1 year. Descriptive endpoints 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 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 Appendix 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 an 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 former 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

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



[a] The initial protocol specified a threshold of 7 g/dL. This was changed to 8 g/dL to maximize investigator adherence to the protocol before inclusion of the first patient. Enrollment took place at any time during hospitalization. No screening log was maintained.

and n_{21} is the event number and n_2 is the total number of patients in the liberal group. Ninety-five percentCIswereestimatedusingtheWaldmethod.Theanalysis was performed among both the as-treated population, which included all patients without a major protocol violation (including eligibility criteria not fulfilled), and the asrandomized population, which included all randomized patientswiththeexceptionof2patients(1withoutaconsentform and 1 who withdrew consent immediately after randomization).Concordanceinthenoninferiorityanalysisbetweenthe as-randomized and the as-treated populations was required to establish noninferiority. The use of multiple imputation methodswasplannedinthestatisticalanalysisplaninthecase ofmissingdataforthepri maryclinicaloutcome.Giventheabsence of missing data at day 30, imputation was not needed. Because the trial was conducted at multiple sites, site effect wasaccountedforinaposthocsensitivityanalysisusingageneralized linear regression mixed model with binary distributionandaloglinkfunctionwithstrategyasafixedeffectand 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		
Units transfused, No. of packed red blood cells	342	758
Per patient transfused, mean (SD)	2.9 (3.7)	2.8 (2.7)
Patients who received ≥1 unit	122 (35.7)	323 (99.7)[a]
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 recensored 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 endpoints 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

absenceofdiabetes,smokingstatus,presenceorabsenceofhypertension,presenceorabsenceofdyslipidemia,Killipclass,kidneyfunction[creatinineclearance],presenceorabsenceofactivebleeding,hemoglobinlevelsatthetimeofrandomization, ST-vsnon–ST-segmentelevationmyocardialinfarction,andrevascularizationbypercutaneouscoronaryinterventionforthe indexeventbeforeorafterrandomization);theinteractionbetween 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. Allsuperioritytestsand95%CIwere2-sided,and*P*values<.05 were considered significant. Statistical analyses were performedusingSASversion9.4(SASInstituteInc)andRversion 3.6.3 (R Foundation for Statistical Computing).

Results

Descriptive Findings

FromMarch2016toSeptember2019,atotalof668patientswith AMIandanemiawereconsecutivelyenrolledinthetrial(in26 centersinFranceand9centersinSpain;Figure1).Baselinecharacteristics of the as-randomized population were similar between the groups (Table1). The median age of patients was 77 years,385(57.8%)weremen,and334(50.2%)haddiabetes.In most patients, the cause of anemia was unknown; 43 patients (6.5%) had a history of bleeding requiring hospitalization and transfusion.Thequalifyingmyocardialinfarctionwasnon–STelevationmyocardialinfarctioninapproximatelytwo-thirdsof 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 Supplement2.Mostpatientsunderwentcoronaryangiography(81.9% intherestrictivegroupand79.3%intheliberalgroup)andapproximatelytwo-thirdsunderwentmyocardialrevascularization. Treatmentsbeforehospitalizationandduringthefirst24hours of admission are shown in eTable 3 in Supplement 2. Most patientsreceiveddualantiplatelettherapyforthequalifyingmyocardialinfarction.Baselinecharacteristicsandtreatmentofthe as-treatedpopulationareshowninTable4inSupplement2and wereconsistentwiththeas-randomizedpopulation.

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 numberofredbloodcellunitstransfusedperpatientisshown in Table 2. In the liberal group, the majority of patients received2ormoreunits.Therestrictivegroupused342redblood 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 hospitalizationwas7.0(3.0-13.0)daysinbothgroups;56patientsinboth the restrictive strategy (16.4%) and liberal strategy (17.3%) groups were hospitalized in an intensive care unit. At discharge,mean(SD)hemoglobinwas9.7(1.0)g/dLintherestrictivegroupcomparedwith11.1(1.4)g/dLintheliberalgroup(difference, −1.4 [95% CI, −1.6 to −1.2]; Table 2). Data for the astreated population are provided in eTable 5 in Supplement 2.

