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ORIGINAL ARTICLE

Restrictive versus Liberal Transfusion in Myocardial Infarction — A Patient-Level Meta-Analysis

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Abstract

BACKGROUND Clinical guidelines have concluded that there are insufficient data to provide recommendations for the hemoglobin threshold for the use of red cell transfusion in patients with acute myocardial infarction (MI) and anemia. After the recent publication of the Myocardial Infarction and Transfusion (MINT) trial, we performed an individual patient-level data meta-analysis to evaluate the effect of restrictive versus liberal blood transfusion strategies.

METHODS We conducted searches in major databases. Eligible trials randomly assigned patients with MI and anemia to either a restrictive (i.e., transfusion threshold of 7–8 g/dl) or liberal (i.e., transfusion threshold of 10 g/dl) red cell transfusion strategy. We used individual patient data from each trial. The primary outcome was a composite of 30-day mortality or MI.

RESULTS We included 4311 patients from four trials. The primary outcome occurred in 334 patients (15.4%) in the restrictive strategy and 296 patients (13.8%) in the liberal strategy (relative risk [RR] 1.13, 95% confidence interval [CI], 0.97 to 1.30). Death at 30 days occurred in 9.3% of patients in the restrictive strategy and in 8.1% of patients in the liberal strategy (RR 1.15, 95% CI, 0.95 to 1.39). Cardiac death at 30 days occurred in 5.5% of patients in the restrictive strategy and in 3.7% of patients in the liberal strategy (RR 1.47, 95% CI, 1.11 to 1.94). Heart failure (RR 0.89, 95% CI, 0.70 to 1.13) was similar in the transfusion strategies. All-cause mortality at 6 months occurred in 20.5% of patients in the restrictive strategy compared with 19.1% of patients in the liberal strategy (hazard ratio 1.08, 95% CI, 1.05 to 1.11).

CONCLUSIONS Pooling individual patient data from four trials did not find a definitive difference in our primary composite outcome of MI or death at 30 days. At 6 months, a restrictive transfusion strategy was associated with increased all-cause mortality. (Partially funded by a grant from the U.S. National Heart, Lung, and Blood Institute [R01HL171977].)

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Introduction

Red cell transfusion guidelines have recommended adopting a restrictive transfusion strategy in most clinical settings because mortality and major clinical outcomes (e.g., infections) are comparable to a liberal strategy, and the restrictive strategy uses fewer resources.[1] However, a lack of randomized trial data has precluded recommendations in patients with myocardial infarction (MI), who may be at higher risk of ongoing myocardial ischemia and might benefit from a higher hemoglobin threshold. A recent trial-level meta-analysis informing these guidelines identified just three trials in 820 patients with MIs and found inconsistent results among the trials.[1-4]

The Myocardial infarction and Transfusion Trial (MINT) has subsequently been published, in which 3504 patients with an acute MI and anemia were randomly allocated to a restrictive (transfusion when the hemoglobin ≤8 g/dl) or liberal (transfusion when the hemoglobin ≤10 g/dl) transfusion strategy.[5] In MINT, the primary outcome of all-cause mortality or MI at 30 days occurred in 16.9% of patients in the restrictive strategy and 14.5% in the liberal strategy, with a relative risk (RR) of 1.15 with a 95% confidence interval (CI) from 0.99 to 1.34 (P=0.07).

Prior to completing the MINT,[5] we planned an individual patient data meta-analysis to generate more precise estimates of treatment effects using the totality of available randomized evidence. This approach became even more relevant given the potentially important findings of MINT that overall favored a liberal transfusion strategy, but with a CI around the point estimate that included no difference. Individual patient meta-analysis allows adjustment for individual patient characteristics and risk factors, aligns outcomes across trials, and allows exploration of treatment effects across clinically meaningful subgroups.

Methods

IDENTIFICATION OF RANDOMIZED CLINICAL TRIALS

In addition to MINT, we performed literature searches for new randomized trials as described in the most recent Cochrane review up to August 14, 2023.[6] Searches were conducted in MEDLINE, Embase, the Cochrane Library, PubMed, Transfusion Evidence Library, Web of Science Conference Proceedings Citation Index, ClinicalTrials.gov and WHO International Clinical Trials Registry. Two investigators (J.L.C. and S.J.S.) independently screened the titles and abstracts of the search results and identified trials that met eligibility criteria. To be eligible, trials had to randomly assign patients with MI to either a lower hemoglobin threshold (restrictive transfusion strategy) or a higher transfusion hemoglobin threshold (liberal transfusion strategy). Risk of bias was assessed by two reviewers independently and disagreements between reviewers' judgements were resolved by consensus (Table S1 in the Supplementary Appendix).

DATA COLLECTION AND PROCUREMENT

Principal investigators for each of the eligible trials were contacted and asked to participate in our individual patient data meta-analysis. We secured data use agreements for all trials and the individual patient data from each trial participant were provided to Rutgers Robert Wood Johnson Medical School for analysis. In collaboration with investigator teams, we developed a standardized list of variables with common definitions and coding for each covariate and outcome variable. The variables included baseline demographic, clinical history, and laboratory data, assigned intervention group, transfusion treatment variables, hemoglobin concentrations, and clinical outcomes. Most baseline variables among the trials were defined similarly, and the individual trial definitions were used (Table S2). The Rutgers data team replicated and merged the results of the published trials using data files from each of the trials, and, where there were discrepancies, consulted with the trial investigators to identify reasons for the different findings. No important issues were identified in checking data.

