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Restrictive Versus Liberal Transfusion in Patients with Type 1 or Type 2 Myocardial Infarction: A Prespecified Analysis of the Myocardial Ischemia and Transfusion (MINT) Trial

Running Title: *DeFilippis et al.; Transfusion in Patients with Type 1 or Type 2 MI*

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Abstract

Background: The MINT trial raised concern for harm from a restrictive versus liberal transfusion strategy in patients with acute myocardial infarction (MI) and anemia. Type 1 and type 2 MI are distinct pathophysiological entities that may respond differently to blood transfusion. This analysis sought to determine if the effects of transfusion varied among patients with a type 1 or a type 2 MI and anemia. We hypothesized that the liberal transfusion strategy would be of greater benefit in type 2 than in type 1 MI.
Methods: We compared rates of death or MI at 30 days in patients with type 1 (n=1460) and type 2 (n=1955) MI and anemia who were randomly allocated to a restrictive (threshold of 7 to 8 g/dL) or a liberal (threshold of 10 g/dL) transfusion strategy.
Results: The primary outcome of death or MI was observed in 16% of type 1 MI and 15.4% of type 2 MI patients. The rate of death or MI was higher in patients with type 1 MI randomized to a restrictive (18.2%) versus liberal (13.2%) transfusion strategy (RR 1.32, 95% CI 1.04 - 1.67) with no difference observed between the restrictive (15.8%) and liberal (15.1%) transfusion strategies in patients with type 2 MI (RR 1.05 95% CI 0.85-1.29). The test for a differential effect of transfusion strategy by MI type was not statistically significant ($P\text{-}_{interaction} = 0.16$).
Conclusions: The concern for harm with a restrictive transfusion strategy in patients with acute MI and anemia raised in the MINT primary outcome manuscript may be more apparent in patients with type 1 than type 2 MI.
Clinical Trial Registration: ClinicalTrials.gov number, NCT02981407

Key Words: Myocardial infarction; Type 1 Myocardial Infarction; Type 2 Myocardial Infarction; Acute Coronary Syndrome; Blood Transfusion; Critical Care Cardiology

Non-Standard Abbreviations and Acronyms: MI, myocardial infarction; CI confidence interval; RR, risk ratio; MINT, Myocardial Ischemia and Transfusion; CONSORT, Consolidated Standards of Reporting Trials; IRB, institutional review board; SD, standard deviation; Q, quartile; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; Death/MI/revasc/readmit, Death, MI, ischemia driven unscheduled revascularization, unscheduled readmission for ischemic cardiac diagnosis

Clinical Perspective

What is new?

- The primary outcome analysis of the MINT trial raised concern for harm from a restrictive versus liberal transfusion strategy in patients with acute MI and anemia.

What are the clinical implications?

- This prespecified subgroup analysis suggests that harm from a restrictive versus liberal transfusion strategy may be more apparent in patients with type 1 than type 2 MI.
- Data establishing the safety of a restrictive transfusion strategy in multiple other patient populations should not be applied to patients with acute MI and anemia, particularly type 1 MI.

Introduction

Anemia is common in patients with a myocardial infarction (MI).[1,2] While a restrictive transfusion threshold has been established to be safe in many patient populations,[3] until more recently, the evidence in acute MI has not been sufficient to guide clinical practice.[4] The Myocardial Ischemia and Transfusion (MINT) trial[5] randomized patients with acute MI (including type 1 and type 2) and a hemoglobin concentration less than 10 g/dL to a restrictive or a liberal transfusion strategy. The MINT primary results demonstrated that acute MI patients randomized to a restrictive versus liberal transfusion strategy had a relative risk of MI or death of 1.15; 95% confidence interval (CI), 0.99 to 1.34; P = 0.07, suggesting potential harm with a restrictive strategy. Indeed, in a Bayesian analysis of the MINT trial data, an independent group of investigators suggested that the probability of harm from a restrictive versus liberal transfusion strategy is over 90%.[6]

Reflecting the greater understanding of the diverse causes of MI, the Universal Definition of MI defines five etiologically distinct types of acute MI.[7,8] The two most common are type 1 MI, resulting from a coronary thrombus overlying a disrupted atherosclerotic plaque (rupture or erosion) and type 2 MI, resulting from a mismatch in myocardial oxygen supply and demand unrelated to atherothrombosis. Despite differences in underlying pathophysiology between type 1 and type 2 MIs, most clinical trials have not differentiated or limited enrollment to specific types of MI. Therefore, the effectiveness of therapies for the treatment of patient with type 1 versus type 2 MI are unknown and may differ.[9] Potential benefit from liberal transfusion for both type 1 and type 2 MI may include increased oxygen delivery to limit or reverse ischemia. Potential harm from liberal transfusion may include volume overload (heart failure), nitric oxide sequestration (coronary constriction), or harm more specific to type 1 MI from vascular

inflammation (integral to plaque disruption) and thrombosis from platelet activation and higher blood viscosity.[10-13]

We performed a prespecified subgroup analysis to compare restrictive versus liberal transfusion strategies in patients presenting with acute type 1 and type 2 MI. We hypothesized that the liberal transfusion strategy would be of greater benefit in type 2 than in type 1 MI.

Methods

Anonymized data and materials will be made publicly available at the NIH/NHLBI Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) and can be accessed at https://biolincc.nhlbi.nih.gov after 12/28/2025 through a BioLINCC application process.

We previously reported the primary results of the MINT trial; detailed methods including a statistical plan are available at ClinicalTrials.gov number, NCT02981407.[5,14] Briefly, MINT randomized patients with acute MI and anemia to either a restrictive or liberal treatment strategy. The MINT trial was conducted at 144 sites in the United States, Canada, France, Brazil, New Zealand and Australia between April 2017 - April 2023. All sites received institutional review board (IRB) or ethics committee approval and all study patients, or their legal authorized representative, provided informed consent prior to participation. An independent data and safety monitoring committee reviewed unblinded data every six months to ensure patient safety as well as protocol-specified statistical interim monitoring for efficacy on an annual basis.

Trial Population

In the full trial, we enrolled patients 18 years or older with an acute MI including types 1, 2, 4b, or 4c, as defined by the Third Universal Definition of MI[7] and anemia defined as a hemoglobin concentration less than 10 g/dL within 24 hours prior to randomization. We excluded patients

with uncontrolled bleeding, receiving only palliative treatment, scheduled for cardiac surgery during the index admission, who declined blood transfusion, were previously enrolled in MINT, or would not be able to complete 30-days of follow-up.

