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RESEARCH LETTER

One-Year Major Cardiovascular Events After Restrictive Versus Liberal Blood Transfusion Strategy in Patients With Acute Myocardial Infarction and Anemia: The REALITY Randomized Trial

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Uncertainty exists on the optimal transfusion strategy in patients with anemia and acute myocardial infarction (AMI). Observational studies and 2 small randomized trials examining the effect on clinical outcomes of various transfusion strategies in AMI patients with anemia have yielded conflicting results, emphasizing the need for larger randomized clinical trials.[1]

The REALITY trial (Restrictive and Liberal Transfusion Strategies in Patients With AMI; NCT02648113; https://clinicaltrials.gov/ct2/show/NCT00235092) is a randomized, noninferiority trial in 666 patients with AMI with anemia (hemoglobin concentration between 7 and 10 g/dL), comparing management with a restrictive transfusion strategy (transfusion triggered by hemoglobin ≤8 g/dL, with a target between 8 and 10 g/dL) or a liberal strategy (transfusion triggered by hemoglobin ≤10 g/dL, with a target >11 g/dL), used as reference.[2] The primary outcome was cost–effectiveness ratio, and the main clinical end point was the composite of all-cause death, recurrent myocardial infarction, or emergency revascularization (major adverse cardiovascular event [MACE]) at 30 days. At 30 days, the main clinical outcome occurred in 11% versus 14% of patients in the restrictive and liberal arms, respectively (relative risk, 0.79 [1-sided 97.5% CI, 0—1.19]), meeting the prespecified noninferiority margin <1.25.[3]

As prespecified, follow-up was continued to 1 year, to describe 1-year outcomes and test whether the restrictive strategy remained clinically noninferior to the liberal strategy in both intention-to-treat (n=666) and per-protocol populations (n=659; consent withdrawal in 2 and 5 patients from the restrictive and liberal strategies, respectively). The study was approved by an institutional review committee, and subjects gave written informed consent. The data that support the findings are available from the corresponding author on reasonable request.

A Cox proportional-hazards model stratified on center was used to estimate the hazard ratios and 95% CIs for the effect of transfusion strategy on outcomes. Survival and MACE-free survival during 1 year are also described using Kaplan-Meier curves. In addition, relative risk was calculated for MACE.

At 1 year, MACE occurred in 111 patients and 92 patients in the restrictive and liberal groups, respectively (hazard ratio, 1.16 [95% CI, 0.88—1.53]). The relative risk for MACE was 1.13, and the 1-sided 97.5% CI, 0—1.43,

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was no longer within the prespecified noninferiority margin of 1.25 (Figure [A]). MACE event curves appeared to cross at approximately month 5 (Figure [B]). In a post hoc exploratory analysis, the hazard ratio was 1.00 (95% CI, 0.72—1.38) <5 months and 1.71 (95% CI, 1.00—2.94) ≥5 months. All-cause death occurred in 79 patients versus 66 patients in restrictive and liberal groups, respectively.

The baseline characteristics of surviving patients at day 30 did not differ between treatment groups. In a post hoc analysis of MACE between day 30 and 1 year, MACE occurred more frequently in the restrictive group (hazard ratio, 1.44 [95% CI, 1.01—2.03]).

At least 1 safety event was documented in 11.8% versus 11.3% of the patients in the restrictive and the liberal groups, respectively. Safety outcomes at 1 year did not differ from those reported at day 30.[3]

This analysis has several limitations. First, the REALITY trial was of moderate size and did not establish definitive superiority of either strategy. A larger ongoing trial with a similar design (MINT trial [Myocardial Ischemia and Transfusion]; NCT02981407) is powered to test clinical superiority of the liberal strategy using the composite outcome of all-cause death or nonfatal recurrent AMI at 6 months. Second, the trial was open-label because of the