OUTCOME MEASURES

The primary outcome was a composite of death or MI at 30 days. This outcome was declared a priori as the primary outcome for this meta-analysis (and MINT) because it is both clinically important and potentially modifiable by different transfusion strategies (ClinicalTrials.gov number NCT02981407; PROSPERO CRD42023446878). Secondary outcomes included the components of the primary outcome (death, recurrent MI), major adverse cardiac events (MACE [defined as all-cause death, MI, or stroke]), cardiac death, the composite of death, MI, or unscheduled coronary revascularization, heart failure, unscheduled coronary revascularization, acute renal failure, stroke, pulmonary embolism, or deep venous thrombosis, pneumonia, bacteremia, bleeding, all-cause death, and cause-specific death. The cause of death was classified as cardiac, non-cardiac, or unknown.

At 6 months, the only outcome assessed was mortality. The cause of death was classified by sites in three trials (Restrictive and Liberal Transfusion Strategies in Patients With Acute Myocardial Infarction [REALITY], MINT Pilot, and MINT)[2,3,5] and centrally adjudicated in two trials (REALITY and MINT Pilot).[2,3]

DATA ANALYSIS

We compared a restrictive transfusion strategy with a liberal transfusion strategy using an intention-to-treat approach. A one-stage individual patient data meta-analysis was conducted to synthesize all data simultaneously while accounting for clustering within each of the trials. Specifically, a multilevel generalized linear model was performed with trial-specific random effects to analyze the treatment effect for dichotomous 30-day outcomes. We did not include a trial-specific random treatment effect in the model because two of the four trials were too small and showed model overfit when included. We calculated risk ratios and absolute differences with 95% CIs from these models. A secondary analysis was conducted to adjust for specified baseline variables: age (continuous), sex, pre-random-assignment hemoglobin level (continuous), ST-segment elevation MI (STEMI) versus non-ST-segment elevation MI (NSTEMI), pre-random-assignment coronary revascularization, history of heart failure, prior history of anemia, diabetes mellitus, and history of renal disease. For 6-month time-to-event outcomes, follow-up was censored at 180 days for all patients. We used Cox regression models with trial-specific random effects to estimate the hazard ratios and 95% CIs for the overall risk of death at 6 months and 1 year. The proportional hazard assumption was assessed by testing the interaction between assigned treatment strategy and time, and the proportional hazard assumption was satisfied (P=0.60). We estimated the risk of cause-specific death at 6 months from cumulative incidence functions using an extension of the Fine–Gray competing risk model that incorporates the correlation among patients within each trial to estimate hazard ratios and 95% CIs. We assessed and confirmed the proportional hazard assumption for Cox models.

Subgroup analyses for the composite primary outcome of 30-day mortality or MI were conducted within the following baseline subgroups: STEMI or NSTEMI, coronary revascularization, sex, history of heart failure, renal failure, diabetes, history of anemia, age (<60, 60–69, 70–79, ≥80 years of age), hemoglobin concentration prior to random assignment (<8 g/dl, 8 to <9 g/dl, ≥9 g/dl), and administration of red blood cells pre random assignment. Our protocol did not specify a plan to adjust for multiple comparisons for the evaluation of secondary outcomes; CIs are not adjusted for multiplicity and should not be used in place of hypothesis testing.

SAS version 9.4 (Cary, North Carolina) was used for all analyses. The analysis was approved by the Rutgers University Institutional Review Board. The meta-analysis was preregistered in PROSPERO[7] and the content of this report is consistent with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.[8] Dr. Carson with the assistance of other authors designed the study, obtained data use agreements with the principal investigators of the trials, vouched for the data, and wrote the first draft of the manuscript. Helaine Noveck analyzed the data under the direction of the statisticians and investigators. All the authors contributed to writing the paper and decided to publish the article. Data use agreements preclude sharing the data.

Results

DESCRIPTION OF TRIALS

In addition to MINT,[5] three trials (Conservative Versus Liberal Red Cell Transfusion in Acute Myocardial Infarction [CRIT], REALITY, and the MINT Pilot) were identified[2,4,9] (Fig. 1). Investigators of the four trials agreed to participate in this individual patient data meta-analysis.

The four trials had sample sizes ranging from 45 to 3504 participants, with a total of 4325 participants. A total of 14 participants without an MI enrolled in the MINT Pilot[3] were excluded, yielding 4311 participants included in the current analyses (Table 1). The eligibility criteria were similar across trials, and all trials included patients with acute MI and anemia with a hemoglobin concentration less than 10 g/dl. Two trials were pilot feasibility trials;[3,4] the REALITY trial's primary objective was to evaluate cost-effectiveness and the trial was designed to determine whether a restrictive transfusion strategy was clinically noninferior to a liberal transfusion strategy,[2] and MINT compared 30-day death or MI between transfusion strategies.[5] All trials recorded deaths; the duration of follow-up varied from 30 days[4] to 1 year.[2] Recurrent MI was adjudicated in three of the four trials by a committee blinded to the randomly assigned transfusion strategy.[2,3,5] The overall risk of bias was low (Table S1).

TRIAL BASELINE CHARACTERISTICS AND TRANSFUSIONS

Overall, the mean age of participants was 72.2 years, and 54.9% were men. MINT included MI types 1, 2, 4b,