Per study protocol, diagnosis and categorization of the index MI was performed by site investigators based on the Universal Definition of MI definitions.[7] We specifically asked investigators to reassess MI subtype in cases where a "missing/unknown" value had been originally recorded prior to database lock. For this subgroup analysis, we included patients with an index type 1 or type 2 MI, excluding the infrequently occurring types 4b (n=22), 4c (n=12), and those where the type of MI was unknown/missing (n=55).

Transfusion Strategies

In the restrictive arm, transfusion was permitted, but not required, when the hemoglobin concentration was less than 8 g/dL and strongly recommended when less than 7 g/dL. In the liberal arm, transfusions were given to maintain the hemoglobin concentration at or above 10 g/dL. The protocol was followed through the index hospital discharge or 30 days. Exceptions to either strategy included providing transfusions for surgery, uncontrolled angina symptoms in the restrictive arm and delaying transfusions for volume overload pending diuresis or dialysis for those with end stage renal disease. For both strategies, transfusion was administered one unit at time followed by measurement of hemoglobin concentration. The transfusion strategy was not masked to the care team or patients.

Measurements, Assessments, and Trial Outcomes

Electrocardiogram, hemoglobin concentration, and troponin measurements were required within 24 hours before randomization and daily for 3 days after randomization (two troponin values were required on day 1) until discharge or death. Additionally, all clinically available

hemoglobin and troponin levels during the index hospitalization were recorded. Patients were contacted at 30 days to assess vital status and readmission to the hospital or emergency room. Study staff reviewed medical records from the index hospitalization, and all subsequent hospital or emergency room admissions to identify potential clinical events and recorded all available troponin levels.

The primary outcome was a composite of all-cause death or MI up to 30 days following randomization.[5] A Clinical Events Committee masked to treatment assignment systematically screened all protocol required and clinically measured troponin values. Event Committee-identified potential events and site-reported MIs triggered the acquisition of hospital records related to the event. MI adjudication was performed using Third Universal Definition of MI criteria and taxonomy.[7] Pre-specified secondary outcomes included the individual components of the primary outcome (30-day death and 30-day MI), and the composite outcome of all-cause death, MI, ischemia driven unscheduled coronary revascularization, or readmission to the hospital for an ischemic cardiac diagnosis within 30 days. Additional 30 day outcomes included hospital length of stay, coronary revascularization procedures, unscheduled readmission to the hospital or emergency department, heart failure, stroke, pulmonary embolism, deep venous thrombosis, bleeding event, and other trial defined adverse events. Cause of death was classified by the enrolling site as cardiac, non-cardiac, or undetermined. The only centrally adjudicated outcome was non-fatal MI.

Acute anemia was defined as a drop in hemoglobin ≥ 2 g/dL between the first hemoglobin measurement and the closest hemoglobin measurement prior to randomization. If a participant had received a blood transfusion between hospital admission and randomization, an unobserved drop of 1 g/dL was assumed for each transfused unit. Additional details for the

definition of acute and chronic anemia can be found in the appendix. Outcome bleeding events were defined as bleeding that resulted in hemodynamic compromise, lead to a transfusion or death or clinical bleeding defined as recognized bleeding by either symptoms (e.g., hematemesis, melena, hematochezia), signs (e.g., hypotension, tachycardia) or imaging (e.g., bleeding scans, angiogram consistent with bleeding, CT or MRI identified bleeding/hematoma).

At 6 months, the cause of death was classified by the sites.

Statistical Analysis

The complete MINT trial statistical plan has been published[5]. For this sub study, distributional assumptions were verified prior to analyses. For comparing descriptive quantities, summaries included mean ± standard deviation (SD), median (25^{th}, 75th) which were tested with t-tests, Wilcoxon rank, chi-square or Fisher's-exact test, as appropriate. Baseline variables with missing values are excluded from proportions reported in Table 1. For the primary outcome, log-binomial models were used to estimate and compare the relative risks, by MI type or by randomization assignment. To determine if the effect of restrictive versus liberal strategies varied by MI type, the assigned treatment, MI type and their interaction were included in the model and with appropriate contrasts were computed. Cumulative risk of death/MI, death and non-fatal MI were calculated by MI type and assigned treatment using Kaplan-Meier methods and log-rank statistics. Censoring occurred at the time of a patient's withdrawal or at 30 days. For participants with incomplete outcome data (due to withdrawals or lost to follow-up after the index hospitalization), we assumed there were no unobserved events and based the outcomes on their time observed in the study. All units are in System International units, with the exception of hemoglobin (reported as g/dL, multiply by 10 to obtain g/L) and creatinine (reported as mg/dL, multiply by 88.4 to obtain μmol/L). Analyses were performed using SAS 9.4 (SAS Institute Inc;

Cary, NC, USA) and R version 4.3.1. GraphPad Prism version 10.1.2 was used to generate figures (GraphPad Software, Inc.; La Jolla, CA, USA).

Results

The MINT trial enrolled 3,504 patients of whom 1,460 (42%) were identified as having a type 1 and 1,955 (56%) were identified as having a type 2 index MI (Figure 1). The majority of trial patients were enrolled in the United States with significant variability in the proportion of patients enrolled with a type 1 versus type 2 MI by country, including a high of 81% type 1 in Brazil to a low of 34% type 1 in the United States.

Compared to patients enrolled with a type 1 MI, those with a type 2 MI were similar in age and sex, had a similar or higher baseline prevalence of cardiovascular risk factors (except current smoking) and more chronic illnesses, including a prior history of anemia, but a lower rate of a prior diagnosis of coronary artery disease. At the time of the index MI, symptoms of ischemia were highly prevalent in both MI types but more frequent in patients with type 1 MI (89%) than patients with type 2 MI (73%) (Table 1 & Supplemental Table 1).

Electrocardiographic changes at the time of the index MI, were also highly prevalent in both MI types but were more frequent in patients with type 1 MI (72%) than patients with type 2 MI (57%). Development of Q-waves, imaging evidence of new loss of viable myocardium, and identification of an intracoronary thrombus were all more frequent in patients with type 1 than type 2 MI. During the index hospitalization prior to randomization, a larger proportion of patients with type 1 MI had invasive angiography, percutaneous coronary interventions, heart failure, and meet criteria for acute anemia, but fewer had received a pre-randomization blood transfusion compared to patients with type 2 MI (Table 1). Compared to patients with type 1 MI, those with type 2 MI were less likely to be discharged on a P2Y12 receptor inhibitor, aspirin,

dual anti-platelet therapy, beta blocker, and statin but more likely to be discharged on oral anticoagulation (Table 1).

