Liberal Versus Restrictive Transfusion Thresholds For Patients With Symptomatic Coronary Artery Disease

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Abstract

Background—Prior trials suggest it is safe to defer transfusion at hemoglobin levels above 7–8 g/dL in most patients. Patients with acute coronary syndrome may benefit from higher hemoglobin levels.

Methods—We performed a pilot trial in 110 patients with acute coronary syndrome or stable angina undergoing cardiac catheterization and a hemoglobin < 10 g/dL. Patients in the liberal transfusion strategy received one or more units of blood to raise the hemoglobin level ≥ 10 g/dL. Patients in the restrictive transfusion strategy were permitted to receive blood for symptoms from anemia or for a hemoglobin < 8 g/dL. The predefined primary outcome was the composite of death, myocardial infarction, or unscheduled revascularization 30 days post randomization.

Results—Baseline characteristics were similar between groups except age (liberal-67.3, restrictive-74.3). The mean number of units transfused was 1.6 in the liberal group and 0.6 in the restrictive group. The primary outcome occurred in 6 patients (10.9%) in the liberal group and 14 (25.5%) in the restrictive group (risk difference= 15.0%; 95% confidence interval of difference 0.7% to 29.3%; p=0.054 and adjusted for age p=0.076). Death at 30 days was less frequent in liberal group (n=1, 1.8%) compared to restrictive group (n=7, 13.0%; p=0.032).

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Conclusions—The liberal transfusion strategy was associated with a trend for fewer major cardiac events and deaths than a more restrictive strategy. These results support the feasibility of and the need for a definitive trial.

Introduction

Recently, published guidelines recommended that clinicians adopt a restrictive transfusion strategy in most acutely ill patients.[1, 2] Patients with coronary artery disease frequently become anemic and receive transfusion because they have pre-existing anemia, undergo invasive procedures, and receive multiple classes of anticoagulants.[3] Moderate anemia may result in increased rates of myocardial ischemia and infarction in patients with pre-existing coronary lesions that limit myocardial oxygen delivery.[4] Observational studies examining the association between transfusion and outcomes document an association between transfusion and increased.[5] These studies are limited by confounding (more severely ill patients also get more transfusions), making causal inferences impossible.[6, 7] However, there are no clinical trials to guide transfusion decisions in patients with acute coronary syndrome. The absence of high quality evidence contributes to the ongoing large variation in clinical practice[8]

Given this uncertainty, we undertook a multicenter pilot trial to evaluate the feasibility and outcomes of a liberal transfusion strategy compared to a restrictive transfusion strategy in patients with symptomatic coronary artery disease including acute coronary syndromes.

Methods

Study Population

We enrolled patients from 8 US hospitals from March 15, 2010 to May 8, 2012 who were: 1) greater than 18 years of age; 2) had either a) ST segment elevation myocardial infarction, b) Non ST segment elevation myocardial infarction, c) unstable angina, or d) stable coronary artery disease undergoing a cardiac catheterization; and 3) had a hemoglobin concentration less than 10 g/dL at the time of random allocation. We excluded patients who had active bleeding from cardiac catheterization puncture site, including retroperitoneal, judged to be uncontrolled or needing surgical repair or resulting in hemodynamic instability at any time during the index admission; symptoms of anemia at the time of randomization; or other health concerns (i.e., acute psychiatric illness) that would interfere with the reporting of symptoms and adherence to treatment protocols. The institutional review board at all participating hospitals approved the protocol. Written informed consent was obtained from all patients. An independent data and safety monitoring board also approved the protocol and monitored the trial.

Definitions of diagnostic categories—We defined an ST elevation myocardial infarction as symptoms of cardiac ischemia at rest with at least one episode lasting 10 minutes and who had ST-segment elevation of 1 mm or more in two or more contiguous leads, new left bundle-branch block, cardiac biomarkers (troponin or creatine kinase MB) above the upper limit of the normal range. We defined a Non ST elevation myocardial infarction as symptoms of cardiac ischemia at rest with at least one episode lasting 10 minutes AND a level of troponin or creatine kinase MB above the upper limit of the normal range. The diagnosis of unstable angina required symptoms of cardiac ischemia at rest with at least one episode lasting 10 minutes AND ST-segment depression of 0.01 mV or more or transient [<30-minute] ST-segment elevation of 0.1 mV or more in two or more contiguous leads), OR prior documented coronary artery disease (myocardial infarction, percutaneous cardiac intervention, coronary artery bypass graft surgery), or age >55 with diabetes mellitus or peripheral arterial disease and no biomarker elevation. For stable coronary artery disease,

we required the presence of coronary artery disease (one cardiac artery with at least 70% obstruction by visual inspection based on cardiac catheterization or undergoing a percutaneous cardiac intervention, during index admission).

Randomization and Intervention

Using an automated telephone system, we implemented a permuted block randomization process stratified by clinical site and clinical diagnosis (acute coronary syndrome or stable coronary artery disease).