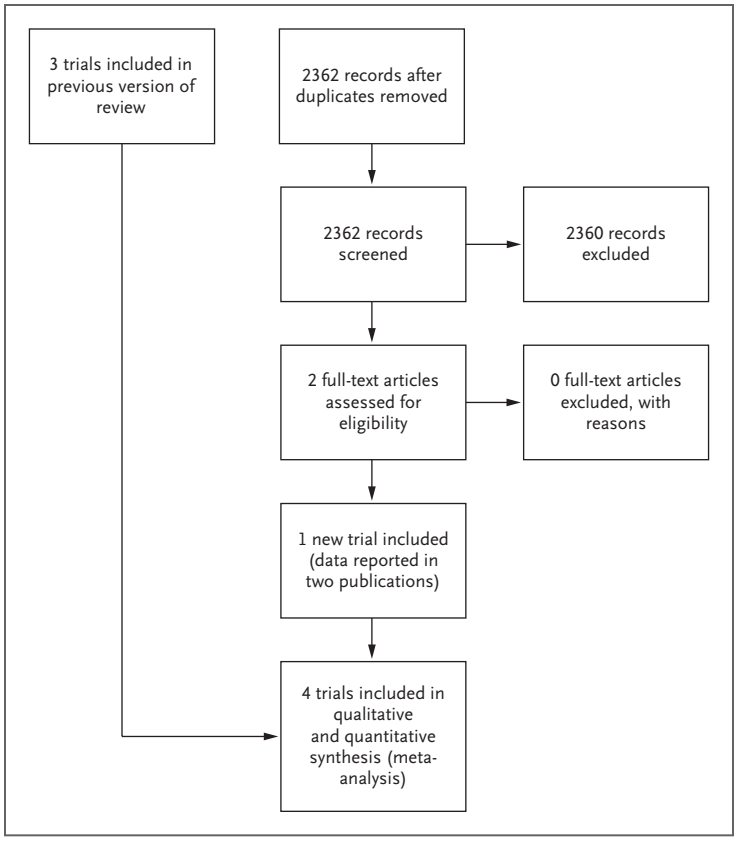

Figure 1. Transfusion Threshold Trials in Patients with Acute Myocardial Infarction.

Table 1. Characteristics of Trials.*

	Trial Name	Population	Dates	Restrictive Transfusion	Liberal Transfusion	Restrictive N	Liberal N
Cooper et al. 2011	CRIT†	Hgb <10 g/dl	May 2003 to October 2009	Transfusion occurred when HCT <24% to maintain HCT between 24 and 27%	Transfusion occurred when HCT <30% to maintain HCT between 30 and 33%	24	21
Carson et al. 2013	MINT Pilot‡	Undergoing cardiac catheterization, Hgb <10 g/dl	March 2010 to May 2012	Transfusion if participants developed symptoms of anemia or if Hgb fell to <8 g/dl	1 unit of RBCs following random assignment and enough blood to maintain Hgb >10 g/dl	50	46
Ducrocq et al. 2021	REALITY§	Acute MI, Hgb <10 g/dl	March 2016 to September 2019	Transfusion when Hgb<8 g/dl with target 8 g/dl to 10 g/dl	Transfusion when Hgb<10 g/dl with target >11 g/dl	342	324
Carson et al. 2023	MINT¶	Acute MI Hgb <10 g/dl	April 2017 to April 2023	Transfusion permitted, when the hemoglobin concentration was less than 8 g/dl or for anginal symptoms not controlled with medications	Transfused to maintain the hemoglobin concentration at ≥10 g/dl	1749	1755

* Hgb denotes hemoglobin concentration; HCT, hematocrit; MI, myocardial infarction; and RBC, red blood cell.
† CRIT denotes Conservative Versus Liberal Red Cell Transfusion in Acute Myocardial Infarction.
‡ MINT denotes Myocardial Infarction and Transfusion Trial.
§ REALITY denotes Restrictive Versus Liberal Blood Transfusion strategy on Major Cardiovascular Events Among Patients with Acute Myocardial Infarction and Anemia.
¶ Excluded 14 patients who did not have MI.

Table 2. Baseline Characteristics of Trial Participants.*

	Overall N (%)	Restrictive Transfusion N (%)	Liberal Transfusion N (%)
Age, mean (SD), years	72.2±11.7	72.3±11.7	72.1±11.7
Male	2368/4311 (54.9)	1214/2165 (56.1)	1154/2146 (53.8)
Hypertension	3620/4309 (84.0)	1808/2163 (83.6)	1812/2146 (84.4)
Diabetes	2314/4309 (53.7)	1164/2163 (53.8)	1150/2146 (53.6)
Prior MI	1417/4301 (32.9)	733/2158 (34.0)	684/2143 (31.9)
History of heart failure	1185/4309 (27.5)	593/2163 (27.4)	592/2146 (27.6)
Prior PCI	1475/4305 (34.3)	762/2161 (35.3)	713/2144 (33.3)
Prior CABG	887/4311 (20.6)	436/2165 (20.1)	451/2146 (21.0)
History stroke	724/4309 (16.8)	371/2163 (17.2)	353/2146 (16.4)
Renal insufficiency	507/4299 (11.8)	247/2157 (11.5)	260/2142 (12.1)
COPD	930/4264 (21.8)	475/2139 (22.2)	455/2125 (21.4)
Chronic anemia	1653/4264 (38.8)	816/2139 (38.1)	837/2125 (39.4)
Current admission			
Index MI STEMI	908/4311 (21.1)	454/2165 (21.0)	454/2146 (21.2)
Revascularization prior to random assignment	1380/4311 (32.0)	695/2165 (32.1)	685/2146 (31.9)
Hemoglobin concentration prior to random assignment	1258/4266 (29.5)	609/2141 (28.4)	649/2125 (30.5)
Hemoglobin prior to random assignment, g/dl			
<7.0	105/4302 (2.4)	50/2163 (2.3)	55/2139 (2.6)
7.0–7.9	790/4302 (18.4)	410/2163 (19.0)	380/2139 (17.8)
8.0–8.9	1591/4302 (37.0)	803/2163 (37.1)	788/2139 (36.8)
≥9.0	1816/4302 (42.2)	900/2163 (41.6)	916/2139 (42.8)

*CABG denotes coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; SD, standard deviation; and PCI, percutaneous coronary intervention.

and 4c (definitions of the type of MI are included in the Supplementary Appendix); the other trials did not specify the type of MI. The baseline characteristics were similar between restrictive and liberal transfusion strategies (Table 1 and Table S3). The mean hemoglobin concentration prior to random assignment was 8.7±0.8 g/dl and the number of units transfused after random assignment was 0.8±1.8 g/dl in the restrictive transfusion strategy group and 2.5±2.3 g/dl in the liberal transfusion strategy group (Table 2). The frequency of 30-day death or MI, death, MI, MACE, and cardiac death varied among the trials and was highest in the MINT Pilot (Table 3).