Transfusion Strategy Implementation

Baseline characteristics were well balanced among patients with type 1 and type 2 MI randomized to the restrictive or liberal transfusion strategy with only small differences observed in age and pre-randomization PCI (Supplemental Table 2). Randomization to liberal or restrictive transfusion strategy resulted in clear separation in the mean hemoglobin values on the three days after enrollment in patients with type 1 and type 2 MI (Supplemental Fig. 1).

Outcomes by MI Type at Enrollment

The rate of the primary outcome (all-cause death or non-fatal myocardial infarction at 30-days) was similar in patients with a type 1 or type 2 MI (16.0% vs. 15.4%, p = 0.64; Table 2). Secondary outcomes including death, MI and the composite of death, MI, revascularization, or readmission for an ischemic cardiac diagnosis also did not differ by MI type. However, patients with type 1 MI had shorter hospital length of stay, more cardiac death at 30 days (5.5% vs 3.4%, p = 0.003) and 6 months (8.6% vs 6.6%, p = 0.03), incident acute renal failure (15.3% vs. 11.6%, p = 0.001), percutaneous coronary intervention at 30 days (18.4% vs 10.1%, p<0.001) and less non-cardiac death at 30 days (2.5% vs 4.5%, p = 0.002) and 6 months (7.0% vs 10.5%, p < 0.001) as compared with patients with type 2 MI (Table 2).

Impact of Transfusion Strategy by MI Type at Enrollment

Patients with type 1 MI randomized to a restrictive transfusion strategy, had a higher rate of the primary outcome (18.2% vs 13.8%; RR 1.32, 95% confidence interval [CI] 1.04-1.67), the secondary outcome of all-cause death at 30 days (10.5% vs 7.5%; RR 1.40, 95% CI 1.01-1.95) and the outcome of cardiac death at 30 days (6.8% vs 4.2%; RR 1.61, 95% CI 1.04-2.49) and 6

months (10.6% vs 6.7%; RR 1.57, 95% CI 1.12 – 2.21) as compared to a liberal transfusion strategy (Figure 2, Table 3). Kaplan-Meier survival analysis demonstrates a higher rate of the primary outcome of death or MI (18.3% vs 14.0% at day 30, p= 0.02) among patients with type 1 MI randomized to a restrictive transfusion strategy that was evident at day 5 and persisted to day 30 post enrollment (Figure. 3). Kaplan-Meier curves for the 6-month outcome of all cause death are presented in supplemental figure 2. There was no difference in the primary outcome, or any of the secondary outcomes among patients with a type 2 MI randomized to a restrictive versus liberal transfusion strategy, however the risk of cardiac death was higher at 30 days (4.6% vs 2.3%; RR 1.95, 95% CI 1.19-3.21) and at 6 months (7.8% vs 5.5%, RR 1.42, 95% CI 1.01 - 1.99) (Figures 2 & 3, Table 3). Tests for interaction between the transfusion strategy effect and MI type at enrollment were not significant for any of the a priori study outcome comparisons (Figure 2, Table 3).

In a sensitivity analysis limited to participants who did not receive a pre-randomization transfusion, findings were similar to analyses including all MINT participants (Supplemental Table 3).

Discussion

The MINT trial design allowed for the evaluation of a therapeutic intervention (transfusion strategy) in patients with type 1 or type 2 MI and anemia. More than 50% of MINT patients had a type 2 MI and irrespective of transfusion strategy, the 30-day primary event rate of death or MI was similarly high in type 1 (16%) and type 2 (15.4%) MI patients. We observed that patients with type 1 MI randomized to a restrictive versus liberal transfusion strategy had higher rates of the primary outcome, 30-day death or MI, compared to a liberal transfusion strategy, unlike patients with type 2 MI who had similar rates of death or MI with the two transfusion

strategies. Additionally, the secondary outcome of all-cause death was higher in type 1 but not type 2 MI patients randomized to the restrictive strategy. However, statistical testing for a differential effect of a restrictive versus liberal transfusion strategy in type 1 versus type 2 MI was not significant. Therefore, this pre-specified subgroup analysis did not provide definitive evidence that a restrictive versus liberal transfusion strategy affected patients with type 1 or type 2 MI differently. However, given the high likelihood for harm with a restrictive and low likelihood of harm with a liberal transfusion strategy, this data is supportive of a liberal transfusion strategy in patients with type 1 MI and anemia, contrary to data in multiple other disease states where a restrictive strategy is preferred.

While the pathophysiology leading to myocardial injury and the patient affected by type 1 and type 2 MI differs,[7,8,15] in the setting of anemia the rate of death or MI was similar and high at 30 days in patients with type 1 and type 2 MI. We hypothesized that transfusion in both type 1 and type 2 MI could reduce adverse cardiac events and death by ameliorating myocardial ischemia / injury. Initially, we hypothesized that this potential benefit would be particularly evident in type 2 MI because of the relative lack of interventions to ameliorate supply-demand mismatch in type 2 MI as opposed to the use of coronary revascularization to correct ischemia caused by acute atherothrombotic obstruction in type 1 MI. Additionally, we hypothesized type 1 MI patients would be more susceptible to some potential harms of transfusion, including vascular inflammation (integral to plaque disruption) and thrombosis from platelet activation and higher blood viscosity.[10-13] However, we found no data to suggest that a liberal transfusion strategy was more efficacious in type 2 MI; instead, the data was compelling for a greater absolute benefit of a liberal transfusion strategy in type 1 MI.

Consistent with prior observational data,(11) patients enrolled in MINT with a type 2 MI had more comorbidities, similar rates of all cause death, but less cardiac death at 30 days as compared to patients with type 1 MI (Table 2). In MINT, at 30 days, 61% of the deaths in type 1 MI patients were cardiac while only 37% of deaths in type 2 MI patients were thought to be cardiac in origin. Therefore, although cardiac death was reduced by a liberal transfusion strategy in both type 1 and type 2 MI patients, deaths were more often cardiac (ischemic) in type 1 MI patients while deaths were predominantly non-cardiac (non-ischemic) in type 2 MI patients. Thus, we speculate that the relative contribution of ischemic complications to adverse events may in part explain why the apparent response to a restrictive versus liberal transfusion strategy might differ among patients with a type 1 and type 2 MI. These findings are consistent with observational studies that have found attenuation of differences in all cause death and major adverse cardiac events (MACE) between patients with type 2 versus type 1 MI after adjusting for non-cardiac comorbidities and competing risk of non-cardiac death, respectively.[15,16]

