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RESEARCH LETTER

Transfusion Thresholds for Acute Coronary Syndromes—Insights From the TRICS-III Randomized Controlled Trial, Systematic Review, and Meta-Analysis

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Both anemia and red blood cell transfusion are associated with morbidity and mortality in patients hospitalized for acute coronary syndromes (ACSs); these exposures are tightly linked, and their attributable risks are difficult to isolate. To reduce unnecessary blood exposure, transfusion should only be administered if/when its net benefits outweigh the risks associated with anemia. Hemoglobin thresholds are currently used for evaluating the severity of anemia and for guiding transfusion therapy; however, there is controversy surrounding the optimal hemoglobin threshold for transfusion in this patient population.[1] Randomized controlled trials (RCT) comparing hemoglobin-guided restrictive versus liberal transfusion strategies are difficult to interpret,[2] and there is a paucity of available data on long-term outcomes. We therefore performed a subset analysis of patients with acute myocardial infarction (AMI) in the TRICS-III (Transfusion Thresholds in Cardiac Surgery) RCT to add evidence addressing this important clinical question and further interpret the results using a systematic-review, meta-analysis, and trial-sequential analysis.

The previously described[3] multinational TRICS-III trial (NCT02042898) randomly assigned patients with a moderate-to-high risk of death undergoing cardiac surgery on cardiopulmonary bypass to a restrictive transfusion strategy (transfuse at a hemoglobin level <7.5 g/dL) or liberal strategy (operating room and intensive care unit: transfuse at a hemoglobin level <9.5 g/dL; ward: <8.5 g/dL). Appropriate ethical board review and approval were obtained from each participating site, and informed consent was obtained from all participants. Patients with AMI were those with a recent myocardial infarction (MI) (<90 days of surgery) undergoing coronary artery bypass graft surgery and ≥1 of the following enrichment criteria: unstable angina, critical preoperative state, use of preoperative intra-aortic balloon pump, and/or undergoing emergency surgery. The primary outcome was a per-protocol analysis of major adverse cardiac events (MACE) defined as all-cause death, MI, and revascularization at 6 months.

We next performed a systematic search of the MEDLINE and EMBASE databases from inception to April 18, 2022, to identify RCTs evaluating restrictive versus liberal transfusion in patients hospitalized for ACSs. The primary outcome was MACE, defined as all-cause death, MI, and revascularization (when available), at the longest available timepoint.

Key Words: acute coronary syndromes ■ acute myocardial infarction ■ anemia ■ transfusion

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A TRICS-AMI Cohort Characteristics

	Restrictive Strategy (n=89)	Liberal Strategy (n=105)
Age	67.4±9.8	67.5±8.9
Male sex	69/89 (77.5)	85/105 (81.0)
Body mass index	28.1±4.2	27.4±4.3
EuroSCORE I	9.2±2.0	9.5±2.3
Preserved left ventricular function (ejection fraction >50%)	32/89 (36.0)	29/104 (27.9)
Treated hypertension	73/89 (82.0)	84/105 (80.0)
Normal renal function (creatinine clearance >85 ml/min)	47/88 (53.4)	63/104 (60.6)
Preoperative use of aspirin	72/89 (80.9)	75/105 (71.4)
Preoperative anemia (male hemoglobin <13 g/L; female <12 g/dL)	46/89 (51.7)	48 /105 (45.7)
Duration of cardiopulmonary bypass, minutes	105±35	108±48
≥1 Red blood cell transfusion post-randomization	47/89 (52.8)	83/105 (79.0)
Number of units	1.82 ± 3.56	3.61 ± 4.61

B Meta-Analysis of Randomized Controlled Trials

Major Adverse Cardiovascular Events (all-cause death, myocardial infarction, and revascularization)

Trial	Restrictive, n (%)	Liberal, n (%)	Weight	Risk Difference (95% Confidence Interval)	Certainty of Evidence
CRIT	2/23 (9%)	2/19 (11%)	8.2%	-2% (-20% to 16%)	--
MINT Pilot	20/54 (37%)	15/55 (27%)	8.7%	10% (-8% to 27%)	--
REALITY	111/342 (32%)	92/324 (28%)	54.5%	4% (-3% to 11%)	--
TRICS-AMI	12/84 (14%)	11/101 (11%)	28.6%	3% (-6% to 13%)	--
Total	**145/503 (29%)**	**120/499 (24%)**	**100%**	**4% (-1% to 9%)**	⊕⊕⊕○ Moderate

Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 3 (P = 0.84); I² = 0%
Test for overall effect: Z = 1.48 (P = 0.14)

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Death

Trial	Restrictive, n (%)	Liberal, n (%)	Weight	Risk Difference (95% Confidence Interval)	Certainty of Evidence
CRIT	2/23 (9%)	1/19 (5%)	8.3%	3% (-12% to 19%)	--
MINT Pilot	10/54 (19%)	7/55 (13%)	10.5%	6% (-8% to 19%)	--
REALITY	79/342 (23%)	66/324 (20%)	49.7%	3% (-4% to 9%)	--
TRICS-AMI	7/85 (8%)	8/101 (8%)	31.5%	0% (-8% to 8%)	--
Total	**98/504 (19%)**	**82/499 (16%)**	**100%**	**2% (-2% to 7%)**	⊕⊕⊕○ Moderate

Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 3 (P = 0.91); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)

