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Restrictive versus Liberal Transfusion in Patients with Diabetes Undergoing Cardiac Surgery: An Open-Label Randomized, Blinded Outcome Evaluation Trial

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Structured Abstract:

Aim: To characterize the association between diabetes and transfusion and clinical outcomes in cardiac surgery, and to evaluate whether restrictive transfusion thresholds are harmful in these patients.

Materials and methods: The multinational, open-label, randomized controlled TRICS-III trial assessed a restrictive transfusion strategy (hemoglobin [Hb] transfusion threshold <75 g/L) compared to a liberal strategy (Hb <95g/L for operating room or ICU; or <85g/L for ward) in patients undergoing cardiac surgery on cardiopulmonary bypass with a moderate-to-high risk of death (EuroSCORE ≥6). Diabetes status was collected preoperatively. The primary composite outcome was all-cause death, stroke, myocardial infarction, and new-onset renal failure requiring dialysis at 6 months. Secondary outcomes included components of the composite outcome at 6 months, and transfusion and clinical outcomes at 28 days.

Results: Of the 5092 patients analyzed, 1396 (27.4%) had diabetes (Restrictive: n=679, Liberal n=717). Patients with diabetes had more cardiovascular disease than patients without diabetes. Neither the presence of diabetes (OR [95%CI]1.10[0.93-1.31]) or the restrictive strategy increased the risk for the primary composite outcome (diabetes OR [95%CI]1.04[0.68-1.59] vs. no diabetes OR 1.02[0.85-1.22],$p_{interaction}$=0.92). In patients with versus without diabetes, a restrictive transfusion strategy was more effective at reducing red blood cell transfusion (diabetes OR [95%CI] 0.28[0.21-0.36]; no diabetes OR [95%CI] 0.40[0.35-0.47];$p_{interaction}$=0.04).

Conclusions: The presence of diabetes did not modify the effect of a restrictive transfusion strategy on the primary composite outcome, but improved its efficacy on red cell transfusion.

Restrictive transfusion triggers are safe and effective in patients with diabetes undergoing cardiac surgery.

Clinicaltrials.gov registration: NCT02042898

Introduction:

The association between diabetes and transfusion outcomes is not well characterized in patients undergoing cardiac surgery. Current clinical practice guidelines recommend a restrictive hemoglobin (Hb) trigger of <75g/L for red blood cell (RBC) transfusion in patients undergoing cardiac surgery;[1,2] however, it remains unclear whether restrictive transfusion thresholds are safe for patients with diabetes. Patients with diabetes have abnormalities in blood cell structure and function, contributing to impaired platelet function[3] resulting in increased antiplatelet agent use, RBC-mediated endothelial dysfunction,[4] increased circulation of proinflammatory cell types,[5] and regenerative cell exhaustion.[6] These factors may result in an increase in bleeding risk, an impairment in the ability for blood cell regeneration, and vasculopathy; and ultimately may result in microvascular perfusion-related morbidity and mortality.[6] The additional risk from macrovascular and microvascular complications of diabetes may result in clinicians selectively transfusing these patients at higher hemoglobin thresholds, potentially exposing these patients to unnecessary transfusions.[7]

Furthermore, presence of diabetes is associated with a higher risk for fatal acute coronary events,[8] and optimal transfusion management may mitigate some of this risk. There is controversy as to the optimal transfusion threshold for managing patients with acute coronary syndromes. The results from small randomized studies suggest that liberal transfusion triggers may be favoured in patients with acute myocardial infarction.[9] Conversely, the results from a recent larger randomized study have been inconclusive.[10,11]

We therefore conducted a planned analysis of the transfusion requirements in cardiac surgery (TRICS-III) trial[12,13] to: 1) characterize the association of diabetes with transfusion and postoperative outcomes in a contemporary multinational cardiac surgical cohort; and to 2)

evaluate if a restrictive transfusion strategy, as compared to a liberal strategy, is harmful in patients with diabetes undergoing cardiac surgery.

Materials and Methods:

Study design:

TRICS-III was an open-labelled, randomized, controlled, non-inferiority trial comparing a restrictive to liberal transfusion strategy in patients undergoing cardiac surgery on cardiopulmonary bypass with a moderate-to-high risk of death. The TRICS-III study design[14] and primary findings[12,13] have been previously reported (NCT02042898). From January 2014 to March 2017, 5035 patients were randomized from 73 sites, representing 19 countries and 6 continents. Additionally, this analysis included 208 patients who were randomized in the TRICS-II pilot study, whose data were kept blinded until TRICS-III study completion. Appropriate ethical board review and approval was obtained for each participating site.

The trial included adults undergoing cardiac surgery on cardiopulmonary bypass with a EuroSCORE I value ≥6. Patients were randomized 1:1 via a web-based system, stratified according to centre, in randomly permutated computer-generated blocks. Patients randomized to the restrictive transfusion strategy were administered RBC transfusions when Hb <75g/L in the operating room, in the ICU, or on the ward; and patients randomized to the liberal strategy were administered RBC transfusions when Hb <95g/L in the operating room or intensive care unit, or <85 g/L on the ward. Patients received transfusions as per their allocated treatment protocol until the first of hospital discharge or 28 days after surgery. It was not possible to mask the healthcare staff and patients to the assigned transfusion strategy; however, participants were not actively informed of their treatment assignment and outcome adjudicators were blinded to the treatment allocation. Diabetes status as a binary variable was collected during the preoperative assessment visit (before randomization) as reported by patient history. Patients who were identified as having diabetes were classified as either requiring insulin or not. The TRICS-III study did not

include a specific diabetes screening procedure, and thus did not collect information on type of diabetes, duration of diabetes, or glycated hemoglobin levels.

Outcomes:

The primary outcome for this study was a composite of all-cause mortality, stroke, myocardial infarction, and new-onset renal failure requiring dialysis at 6 months after surgery. Secondary clinical outcomes included components of the primary composite, as well as an expanded composite outcome, and its components of myocardial revascularization and healthcare utilization (defined as emergency department visits and/or and hospital readmission) at 6 months.

Bleeding outcomes, RBC transfusion, ICU and hospital length of stay, duration of mechanical ventilation, prolonged low cardiac output state, infection, gut infarction, seizure, acute kidney injury (KDIGO criteria), encephalopathy, and delirium were collected until the first of hospital discharge or 28 days.

The primary objectives for this study were to: 1) characterize the association between presence of diabetes and transfusion and clinical outcomes; and 2) evaluate whether a restrictive transfusion strategy was harmful in patients with diabetes. We performed a modified intention-to-treat analysis which included all randomized patients who underwent their planned surgical procedure and who did not withdraw consent preoperatively.