Therapeutic strategies are well established for patients with type 1 MI,[17-19] but no compelling data exist for the treatment of patients with type 2 MI. Thus, evidence-based treatment guidelines have not been established for type 2 MI despite similar (or greater) prevalence and comparable all-cause mortality to that of type 1 MI seen in this trial and other observational studies.[15] The MINT trial highlights the feasibility of studying patients with both type 1 and type 2 MI types in multicenter, randomized controlled clinical trials. The trial provides information to help guide physician decision-making regarding the use of red blood cell transfusion in both type 1 and type 2 MI patients with anemia. In this planned subgroup analysis, we found no evidence to support our *a priori* hypothesis that a liberal transfusion strategy would be most efficacious in type 2 MI. On the contrary, the clinical outcomes suggest

that a liberal strategy may be more efficacious in patients with type 1 MI and anemia. Although the test of interaction for a differential effect of transfusion by MI type was not statistically significant, the point estimate and 95% CI for the primary outcome of death or MI suggests a high likelihood of harm for the restrictive transfusion strategy in patients with type 1 MI and anemia with no observed harm for use of a liberal transfusion strategy in these patients. This data is supportive of a liberal transfusion strategy with a hemoglobin target of 10 mg/dL in patients with type 1 MI and anemia, contrary to data in multiple other disease states in which a restrictive strategy is preferred.[3]

Study Limitations

The explanation for the observed variation in the proportion of patients with type 1 and type 2 MIs in different countries in unclear. We speculate this may be related to the screening approach used to identify MI patients in each hospital. For example, study investigators working in a cardiac intensive care or cardiology ward may preferentially identify type 1 MI patients in contrast to those in a medical/surgical intensive care or internal medicine ward setting who may more readily identify type 2 MI patients. The MINT trial began enrollment when the Third, as opposed to the Fourth, Universal Definition of MI was available.[7,8] However, with the exception of the rare occurrence of spontaneous coronary artery dissection, the Third and Fourth Universal Definitions define type 1 and type 2 MI similarly. Therefore, the application of either definition is unlikely to change the classification of MI type in the MINT trial. As a pragmatic trial, MINT used the principal investigator's classification of index MI type. The categorization of type 1 versus type 2 MI in a clinical trial is novel and data on precision is limited. While some prior studies have shown limitations of classification of MI type by physicians when accessed from submitted billing codes,[20] others have shown reassuring agreement in the clinical research

setting.[21] Patient characteristics to support a diagnosis of type 2 MI were required, recorded, and reported and are consistent with type 2 MI patients; for example, over 70% reported symptoms of ischemia and over 55% demonstrated new ST-T changes or new left bundle branch block on the electrocardiogram. While misclassification of MI type may have occurred, the methodology used in MINT is consistent with routine clinical practice—making the therapeutic intervention tested in this trial, a restrictive versus liberal transfusion strategy, reflective of what might be expected in clinical practice. While we present data on the acuity of anemia at the time of enrollment, data on the cause of bleeding was not ascertained. The MINT trial was powered for the primary outcome analysis and therefore any subgroup analysis—including type 1 vs. type 2 MI--is likely underpowered.

Conclusions

Death or recurrent MI was common and equally prevalent among patients with type 1 and type 2 MI and anemia. Consistent with the overall MINT trial results, patients with type 1 MI and anemia tended to have a greater reduction in death or recurrent MI at 30 days with a liberal compared to a restrictive transfusion strategy than patients with type 2 MI. Data establishing the safety of a restrictive transfusion strategy in multiple other patient populations should not be applied to patients with acute MI and anemia, particularly in type 1 MI.

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Supplemental Materials

Supplemental Figure 1-2

Supplemental Table 1-3

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Table 1. Baseline Characteristics by MI Type.

Variable	Level	Type 1 MI N=1460	Type 2 MI N=1955	P-Value
Age (years), mean (SD)		72.1 (11.7)	72.3 (11.4)	0.63
Sex, n (%)	Female	693 (47.5%)	863 (44.1%)	0.054
	Male	767 (52.5%)	1092 (55.9%)	
Enrollment location, n (%)	US	714 (48.9%)	1376 (70.4%)	<0.001
	Canada	411 (28.2%)	459 (23.5%)	
	Europe	226 (15.5%)	91 (4.7%)	
	Brazil	85 (5.8%)	20 (1.0%)	
	New Zealand / Australia	24 (1.6%)	9 (0.5%)	
Race collected/available*, n (%)		1139 (78.0%)	1831 (93.7%)	<0.001
Race†,‡, n (%)	White	876 (76.9%)	1459 (79.7%)	<0.001
	Black	149 (13.1%)	257 (14.0%)	
	Other	114 (10.0%)	115 (6.3%)	
Hispanic Latino or Latina†, n (%)		37 (3.2%)	97 (5.3%)	<0.001
Tobacco smoker†, n (%)	Never	570 (41.5%)	726 (39.3%)	0.37
	Current/Former	803 (58.5%)	1122 (60.7%)	
Medical History (Prior to index Hospitalization)				
CAD, n (%)		1307 (89.5%)	1426 (72.9%)	<0.001
MI, n (%)		476 (32.6%)	633 (32.4%)	0.89
PCI† n (%)		498 (34.1%)	652 (33.4%)	0.48
CABG, n (%)		265 (18.2%)	469 (24.0%)	<0.001
Heart Failure, n (%)		769 (52.7%)	1050 (53.7%)	0.55
LV ejection fraction available, n (%)		1124 (77.0%)	1358 (69.5%)	<0.001
Most recent LV ejection fraction (%) within the past year, mean (SD)		45.9 (13.1)	48.7 (13.7)	<0.001
TIA, n (%)		230 (15.8%)	379 (19.4%)	0.006
Atrial fibrillation, n (%)		270 (18.5%)	607 (31.0%)	<0.001
eGFR†, n (%)	<60	725 (49.9%)	1029 (52.7%)	<0.001
	≥60	581 (40.0%)	666 (34.1%)	
	On dialysis at baseline	148 (10.2%)	258 (13.2%)	
Diabetes, n (%)		755 (51.7%)	1091 (55.8%)	0.02
Hypertension, n (%)		1185 (81.2%)	1715 (87.7%)	<0.001
Dyslipidemia, n (%)		902 (61.8%)	1306 (66.8%)	0.002
COPD/asthma, n (%)		285 (19.5%)	535 (27.4%)	<0.001
Anemia, n (%)		520 (35.6%)	936 (47.9%)	<0.001
Index MI Characteristics				
ST-elevation, n (%)		546 (37.4%)	89 (4.6%)	<0.001
Symptoms of ischemia, n (%)		1297 (88.8%)	1433 (73.3%)	<0.001
New ST-T changes or new left bundle branch block, n (%)		1054 (72.2%)	1122 (57.4%)	<0.001
Development of pathological Q waves†, n (%)		163 (11.2%)	52 (2.7%)	<0.001
New loss of viable myocardium or regional wall motion abnormality†, n (%)		346 (23.7%)	210 (10.7%)	<0.001
Identification of an intracoronary thrombus†, n (%)		291 (19.9%)	43 (2.2%)	<0.001
Index Hospitalization, Pre-Randomization				
Number of days between index MI and randomization, median (Q1, Q3)		2 (1, 4.5)	2 (1, 3)	<0.001
Angiography performed§, n (%)		1036 (71.0%)	648 (33.2%)	<0.001
PCI#, n (%)		776 (53.2%)	244 (12.5%)	<0.001
HF, n (%)		351 (24.0%)	412 (21.1%)	0.04
Intubated on ventilator, n (%)		215 (14.7%)	250 (12.8%)	0.10
Received red blood cell transfusion, n (%)		406 (27.8%)	805 (41.2%)	<0.001
Anemia, n (%)	Acute	505 (41.8%)	550 (34.2%)	<0.001
	Chronic	704 (58.2%)	1057 (65.8%)	
Laboratory Values				
Baseline hemoglobin‖, g/dL, mean (SD)		8.7 (0.9)	8.6 (0.8)	0.002