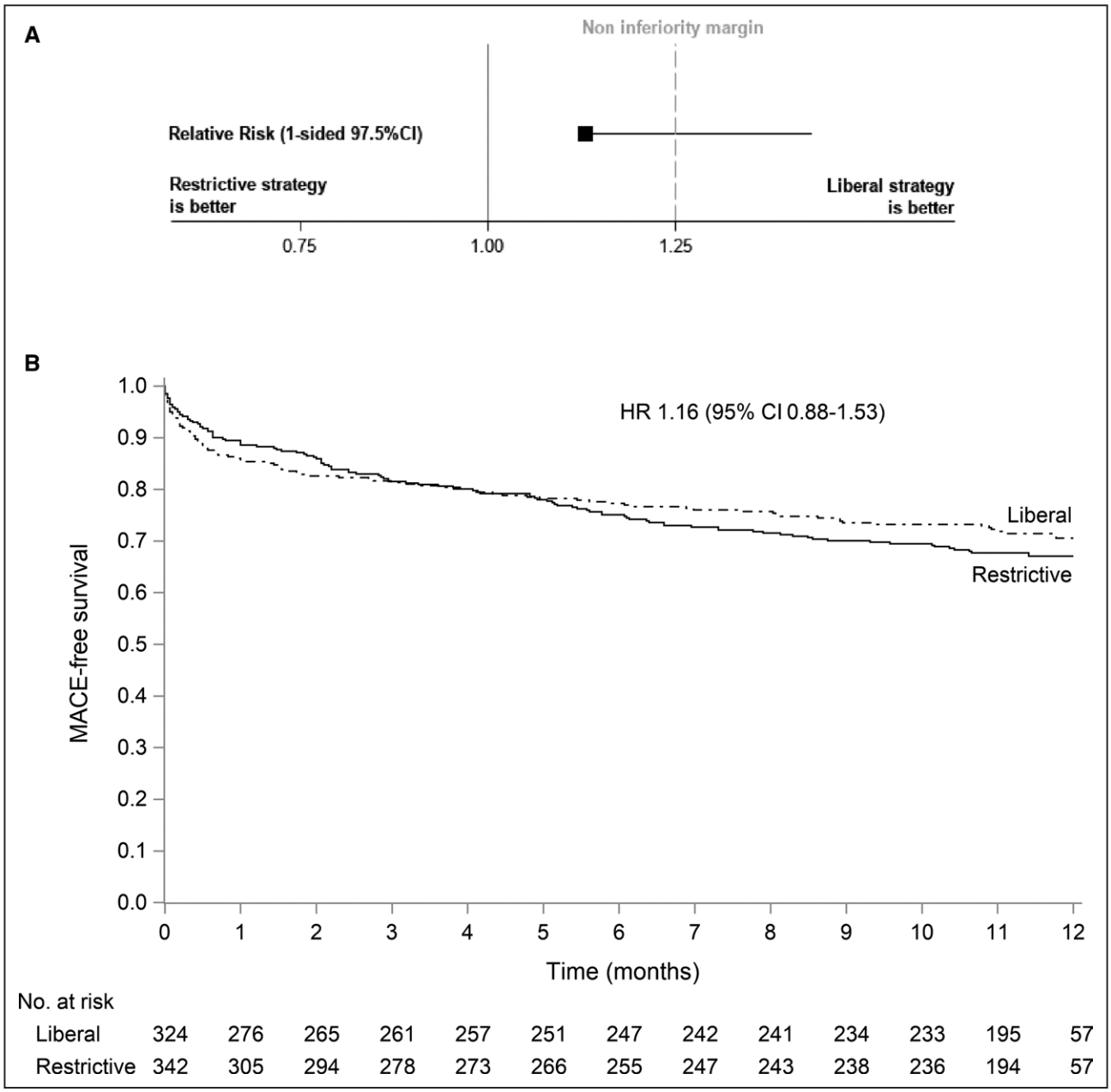

Figure. One-year major cardiovascular events.
A, Relative risk of major adverse cardiovascular event (MACE; for the restrictive vs liberal groups) and 97.5% unilateral CI (intention-to-treat population). **B**, MACE-free survival from randomization to 1 year (intention-to-treat population). MACE is defined as the composite of all-cause death, nonfatal stroke, nonfatal recurrent myocardial infarction, or emergency revascularization prompted by ischemia. HR indicates hazard ratio.

logistical challenges of blinding transfusion in the setting of AMI. However, assessment of clinical efficacy relied on objective outcomes, which were blindly adjudicated. Third, the post hoc analysis of events occurring between 30 days and 1 year must be interpreted as highly speculative and hypothesis-generating.

The main finding from the 1-year analysis of the randomized REALITY trial performed in AMI patients with anemia is that, in contrast with what was observed at 30 days, a restrictive transfusion strategy versus a liberal strategy did not achieve noninferiority in terms of MACE. This may be a result of a higher rate of events (including all-cause death) in the restrictive strategy group among surviving patients after 30 days. This observation may be a chance finding, given the relatively small sample size, or may reflect potential late harm of the restrictive strategy. A late accrual of MACE in the restrictive group may reflect delayed harm related to persistent anemia, such as an increased risk of sudden death or arrhythmias in that group.[4,5]

In conclusion, in patients with AMI and anemia, a restrictive versus liberal transfusion strategy did not achieve clinical noninferiority at 1 year. These results indicate the need for more evidence on the optimal transfusion strategy in this clinical setting.

ARTICLE INFORMATION

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