PRIMARY OUTCOME: DEATH OR MI AT 30 DAYS

The primary outcome of death or MI within 30 days occurred in 334 of 2165 patients (15.4%) in the restrictive transfusion strategy group and in 296 of 2146 patients (13.8%) in the liberal transfusion strategy group (Fig. 2). The RR for a restrictive strategy versus a liberal strategy in the pooled sample was 1.13 (95% CI, 0.97 to 1.30); the adjusted pooled RR was 1.12 (95% CI, 0.97 to 1.29). The absolute difference in death or MI at 30 days was 1.3 percentage points (95% CI −0.7 to 3.4). The cumulative incidence curves for the composite of death or MI are presented in Figure 3.

SUBGROUPS EFFECTS FOR THE PRIMARY OUTCOME AT 30 DAYS

The effect of a restrictive transfusion strategy compared with a liberal transfusion strategy on the primary outcome of 30-day death or MI (Fig. 4) was consistent across most subgroups, favoring a liberal strategy. For patients without a history of renal failure, a restrictive transfusion strategy was associated with an increased risk of death or MI (RR 1.19, 95% CI, 1.01 to 1.39), which differed from those with a history of renal failure, for whom no similar association was observed (RR 0.83, 95% CI, 0.56 to 1.23).

SECONDARY OUTCOMES AT 30 DAYS

Death at 30 days occurred in 201 patients (9.3%) in the restrictive transfusion strategy group and 174 patients (8.1%) in the liberal transfusion strategy (RR 1.15, 95% CI,

Outcome	Restrictive n/N (%)	Liberal n/N (%)	Absolute Difference (95% CI)	RR (95% CI)
Primary Outcome				
Death or MI	334/2165 (15.4)	296/2146 (13.8)	1.3% (–0.7 to 3.4)	1.13 (0.97 to 1.30)
Other Outcomes				
Death within 30 days	201/2165 (9.3)	174/2146 (8.1)	1.1% (–0.5 to 2.8)	1.15 (0.95 to 1.39)
MI	163/2165 (7.5)	142/2146 (6.6)	0.5% (–0.9 to 1.9)	1.15 (0.92 to 1.42)
MACE (death, MI, or stroke)	351/2165 (16.2)	319/2146 (14.9)	1.1% (–1.1 to 3.2)	1.10 (0.96 to 1.26)
Cardiac death	117/2141 (5.5)	79/2125 (3.7)	1.8% (0.6 to 3.1)	1.47 (1.11 to 1.94)
Death, MI, or unscheduled revascularization	361/2141 (16.9)	322/2125 (15.2)	1.4% (–0.7 to 3.6)	1.12 (0.98 to 1.28)
Unscheduled revascularization	50/2141 (2.3)	45/2125 (2.1)	0.2% (–0.7 to 1.1)	1.10 (0.74 to 1.64)
Heart failure	122/2165 (5.6)	134/2146 (6.2)	–0.5% (–1.8 to 0.9)	0.89 (0.70 to 1.13)
Acute renal failure/dialysis	235/1883 (12.5)	223/1854 (12.0)	0.6% (–1.4 to 2.7)	1.04 (0.88 to 1.23)
Stroke	32/2165 (1.5)	29/2146 (1.4)	0.1% (–0.6 to 0.8)	1.10 (0.67 to 1.81)
PE/DVT	26/2141 (1.2)	38/2125 (1.8)	–0.7% (–1.4 to –0.1)	0.68 (0.42 to 1.12)
Pneumonia	103/1799 (5.7)	94/1801 (5.2)	0.6% (–0.9 to 2.1)	1.10 (0.84 to 1.44)
Bacteremia	95/2141 (4.4)	91/2125 (4.3)	0.2% (–1.1 to 1.4)	1.04 (0.78 to 1.38)
Bleeding	272/2165 (12.6)	255/2146 (11.9)	0.7% (–1.2 to 2.6)	1.05 (0.90 to 1.23)

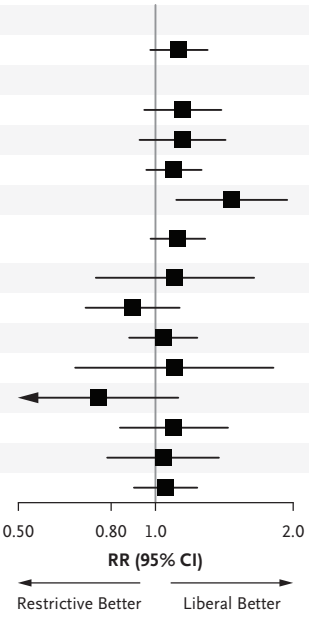

Figure 2. Primary and Secondary 30-Day Outcomes.

Risk difference models using random effects did not converge for bacteremia and we report risk difference estimates that did not use random effects for that outcome. CI denotes confidence interval; DVT, deep venous thrombosis; MACE, major adverse cardiac events; MI, myocardial infarction; PE, pulmonary embolism; and RR, relative risk. Arrow indicates lower limit of confidence interval extends beyond 0.5.