Variable	Level	Type 1 MI N=1460	Type 2 MI N=1955	P-Value
Most recent creatinine prior to randomization[||], mg/dL, median (Q1, Q3)		1.3 (0.9, 2.4)	1.5 (1.0, 2.7)	0.002
Discharge Medications[†]		**N = 1349**	**N = 1759**	
P2Y12 inhibitor, n (%)		1097 (81.3%)	760 (43.2%)	<0.001
Aspirin, n (%)		1134 (84.1%)	1263 (71.8%)	<0.001
Dual antiplatelet therapy[**], n (%)		968 (71.8%)	635 (36.1%)	<0.001
Oral anticoagulant, n (%)		307 (22.8%)	488 (27.7%)	0.002
Beta blocker, n (%)		1119 (83.0%)	1306 (74.3%)	<0.001
Statin, n (%)		1219 (90.4%)	1445 (82.2%)	<0.001

[*] Race and ethnicity were collected in sites from the United States, Canada, New Zealand and Australia. Race was not collected in the European Union. Racial categories in Brazil do not map well to the United States racial categories and are not included.

[†] Participants with missing data are not included in the proportions for the following variables: race (n=445) ; European Union or Brazil [n=422]; missing [n=23]), ethnicity (n=484; European Union or Brazil [n=422], missing=62), smoking status (n=194), history of PCI (n=1), eGFR (n=8), development of pathological Q waves (n=1), new loss of viable myocardium or regional wall motion abnormality (n=1), identification of an intracoronary thrombus (n=1); anemia (missing [n=599]), discharge medication data (n=307)

[‡] Participants were able to choose as many as possible races from a list that included American Indian or Alaska Native, Asian, Black or African-American, First Nations, Inuit or Metis Native Hawaiian or Pacific Islander, White or Caucasian, Other or Unknown. The General Data Protection Regulation (GDPR) did not allow us to collect this information in France. All participants from Brazil were recorded as having missing race as the above racial categories are not appropriate in Brazil.

[§] Does not include angiograms conducted post-randomization.

[||] All units are in System International units, with the exception of hemoglobin (reported as g/dL, multiply by 10 to obtain g/L) and creatinine (reported as mg/dL, multiply by 88.42 to obtain μmol/L).

Abbreviations: CAD=Coronary Artery Disease; MI=Myocardial Infarction; PCI= Percutaneous Coronary Intervention; CABG=Coronary Artery Bypass Graft; LV=Left Ventricle; TIA=Transient Ischemic Attack; eGFR = estimated Glomerular Filtration Rate; COPD=Chronic Obstructive Pulmonary Disease; Q1=1st quartile; Q3=3rd quartile; SD=Standard Deviation

[#] Does not include PCI performed for the index MI performed after randomization

[**]Dual antiplatelet therapy is defined as being prescribed both aspirin and a P2Y12 inhibitor at discharge.

Table 2. Primary, Secondary and Tertiary Outcome Rates by Index MI Type

	Total N=3415	Type 1 MI N=1460	Type 2 MI N=1955	P value
Primary Outcome				
Death (30 day)/MI*	536 (15.7)	234 (16.0)	302 (15.4)	0.64
Secondary Outcomes				
Death (30 day)*	312 (9.1)	132 (9.0)	180 (9.2)	0.87
MI	268 (7.8)	121 (8.3)	147 (7.5)	0.41
Death (30 day), MI, ischemia driven unscheduled revascularization, unscheduled readmission for ischemic cardiac diagnosis*	631 (18.5)	274 (18.8)	357 (18.3)	0.71
Tertiary Outcomes				
Death (6 month)	712 (20.9)	285 (19.5)	427 (21.8)	0.10
Heart failure	199 (5.8)	85 (5.8)	114 (5.8)	0.99
Stroke	54 (1.6)	28 (1.9)	26 (1.3)	0.17
Pulmonary Embolism / Deep Vein Thrombosis	60 (1.8)	26 (1.8)	34 (1.7)	0.93
Bleeding event	381 (11.2)	168 (11.5)	213 (10.9)	0.57
Length of hospital stay, number of days, median (Q1, Q3)	5 (2, 10)	5 (2, 9)	5 (2, 10)	0.005
Cause-Specific Death (30 day)				
Cardiac	148 (4.3)	81 (5.5)	67 (3.4)	0.003
Non-Cardiac	125 (3.7)	37 (2.5)	88 (4.5)	0.002
Unknown	39 (1.1)	14 (1.0)	25 (1.3)	0.42
Cause-Specific Death (6 month)				
Cardiac	255 (7.5)	126 (8.6)	129 (6.6)	0.03
Non-Cardiac	307 (9.0)	102 (7.0)	205 (10.5)	<0.001
Unknown	150 (4.4)	57 (3.9)	93 (4.8)	0.23
Atrial Fibrillation	369 (10.8)	164 (11.2)	205 (10.5)	0.49
Acute Renal Failure	451 (13.2)	224 (15.3)	227 (11.6)	0.001
Infection (bacteremia or pneumonia)	310 (9.1)	134 (9.2)	176 (9.0)	0.86
PCI†	466 (13.6)	269 (18.4)	197 (10.1)	<0.001
CABG	59 (1.7)	24 (1.6)	35 (1.8)	0.75

*All-cause mortality within 30-days.

Heart failure defined as evidence of signs, symptoms, and treatment suggestive of congestive heart failure. Acute renal failure is site-reported.

Abbreviations: MI: myocardial infarction; Q1: quartile 1; Q3: quartile 3; EQ-5D: EuroQol 5 Dimension; SD: standard deviation; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft.