Outcome	No. (%)		Difference (95% CI), %	Relative risk (1-sided 97.5% CI)
	Restrictive	Liberal		
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	(5.6)	25 (7.7)		
Cardiovascular	(68.4)	21 (84.0)		
Noncardiovascular	(15.8)	2 (8.0)		
Unknown	(15.8)	2 (8.0)		
Nonfatal recurrent myocardial infarction[c]	(2.1)	10 (3.1)		
ST-segment elevation recurrent myocardial infarction	3 (30.0)			
Non–ST-segment elevation recurrent myocardial infarction	(100.0)	7 (70.0)		
Type 1: spontaneous recurrent myocardial infarction	(57.1)	4 (40.0)		
Type 2: recurrent myocardial infarction secondary to an ischemic imbalance	(28.6)	5 (50.0)		
Type 4b: recurrent myocardial infarction related to stent thrombosis	(14.3)	1 (10.0)		
Emergency revascularization	(1.5)	6 (1.9)		
Nonfatal ischemic stroke	(0.6)	2 (0.6)		

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

[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

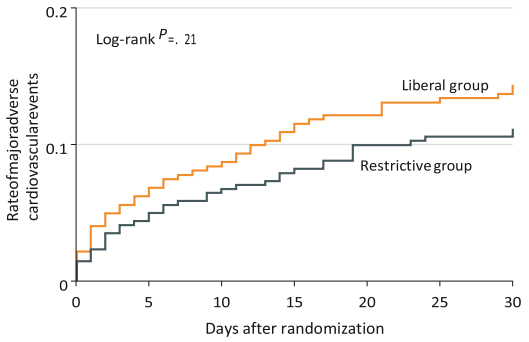
Follow-up data for 30-day MACE were complete for all 666 patients who consented and were randomized. In the as-treated population, 30-day MACE occurred in 36 patients (11.0% [95% CI, 7.5%-14.6%]) in the restrictive group and in 45 patients (14.0% [95% CI, 10.0%-17.9%]) in the liberal group (relative 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 (astreated 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-sided97.5%CI>1.00).[19]Subgroupanalysesbasedonage;sex; bodyweight;smokingstatus;Killipclass;kidneyfunction(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 ofthetestsforinteractionwerenotstatisticallysignificant(eFigure in Supplement 2).

Secondary Efficacy Outcomes

ComponentsofMACEaredetailedinTable3.Intherestrictive group vs the liberal group, all-cause death occurred in5.6%vs7.7%ofpatients,recurrentmyocardialinfarctionoccurred 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 astreatedpopulationareprovidedineTable6inSupplement2.

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.

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

	No. (%)	
Adverse event	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

AdverseeventsarepresentedinTable4fortheas-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 withworseclinicaloutcomes.[1]Intheory,transfusionshouldincrease oxygen delivery, which would argue for a liberal transfusionstrategyinpatientswithacutemyocardialischemia.However, data suggest that oxygen delivery is not necessarily increased in patients receiving transfusions, due to red blood celldepletioninnitricoxideand2,3-diphosphoglycericacidduringstorage,andthat,conversely,transfusionmayincreaseplateletactivationandaggregationandproducevasoconstriction.[20,21] Observational studies have yielded uncertain results and are susceptibletounmeasuredconfounding,[22]highlightingtheneed for randomized trials.[23] To our knowledge, only 2 small randomizedtrialsthatexaminetransfusioninindividualswithmyocardialinfarctionareavailable,andtheyreportedoppositeconclusions. The first trial, which included 45 patients, found

apparentbenefitofarestrictiveoveraliberaltransfusionstrategyandtheseco ndpilottrial,whichincluded110patients,found numericallyfewercardiaceventsanddeathswithaliberalstrategy, but no statistically significant difference, and led the authorstosupporttheneedforadefinitivetrial.[6,22]Thereiswide variationinclinicalpracticeregardingtheuseoftransfusionfor patientswithAMI.[24]Giventhepersistentequipoiseintheclinicalcommunity regardingwhattransfusionstrategyisoptimal inthespecificsettingofAMI,therehavebeenmultiplecallsfor generating more evidence from randomized trials.[4,11,22,25]