0.95 to 1.39). Cardiac death occurred in 5.5% of patients in the restrictive transfusion strategy and 3.7% of patients in the liberal transfusion strategy (RR 1.47, 95% CI, 1.11 to 1.94). MI and MACE occurred more frequently in patients in the restrictive transfusion strategy than in patients in the liberal transfusion strategy, but the 95% CIs included 1.00. Adjustment for baseline characteristics had no meaningful effect on the RR estimates (Fig. S1). All other 30-day efficacy outcomes were similar between the restrictive and liberal strategies (Fig. 2).

Among safety outcomes, pneumonia occurred in 5.7% of patients in the restrictive transfusion strategy group and 5.2% of patients in the liberal transfusion strategy (RR 1.10, 95% CI, 0.84 to 1.44), and the rates of bacteremia were nearly the same (Fig. 2). Heart failure occurred in 5.6% of patients in the restrictive transfusion strategy and 6.2% of patients in the liberal transfusion strategy (RR 0.89, 95% CI, 0.70 to 1.13), and pulmonary embolism or deep venous thrombosis occurred in 1.2% of patients in the restrictive transfusion strategy group and 1.8% of patients in the liberal transfusion strategy (RR 0.68, 95% CI, 0.42 to 1.12) (Table 4).

DEATH AT 6 MONTHS

The duration of follow-up varied among the trials; three trials followed patients for at least 6 months (n=4266).[2,3,5] The restrictive, compared with liberal, transfusion strategy was associated with an increased risk of all-cause death at 6 months (hazard ratio 1.08, 95% CI, 1.05 to 1.11), with cumulative incidence curves remaining parallel from 30 days to 6 months (Fig. 3). The risk of cardiac death at 6 months was higher with a restrictive transfusion strategy than with a liberal transfusion strategy (hazard ratio 1.38, 95% CI, 1.08 to 1.76) (Fig. S2).

Discussion

In this individual patient data meta-analysis of 4311 patients with acute MI and anemia, a restrictive transfusion strategy resulted in a 13% relative (1.6 percentage point absolute) increase in a composite outcome of death or MI at 30 days, but with a 95% CI that included 1.0. The adoption of a restrictive transfusion strategy compared with a liberal transfusion strategy was associated with increased

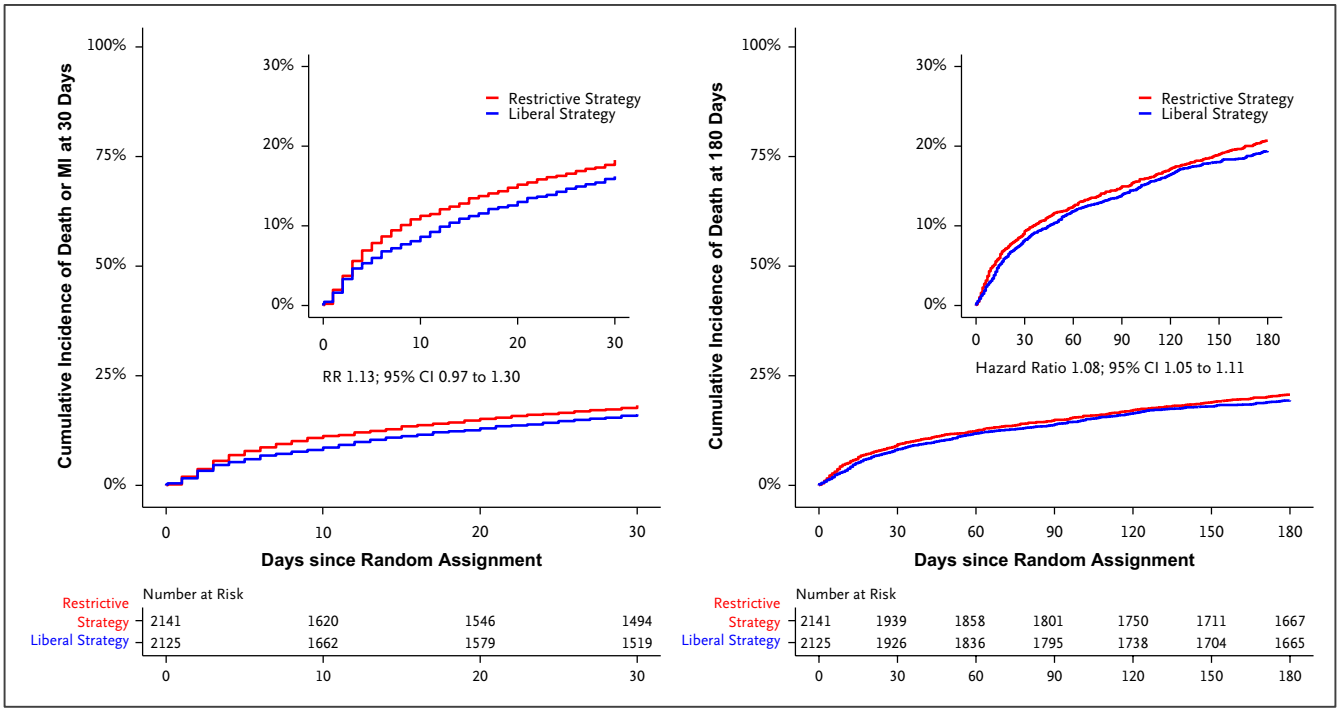

Figure 3. Cumulative Incidence of Death or Myocardial Infarction at 30 Days and All-Cause Death at 180 Days.

The rate of death or MI at 30 days was 15.4% in the restrictive transfusion strategy and 13.8% in the liberal transfusion strategy. The rate of all-cause death at 30 days was 9.3% in the restrictive transfusion strategy and 8.1% in the liberal transfusion strategy. The rate of all-cause death at 180 days was 20.5% in the restrictive transfusion strategy and 19.1% in the liberal transfusion strategy. CI denotes confidence interval; MI, myocardial infarction; and RR, relative risk.

all-cause mortality at 6 months. The risks of heart failure and other safety outcomes were similar between the two transfusion strategies.