† Outcome PCI does not included PCI performed as part of the initial treatment plan for the index MI

Abbreviations: MI: myocardial infarction; Q1: quartile 1; Q3: quartile 3; EQ-5D: EuroQol 5 Dimension; SD: standard deviation; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft.

Table 3. Event Rates and Risk Ratios by MI Type

	Type 1 MI N=1460			**Type 2 MI N=1955**			
	R N=730	L N=730	RR (95% CI) R vs L	R N=967	L N=988	RR (95% CI) R vs L	p-value (interaction)
Primary Outcome							
Death (30 day) or MI*	133 (18.2)	101 (13.8)	1.32 (1.04, 1.67)	153 (15.8)	149 (15.1)	1.05 (0.85, 1.29)	0.16
Secondary Outcomes							
Death (30 day)*	77 (10.5)	55 (7.5)	1.40 (1.01, 1.95)	93 (9.6)	87 (8.8)	1.09 (0.83, 1.44)	0.26
MI	68 (9.3)	53 (7.3)	1.28 (0.91, 1.81)	75 (7.8)	72 (7.3)	1.06 (0.78, 1.45)	0.43
Death (30 day), MI, ischemia driven unscheduled revascularization, unscheduled readmission for ischemic cardiac diagnosis*	148 (20.3)	126 (17.3)	1.17 (0.95, 1.46)	183 (18.9)	174 (17.6)	1.07 (0.89, 1.30)	0.54
Tertiary Outcomes							
Death (6 month)	154 (21.1)	131 (18.0)	1.18 (0.95, 1.45)	213 (22.0)	214 (21.7)	1.02 (0.86, 1.20)	0.29
Heart failure	36 (4.9)	49 (6.7)	0.73 (0.48, 1.12)	56 (5.8)	58 (5.9)	0.99 (0.69, 1.41)	0.29
Stroke	14 (1.9)	14 (1.9)	1.00 (0.48, 2.08)	16 (1.7)	10 (1.0)	1.63 (0.75, 3.58)	0.37
Pulmonary Embolism / Deep Vein Thrombosis	13 (1.8)	13 (1.8)	1.00 (0.47, 2.14)	13 (1.3)	21 (2.1)	0.63 (0.32, 1.26)	0.38
Bleeding event	83 (11.4)	85 (11.6)	0.98 (0.73, 1.30)	109 (11.3)	104 (10.5)	1.07 (0.83, 1.38)	0.64
Length of hospital stay, number of days, median (Q1, Q3)‡	5 (2, 9)	4 (2, 9)	1.03 (0.94, 1.14)	5 (2, 10)	5 (2, 10)	0.96 (0.89, 1.04)	0.26
Other Outcomes							
Cause-Specific Death							
Cardiac	50 (6.8)	31 (4.2)	1.61 (1.04, 2.49)	44 (4.6)	23 (2.3)	1.95 (1.19, 3.21)	0.57
Non-Cardiac	21 (2.9)	16 (2.2)	1.31 (0.69, 2.49)	37 (3.8)	51 (5.2)	0.74 (0.49, 1.12)	0.14
Unknown	6 (0.8)	8 (1.1)	0.75 (0.26, 2.15)	12 (1.2)	13 (1.3)	0.94 (0.43, 2.06)	0.73
Cause-Specific Death (6 month)							
Cardiac	77 (10.6)	49 (6.7)	1.57 (1.12, 2.21)	75 (7.8)	54 (5.5)	1.42 (1.01, 1.99)	0.68
Non-Cardiac	52 (7.1)	50 (6.9)	1.04 (0.72, 1.51)	92 (9.5)	113 (11.4)	0.83 (0.64, 1.08)	0.34
Unknown	25 (3.4)	32 (4.4)	0.78 (0.47, 1.30)	46 (4.8)	47 (4.8)	1.00 (0.67, 1.49)	0.45
Atrial Fibrillation	83 (11.4)	81 (11.1)	1.02 (0.77, 1.37)	101 (10.4)	104 (10.5)	0.99 (0.77, 1.29)	0.87
Acute Renal Failure	106 (14.5)	118 (16.2)	0.90 (0.71, 1.14)	117 (12.1)	110 (11.1)	1.09 (0.85, 1.39)	0.28
Infection (bacteremia or pneumonia)	70 (9.6)	64 (8.8)	1.08 (0.78, 1.49)	88 (9.1)	88 (8.9)	1.02 (0.77, 1.35)	0.76
PCI†	139 (19.0)	130 (17.8)	1.07 (0.86, 1.33)	96 (9.9)	101 (10.2)	0.97 (0.75, 1.27)	0.58
CABG	9 (1.2)	15 (2.1)	0.60 (0.26, 1.36)	19 (2.0)	16 (1.6)	1.21 (0.63, 2.35)	0.19

*All-cause mortality within 30-days.

† Outcome PCI does not included PCI performed as part of the initial treatment plan for the index MI

‡ Effect estimates and interaction p-values from negative binomial model.

Heart failure defined as evidence of signs, symptoms, and treatment suggestive of congestive heart failure. Acute renal failure is site-reported.

Abbreviations: MI: myocardial infarction; Q1: quartile 1; Q3: quartile 3; EQ-5D: EuroQol 5 Dimension; SD: standard deviation; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft.