Statistical Analysis:

The association between presence of diabetes and binary outcomes (composite outcomes and their components at 6 months; transfusion outcomes, prolonged low output state, infection, gut infarction, seizure, acute kidney injury, encephalopathy, and delirium at 28 days) was evaluated with logistic regression models adjusted for treatment group, prognostic factors (sex, age,

preoperative renal function, preoperative chronic pulmonary disorder, left ventricular function, and preoperative hemoglobin level), and mediators (type of surgery). Time-to-event outcomes (duration of mechanical ventilation, ICU length of stay, and hospital length of stay) were censored at 28 days, and were analyzed using adjusted cox proportional-hazards models. Bleeding outcomes were analyzed using adjusted linear regression models. Count components from adjusted zero-inflated Poisson regression models were used to estimate relative rates of RBC transfusion among those receiving at least one RBC transfusion after randomization. These models included an offset term for hospital length of stay (censored at 28 days). P values were obtained by adjusted Wald Chi-squared tests.

To evaluate the effect modification of diabetes on randomized strategy, we fitted separate models that included a diabetes-by-treatment interaction term. P values were obtained by Wald Chi-squared tests adjusted for all interactions in the model. The respective adjusted treatment effects and two-sided 95% CIs were expressed as odds ratios, hazard ratios, and rate ratios for binary, time-to-event, and count outcomes respectively. A P value <0.05 was taken to be statistically significant. The sample size was determined by the TRICS-III cohort, and post hoc power calculations were not performed. All analyses were performed with R software (version 3.6.3).

Subgroup, post-hoc, and sensitivity analyses:

We performed a subgroup analysis stratifying patients with diabetes by insulin requirement status. For this analysis, we created a three-level variable categorizing patients as either having: 1) diabetes requiring insulin; 2) diabetes not requiring insulin; and 3) no diabetes (reference group). For this subgroup analysis, we fitted adjusted regression models that included an interaction term between the three-level diabetes status variable and treatment, and P values were obtained as previously described by Wald Chi-squared tests.

Furthermore, we performed a post-hoc analysis to determine whether presence of symptomatic coronary disease modified the randomized treatment effect on clinical outcomes at 6 months among patients with diabetes, as there is controversy as to the optimal transfusion strategy for these patients.[9] Symptomatic coronary disease was defined as the presence of either: 1) myocardial infarction within 30 days preceding surgery; 2) unstable angina; 3) Canadian Cardiovascular Society (CCS) Class 4 angina; and/or 4) New York Heart Association (NYHA) Class III/IV heart failure. We hypothesized that among patients with diabetes, a restrictive transfusion strategy may be more harmful among patients with symptomatic coronary disease compared to patients without symptomatic coronary disease.

Other subgroup and sensitivity analyses included an assessment of transfusion strategy in patients with diabetes across different definitions of preoperative cardiac or renal risk strata, including: 1) heart failure (by NYHA classification and by LV grade); 2) angina (by presence of CCS class 4 angina or by presence of unstable angina); 3) myocardial infarction (within 90 days of surgery); and 4) renal dysfunction (by creatinine clearance and creatinine level). Additionally, we compared the treatment effect of transfusion strategy in patients with vs. without diabetes after stratifying by age group.

Results:

Patient Characteristics:

From a total of 5243 patients randomized, 151 patients were excluded for the following reasons: not having surgery or having surgery without cardiopulmonary bypass (n=117), patient withdrew consent before surgery (n=63), or other reasons (n=34). As a result, 5092 patients were included in the modified intention-to-treat analysis. Diabetes information was available for all patients. Of the 1396 (27.4%) patients with diabetes, 679 were randomized to the restrictive transfusion strategy and 717 were randomized to the liberal strategy; and of the 3696 (72.6%) patients without diabetes, 1876 were randomized to the restrictive strategy and 1820 were randomized to the liberal strategy. Of the patients with diabetes, 538 (38.5%) required insulin (restrictive n=266, liberal n=272) and 858 (61.5%) did not require insulin (restrictive n=413, liberal n=445). A participant flow diagram is provided in the Supplementary Appendix (Figure S1).

Patients with diabetes had a higher preoperative cardiovascular risk-profile compared to patients without diabetes. Patients with diabetes had more preoperative extracardiac arteriopathy, worse left ventricular function, worse renal function, more symptomatic coronary disease, more treated hypertension, and more use of antiplatelet agents (Table 1). Patients with diabetes underwent more CABG procedures. The magnitude of the differences increased with insulin requirement (Table S1). Baseline and procedural characteristics were well balanced among randomization arms for patients after stratifying by diabetes presence (Table S2) and across insulin requirement subgroups (Table S3).

Hemoglobin Concentrations, Bleeding, and Transfusion Outcomes:

Preoperative, intraoperative, and early postoperative hemoglobin concentrations were lower in patients with diabetes. Perioperative hemoglobin concentrations were lower among patients treated according to a restrictive transfusion strategy (Figure S2).

Presence of diabetes was associated with less intraoperative estimated blood loss (Figure 1). A restrictive transfusion strategy was associated with a larger reduction in intraoperative bleeding among patients with diabetes compared to patients without diabetes (diabetes: mean difference [MD] -82mL, 95% CI -149mL to -15mL; no diabetes: MD 28mL, 95% CI -13mL to 70mL, $p_{interaction}$=0.02; Figure 2).

Diabetes was associated with a non-significant trend towards an increased incidence for RBC transfusion (OR: 1.14, 95% CI 0.98-1.33; Figure 1). Diabetes was associated with a lower relative rate of RBC transfusion (rate ratio [RR]: 0.93, 95% CI 0.89-0.97; Figure 1).

In patients with diabetes versus without diabetes, a restrictive transfusion strategy was more effective at reducing the incidence of RBC transfusion (diabetes: OR, 0.28, 95% CI 0.21-0.36; no diabetes: OR 0.40, 95% CI 0.35-0.47, $p_{interaction}$=0.04; Figure 2) and relative rate of RBC transfused (diabetes: RR, 0.62, 95% CI 0.58-0.66; no diabetes: RR, 0.81, 95% CI 0.77-0.84; $p_{interaction}$<0.001; Figure 2).

Clinical Outcomes:

The presence of diabetes did not have a meaningful association with the primary composite outcome (OR: 1.10, 95% CI, 0.93-1.31), expanded composite outcome (OR: 0.94, 95% CI, 0.82-1.08), nor any of its components at six months, including myocardial infarction (OR: 1.13, 95% CI, 0.88-1.46) (Figure 1). Time-to-death is shown in the supplementary appendix (Figure S3).

Presence of diabetes was associated with an increased risk of acute kidney injury (OR: 1.22, 95% CI 1.06-1.40) and delirium (OR: 1.29, 95% CI, 1.06-1.56; Figure 1) within 28 days.

Presence of diabetes did not modify the effect of a restrictive transfusion strategy on the primary composite outcome (diabetes, OR: 1.04, 95% CI 0.68-1.59; no diabetes, OR: 1.02, 95% CI 0.85-1.22, $p_{interaction}$=0.92). We observed no difference in the effect of transfusion strategy on clinical outcomes 6 months or at 28 days between patients with and without diabetes (Figure 3).

Subgroup Analysis – Patients with Diabetes Stratified by Insulin Requirement Status:

The association between diabetes stratified by insulin requirements and bleeding and transfusion outcomes is shown in Table S4. A restrictive transfusion strategy was associated with a lower relative rate of RBC transfusion in patients with diabetes requiring insulin and patients with diabetes not requiring insulin when compared to patients without diabetes (Table S5).