Patients randomly allocated to the liberal transfusion strategy received one unit of packed red blood cells following randomization and then received enough blood to raise the hemoglobin concentration to 10 g/dL or above any time the hemoglobin concentration was detected to be below 10g/dL during the hospitalization for up to 30 days. Patients randomized to the restrictive transfusion strategy were permitted to receive a transfusion if they developed symptoms related to anemia. A blood transfusion was also permitted, but not required, in the absence of symptoms if the hemoglobin concentration fell below 8 g/dL. There was no lower threshold for which blood was required in the restrictive group. Blood was to be administered one unit at a time and the presence of symptoms reassessed. Only enough blood was given to relieve symptoms or to increase the hemoglobin concentration above 8 g/dL. Symptoms of anemia that were indications for transfusion included definite angina requiring treatment with sublingual nitroglycerin or equivalent therapy, and unexplained tachycardia or hypotension. Leukoreduction was not required.

Study Outcomes

The primary clinical endpoint was the composite rate of all cause mortality, myocardial infarction or unscheduled coronary revascularization up to 30 days after randomization. Secondary outcomes were: i) composite 6 month rates of all cause mortality, recurrent myocardial infarction, or unscheduled coronary revascularization. ii) Rates of each of the individual components of the composite outcome at 30 days and 6 months. iii) Mortality from cardiac cause at 30 days and 6 months. iv) Unscheduled hospital admission at 30 days and 6 months for any reason, for cardiac reason, or infection. v) Stroke at 30 days and 6 months. vi) Congestive heart failure at 30 days and 6 months. vii) Stent thrombosis at 30 days and 6 months. viii) Deep vein thrombosis or pulmonary embolism at 30 days and 6 months. ix) Composite 30 day and 6 month infection outcome of pneumonia and blood stream infection. x) Each of the components of the composite infection outcome at 30 days and 6 months. xi) Composite 30 day rates of all cause mortality, myocardial infarction, unscheduled coronary revascularization, and pneumonia. xii) Composite 6 month rates of all cause mortality, recurrent myocardial infarction, unscheduled coronary revascularization and pneumonia.

Outcome adjudications and event classifications were performed by a committee composed of two cardiologists or infectious disease specialist (for infections) masked to the assignment group. Disagreements were settled by consensus.

Vital status was determined by telephone follow-up and a review of medical records. Deaths were classified as definite cardiac death (sudden cardiac death, definite myocardial infarction, congestive heart failure, cardiac procedure, cardiogenic shock, stent thrombosis, or other), probable cardiac death (probable myocardial infarction, unwitnessed death beyond one hour, other), cerebrovascular (stroke, other), noncardiac death (infection, cancer, pulmonary, renal, accident, trauma/suicide, other).[9]

Myocardial infarction was defined using The Joint European Society of Cardiology/ American College of Cardiology Committee definitions.[10] The diagnosis of myocardial

infarction required rise and/or fall of cardiac biomarkers (preferably troponin) together with evidence of myocardial ischemia and either symptoms of ischemia or electrocardiogram changes indicative of new ischemia. Myocardial infarction was classified as ST-segment elevation or non-ST segment elevation.

Unstable angina was defined as: 1) the absence of elevated cardiac biomarkers and 2) presence of ischemic symptoms or electrocardiogram changes indicative of ischemia or 3) chest pain or angina equivalent leading to a coronary artery intervention (e.g., coronary angioplasty) and 4) hospitalization.

Re-admission to hospital was classified, overall, for primary cardiac diagnosis (acute coronary artery syndrome, congestive heart failure, or other), stroke, infection, or noncardiac.

Congestive heart failure required at least one of the following symptoms or signs, new or worsening including: dyspnea at rest, orthopnea, or paroxysmal nocturnal dyspnea, AND radiological evidence of heart failure or worsening heart failure AND additional/increased therapy. Hospitalization for congestive heart failure required an admission to an inpatient unit for at least a 12-hour stay (or a date change if the time of admission/discharge is not available). Biomarker results (e.g., brain natriuretic peptide) consistent with congestive heart failure were considered supportive but not diagnostic of the diagnosis.

Stent thrombosis[11] and pneumonia[12] were also adjudicated by committee. Based on medical record review, unscheduled coronary artery bypass surgery or percutaneous cardiac intervention, stroke, deep vein thrombosis or pulmonary embolism, laboratory confirmed blood stream infection were recorded.

We documented the number of eligible study subjects and enrollment rate. We characterized the patients randomized in the trial, and assessed the adherence to the transfusion protocol including the mean hemoglobin concentrations and the median number of units of red blood cell transfusions in the two study arms. The observed frequencies of the proposed primary and secondary outcomes were documented for study planning purposes.