The observed association for the difference in mortality at 30 days persisted to 6 months, and the absolute difference remained constant. At 6 months, more deaths occurred in the restrictive transfusion arm (20.5%) than in the liberal transfusion arm (19.1%). The cause-specific mortality findings suggest that a restrictive transfusion strategy was associated with a higher risk of death due to cardiac causes. However, the best assessment of the effect of transfusion on mortality is all-cause mortality, which is also the most meaningful assessment of the efficacy and safety of a given strategy, making the association between restrictive strategy and increased mortality up to 6 months particularly notable.

As we hypothesized in MINT and our individual patient data meta-analysis protocol, there is biological plausibility for why a restrictive transfusion strategy may be harmful in acute MI as oxygen delivery to the myocardium is flow dependent. Oxygen delivery to the myocardium can increase substantially only with an increase in blood flow[10] since the heart consumes 60 to 75% (extraction ratio) of all oxygen delivered by the coronary circulation.[11-13] Therefore, myocardial ischemia may be precipitated or worsened by low hemoglobin concentrations, especially in patients with coronary stenosis and/or complete obstruction that leads to MI.

Combining trials using individual patient data allows examination of less frequent, but important, outcomes such as mortality, and provides the most precise available estimates of treatment effect. Precision was enhanced through several additional steps. Specifically, to combine the REALITY results with the other three trials, we created a composite primary outcome of death or MI at 30 days from REALITY individual patient data that had not been previously reported by the trial. We also conducted an adjusted analysis for important patient-level baseline characteristics, which cannot be performed in a trial-level meta-analysis. Finally, we examined 6-month mortality in the three

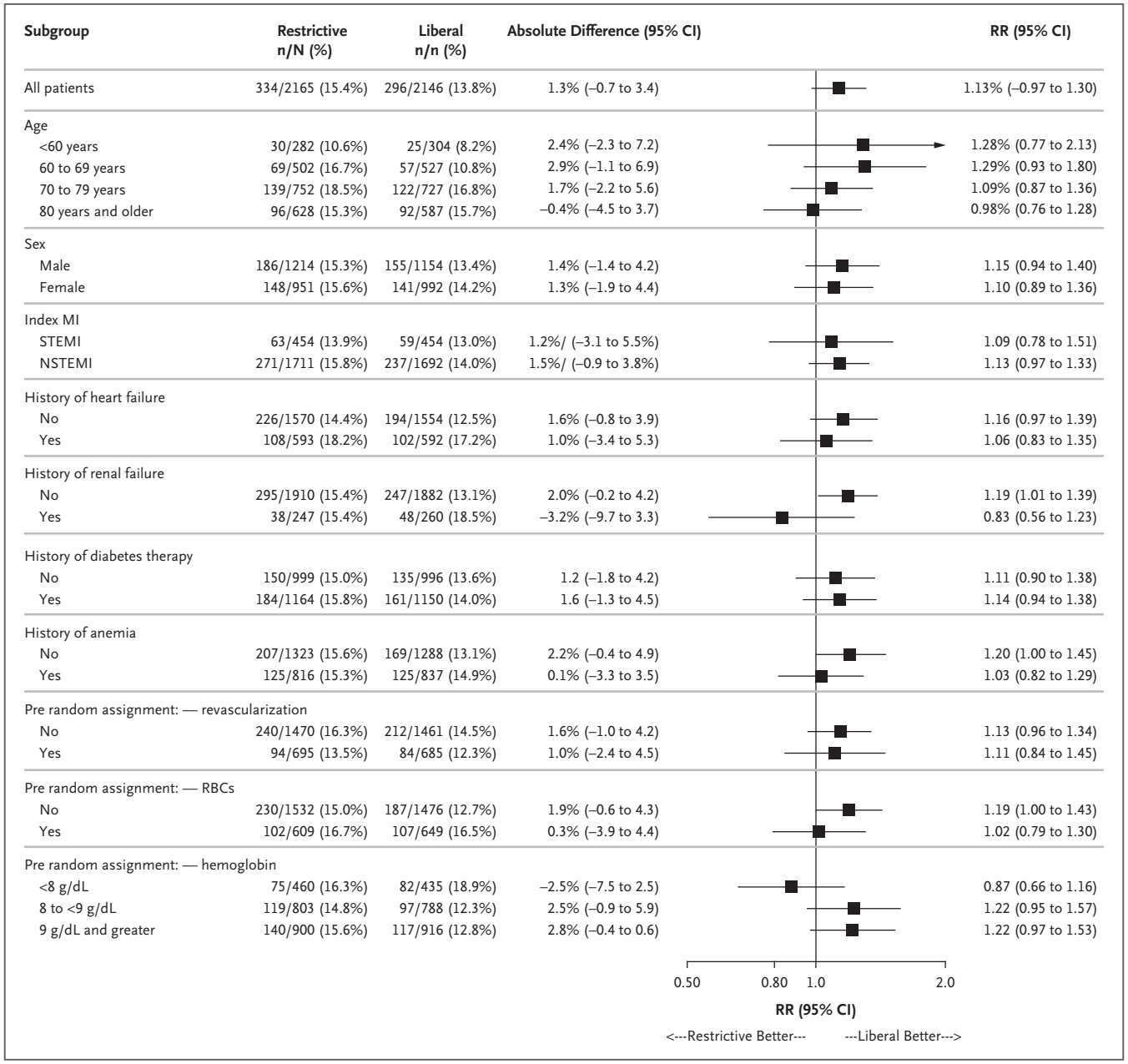

Figure 4. Subgroup Analysis for Primary Outcome of Death or Myocardial Infarction at 30 Days.