The association between diabetes and an elevated risk for acute kidney injury and delirium increased in magnitude with insulin requirements (Table S6). Diabetes not requiring insulin was associated with a reduced risk for the expanded composite outcome at 6 months compared to patients with diabetes requiring insulin, which was related to a reduction in emergency department visits. Insulin requirement status in patients with diabetes did not modify the effect of a restrictive transfusion strategy on the primary composite outcome, nor other clinical outcomes 6 months or at 28 days (Table S7).

The results of this and other subgroup analyses may not be adequately powered and should be interpreted as hypothesis-generating.

Post-hoc Analysis – Effect of Transfusion Strategy in Patients with Diabetes and Symptomatic Coronary Disease:

Symptomatic coronary disease status could be ascertained in 1348 (96.6%) of patients with diabetes; and was present among 960 of these patients (71.2%; restrictive n=468, liberal n=492) and not present in 388 patients (28.8%; restrictive n=187, liberal n=201). There was no difference in the effect of transfusion strategy between patients with versus without symptomatic coronary disease on the primary composite outcome (symptomatic coronary disease, OR: 1.22, 95% CI 0.88-1.70; no symptomatic coronary disease, OR: 0.75, 95% CI 0.44-1.27, $p_{interaction}$=0.25) or other clinical outcomes at 6 months (Figure 4).

Other Subgroup and Sensitivity Analyses:

We observed no difference in treatment effect across different definitions of heart failure, angina, and renal dysfunction risk strata; and by presence of recent myocardial infarction (Figure S4). There was no difference in treatment effect between patients with vs. without diabetes after stratifying the cohort by age groups (Table S8).

Discussion:

We found that a restrictive transfusion strategy was more effective at reducing RBC transfusion among patients with diabetes without modifying the effect of transfusion strategy on clinical outcomes. The result of our primary outcome was consistent across all subgroup and sensitivity analyses.

The decision to transfuse blood is complex and multifactorial, and involves balancing risks associated with: 1) anemia; 2) RBC transfusion; 3) patient comorbidities; 4) medical treatment; and 5) surgical intervention.[15] Emerging evidence suggests that optimal transfusion strategies may be context-specific, and vary across patient and clinical characteristics.[16] For example, in the primary TRICS-III analysis, we observed that age may modify the treatment effect of transfusion strategy in cardiac surgery.[12,13] In the current study, we did not observe further effect modification due to diabetes in our sensitivity analysis stratifying by age group.

A restrictive transfusion strategy reduced RBC transfusion by a larger magnitude in patients with diabetes compared to patients without diabetes. This larger reduction in RBC transfusion among patients with diabetes did not increase the risk for clinical outcomes including acute kidney injury and delirium, despite these patients having a higher cardiovascular risk-profile. There is controversy as to the optimal transfusion strategy for patients hospitalized for acute coronary syndromes. This has been recently illustrated by the REALITY trial,[10] which reported early non-inferiority of a restrictive strategy compared to a liberal strategy in anemic patients hospitalized for acute myocardial infarction with respect to a primary composite outcome of major adverse cardiovascular events.[10] However, the Kaplan-Meier curves crossed at 5 months, after which a restrictive strategy was associated with potential harm and was no longer non-inferior at 1 year.[11] This uncertainty, in the context of more cardiovascular comorbidities present among patients

with diabetes, may predispose patients with diabetes to receive more transfusions at higher hemoglobin levels. In our subgroup and sensitivity analysis, a restrictive strategy did not increase the risk for adverse outcomes across cardiac and renal risk groups. Additionally, this observation persisted in our post-hoc analysis of patients with diabetes and symptomatic coronary disease. Restrictive transfusion strategies may reduce unnecessary transfusion in patients with diabetes undergoing cardiac surgery, including those receiving intervention for symptomatic coronary diseases, and may reduce the risk for transfusion-related injury and improve RBC resource optimization.[7]

Our study adds to the literature as few studies have evaluated the association between diabetes and bleeding, and diabetes and transfusion, in the cardiac surgical setting. We observed that diabetes was associated with less intraoperative bleeding, a reduced rate of RBC transfusion, and a more efficacious effect of a restrictive transfusion strategy; contrasting previous studies identifying diabetes as an independent predictor for bleeding[17,18] and transfusion.[18-20] Interestingly, the effect of reduced bleeding in patients with diabetes is pronounced in patients transfused using a restrictive strategy. Further research is needed to elucidate whether this effect in patients with diabetes is due to their cardiovascular status; and whether a restrictive transfusion approach is of benefit or a liberal transfusion strategy promotes bleeding in these patients.

Diabetes-induced microvascular dysfunction may have contributed to the increased incidence of delirium and acute kidney injury observed at 28 days. This microvascular dysfunction, combined with macrovascular disease present in patients with diabetes, may be another factor contributing to clinicians transfusing these patients at higher hemoglobin thresholds. Hyperglycemia has been demonstrated to increase oxidative stress and inflammation, contributing to endothelial

dysfunction and injury.[21] Also, the diabetic milieu has been shown to disrupt the integrity of the blood-brain barrier, leading to altered brain interstitial fluid;[21] and induce glomerular hyperfiltration and hypertension, leading to increased renal tissue hypoxia, podocytopathy, and ultimately deterioration of the filtration barrier and proteinuria.[21,22] This, in the context of further blood-brain barrier disruption[23] and renal-reperfusion injury[24] due to CPB may increase the risk for delirium and acute kidney injury as seen in our and other studies.[25,26] Further studies are required to delineate the mechanism for these associations.

We provide results from a large contemporary generalizable multinational cohort with detailed bleeding and transfusion data and blinded outcome adjudication. Despite this, some limitations of our analysis should be noted. Detailed information on the type of diabetes, duration of diabetes, prescribed diabetes medications, and glycosylated hemoglobin levels were not captured in the TRICS-III database. However, in our subgroup analysis stratifying patients with diabetes by insulin requirement status, the magnitude of associations consistently increased with insulin requirements, providing a rudimentary biological gradient for our observations.

The selection criteria and short-term follow-up duration of the TRICS-III trial may explain our unexpected observation of a lack of association between diabetes and mortality or major adverse outcomes. Analyses of clinical registry and administrative databases have identified long-term associations between diabetes and outcomes;[27-29] however, the short-term results of these studies are inconsistent.[27,30,31] Our analysis supports that diabetes does not increase the risk for clinical outcomes at 6-months after surgery, and that insulin requirements is not associated with an increased risk. Future studies, such as the OCTOPuS Trial[32] (ISRCTN10170306), will provide insight characterizing the association between diabetes and patient-oriented outcomes, and

whether improved preoperative optimization of these patients is associated with better postoperative outcomes.

Differences in operative characteristics such as duration of CPB and aortic cross-clamp time may have contributed to the observed reduction in intraoperative bleeding and rate of RBC transfusion in patients with diabetes.[33,34] However, in our analysis, which included statistical adjustment for type of surgery, presence of diabetes did not increase the risk for bleeding and transfusion outcomes in cardiac surgery. Lastly, this was a planned secondary analysis, and our findings may be biased by unmeasured or residual confounding. However, the prospective randomized design and protocolized data collection of this analysis is less prone to bias compared to retrospective analyses.