Follow-up

We recorded daily hemoglobin concentrations for the first 3 days following randomization. We did not mandate daily measurements thereafter but recorded all other hemoglobin concentrations during the hospitalization (up to 30 days). We performed a baseline electrocardiogram and troponin concentration prior to randomization and collected all electrocardiograms, troponin and CK results obtained for clinical purposes. After randomization, troponin values were obtained every 12 hours for 1 day, and then daily for 2 days or until discharge from the hospital. An electrocardiogram was performed daily up to 3 days after randomization or discharge, or when clinically indicated.

We contacted all surviving patients discharged from the hospital by telephone at 30 days and 6 months after randomization to learn of their vital status and repeated hospital admissions. Follow-up telephone calls were performed centrally by the Clinical Coordinating Center. If a patient was admitted to the hospital, copies of medical records were obtained.

Sample size and Analysis

We planned to enroll 200 patients. However, we terminated recruitment with the approval the Data Safety Monitoring Committee at the end of 18 months. 110 patients had been enrolled providing sufficient information about implementation and rates of clinical outcomes to plan a larger trial.

We used the intention to treat principle for all randomized comparisons. Baseline characteristics of the patients in each of the two arms of the trial were described (e.g., means, standard deviations, medians, interquartile ranges, and proportions) and statistically compared using chi-square statistics for categorical variables and t-tests or Wilcoxon rank sum statistics for continuous variables. We compared the number of units transfused and the mean hemoglobin concentration each day between the randomized transfusion groups using a Spearman and Wilcoxon rank sum statistics.

We used a stratified Mantel-Haenszel chi-square statistic to compare event rates for the primary composite clinical outcome between treatment groups; alpha level of 0.05 was used for the primary outcome. As a sensitivity analysis, a logistic regression model was created to estimate the assigned treatment effect on the primary composite outcome adjusting for measured baseline variables that were significantly different (p<0.05) between the two assigned groups. The other pre-specified 30-day clinical events were compared using standard chi-square statistics (since there were often too few events for stratification). Randomized comparisons of time to event outcomes at 6-months were analyzed with Kaplan Meier estimates and log rank statistics. An alpha level of 0.01 was used for all secondary outcomes to adjust for multiple comparisons.

Results

A total of 1920 patients with a hemoglobin concentration less than 11 g/dL were screened. The most common reasons for exclusion (Figure 1) were the hemoglobin > 10 g/dL (n=644), patient declined (n=198), cardiac surgery was planned within 30 days (n=156), patient was unable to provide consent (n=144), or severe illness (n=139). The incidence of hemoglobin concentration < 10 g/dL was 24.2%. Among patients approached, consent was obtained in 25% of patients. We randomly allocated 110 patients; Robert Wood Johnson University Hospital= 32, Montefiore-Weiler Division=24, Rhode Island Hospital=21, Montefiore-Moses Division=15, University of Pittsburgh Medical Center-Presbyterian Hospital=12, Duke University=2, University of Pittsburgh Medical Center-Passavant Hospital=2, Brigham and Women's Hospital=2. One patient was lost to follow-up (Figure 1).

Study Population

Clinical characteristics (table 1) were similar between the two transfusion groups with exception of age: 74.3 years in the restrictive group compared to 67.3 years in the liberal group; p=0.004. Pre-existing anemia was present in 41% of patients and active bleeding in only 14% of patients.

Hemoglobin Levels and Transfusion

The mean hemoglobin concentration was between 1.3 and 1.8 g/dL higher in the liberal transfusion group than restrictive transfusion group (all p-value < 0.001) (Table 2). On average, the patients in the liberal arm received about 3 times as many transfusions as those in the restrictive arm (total number of units 87 versus 27; p < 0.001). Of note, 72.7% of patients in the restrictive arm did not receive blood transfusion. Consistent with the protocol, the mean hemoglobin concentration at the time transfusion was implemented was 1.4 g/dL higher in the liberal group than in the restrictive group (P<0.001) (Table 2).

Violations in the transfusion protocol occurred in five patients (9.1%) in the liberal group and one patient (1.8%) in the restrictive group. The most common reason for protocol

violation was insufficient time to administer a transfusion prior to discharge in the liberal group.

Thirty day and 6-month Study Outcomes

The pre-defined primary outcome of death, myocardial infarction, and unscheduled revascularization occurred within 30 days in six patients (10.9%) in the liberal-transfusion strategy and 14 (25.5%) in the restrictive-transfusion strategy (risk difference= 15.0%; 95% confidence interval of difference 0.7% to 29.3%; p=0.054). Death at 30 days was less frequent among liberal transfusion patients (n=1, 1.8%) compared to restrictive transfusion patients (n=7, 13.0%); risk difference=11.1%, 95% confidence interval of difference 1.5% to 20.8%; p=0.032). All deaths were classified as cardiac. Most of the other adverse cardiac outcomes were more frequent in restrictive transfusion compared with the liberal transfusion group (Table 3).