Risk difference models using random effects did not converge for the subgroup age and subgroup random assignment hemoglobin. For each of these, we report risk difference estimates that do not use random effects. CI denotes confidence interval; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; RBC, red blood cell; and RR, relative risk. Arrow indicates upper limit of confidence interval extends beyond 2.0.

largest trials that followed patients beyond hospitalization. These results are consistent with three published trial-level meta-analyses.[14-16]

The results of this meta-analysis in patients with MI differ from those observed in other clinical settings.[6] In patients with acute blood loss, including gastrointestinal bleeding, a restrictive transfusion strategy may be superior to a liberal transfusion strategy.[17] In other clinical settings, including orthopedic surgery, critical care, and cardiac surgery, trials have consistently demonstrated no evidence to support the use of a liberal transfusion strategy in

Table 3. Primary and Secondary Outcomes for the Four Trials.*

Outcome	N/N (%)	Restrictive Transfusion N/N (%)	Liberal Transfusion N/N (%)	RR (95% CI)
Death or MI within 30 days	630/4311 (14.6)	334/2165 (15.4)	296/2146 (13.8)	1.13 (0.97 to 1.30)
MINT	550/3250 (15.7)	295/1749 (16.9)	255/1755 (14.5)	1.16 (1.00 to 1.35)
REALITY	59/666 (8.9)	26/342 (7.6)	33/324 (10.2)	0.75 (0.46 to 1.22)
MINT Pilot	17/96 (17.7)	11/50 (22.0)	6/46 (13.0)	1.69 (0.68 to 4.19)
CRIT	4/45 (8.9)	2/24 (8.3)	2/21 (9.5)	0.88 (0.13 to 5.68)
Death within 30 days	375/4311 (8.7)	201/2165 (9.3)	174/2146 (8.1)	1.15 (0.95 to 1.39)
MINT	319/3504 (9.1)	173/1749 (9.9)	146/1755 (8.3)	1.19 (0.96 to 1.47)
REALITY	46/666 (6.9)	20/342 (5.8)	26/324 (8.0)	0.73 (0.42 to 1.28)
MINT Pilot	7/96 (7.3)	6/50 (12.0)	1/46 (2.2)	5.52 (0.69 to 44.13)
CRIT	3/45 (6.7)	2/24 (8.3)	1/21 (4.8)	1.75 (0.17 to 17.95)
MI	305/4311 (7.1)	163/2165 (7.5)	142/2146 (6.6)	1.15 (0.92 to 1.42)
MINT	275/2504 (7.8)	149/1749 (8.5)	126/1755 (7.2)	1.19 (0.94 to 1.49)
REALITY	17/666 (2.6)	7/342 (2.0)	10/324 (3.1)	0.66 (0.26 to 1.72)
MINT Pilot	12/96 (12.5)	7/50 (14.0)	5/46 (10.9)	1.29 (0.44 to 3.78)
CRIT	1/45 (2.2)	0/24 (0)	1/21 (4.8)	—
MACE (death, MI, or stroke)	670/4311 (15.5)	351/2165 (16.2)	319/2146 (14.9)	1.10 (0.96 to 1.26)
MINT	585/3594 (16.7)	310/1749 (17.7)	275/1755 (15.7)	1.31 (0.98 to 1.31)
REALITY	63/666 (9.5)	28/342 (8.2)	35/324 (10.8)	0.76 (0.47 to 1.22)
MINT Pilot	18/96 (18.8)	11/50 (22.0)	7/46 (15.2)	1.45 (0.61 to 3.41)
CRIT	4/45 (8.9)	2/24 (8.3)	2/21 (9.5)	0.88 (0.13 to 5.68)
Cardiac death	196/4266 (4.6)	117/2141 (5.5)	79/2125 (3.7)	1.47 (1.11 to 1.94)
MINT	153/3504 (4.4)	97/1749 (5.5)	56/1755 (3.2)	1.74 (1.26 to 2.40)
REALITY	36/666 (5.4)	14/342 (4.1)	22/324 (6.8)	0.60 (0.31 to 1.16)
MINT Pilot	7/96 (7.3)	6/50 (12.0)	1/46 (2.2)	5.52 (0.69 to 44.1)
CRIT	N/A			
Death, MI, or unscheduled revascularization	683/4266 (16.0)	361/2141 (16.9)	322/2125 (15.2)	1.12 (0.98 to 1.28)
MINT	600/3504 (17.1)	319/1749 (49.9)	281/1755 (16.0)	1.14 (0.98 to 1.32)
REALITY	64/666 (9.6)	29/342 (8.5)	35/324 (10.8)	0.79 (0.49 to 1.25)
MINT Pilot	19/96 (19.8)	13/50 (26.0)	6/46 (13.0)	1.99 (0.83 to 4.80)
CRIT	N/A			

*CI denotes confidence interval; CRIT, Conservative Versus Liberal Red Cell Transfusion in Acute Myocardial Infarction; MACE, major adverse cardiac event; MI, myocardial infarction; MINT, Myocardial Ischemia and Transfusion; REALITY, Restrictive Versus Liberal Blood Transfusion strategy on Major Cardiovascular Events Among Patients with Acute Myocardial Infarction and Anemia; and RR, relative risk.

adults or children. When trials comparing restrictive with liberal transfusion strategies in all populations are combined, the summary RR for 30-day mortality was 1.00 (95% CI, 0.86 to 1.16). This leads to the conclusion that transfusion threshold has no effect on mortality,[1] informing a general recommendation for restrictive transfusion policies in guidelines.[1,18] However, patients with MI may respond differently to blood transfusion and thus need to be studied separately.