In conclusion, a restrictive strategy did not have a meaningful association with clinical outcomes, and is more effective at reducing RBC transfusion in patients with diabetes undergoing cardiac surgery. Thus, restrictive transfusion thresholds are safe in patients with diabetes in this setting.

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Conflicts of Interest: D.F. reports speaker honoraria from Werfen Company, Instrumentation Laboratory, Eurasia Heart Foundation & Krems Donau University, Austria, and American Society of Anesthesiology. P.J. reports serving as an unpaid steering committee member for Astra Zeneca, Biotronik, Biosensors, Abbott, and the Medicines Company, and reported receiving consulting fees from Amgen, Ava, and Fresenius. S.V. reports holding a Tier 1 Canada Research Chair in Cardiovascular Surgery; reported receiving research grants and speaking honoraria from Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, EOCI Pharmacomm, Ltd, HLS Therapeutics, Janssen, Merck, Novartis, Novo Nordisk, PhaseBio, Sanofi, Sun Pharmaceuticals, and the Toronto Knowledge Translation Working Group; and reported being the President of the Canadian Medical and Surgical Knowledge Translation Research Group, a federally incorporated not-for-profit physician organization. C.D.M reports receiving advisory board fees from Amgen, AstraZeneca, Boehringer Ingelheim, and Octapharma. All other authors report no potential conflicts of interest.

Author Contributions: C.D.M attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. N.M., N.S., D.N.W, K.E.T, P.J., G.M.T.H., D.T.K., S.V., and C.D.M contributed to the study design. N.S., P.C., D.B., R.H., F.M.C, C.S.A., E.E.T., A.G.R., C.R., D.F., C.M., T.S., J.C.V., A.J.G., K.E.T., P.J., G.M.T.H., S.V., and C.D.M. contributed to study conduct/data collection. N.M., K.E.T., and C.D.M. contributed to data analysis. All authors contributed to interpretation of data. N.M and C.D.M wrote the initial draft of the manuscript, and all authors critically reviewed and approved the final version. N.M. and C.D.M. are the guarantors of this work and, as such, have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Legends to Figures:

Figure 1: Association between diabetes and bleeding, transfusion, and clinical outcomes. Effect estimates adjusted for Values presented as number (%), mean ± standard deviation, or median (interquartile range). ICU, intensive care unit; RBC, red blood cell; ED, emergency department. †This value is a rate ratio. ‡This value is a hazard ratio

Figure 2: Effect of transfusion strategy on bleeding and transfusion outcomes stratified by presence of diabetes. Values presented as number (%) or mean ± standard deviation. ICU, intensive care unit; RBC, red blood cell. †This value is a rate ratio

Figure 3: Effect of transfusion strategy on clinical outcomes stratified by presence of diabetes. Values presented as number (%) or median (interquartile range). ED, emergency department. †This value is a hazard ratio

Figure 4: Effect of transfusion strategy on clinical outcomes at 6 months in patients with diabetes stratified by presence of symptomatic coronary disease. ED, emergency department.

Table 1: Preoperative and Procedural Characteristics**.**

	Diabetes (N=1396)	No Diabetes (N=3696)	P
Preoperative Characteristics			
Age	72.7±8.1	72.2±10.8	0.07
Male sex	916/1396 (65.6)	2354/3696 (63.7)	0.20
BMI	29.5±5.6	27.4±5.0	<0.01
EuroSCORE 1	8.0±1.9	7.8±1.9	0.04
Previous cardiac surgery	131/1396 (9.4)	493/3696 (13.3)	<0.01
Emergency surgery	21/1396 (1.5)	53/3696 (1.4)	0.85
Extracardiac arteriopathy†	332/1396 (23.8)	535/3696 (14.5)	<0.01
Critical preoperative state‡	81/1395 (5.8)	129/3695 (3.5)	<0.01
Left ventricular function			<0.01
Good	755/1394 (54.2)	2389/3695 (64.7)	
Moderate	472/1394 (33.9)	1048/3695 (28.4)	
Poor	134/1394 (9.6)	203/3695 (5.5)	
Very Poor	33/1394 (2.4)	55/3695 (1.5)	
Renal Function			<0.01
Normal (CC >85ml/min)	508/1336 (38.0)	1271/3548 (35.8)	
Moderate (CC >50 and <85)	513/1336 (38.4)	1732/3548 (48.8)	
Severe (CC <50)	277/1336 (20.7)	518/3548 (14.6)	
Dialysis (regardless of CC)	38/1336 (2.8)	27/3548 (0.8)	
Recent MI (<90 days)	504/1396 (36.1)	704/3696 (19.0)	<0.01
Unstable angina	119/1396 (8.5)	118/3696 (3.2)	<0.01
CCS class 4 angina	145/1333 (10.9)	191/3541 (5.4)	<0.01
NYHA Class			<0.01
I	244/1308 (18.7)	733/3478 (21.1)	
II	474/1308 (36.2)	1410/3478 (40.5)	
III	501/1308 (38.3)	1164/3478 (33.5)	
IV	89/1308 (6.8)	171/3478 (4.9)	

Treated hypertension	1217/1396 (87.2)	2566/3696 (69.4)	<0.01
Use of aspirin	874/1393 (62.7)	1814/3689 (49.2)	<0.01
Use of thienopyridine	193/1395 (13.8)	313/3694 (8.5)	<0.01
Use of anticoagulant	312/1395 (22.4)	826/3695 (22.4)	0.99
Hemoglobin concentration (g/L)	125.0±18.1	132.8±17.1	<0.01
Blood product transfusion before randomization	48/1395 (3.4)	68/3695 (1.8)	<0.01
Procedural Characteristics			
Surgery Type			<0.01
CABG Only	546/1395 (39.1)	764/3694 (20.7)	
CABG and Valve	327/1395 (23.4)	669/3694 (18.1)	
Other Surgery and CABG	117/1395 (8.4)	319/3694 (8.6)	
Valve Only	292/1395 (20.9)	1182/3694 (32.0)	
Other Non-CABG Surgery	113/1395 (8.1)	760/3694 (20.6)	
Duration of CPB	117.2±56.1	123.6±61.4	<0.01
Total cross-clamp time	84.5±42.2	90.3±47.1	<0.01
Nadir hemoglobin on CPB	84.8±15.5	88.7±15.1	<0.01
Return to operating room	126/1391 (9.1)	401/3681 (10.9)	0.06

Data presented as n (%) or mean ± standard deviation; BMI, body mass index; CC, creatinine clearance; MI, myocardial infarction; CCS, Canadian College of Cardiology; NYHA, New York Heart Association; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; †as defined by EuroSCORE 1: any one or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta limb arteries or carotids; ‡as defined by EuroSCORE 1: any one or more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anaesthetic room, preoperative inotropic support, intraaortic balloon counterpulsation or preoperative acute renal failure (anuria or oliguria<10 ml/hour)

Figure 1: Association between diabetes and bleeding, transfusion, and clinical outcomes. Effect estimates adjusted for Values presented as number (%), mean ± standard deviation, or median (interquartile range). ICU, intensive care unit; RBC, red blood cell; ED, emergency department. †This value is a rate ratio. ‡This value is a hazard ratio