The trend favoring liberal transfusion persisted throughout follow-up although the risk of death, myocardial infarction, unscheduled revascularization was not statistically different in the two groups (27.3% Liberal versus 37.0% Restrictive; risk difference=9.7%, 95% confidence interval of difference -5.3% to 24.7%; p=0.26) (Figure 2). Similarly, the risk of death and of death or myocardial infarction did not differ significantly by transfusion strategy (death 12.7% Liberal versus 18.5% Restrictive, p=0.26; death/MI 23.6% Liberal versus 33.2% Restrictive p=0.28; Figure 3B and 3C). The curves suggest that the event rates separate by 30 days and remain parallel for 6 months.

We performed a post-hoc analysis to adjust for age, the one variable that was significantly different between assigned groups. The unadjusted odds of death, myocardial infarction, or unscheduled revascularization within 30 days was higher in the restrictive group than the liberal group (odds ratio=2.86, 95% confidence interval, 1.01 to 8.12, p=0.049). Adjusting for age, the 30-day death, myocardial infarction, or unscheduled revascularization estimate for the restrictive versus liberal strategy was slightly attenuated and was not statistically significant (odds ratio=2.65; 95% confidence interval 0.90 to 7.78; p=0.076).

Discussion

In this multicenter pilot trial, patients transfused using a restrictive strategy had more than 2 times the rate of death, myocardial infarction or unscheduled revascularization in the first 30 days of care compared with those transfused using a liberal strategy. Although there was a trend strongly favoring the liberal arm, we believe these data should be interpreted cautiously. The study was small and the apparent impact of transfusion was much larger than expected. Furthermore, the restrictive group was 6 years older than the liberal group.

We successfully implemented this pilot randomized trial in eight US centers. We noted that patients hemoglobin levels less than 10 g/dL were common, occurring in 24.2% of patients with acute coronary syndrome. In adopting our transfusion strategies hemoglobin levels averaged 1.5 g/dL higher in the liberal transfusion group as compared to the restrictive transfusion group. Also, the liberal transfusion group received 3 fold more blood transfusions. Adherence to the protocol exceeded 94% and follow-up at six months was achieved in 99.1% of patients. The observed rates for death and key cardiac outcomes were high.

Prior to initiating the pilot, we anticipated enrolling a large number of patients with anemia that resulted from bleeding. Instead, we found bleeding to be infrequent (only 14%) and pre-existing anemia to be common (41%) resulting in fewer patients eligible for the trial. The low rate of bleeding may reflect the widespread use of lower risk anticoagulants. Thus, we

tested the impact of transfusion in patients with chronic anemia or modest bleeding rather than the hemorrhaging patient. Importantly, these patients had extensive co-morbidity, and as we found in this trial, anemia is a marker for poor outcome in patients with acute coronary disease.[3]

We were unable to blind the treating physician or patient to the transfusion strategy. However, we did classify outcomes blinded to treatment assignment. We do not know if process of care differed between the two groups of patients although adherence to the protocol was similar.

We did learn several important lessons from the pilot that will inform the conduct of larger trial. We plan to reduce exclusions (patients who could not consent for themselves, patients with hemodynamic instability, and patients with life expectancy less than 6 months) to simplify the enrollment process, increase enrollment of patients at risk of adverse consequences of both anemia and transfusion, and enhance generalizability. We will also include patients with demand ischemia because they represent about 15% of patients with acute myocardial infarction and may benefit from a liberal approach to transfusion

In the critically ill and in surgery patients with stable cardiovascular disease or cardiac risk factors, prior randomized trials support that a more restrictive approach to transfusion leads to similar clinical outcomes compared to a liberal approach.[13–15] However, patients with acute coronary disease may require higher hemoglobin concentrations than patients without cardiovascular disease. Oxygen delivery to the myocardium is flow dependent since the heart extracts a high percentage of oxygen, and myocardial ischemia and ventricular arrhythmias may be precipitated by anemia.[16–18]

In contrast to the findings of our trial, the only other randomized trial comparing transfusion triggers in 45 patients with acute coronary syndrome documented an increase in the combined rates of death, recurrent myocardial infarction, and new or worsening congestive heart failure in liberal transfusion group.[19] The apparent difference seen in that study was explained by increase risk of congestive heart failure in the liberal group. Observational studies demonstrate conflicting results with one study finding benefit of liberal transfusion[20] but most studies suggesting harm of transfusion.[5] The inconsistent results among these two small clinical trials and multiple observational studies further support equipoise on this issue and underscore the need for a definitive trial.

This study was designed as a pilot trial, and thus, the primary goals were to assess feasibility of enrollment, characterize the patient population with coronary disease and anemia, identify protocol challenges, and estimate event rates. While our results are provocative, this pilot trial was not designed to enroll enough patients to answer the transfusion dilemma currently facing clinicians in practice.

This pilot was successful in recruiting anemic ill patients predominately with acute coronary syndrome and implementing transfusion protocol and follow-up. The MINT pilot trial results suggest that liberal transfusion strategy might improve outcome, although there were few events, and large treatment differences that could be explained by chance. A large multicenter trial is feasible and essential to definitively establish whether patients with acute coronary syndrome benefit from liberal transfusion.