Figure Legends

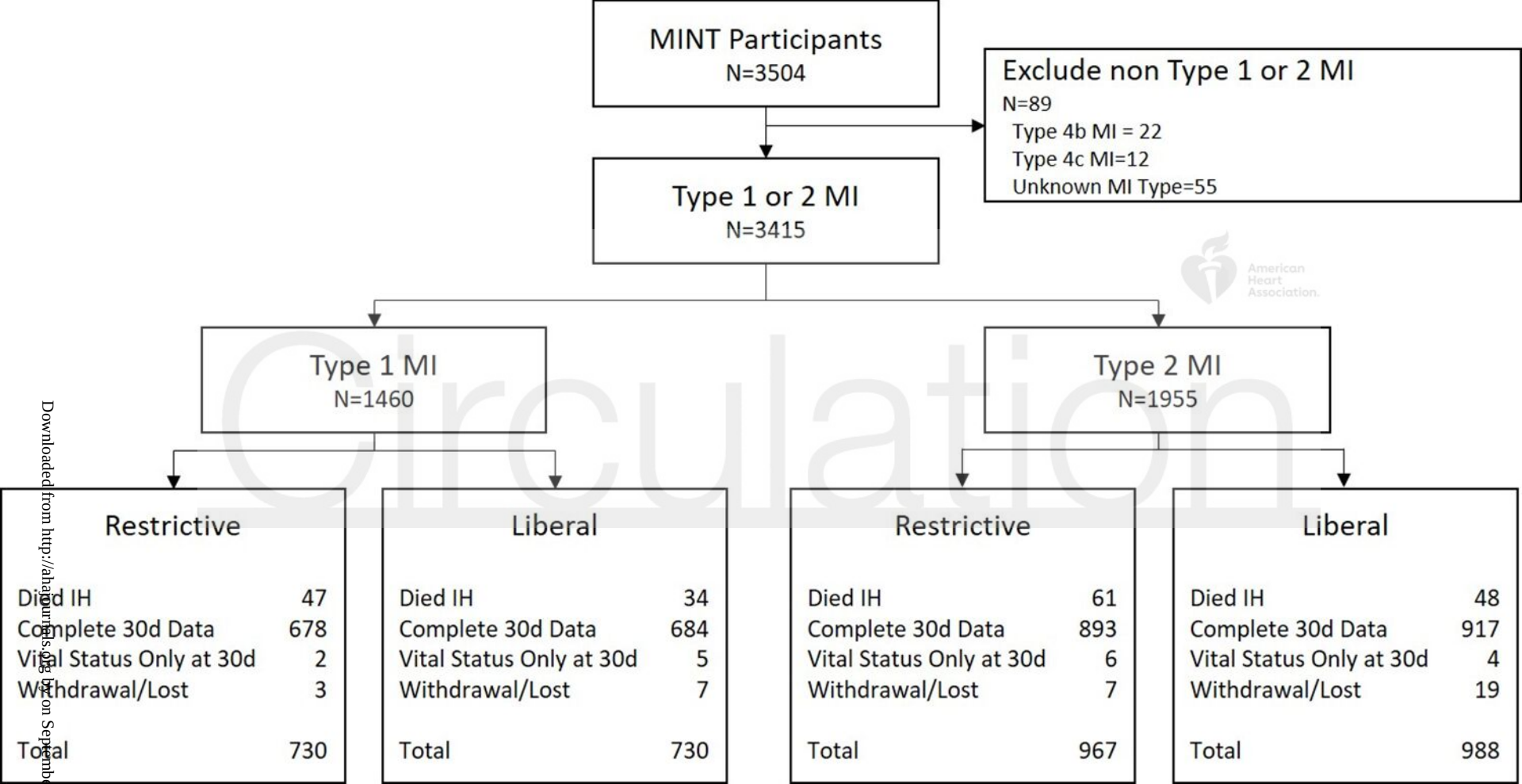
Figure 1. Study flowchart.

Figure 2: Forest Plot Comparing the Effect of Restrictive versus Liberal Transfusion Strategies by MI Type for Select Outcomes.

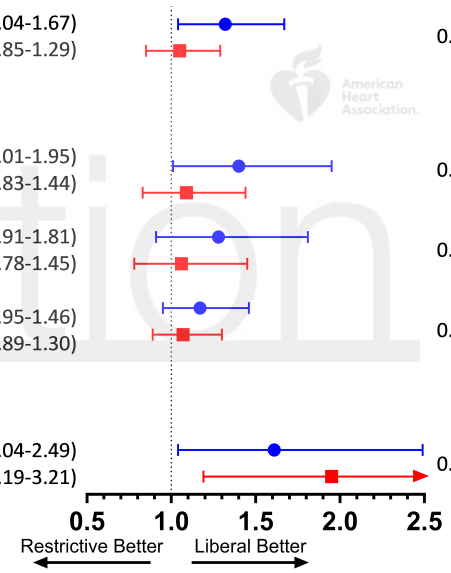
Abbreviations: CI: confidence interval; RR: risk ratio; MI: myocardial infarction; Death/MI/revasc/readmit: Death, MI, ischemia driven unscheduled revascularization, unscheduled readmission for ischemic cardiac diagnosis. All death outcomes represent deaths within 30 days.

Figure 3: Kaplan Meier Curves for Death or MI or Death at 30 Days.

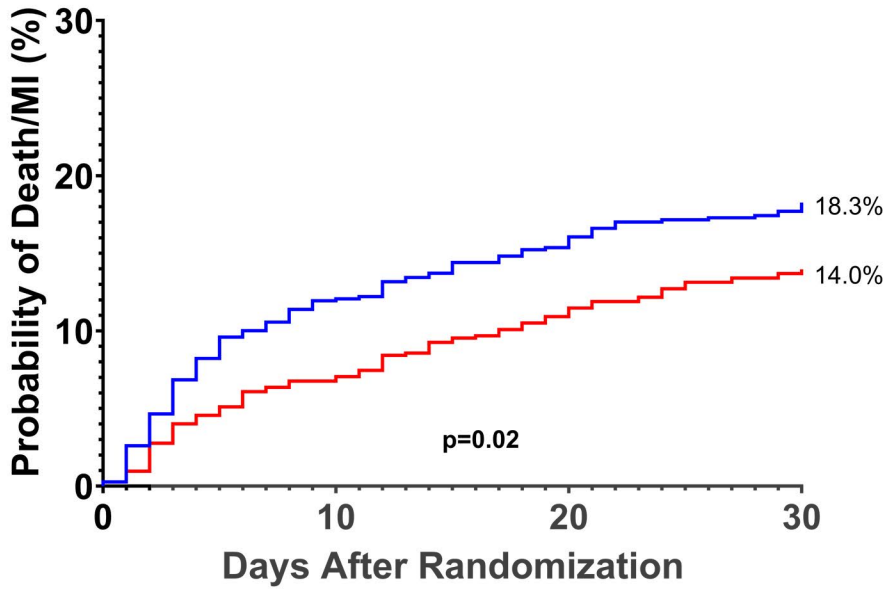
Abbreviations: MI: myocardial infarction



	Restrictive	Liberal	Absolute Risk Difference (%) (95% CI)	Risk Ratio (95% CI)	RR (95% CI)	P-value (interaction)
PRIMARY OUTCOME						
Death / MI						
Type 1	133/730 (18.2%)	101/730 (13.8%)	4.4 (0.6, 8.1)	1.32 (1.04-1.67)		0.16
Type 2	153/967 (15.8%)	149/988 (15.1%)	0.7 (-2.5, 4.0)	1.05 (0.85-1.29)		
SECONDARY OUTCOMES						
Death						
Type 1	77/730 (10.5%)	55/730 (7.5%)	3.0 (0.1, 6.0)	1.40 (1.01-1.95)		0.26
Type 2	93/967 (9.6%)	87/988 (8.8%)	0.8 (-1.8, 3.4)	1.09 (0.83-1.44)		
MI						
Type 1	68/730 (9.3%)	53/730 (7.3%)	2.1 (-0.8, 4.9)	1.28 (0.91-1.81)		0.43
Type 2	75/967 (7.8%)	72/988 (7.3%)	0.5 (-1.9, 2.8)	1.06 (0.78-1.45)		
Death/MI/revasc/readmit						
Type 1	148/730 (20.3%)	126/730 (17.3%)	3.0 (-1.0, 7.0)	1.17 (0.95-1.46)		0.54
Type 2	183/967 (18.9%)	174/988 (17.6%)	1.3 (-2.1, 4.7)	1.07 (0.89-1.30)		
OTHER OUTCOMES						
Cardiac death						
Type 1	50/730 (6.8%)	31/730 (4.2%)	2.6 (0.3, 5.0)	1.61 (1.04-2.49)		0.57
Type 2	44/967 (4.6%)	23/988 (2.3%)	2.2 (0.6, 3.8)	1.95 (1.19-3.21)		