	Diabetes (N=1396)	No Diabetes (N=3696)	Adjusted Effect Estimate (95% Confidence Interval)
Bleeding Outcomes			*Mean Difference*
Intraoperative estimated blood loss (mL)	524.5±549.3	561.3±624.2	-28 (-69 to 13)
Chest tube drainage upon ICU arrival (mL)	121.8±238.9	116.6±189.9	-2 (-15 to 11)
Chest tube drainage within 24h (mL)	588.7±556.8	634.5±587.8	-78 (-114 to -41)
Transfusion Outcomes			*Odds Ratio*
RBC transfusion post-randomization (≥1)	994/1396 (71.2)	2257/3696 (61.1)	1.14 (0.98 to 1.33)
Number of Units	3.0±4.6	2.6±4.2	0.93 (0.89 to 0.97)†
Intraoperative RBC transfusion (≥1)	682/1396 (48.9)	1396/3696 (37.8)	1.13 (0.97 to 1.31)
Postoperative ICU RBC transfusion (≥1)	676/1396 (48.4)	1608/3696 (43.5)	0.92 (0.80 to 1.06)
Postoperative ward RBC transfusion (≥1)	162/1396 (11.6)	393/3696 (10.6)	0.95 (0.77 to 1.17)
Clinical Outcomes at 6 Months			
Primary Composite	283/1335 (21.2)	595/3537 (16.8)	1.10 (0.93 to 1.31)
Death	99/1312 (7.5)	232/3499 (6.6)	0.92 (0.71 to 1.20)
Stroke	49/1240 (4)	116/3351 (3.5)	1.13 (0.79 to 1.63)
Myocardial Infarction	105/1259 (8.3)	242/3382 (7.2)	1.13 (0.88 to 1.46)
Dialysis	88/1265 (7)	130/3380 (3.8)	1.22 (0.89 to 1.67)
Expanded Composite	598/1335 (44.8)	1543/3539 (43.6)	0.94 (0.82 to 1.08)
Revascularization	15/1239 (1.2)	21/3344 (0.6)	1.56 (0.77 to 3.15)
Healthcare Utilization	429/1256 (34.2)	1178/3359 (35.1)	0.91 (0.78 to 1.05)
ED Visits	312/1247 (25)	883/3340 (26.4)	0.90 (0.77 to 1.05)
Hospital Readmission	319/1246 (25.6)	841/3348 (25.1)	0.97 (0.83 to 1.14)
Clinical Outcomes at 28 days			
Duration of Mechanical Ventilation (days)	0.4 (0.2 to 0.8)	0.4 (0.2 to 0.7)	0.96 (0.90 to 1.03)‡
ICU Length of Stay (days)	2.0 (1.0 to 4.1)	2.0 (1.0 to 3.9)	0.96 (0.90 to 1.03)‡
Hospital Length of Stay (days)	9.0 (7.0 to 14.0)	8.0 (6.0 to 12.0)	0.94 (0.88 to 1.00)‡
Prolonged Low Output State	572/1396 (41.0)	1525/3695 (41.3)	0.89 (0.78 to 1.03)
Infection	90/1395 (6.5)	166/3694 (4.5)	1.23 (0.93 to 1.63)
Gut Infarction	4/1395 (0.3)	13/3694 (0.4)	0.83 (0.26 to 2.66)
Seizure	26/1395 (1.9)	70/3694 (1.9)	0.98 (0.61 to 1.59)
Acute Kidney Injury	520/1337 (38.9)	1165/3547 (32.8)	1.22 (1.06 to 1.40)
Encephalopathy	16/1395 (1.1)	37/3694 (1.0)	0.87 (0.46 to 1.61)
Delirium	192/1395 (13.8)	418/3694 (11.3)	1.29 (1.06 to 1.56)

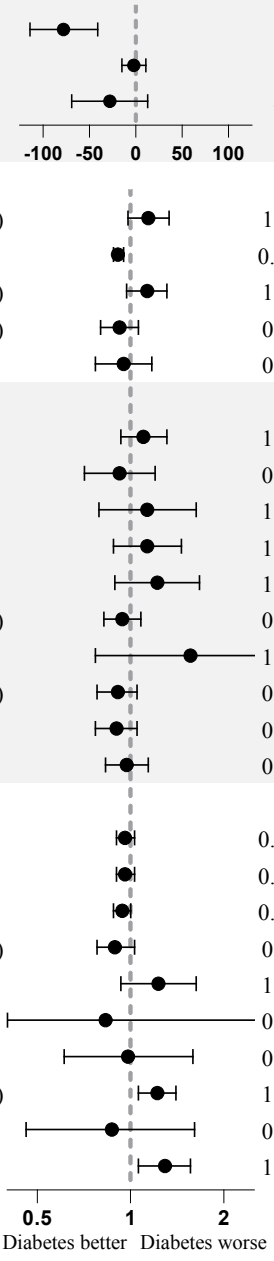


Figure 2: Effect of transfusion strategy on bleeding and transfusion outcomes stratified by presence of diabetes. Values presented as number (%) or mean ± standard deviation. ICU, intensive care unit; RBC, red blood cell. †This value is a rate ratio