Uncertaintyexistsontheoptimaltransfusionstrategyand on what hemoglobin level should trigger transfusion in this population.InpatientswithAMIandanemia,thecurrenttrial showedstatisticalnoninferiorityoftherestrictivestrategycomparedwiththe liberalstrategyinboththeas-randomizedand 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.Thisdeterminationcanbebasedoncomputationofpreservation of at least a fraction of the benefit of an established treatment(oftenintherangeof50%preservationofthebenefit). 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, withanadjustedoddsratioof1.45(95%CI,1.33-1.58)foreach 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 an- ticipated difference in hemoglobin value was expected to exceed 1 g/dL (as was actually observed). The noninferiority marginshouldalsobejustifiableonclinicalgroundsbasedon the estimate of what clinicians would find clinically acceptableasapotentiallossofefficacywithan"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 consumptionofincreasinglyscarcebloodresources,[18]reducedadverseeffe ctsfromtransfusion,potentialcostsavings,andlogisticalbenefitsrelatedtot tive 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 preexistinganemiaorofactivebleedingyieldedresultsconsistentwith the main analysis. Fourth, this report was limited to analysis heimplementationoftransfusion. Thechoiceofa25%relativeincreaseasthemarginfornoninferioritywasmor econservativethanthemarginusedinmany recentlargetrials,[27-31] butdidnoteliminateinferiority.Inany case, it is recommended that clinicians use their own judgmentininterpretingnoninferioritythresholds.[32]Althoughthe 30-dayprimaryclinicaloutcomewasnumericallylowerwith the restrictive strategy, this difference did not achieve statisticalsignificanceforsuperiority.Althoughthedecisiontoinitiate transfusion should not be based on hemoglobin level alone,theobservedresultssuggeststheremaybemerittoarestrictive strategy, which had no apparent downside in terms of logistics. Heart rate was not factored in the decision to initiatetransfusion,particularlybecausemostpatientswithAMI receive β-blockers.

Limitations

Thisstudyhasseverallimitations.First,itwasofmoderatesize and thus was not powered for evaluating the superiority of either strategy. A noninferiority margin of 1.25 includes potentiallyclinicallyimportantharmandmaybeconsideredtoo large.Eventheobservedconfidencelimitrangesuptoan18% increase in cardiac events, which would be clinically meaningful.Alargertrialwithasimilarclinicaldesignisongoingin individualswithAMI(MINTtrial;NCT02981407)andispowered 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 blindingtransfusioninthesettingofAMI.However,assessmentof clinical efficacy relied on objective outcomes, which were blindlyadjudicated.Third,becausequalifyinghemoglobinlevelscouldbec ollectedatanytimeduringhospitalization,some patients may have qualified for enrollment due to shifts after catheterization,repeatedblooddrawsduringalongstay,oracof 30-day outcomes. Longer follow-up to 1 year is being accruedandwillallowevaluationofthepotentiallong-termeffects 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,theCIincludedwhatmaybeaclinicallyimportantharm.