The two largest trials included in this analysis, REALITY and MINT, had outcomes on 30-day death or MI in opposite directions. The most likely explanation for the difference between the trials is chance. REALITY was roughly one fifth the size of MINT, and smaller trials are more likely to produce extreme results and have greater uncertainty with wide CIs. In fact, the CI for the REALITY result includes the point estimate of the MINT primary outcome. There are minor design differences between the trials; however, we do not know whether or how these differences might have impacted the results. The REALITY outcomes included in this analysis, 30-day death or MI, were not its primary outcome. One of the strengths of a meta-analysis is to combine

Table 4. Adverse Effects.*

Outcome	N/N(%)	Restrictive Transfusion N/N (%)	Liberal Transfusion N/N (%)	RR (95% CI)
Acute heart failure	256/4311 (5.9)	122/2165 (5.6)	134/2146 (6.2)	0.89 (0.70 to 1.13)
MINT	213/3504 (6.1)	102/1749 (5.8)	111/1755 (6.3)	0.92 (0.71 to 1.20)
REALITY	23/666 (3.5)	11/342 (3.2)	12/324 (3.7)	0.87 (0.39 to 1.94)
MINT Pilot	8/96 (8.3)	6/50 (12.0)	2/46 (4.3)	2.76 (0.59 to 13.00)
CRIT	12/45 (26.7)	3/24 (12.5)	9/21 (42.9)	0.29 (0.09 to 0.94)
Acute renal failure/dialysis	458/3737 (12.3)	235/1883 (12.5)	223/1854 (12.0)	1.04 (0.88 to 1.23)
MINT	403/3089 (13.0)	202/1546 (13.1)	201/1543 (13.0)	1.00 (0.84 to 1.20)
REALITY	53/611 (8.7)	32/317 (10.1)	21/294 (7.1)	1.41 (0.83 to 2.39)
MINT Pilot	N/A			
CRIT	2/37 (5.4)	1/20 (5.0)	1/17 (5.9)	0.85 (0.06 to 12.6)
Stroke	61/4311 (1.4)	32/2165 (1.5)	29/2146 (1.4)	1.10 (0.67 to 1.81)
MINT	56/3504 (1.6)	30/1749 (1.7)	26/1755 (1.5)	1.16 (0.69 to 1.95)
REALITY	4/666 (0.6)	2/342 (0.6)	2/324 (0.6)	0.95 (0.13 to 6.69)
MINT Pilot	1/96 (1.0)	0/50 (0)	1/46 (2.2)	—
CRIT	0/45 (0)	0/24 (0)	0/21 (0)	—
PE or DVT	64/4266 (1.5)	26/2141 (1.2)	38/2125 (1.8)	0.68 (0.42 to 1.12)
MINT	60/3504 (1.7)	26/1749 (1.5)	34/1755 (1.9)	0.77 (0.46 to 1.27)
REALITY	3/666 (0.5)	0/342 (0)	3/324 (0.9)	—
MINT Pilot	1/96 (1.0)	0/50 (0)	1/46 (2.2)	—
CRIT	N/A			
Bacteremia	186/4266 (4.4)	95/2141 (4.4)	91/2125 (4.3)	1.04 (0.78 to 1.38)
MINT	161/3504 (4.6)	81/1749 (4.6)	80/1755 (4.6)	1.02 (0.75, 1.37)
REALITY	25/666 (3.8)	14/342 (4.1)	11/324 (3.4)	1.21 (0.56 to 2.62)
MINT Pilot	0/96 (0)	0/50 (0)	0/46 (0)	—
CRIT	N/A			
Bleeding	527/4311 (12.2)	272/2165 (12.6)	255/2146 (11.9)	1.05 (0.90 to 1.23)
MINT	389/3504 (11.1)	198/1749 (11.3)	191/1755 (10.9)	1.04 (0.86 to 1.25)
REALITY	129/666 (19.4)	67/342 (19.6)	62/324 (19.1)	1.02 (0.75 to 1.40)
MINT Pilot	5/96 (5.2)	3/50 (6.0)	2/46 (4.3)	1.38 (0.24 to 7.89)
CRIT	4/45 (8.9)	4/24 (16.7)	0/21 (0)	—

*CI denotes confidence interval; CRIT, Conservative Versus Liberal Red Cell Transfusion in Acute Myocardial Infarction; DVT, deep venous thrombosis; MINT, Myocardial Ischemia and Transfusion; N/A, not applicable; REALITY, Restrictive Versus Liberal Blood Transfusion strategy on Major Cardiovascular Events Among Patients with Acute Myocardial Infarction and Anemia; PE, pulmonary embolism; and RR, relative risk.

the results of multiple trials, sometimes with apparently divergent outcomes, to provide the best estimate of the efficacy and safety of an intervention.

There are a number of limitations to this analysis. Because we did not include a provision for correcting for multiplicity, results are reported as point estimates and 95% CIs, and the intervals should not be used to reject or not reject the null hypothesis. There were design differences among the trials that limited our analysis. REALITY did not include patients receiving transfusion prior to random assignment, while the MINT trial did. Both MINT trials screened for recurrent MI using surveillance troponins for 3 days post random assignment, while REALITY did not. Post-random-assignment detailed hemoglobin results were not available for analysis in two of the trials. Comparison of outcomes of type 1 to type 2 MI may be important[19] but was not possible because only MINT classified the type of MI at baseline. Over 80% of the participants in this meta-analysis are from MINT and so these results are necessarily similar to those of MINT. Finally, we were not able to collect nonfatal outcomes beyond 30 days.

Conclusion

By analyzing all patient data from four randomized trials, we did not demonstrate a difference in death or MI at 30 days between liberal and restrictive transfusion thresholds. A restrictive transfusion strategy was associated with an increased risk of 30-day cardiac mortality and 6-month all-cause mortality.

Disclosures

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