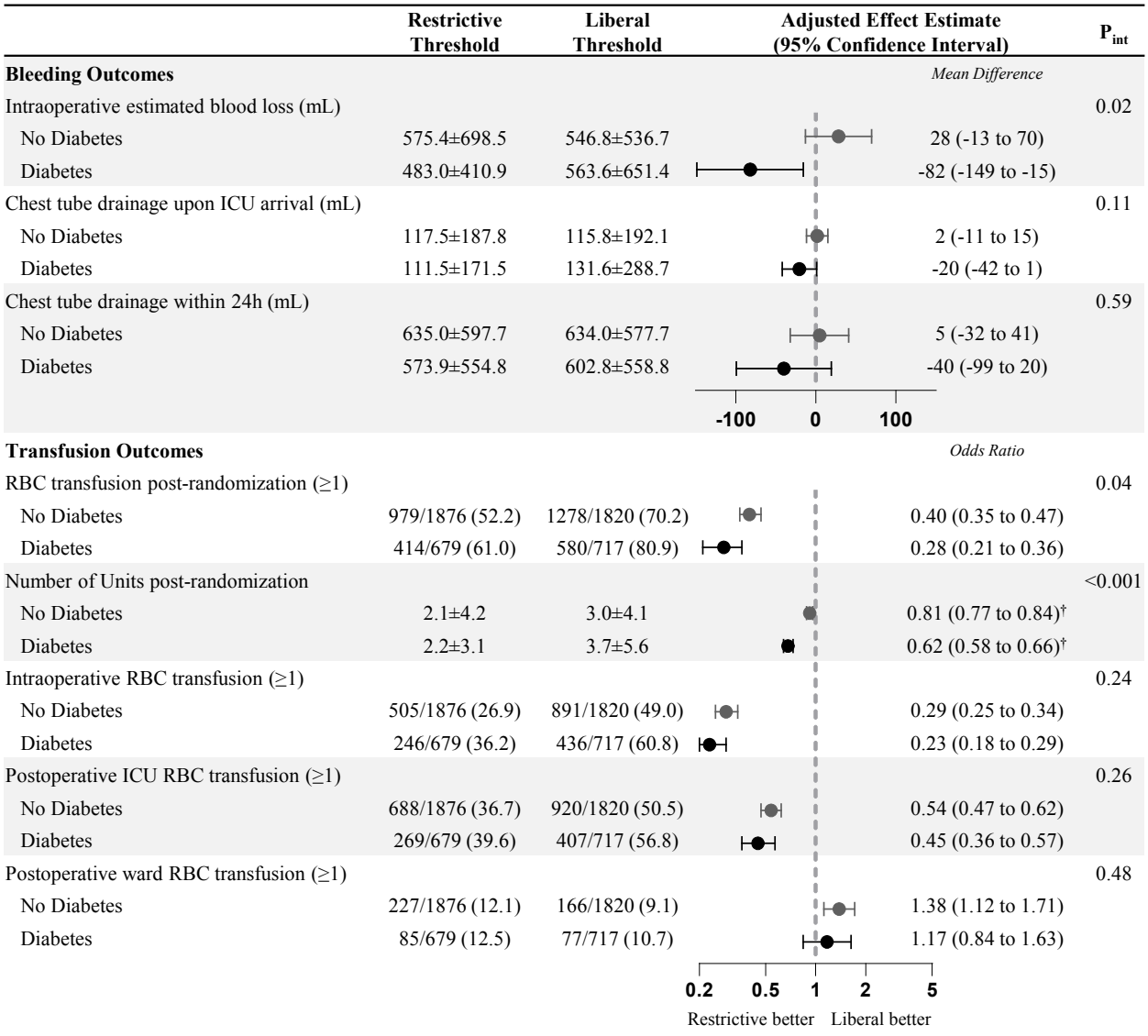
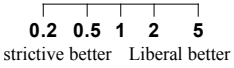


Figure 3: Effect of transfusion strategy on clinical outcomes stratified by presence of diabetes. Values presented as number (%) or median (interquartile range). ED, emergency department. †This value is a hazard ratio

Panel A: Clinical Outcomes at 6 Months

	Restrictive Threshold	Liberal Threshold	Adjusted Odds Ratio (95% Confidence Interval)	P_{int}
Primary Composite Outcome				
No Diabetes	302/1790 (16.9)	293/1747 (16.8)	1.02 (0.85 to 1.22)	
Diabetes	142/644 (22.0)	141/691 (20.4)	1.04 (0.79 to 1.36)	
Death				0.85
No Diabetes	116/1771 (6.5)	116/1728 (6.7)	0.97 (0.74 to 1.27)	
Diabetes	51/635 (8.0)	48/677 (7.1)	1.04 (0.68 to 1.59)	
Stroke				0.92
No Diabetes	64/1696 (3.8)	52/1655 (3.1)	1.24 (0.85 to 1.8)	
Diabetes	26/597 (4.4)	23/643 (3.6)	1.16 (0.65 to 2.07)	
Myocardial Infarction				0.62
No Diabetes	124/1717 (7.2)	118/1665 (7.1)	1.01 (0.78 to 1.32)	
Diabetes	48/608 (7.9)	57/651 (8.8)	0.88 (0.59 to 1.32)	
Dialysis				0.36
No Diabetes	62/1713 (3.6)	68/1667 (4.1)	0.93 (0.65 to 1.35)	
Diabetes	48/613 (7.8)	40/652 (6.1)	1.14 (0.72 to 1.82)	
Expanded Composite Outcome				0.98
No Diabetes	794/1791 (44.3)	749/1748 (42.8)	1.07 (0.94 to 1.23)	
Diabetes	295/644 (45.8)	303/691 (43.8)	1.05 (0.84 to 1.3)	
Revascularization				0.35
No Diabetes	8/1695 (0.5)	13/1649 (0.8)	0.60 (0.25 to 1.45)	
Diabetes	7/598 (1.2)	8/641 (1.2)	0.97 (0.35 to 2.70)	
Healthcare Utilization				0.76
No Diabetes	617/1704 (36.2)	561/1655 (33.9)	1.11 (0.96 to 1.28)	
Diabetes	214/609 (35.1)	215/647 (33.2)	1.07 (0.84 to 1.35)	
ED Visits				0.54
No Diabetes	465/1694 (27.4)	418/1646 (25.4)	1.12 (0.96 to 1.30)	
Diabetes	149/603 (24.7)	163/644 (25.3)	0.95 (0.74 to 1.23)	
Hospital Readmission				0.42
No Diabetes	447/1695 (26.4)	394/1653 (23.8)	1.15 (0.98 to 1.35)	
Diabetes	165/604 (27.3)	154/642 (24.0)	1.17 (0.91 to 1.52)	



Panel B: Clinical Outcomes at 28 Days

	Restrictive Threshold	Liberal Threshold	Adjusted Odds Ratio (95% Confidence Interval)	P_{int}
Duration of Mechanical Ventilation (days)				0.26
No Diabetes	0.4 (0.2 to 0.8)	0.3 (0.2 to 0.7)	0.92 (0.86 to 0.98)†	
Diabetes	0.4 (0.2 to 0.8)	0.4 (0.2 to 0.8)	0.99 (0.89 to 1.10)†	
ICU Length of Stay (days)				0.61
No Diabetes	2.1 (1.0 to 4.0)	1.9 (1.0 to 3.9)	0.90 (0.84 to 0.96)†	
Diabetes	2.2 (1.0 to 4.6)	1.9 (1.0 to 4.0)	0.92 (0.82 to 1.02)†	
Hospital Length of Stay (days)				0.85
No Diabetes	8.0 (7.0 to 12.0)	8.0 (6.0 to 12.0)	0.93 (0.88 to 1.00)†	
Diabetes	9.0 (7.0 to 14.0)	9.0 (7.0 to 13.0)	0.95 (0.86 to 1.06)†	
Prolonged Low Output State				0.21
No Diabetes	788/1875 (42.0)	737/1820 (40.5)	1.04 (0.91 to 1.19)	
Diabetes	269/679 (39.6)	303/717 (42.3)	0.89 (0.71 to 1.11)	
Infection				0.99
No Diabetes	92/1875 (4.9)	74/1819 (4.1)	1.23 (0.89 to 1.69)	
Diabetes	47/678 (6.9)	43/717 (6.0)	1.10 (0.71 to 1.71)	
Gut Infarction				0.6
No Diabetes	9/1875 (0.5)	4/1819 (0.2)	2.10 (0.68 to 7.78)	
Diabetes	2/678 (0.3)	2/717 (0.3)	1.09 (0.13 to 9.13)	
Seizure				0.7
No Diabetes	37/1875 (2.0)	33/1819 (1.8)	1.13 (0.70 to 1.82)	
Diabetes	16/678 (2.4)	10/717 (1.4)	1.53 (0.69 to 3.55)	
Acute Kidney Injury				0.33
No Diabetes	585/1797 (32.6)	580/1750 (33.1)	0.98 (0.85 to 1.12)	
Diabetes	267/650 (41.1)	253/687 (36.8)	1.17 (0.94 to 1.47)	
Encephalopathy				0.71
No Diabetes	21/1875 (1.1)	16/1819 (0.9)	1.31 (0.68 to 2.58)	
Diabetes	8/678 (1.2)	8/717 (1.1)	0.92 (0.33 to 2.55)	
Delirium				0.28
No Diabetes	227/1875 (12.1)	191/1819 (10.5)	1.17 (0.96 to 1.44)	
Diabetes	107/678 (15.8)	85/717 (11.9)	1.39 (1.02 to 1.90)	

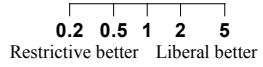


Figure 4: Effect of transfusion strategy on clinical outcomes at 6 months in patients with diabetes stratified by presence of symptomatic coronary disease. ED, emergency department.