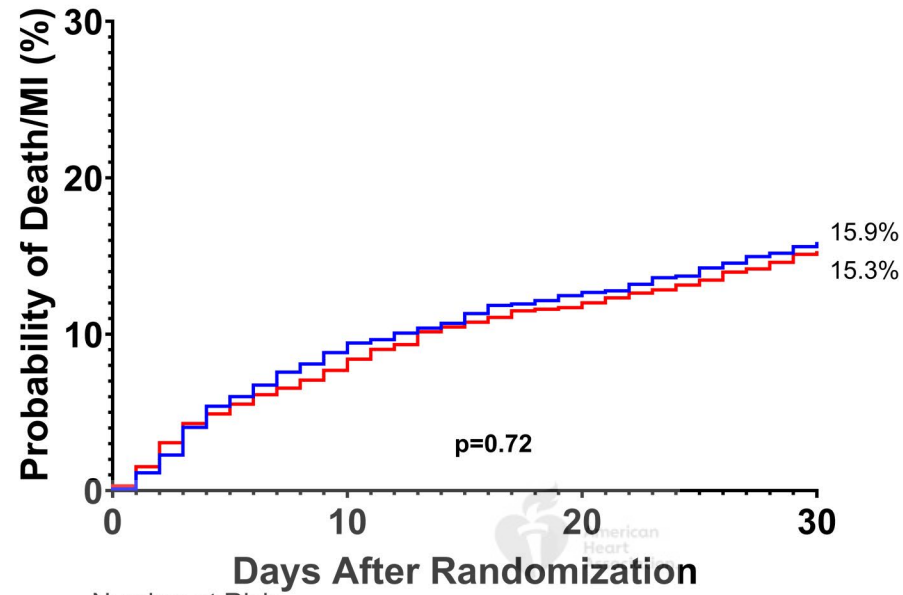
Death/MI Composite, Type 1



Number at Risk

Liberal	730	674	644	617
Restrictive	730	641	616	591

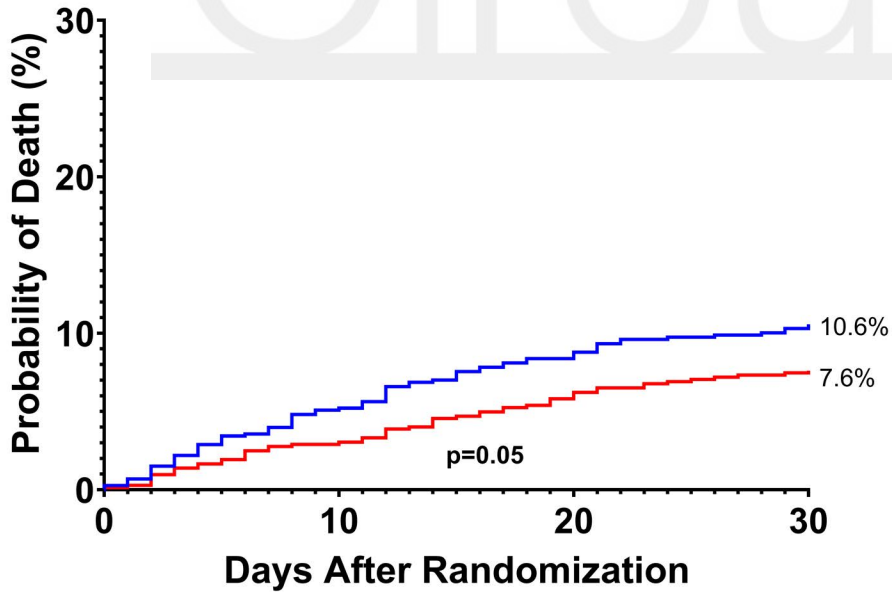
Death/MI Composite, Type 2



Number at Risk

Liberal	988	897	856	820
Restrictive	967	877	841	807

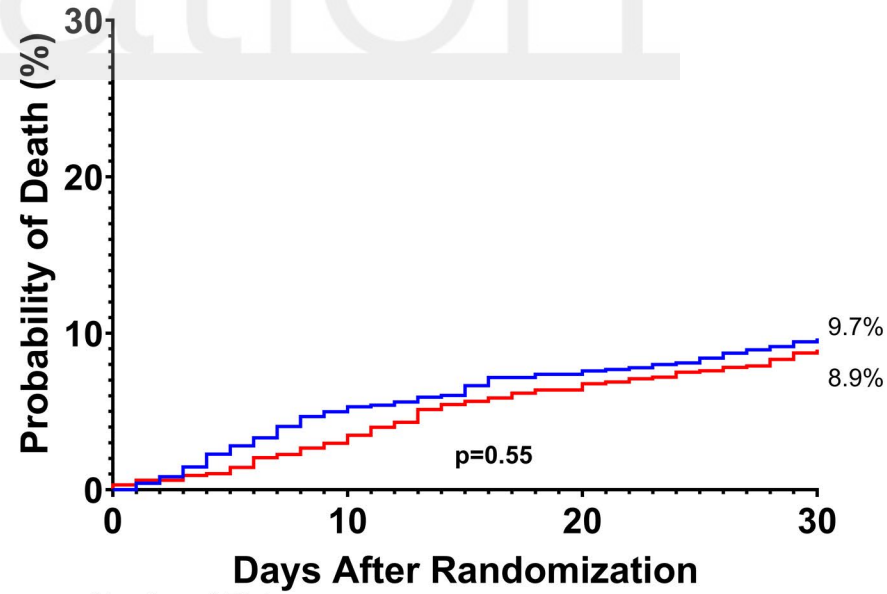
Death, Type 1



Number at Risk

Liberal	730	702	681	669
Restrictive	730	691	667	652

Death, Type 2



Number at Risk

Liberal	988	943	908	885
Restrictive	967	914	890	869