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REFERENCES

1. Sabatine MS, Morrow DA, Giugliano RP, et al.Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. *Circulation*. 2005;111(16):2042-2049. doi:10.1161/01.CIR.0000162477.70955.5F

2. Wu WC, Rathore SS, Wang Y, Radford MJ,Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med*. 2001;345(17):1230-1236. doi:10.1056/NEJMoa010615

3. Chatterjee S, Wetterslev J, Sharma A, LichsteinE, Mukherjee D. Association of blood transfusion with increased mortality in myocardial infarction: a meta-analysis and diversity-adjusted study sequential analysis. *JAMA Intern Med*. 2013;173(2): 132-139. doi:10.1001/2013.jamainternmed.1001

4. Carson JL, Carless PA, Hébert PC. Outcomesusing lower vs higher hemoglobin thresholds for red blood cell transfusion. *JAMA*. 2013;309(1):83-84. doi:10.1001/jama.2012.50429

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(8):1108-1111. doi:10.1016/j.amjcard.2011.06.014

6. Carson JL, Brooks MM, Abbott JD, et al. Liberalversus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. *Am Heart J*. 2013;165(6):964-971. doi:10.1016/j.ahj.2013.03.001

7. Villanueva C, Colomo A, Bosch A, et al.Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med*. 2013;368(1):11-21. doi:10.1056/NEJMoa1211801

8. Docherty AB, O'Donnell R, Brunskill S, et al.Effect of restrictive versus liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting: systematic review and meta-analysis. *BMJ*. 2016;352:i1351. doi:10.1136/bmj.i1351

9. Murphy GJ, Pike K, Rogers CA, et al; TITRe2Investigators. Liberal or restrictive transfusion after cardiac surgery. *N Engl J Med*. 2015;372(11):997-1008. doi:10.1056/NEJMoa1403612

10. Mazer CD, Whitlock RP, Fergusson DA, et al; TRICS Investigators and Perioperative Anesthesia Clinical Trials Group. Six-month outcomes after restrictive or liberal transfusion for cardiac surgery. *N Engl J Med*. 2018;379(13):1224-1233. doi:10.1056/ NEJMoa1808561

11. Rao SV, Sherwood MW. Isn't it about time welearned how to use blood transfusion in patients with ischemic heart disease? *J Am Coll Cardiol*. 2014;63(13):1297-1299. doi:10.1016/j.jacc.2013.11.028

12. Thygesen K, Alpert JS, Jaffe AS, et al; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *Circulation*.

2012;126(16):2020-2035. doi:10.1161/CIR.0b013e31826e1058

13. Puymirat E, Simon T, Steg PG, et al; USIK USIC2000 Investigators; FAST MI Investigators. Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. *JAMA*. 2012;308(10):998-1006. doi:10.1001/2012.jama.11348

14. Hanssen M, Cottin Y, Khalife K, et al; FAST-MI2010 Investigators. French registry on acute ST-elevation and non ST-elevation myocardial infarction 2010: FAST-MI 2010. *Heart*. 2012;98(9): 699-705. doi:10.1136/heartjnl-2012-301700

15. *Statistical Principles for Clinical Trials*. European Medicines Agency; 1998. Accessed November 18, 2020. https://www.ema.europa.eu/en/ich-e9statistical-principles-clinical-trials

16. Steg PG, Simon T. Duration of antiplatelettherapy after DES implantation: can we trust non-inferiority open-label trials? *Eur Heart J*. 2017; 38(14):1044-1047. doi:10.1093/eurheartj/ehx110

17. Pocock SJ, Clayton TC, Stone GW. Challengingissues in clinical trial design: part 4 of a 4-part series on statistics for clinical trials. *J Am Coll Cardiol*. 2015;66(25):2886-2898. doi:10.1016/j.jacc.2015.10. 051

18. Williamson LM, Devine DV. Challenges in themanagement of the blood supply. *Lancet*. 2013;381 (9880):1866-1875. doi:10.1016/S0140-6736(13)60631-5

19. *Non-Inferiority Clinical Trials to Establish Effectiveness: Guidance for Industry*. US Food and Drug Administration; 2016. Accessed August 3, 2020. https://www.fda.gov/media/78504/download

20. Silvain J, Pena A, Cayla G, et al. Impact of redblood cell transfusion on platelet activation and aggregation in healthy volunteers: results of the TRANSFUSION study. *Eur Heart J*. 2010;31(22): 2816-2821. doi:10.1093/eurheartj/ehq209