Literature Cited

1. Napolitano LM, Kurek S, Luchette FA, Corwin HL, Barie PS, Tisherman SA, et al. Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. Crit Care Med. 2009; 37(12): 3124–3157. [PubMed: 19773646]

2. Carson JL, Grossman BJ, Kleinman S, Tinmouth AT, Marques MB, Fung MK, et al. Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB*. Ann Intern Med. 2012; 157(1): 49–58. [PubMed: 22751760]

3. Salisbury AC, Amin AP, Reid KJ, Wang TY, Masoudi FA, Chan PS, et al. Hospital-acquired anemia and in-hospital mortality in patients with acute myocardial infarction. American heart journal. 2011; 162(2):300–309. e3. [PubMed: 21835291]

4. Carson JL, Duff A, Poses RM, Berlin JA, Spence RK, Trout R, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. Lancet. 1996; 348(9034):1055–1060. [PubMed: 8874456]

5. Chatterjee S, Wetterslev J, Sharma A, Lichstein E, Mukherjee D. Association of Blood Transfusion With Increased Mortality in Myocardial Infarction: A Meta-analysis and Diversity-Adjusted Study Sequential Analysis. JAMA internal medicine. 2013; 173(2):132–139. [PubMed: 23266500]

6. Middelburg RA, van de Watering LM, van der Bom JG. Blood transfusions: good or bad? Confounding by indication, an underestimated problem in clinical transfusion research. Transfusion. 2010; 50(6):1181–1183. [PubMed: 20456689]

7. Carson JL, Hebert PC. Here We Go Again-Blood Transfusion Kills Patients?: Comment on "Association of Blood Transfusion With Increased Mortality in Myocardial Infarction: A Meta-analysis and Diversity-Adjusted Study Sequential Analysis". JAMA internal medicine. 2013; 173(2):139–141. [PubMed: 23266861]

8. Alexander KP, Chen AY, Wang TY, Rao SV, Newby LK, LaPointe NM, et al. Transfusion practice and outcomes in non-ST-segment elevation acute coronary syndromes. Am Heart J. 2008; 155(6): 1047–1053. [PubMed: 18513518]

9. Chaitman BR, Hardison RM, Adler D, Gebhart S, Grogan M, Ocampo S, et al. The Bypass Angioplasty Revascularization Investigation 2 Diabetes randomized trial of different treatment strategies in type 2 diabetes mellitus with stable ischemic heart disease: impact of treatment strategy on cardiac mortality and myocardial infarction. Circulation. 2009; 120(25):2529–2540. [PubMed: 19920001]

10. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, et al. Universal definition of myocardial infarction. Circulation. 2007; 116(22):2634–2653. [PubMed: 17951284]

11. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007; 115(17):2344–2351. [PubMed: 17470709]

12. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008; 36(5):309–332. [PubMed: 18538699]

13. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. New England Journal of Medicine. 1999; 340(6):409–417. [see comments]. [PubMed: 9971864]

14. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med. 2011; 365(26):2453–2462. [PubMed: 22168590]

15. Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane database of systematic reviews. 2012; 4 CD002042.

16. Anderson HT, Kessinger JM, McFarland WJ Jr, Laks H, Geha AS. Response of the hypertrophied heart to acute anemia and coronary stenosis. Surgery. 1978; 84(1):8–15. [PubMed: 149386]

17. Hagl S, Heimisch W, Meisner H, Erben R, Baum M, Mendler N. The effect of hemodilution on regional myocardial function in the presence of coronary stenosis. Basic Research in Cardiology. 1977; 72(4):344–364. [PubMed: 901378]

18. Wilkerson DK, Rosen AL, Sehgal LR, Gould SA, Sehgal HL, Moss GS. Limits of cardiac compensation in anemic baboons. Surgery. 1988; 103(6):665–670. [PubMed: 3375993]

19. Cooper HA, Rao SV, Greenberg MD, Rumsey MP, McKenzie M, Alcorn KW, et al. Conservative versus liberal red cell transfusion in acute myocardial infarction (the CRIT Randomized Pilot Study). The American journal of cardiology. 2011; 108(8):1108–1111. [PubMed: 21791325]

20. Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. New England Journal of Medicine. 2001; 345(17):1230–1236. [PubMed: 11680442]
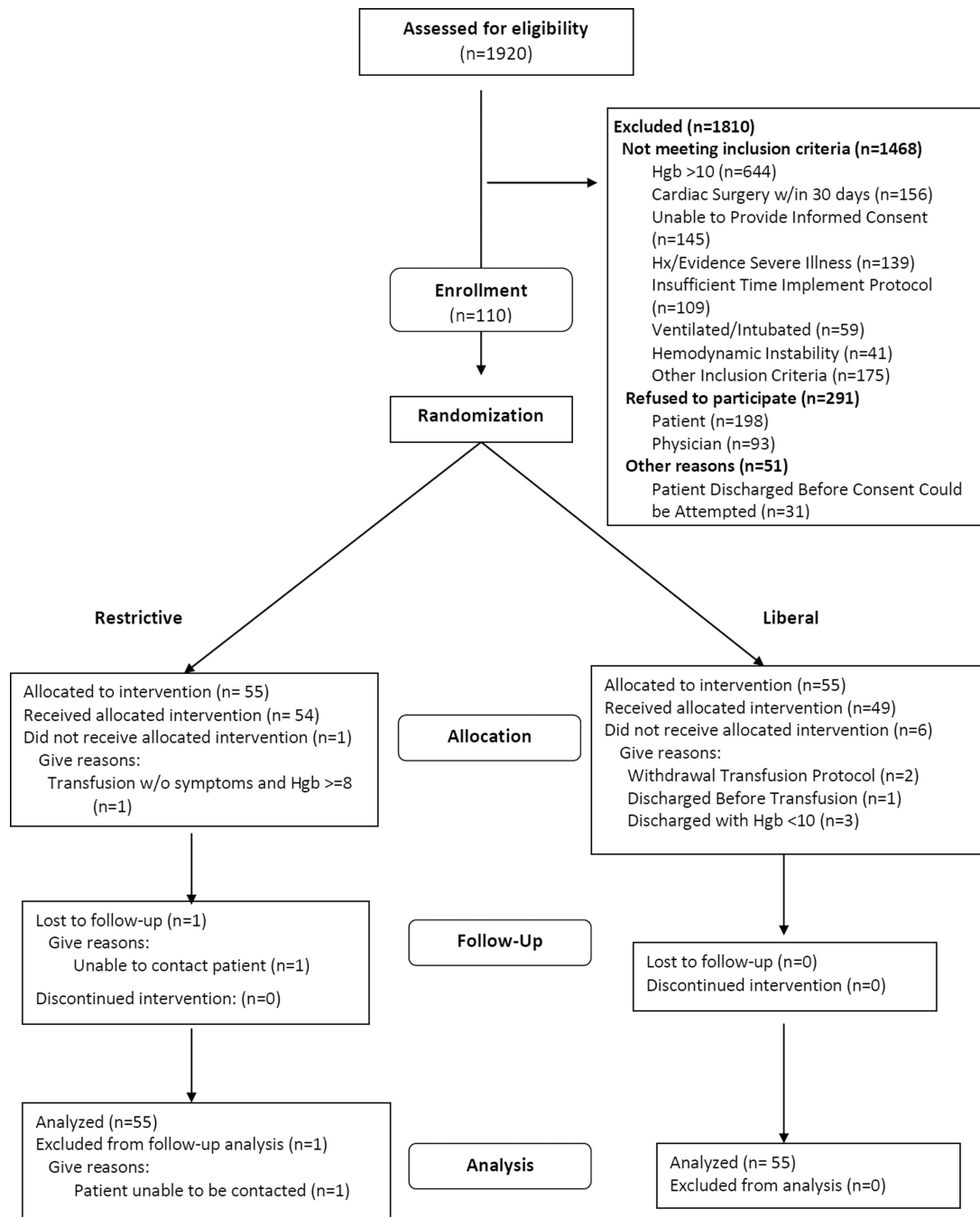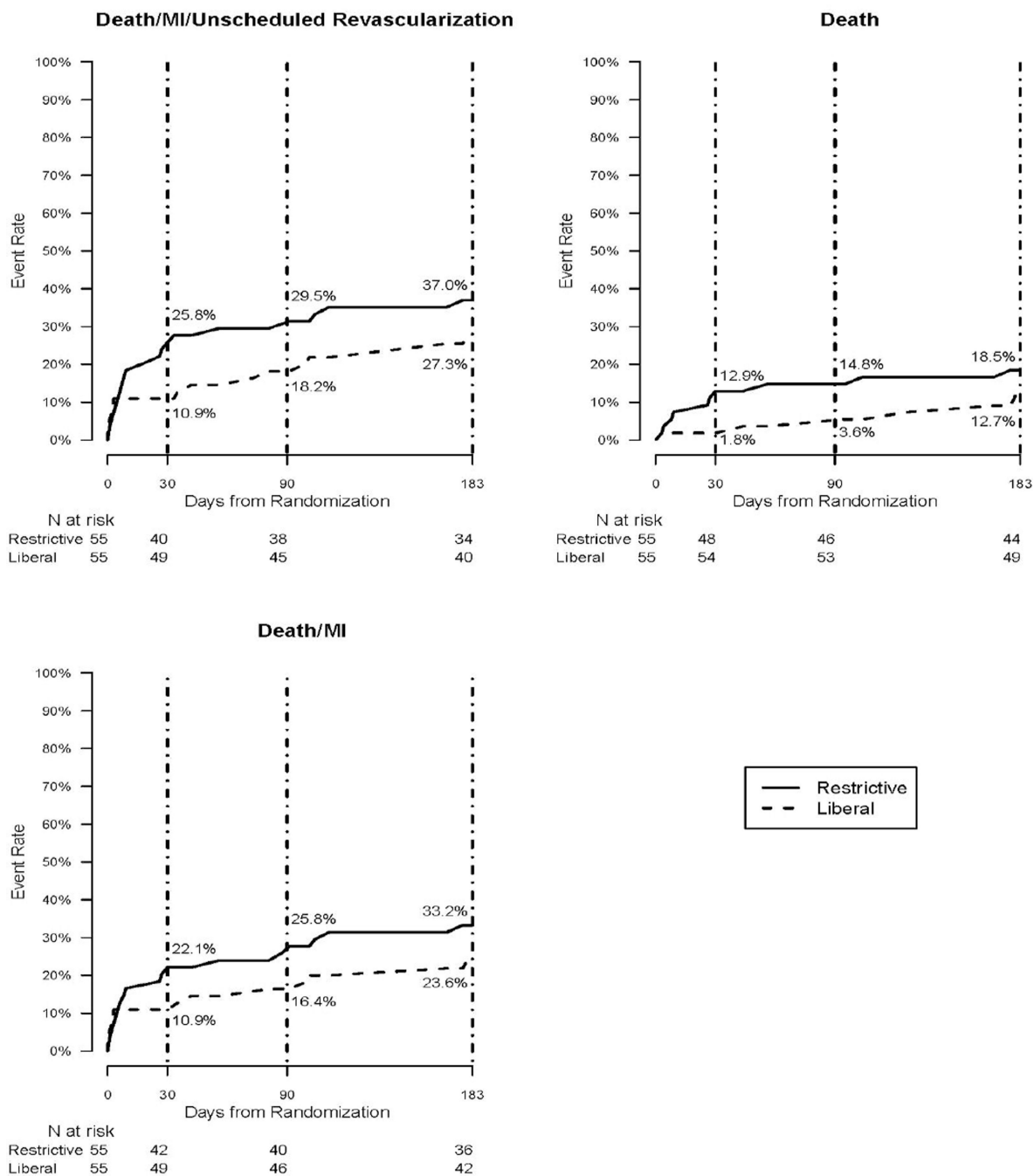
Figure 1.