	Restrictive Threshold	Liberal Threshold	Adjusted Odds Ratio (95% Confidence Interval)	P_{int}
Primary Composite				0.25
No Symptomatic Coronary Disease	32/185 (17.3)	41/199 (20.6)	0.75 (0.44 to 1.27)	
Symptomatic Coronary Disease	104/448 (23.2)	92/478 (19.2)	1.22 (0.88 to 1.70)	
Death				0.64
No Symptomatic Coronary Disease	14/185 (7.6)	12/199 (6.0)	1.21 (0.54 to 2.72)	
Symptomatic Coronary Disease	37/445 (8.3)	36/471 (7.6)	1.03 (0.63 to 1.68)	
Stroke				0.5
No Symptomatic Coronary Disease	5/174 (2.9)	7/190 (3.7)	0.75 (0.23 to 2.44)	
Symptomatic Coronary Disease	21/418 (5.0)	15/446 (3.4)	1.47 (0.74 to 2.92)	
Myocardial Infarction				0.42
No Symptomatic Coronary Disease	11/175 (6.3)	18/189 (9.5)	0.62 (0.28 to 1.37)	
Symptomatic Coronary Disease	31/422 (7.3)	33/449 (7.3)	1.02 (0.61 to 1.70)	
Dialysis				0.08
No Symptomatic Coronary Disease	7/176 (4.0)	11/192 (5.7)	0.56 (0.20 to 1.57)	
Symptomatic Coronary Disease	41/432 (9.5)	27/451 (6.0)	1.51 (0.87 to 2.62)	
Expanded Composite				0.61
No Symptomatic Coronary Disease	82/185 (44.3)	86/199 (43.2)	1.02 (0.68 to 1.55)	
Symptomatic Coronary Disease	205/448 (45.8)	208/478 (43.5)	1.06 (0.81 to 1.38)	
Revascularization				0.8
No Symptomatic Coronary Disease	2/174 (1.1)	3/190 (1.6)	0.72 (0.12 to 4.45)	
Symptomatic Coronary Disease	5/419 (1.2)	5/444 (1.1)	1.08 (0.31 to 3.79)	
Healthcare Utilization				0.54
No Symptomatic Coronary Disease	69/180 (38.3)	59/192 (30.7)	1.41 (0.91 to 2.19)	
Symptomatic Coronary Disease	143/424 (33.7)	154/448 (34.4)	0.95 (0.71 to 1.26)	
ED Visits				0.93
No Symptomatic Coronary Disease	48/178 (27.0)	48/192 (25.0)	1.13 (0.70 to 1.8)	
Symptomatic Coronary Disease	100/420 (23.8)	113/445 (25.4)	0.91 (0.66 to 1.24)	
Hospital Readmission				0.38
No Symptomatic Coronary Disease	53/178 (29.8)	39/192 (20.3)	1.66 (1.02 to 2.68)	
Symptomatic Coronary Disease	111/421 (26.4)	114/443 (25.7)	1.01 (0.74 to 1.38)	

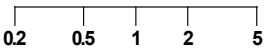
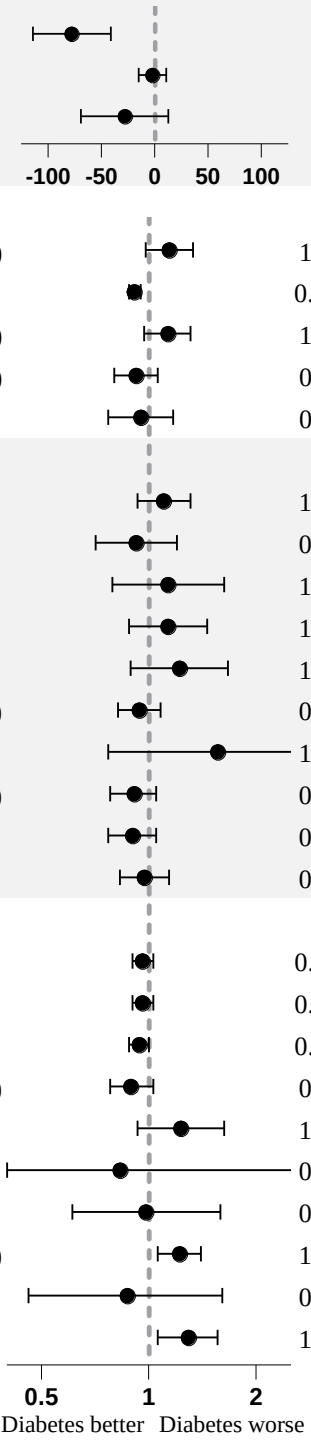