21. Silvain J, Abtan J, Kerneis M, et al. Impact of redblood cell transfusion on platelet aggregation and inflammatory response in anemic coronary and noncoronary patients: the TRANSFUSION-2 study (impact of transfusion of red blood cell on platelet activation and aggregation studied with flow cytometry use and light transmission aggregometry). *J Am Coll Cardiol*. 2014;63(13): 1289-1296. doi:10.1016/j.jacc.2013.11.029

22. Yeh RW, Wimmer NJ. Blood transfusion inmyocardial infarction: opening old wounds for comparative-effectiveness research. *J Am Coll Cardiol*. 2014;64(8):820-822. doi:10.1016/j.jacc.2014.05.041

23. Rao SV, Jollis JG, Harrington RA, et al.Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA*. 2004;292(13):1555-1562. doi:10. 1001/jama.292.13.1555

24. Alexander KP, Chen AY, Wang TY, et al;CRUSADE Investigators. Transfusion practice and outcomes in non-ST-segment elevation acute coronary syndromes. *Am Heart J*. 2008;155(6): 1047-1053. doi:10.1016/j.ahj.2008.01.009

25. Farhan S, Baber U, Mehran R. Anemia and acutecoronary syndrome: time for intervention studies. *J Am Heart Assoc*. 2016;5(11):e004908. doi:10.1161/JAHA.116.004908

26. Piaggio G, Elbourne DR, Altman DG, Pocock SJ,Evans SJ; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA*. 2006;295(10):1152-1160. doi:10.1001/jama.295.10.1152

27. Kim HS, Kang J, Hwang D, et al;HOST-REDUCE-POLYTECH-ACS investigators. Prasugrel-based de-escalation of dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (HOST-REDUCE-POLYTECH-ACS): an open-label, multicentre, non-inferiority randomised trial. *Lancet*. 2020;396(10257):1079-1089. doi:10.1016/S0140-6736(20)31791-8

28. Watanabe H, Domei T, Morimoto T, et al;STOPDAPT-2 Investigators. Effect of 1-Month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA*. 2019;321(24):2414-2427. doi:10.1001/jama.2019.8145

29. Kedhi E, Fabris E, van der Ent M, et al. Sixmonths versus 12 months dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction (DAPT-STEMI): randomised, multicentre, non-inferiority trial. *BMJ*. 2018;363: k3793. doi:10.1136/bmj.k3793

30. Hahn JY, Song YB, Oh JH, et al; SMART-DATEinvestigators. 6-Month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): a randomised, open-label, non-inferiority trial. *Lancet*. 2018;391 (10127):1274-1284. doi:10.1016/S0140-6736(18)30493-8

31. Jabre P, Penaloza A, Pinero D, et al. Effect ofbag-mask ventilation vs endotracheal intubation during cardiopulmonary resuscitation on neurological outcome after out-of-hospital cardiorespiratory arrest: a randomized clinical trial. *JAMA*. 2018;319(8):779-787. doi:10.1001/jama.2018. 0156

32. Mulla SM, Scott IA, Jackevicius CA, You JJ,Guyatt GH. How to use a noninferiority trial: users' guides to the medical literature. *JAMA*. 2012;308 (24):2605-2611. doi:10.1001/2012.jama.11235

33. Ducrocq G, Puymirat E, Steg PG, et al. Bloodtransfusion, bleeding, anemia, and survival in patients with acute myocardial infarction: FAST-MI registry. *Am Heart J*. 2015;170(4):726-734. doi:10.1016/j.ahj.2015.07.004

34. Ducrocq G, Calvo G, González-Juanatey JR,et al Restrictive versus liberal red blood cell transfusion strategies in patients with acute myocardial infarction and anemia: rationale and design of the REALITY trial. *Clin Cardiol*. Published online January 6, 2021. doi:10.1002/clc.23453