Death/MI/Unscheduled Revascularization

Death

Death/MI

Figure 2.
Outcomes at 6 months

Table 1

MINT Trial Baseline Characteristics

	All Patients N=110	Liberal N=55	Restrictive N=55
ST Elevation Myocardial Infarction, %	30.0	30.9	29.1
Non ST Elevation Myocardial Infarction, %	42.7	38.2	47.3
Unstable Angina, %	14.6	14.6	14.6
Stable Coronary Artery Disease, %	12.7	16.4	9.1
Age, mean (sd)[*]	70.8 (12.8)	67.3 (13.6)	74.3 (11.1)
Female, %	50.0	49.1	50.9
White, %	72.7	70.9	74.6
Black, %	20.0	18.2	21.8
Other, %	7.3	10.9	3.6
Prior Percutaneous Coronary Intervention, %	41.8	43.6	40.0
Prior Coronary Artery Bypass Graft Surgery, %	30.9	29.1	32.7
Prior Myocardial Infarction, %	27.3	23.6	30.9
Cerebrovascular Accident, %	8.2	7.3	9.1
Bleeding, %	13.6	10.9	16.4
Congestive Heart Failure, %	30.0	25.5	34.6
Hypertension, %	83.6	85.5	81.8
Diabetes Mellitus (treated with oral meds or insulin), %	57.3	61.8	52.7
Peripheral Arterial Disease, %	9.1	10.9	7.3
Anemia, %	40.9	41.8	40.0
Hypercholesterolemia/Hyperlipidemia, %	67.3	69.1	65.5
Renal Failure/Insufficiency, %	32.7	34.6	30.9
BMI (kg/m^2), mean(sd)	28.7 (6.7)	29.1 (7.2)	28.3 (6.1)
Systolic BP(mmHg) - Most recent prior to randomization, mean (sd)	126.8 (20.6)	125.7 (20.2)	127.8 (21.0)
Congestive Heart Failure at admission, %	22.7	21.8	23.6
Current Tobacco Smoking, %	13.6	12.7	14.6
In-hospital Medication-Prior to randomization,%			
aspirin	90.0	92.7	87.3
clopidogrel	80.9	81.8	80.0
warfarin	3.6	7.3	0.0
heparin	60.0	60.0	60.0
statins	66.4	65.5	67.3
Angiogram within past year, %	94.5	94.5	94.5
Ejection Fraction %, mean (sd) (n=81)	47.9 (15.7)	47.1 (16.4)	48.8 (15.3)
Abnormal (<50%), % (n=87)	47.1	50.0	44.4
Number of Cardiac Vessels 50% Obstruction, %			
0 or 1	31.4	31.4	31.4