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Myocardial Infarction

Trial	Restrictive, n (%)	Liberal, n (%)	Weight	Risk Difference (95% Confidence Interval)	Certainty of Evidence
MINT Pilot	7/54 (13%)	5/55 (9%)	8.2%	4% (-8% to 16%)	--
REALITY	33/342 (10%)	21/324 (6%)	66.7%	3% (-1% to 7%)	--
TRICS-AMI	5/79 (6%)	4/95 (4%)	25.1%	2% (-5% to 9%)	--
Total	**45/475 (9%)**	**30/474 (6%)**	**100%**	**3% (0% to 6%)**	⊕⊕⊕○ Moderate

Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 2 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.73 (P = 0.08)

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Revascularization

Trial	Restrictive, n (%)	Liberal, n (%)	Weight	Risk Difference (95% Confidence Interval)	Certainty of Evidence
MINT Pilot	2/54 (4%)	0/55 (0%)	6.9%	4% (-2% to 10%)	--
REALITY	5/342 (1%)	6/324 (2%)	66.2%	0% (-2% to 2%)	--
TRICS-AMI	0/77 (0%)	1/95 (1%)	26.9%	-1% (-4% to 2%)	--
Total	**7/473 (1%)**	**7/474 (1%)**	**100%**	**0% (-2% to 1%)**	⊕⊕○○ Low

Heterogeneity: Tau² = 0.00; Chi² = 1.94, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.36 (P = 0.72)

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Restrictive safer *Liberal safer*

Citation screening, data abstraction, and assessment of quality and risk of bias were performed in duplicate and as outlined in the Cochrane Handbook for Systematic Reviews and Interventions and Grading of Recommendations Assessment, Development, and Evaluation framework. Inverse variance-weighted random-effects models were used to estimate risk differences (RD) and 95% CIs. We then conducted a

Figure. The effect of restrictive versus liberal transfusion strategies in patients hospitalized for acute coronary syndromes. **A**, Characteristics of patients with AMI in the TRICS-III (Transfusion Thresholds in Cardiac Surgery) randomized controlled trial. **B**, Meta-analysis of randomized controlled trials comparing restrictive versus liberal transfusion in patients with acute coronary syndromes on clinical outcomes at the longest available timepoint. Inverse-variance random-effects models were used for synthesizing data for each outcome. The REALITY Trial was supplemented with data obtained from the summary of a conference proceeding reporting long-term outcomes. AMI indicates acute myocardial infarction; CRIT, conservative versus liberal red cell transfusion in acute myocardial infarction; EuroSCORE, European system for cardiac operative risk evaluation; MINT, myocardial ischemia and transfusion; REALITY, restrictive and liberal transfusion strategies in patients with acute myocardial infarction.

trial-sequential analysis to evaluate the conclusiveness of our meta-analysis of MACE.

The data that support the findings of this study are available from the corresponding author on reasonable request and in accordance with a data-sharing agreement.

Of the 4860 patients included in the primary TRICS-III trial, prerandomization AMI status could be ascertained in 4765 patients (98% of cohort), of which 194 had AMI. A total of 89 patients were allocated to restrictive transfusion and 105 to the liberal strategy. Baseline and procedural characteristics were well balanced between groups (Figure). In the TRICS-AMI population, a restrictive versus liberal transfusion strategy resulted in a numerically higher incidence of MACE at 6 months (14% versus 11%); however, this association was not statistically significant (RD, 3% [95% CI, −6% to 13%]).

Our systematic review identified 274 distinct citations. A total of 3 RCTs met the eligibility criteria,[2,4,5] yielding a total of 4 studies (1015 patients). The transfusion strategies were similar across all studies. Trials evaluating transfusion thresholds are unable to blind study staff and participants to treatment allocation; thus, all trials had a high risk for performance bias. Restrictive transfusion was associated with a trend toward an increased the risk of MACE (RD, 4% [95% CI, −1% to 9%]; I^2 = 0%) and MI (RD, 3% [95% CI, 0%–6%]; I^2 = 0%) at the longest available timepoint (Figure). These CIs exclude major benefits from restrictive transfusion (exclude >1% reduction in absolute risk) and do not exclude important harm (do not exclude ≥6% increases in absolute risk). At 40% of the critical information size, the trial-sequential analysis for MACE did not cross the boundary for superiority or futility, suggesting more evidence is needed to consider this association as conclusive.

Prior meta-analyses demonstrating no clinical benefit of a restrictive or liberal transfusion strategy in ACS have been limited by a lack of availability of data and ability to evaluate only short-term outcomes. We provide new, high-quality, randomized data on long-term outcomes and synthesize the results across RCTs with low clinical, methodological, and statistical heterogeneity. Our findings suggest that liberal transfusion strategies may decrease the risk for long-term MACE and MI. This effect was similar across trials evaluating patients primarily receiving nonsurgical and surgical management of ACS.

It is possible that differences in preexisting anemia or transfusion protocol suspensions may have led to bias in the effect estimates. Emerging evidence suggests that restrictive transfusion strategies are no longer cost-effective after 1 year[6]; therefore, adoption of liberal strategies may improve patient outcomes without increasing cost burden to the health care system. This unrealized benefit may be considerably large, as 5 of 6 respondents from a recent poll by the American College of Cardiology reported using a restrictive transfusion strategy in their current clinical practice for this patient population.[7] Long-term data from the ongoing MI and ischemia RCT (NCT02981407) will provide evidence for establishing the conclusiveness of our findings.

In summary, a liberal transfusion strategy versus restrictive strategy may improve long-term cardiovascular outcomes in patients hospitalized for ACSs. Further investigation is needed to elucidate the mechanisms contributing to this effect and confirm these findings.

ARTICLE INFORMATION

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