	All Patients N=110	Liberal N=55	Restrictive N=55
2	25.5	31.4	19.6
3	43.1	37.3	49.0
PCI –during hospitalization and prior to randomization, %	55.5	63.6	47.3

*
p=0.004

Table 2

Hemoglobin levels and transfusions during initial hospitalization

	Liberal (N=55)	Restrictive (N=55)	p-value
Hemoglobin levels (g/dL) mean (sd)			
Baseline prior to randomization	9.18 (0.64)	8.97 (0.73)	0.24
Day 1	10.30 (1.00)	9.03 (0.82)	<0.001
Day 2	10.78 (0.78)	8.98 (0.80)	<0.001
Day 3	10.64 (0.71)	9.12 (0.75)	<0.001
Units of blood per patient			<0.001
0	3 (5.5%)	40 (72.7%)	
1	33 (60.0%)	9 (16.4%)	
2	9 (16.4%)	3 (5.5%)	
3 or more	10 (18.2%)	3 (5.5%)	
Units of blood per patient, mean (sd)	1.58(1.13)	0.49 (1.03)	<0.001
Total number of units transfused in the trial	87	27	
Age of blood (days) mean (sd)	24.6 (9.1)	23.4 (10.9)	0.48
Leukoreduction (%)	95.4%	92.3%	0.54
Hemoglobin immediately prior to transfusion (g/dL) mean (sd)	9.30 (0.66)	7.89 (0.80)	<0.001

Table 3

MINT Trial Adjudicated 30 day Events

Pilot Study Endpoints	Overall N = 109		Liberal N=55		Restrictive N=54[†]		p-value [*]	Absolute risk difference At 30 days (95% CI)	Relative risk (95% CI)
	n		**n**		**n**				
Death/MI/Unscheduled Revascularization	20	18.3%	6	10.9%	14	25.9%	0.054 [**]	15.0% (0.7%, 29.3%)	2.38 (0.99,5.73)
Death [****]	8	7.3%	1	1.8%	7	13.0%	0.032	11.1% (1.5%, 20.8%)	7.13 (0.91,56.02)
Myocardial Infarction	12	11.0%	5	9.1%	7	13.0%	0.52	3.9% (−7.9%, 15.6%)	1.43 (0.48, 4.22)
Unscheduled Coronary Revascularization [***]	2	1.8%	0	0.0%	2	3.7%	0.24	3.7% (−1.3%, 8.7%)	--
Unscheduled Hospital Admission									
Any Reason	26	23.8%	9	16.4%	17	31.5%	0.064	15.1% (−0.7%, 30.9%)	1.92 (0.94, 3.93)
Cardiac Reason	11	10.1%	3	5.5%	8	14.8%	0.10	9.3% (−1.9%, 20.6%)	2.72 (0.76, 9.70)
Infection	2	1.8%	0	0.0%	2	3.7%	0.24		
Stroke [**]	1	0.9%	1	1.8%	0	0.0%	1.0		
Congestive Heart Failure	9	8.2%	2	3.6%	7	13.0%	0.093	9.3% (−0.9%, 19.6%)	3.56 (0.78, 16.40)
Stent Thrombosis	0	0.0%	0	0.0%	0	0.0%	--		
DVT or Pulmonary Embolism [**]	1	0.9%	1	1.8%	0	0.0%	1.0		
Pneumonia or Blood Stream Infection [**]	2	1.8%	0	0.0%	2	3.7%	0.24		
Pneumonia	2	1.8%	0	0.0%	2	3.7%	0.24		
Blood Stream Infection [**]	0	0.0%	0	0.0%	0	0.0%	--		
Death/MI/Unscheduled Revascularization/Pneumonia	22	20.2%	6	10.9%	16	29.6%	0.015	18.7% (4.0%, 33.4%)	2.72 (1.15, 6.42)
Death/MI	18	16.5%	6	10.9%	12	22.2%	0.11	11.3% (−2.5%, 25.1%)	2.04 (0.82,5.04)
Unstable Angina	5	4.6%	1	1.8%	4	7.4%	0.21	5.6% (−2.2%, 13.4%)	4.07 (0.47,35.29)
Death/MI/Unstable Angina	23	21.1%	7	12.7%	16	29.6%	0.031	16.9% (1.9%, 31.9%)	2.32 (1.04,5.21)
Death/MI/Unscheduled Cardiac Admission	26	23.9%	9	16.4%	17	31.5%	0.064	15.1% (−0.7%, 30.9%)	1.92 (0.94, 3.93)

[*] Fisher exact test p-value reported when any cell had less than 5 observations

[**] Cochran –Mantel-Haenszel p-value reported

[***] Events not classified by adjudication committee.

†One patient had no MINT contact after 3 days and was excluded from the analysis.

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All deaths were classified as cardiac