Table 1: Preoperative and Procedural Characteristics**.**

	Diabetes (N=1396)	No Diabetes (N=3696)	P
Preoperative Characteristics			
Age	72.7±8.1	72.2±10.8	0.07
Male sex	916/1396 (65.6)	2354/3696 (63.7)	0.20
BMI	29.5±5.6	27.4±5.0	<0.01
EuroSCORE 1	8.0±1.9	7.8±1.9	0.04
Previous cardiac surgery	131/1396 (9.4)	493/3696 (13.3)	<0.01
Emergency surgery	21/1396 (1.5)	53/3696 (1.4)	0.85
Extracardiac arteriopathy†	332/1396 (23.8)	535/3696 (14.5)	<0.01
Critical preoperative state‡	81/1395 (5.8)	129/3695 (3.5)	<0.01
Left ventricular function			<0.01
Good	755/1394 (54.2)	2389/3695 (64.7)	
Moderate	472/1394 (33.9)	1048/3695 (28.4)	
Poor	134/1394 (9.6)	203/3695 (5.5)	
Very Poor	33/1394 (2.4)	55/3695 (1.5)	
Renal Function			<0.01
Normal (CC >85ml/min)	508/1336 (38.0)	1271/3548 (35.8)	
Moderate (CC >50 and <85)	513/1336 (38.4)	1732/3548 (48.8)	
Severe (CC <50)	277/1336 (20.7)	518/3548 (14.6)	
Dialysis (regardless of CC)	38/1336 (2.8)	27/3548 (0.8)	
Recent MI (<90 days)	504/1396 (36.1)	704/3696 (19.0)	<0.01
Unstable angina	119/1396 (8.5)	118/3696 (3.2)	<0.01
CCS class 4 angina	145/1333 (10.9)	191/3541 (5.4)	<0.01
NYHA Class			<0.01
I	244/1308 (18.7)	733/3478 (21.1)	
II	474/1308 (36.2)	1410/3478 (40.5)	
III	501/1308 (38.3)	1164/3478 (33.5)	
IV	89/1308 (6.8)	171/3478 (4.9)	
Treated hypertension	1217/1396 (87.2)	2566/3696 (69.4)	<0.01
Use of aspirin	874/1393 (62.7)	1814/3689 (49.2)	<0.01
Use of thienopyridine	193/1395 (13.8)	313/3694 (8.5)	<0.01
Use of anticoagulant	312/1395 (22.4)	826/3695 (22.4)	0.99
Hemoglobin concentration (g/L)	125.0±18.1	132.8±17.1	<0.01
Blood product transfusion before randomization	48/1395 (3.4)	68/3695 (1.8)	<0.01
Procedural Characteristics			
Surgery Type			<0.01
CABG Only	546/1395 (39.1)	764/3694 (20.7)	
CABG and Valve	327/1395 (23.4)	669/3694 (18.1)	
Other Surgery and CABG	117/1395 (8.4)	319/3694 (8.6)	
Valve Only	292/1395 (20.9)	1182/3694 (32.0)	
Other Non-CABG Surgery	113/1395 (8.1)	760/3694 (20.6)	
Duration of CPB	117.2±56.1	123.6±61.4	<0.01
Total cross-clamp time	84.5±42.2	90.3±47.1	<0.01
Nadir hemoglobin on CPB	84.8±15.5	88.7±15.1	<0.01
Return to operating room	126/1391 (9.1)	401/3681 (10.9)	0.06

Data presented as n (%) or mean ± SD; BMI, body mass index; CC, creatinine clearance; MI, myocardial infarction; CCS, Canadian College of Cardiology; NYHA, New York Heart Association; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; †as defined by EuroSCORE 1: any one or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta limb arteries or carotids; ‡as defined by EuroSCORE 1: any one or more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anaesthetic room, preoperative inotropic support, intraaortic balloon counterpulsation or preoperative acute renal failure (anuria or oliguria<10 ml/hour)

	Diabetes (N=1396)	No Diabetes (N=3696)	Adjusted Effect Estimate (95% Confidence Interval)
Bleeding Outcomes			*Mean Difference*
Intraoperative estimated blood loss (mL)	524.5±549.3	561.3±624.2	-28 (-69 to 13)
Chest tube drainage upon ICU arrival (mL)	121.8±238.9	116.6±189.9	-2 (-15 to 11)
Chest tube drainage within 24h (mL)	588.7±556.8	634.5±587.8	-78 (-114 to -41)
Transfusion Outcomes			*Odds Ratio*
RBC transfusion post-randomization (≥1)	994/1396 (71.2)	2257/3696 (61.1)	1.14 (0.98 to 1.33)
Number of Units	3.0±4.6	2.6±4.2	0.93 (0.89 to 0.97)†
Intraoperative RBC transfusion (≥1)	682/1396 (48.9)	1396/3696 (37.8)	1.13 (0.97 to 1.31)
Postoperative ICU RBC transfusion (≥1)	676/1396 (48.4)	1608/3696 (43.5)	0.92 (0.80 to 1.06)
Postoperative ward RBC transfusion (≥1)	162/1396 (11.6)	393/3696 (10.6)	0.95 (0.77 to 1.17)
Clinical Outcomes at 6 Months			
Primary Composite	283/1335 (21.2)	595/3537 (16.8)	1.10 (0.93 to 1.31)
Death	99/1312 (7.5)	232/3499 (6.6)	0.92 (0.71 to 1.20)
Stroke	49/1240 (4)	116/3351 (3.5)	1.13 (0.79 to 1.63)
Myocardial Infarction	105/1259 (8.3)	242/3382 (7.2)	1.13 (0.88 to 1.46)
Dialysis	88/1265 (7)	130/3380 (3.8)	1.22 (0.89 to 1.67)
Expanded Composite	598/1335 (44.8)	1543/3539 (43.6)	0.94 (0.82 to 1.08)
Revascularization	15/1239 (1.2)	21/3344 (0.6)	1.56 (0.77 to 3.15)
Healthcare Utilization	429/1256 (34.2)	1178/3359 (35.1)	0.91 (0.78 to 1.05)
ED Visits	312/1247 (25)	883/3340 (26.4)	0.90 (0.77 to 1.05)
Hospital Readmission	319/1246 (25.6)	841/3348 (25.1)	0.97 (0.83 to 1.14)
Clinical Outcomes at 28 days			
Duration of Mechanical Ventilation (days)	0.4 (0.2 to 0.8)	0.4 (0.2 to 0.7)	0.96 (0.90 to 1.03)‡
ICU Length of Stay (days)	2.0 (1.0 to 4.1)	2.0 (1.0 to 3.9)	0.96 (0.90 to 1.03)‡
Hospital Length of Stay (days)	9.0 (7.0 to 14.0)	8.0 (6.0 to 12.0)	0.94 (0.88 to 1.00)‡
Prolonged Low Output State	572/1396 (41.0)	1525/3695 (41.3)	0.89 (0.78 to 1.03)
Infection	90/1395 (6.5)	166/3694 (4.5)	1.23 (0.93 to 1.63)
Gut Infarction	4/1395 (0.3)	13/3694 (0.4)	0.83 (0.26 to 2.66)
Seizure	26/1395 (1.9)	70/3694 (1.9)	0.98 (0.61 to 1.59)
Acute Kidney Injury	520/1337 (38.9)	1165/3547 (32.8)	1.22 (1.06 to 1.40)
Encephalopathy	16/1395 (1.1)	37/3694 (1.0)	0.87 (0.46 to 1.61)
Delirium	192/1395 (13.8)	418/3694 (11.3)	1.29 (1.06 to 1.56)



	Restrictive Threshold	Liberal Threshold	Adjusted Effect Estimate (95% Confidence Interval)	P_{int}
Bleeding Outcomes			*Mean Difference*	
Intraoperative estimated blood loss (mL)				0.02
No Diabetes	575.4±698.5	546.8±536.7	28 (-13 to 70)	
Diabetes	483.0±410.9	563.6±651.4	-82 (-149 to -15)	
Chest tube drainage upon ICU arrival (mL)				0.11
No Diabetes	117.5±187.8	115.8±192.1	2 (-11 to 15)	
Diabetes	111.5±171.5	131.6±288.7	-20 (-42 to 1)	
Chest tube drainage within 24h (mL)				0.59
No Diabetes	635.0±597.7	634.0±577.7	5 (-32 to 41)	
Diabetes	573.9±554.8	602.8±558.8	-40 (-99 to 20)	
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Transfusion Outcomes			*Odds Ratio*	
RBC transfusion post-randomization (≥1)				0.04
No Diabetes	979/1876 (52.2)	1278/1820 (70.2)	0.40 (0.35 to 0.47)	
Diabetes	414/679 (61.0)	580/717 (80.9)	0.28 (0.21 to 0.36)	
Number of Units post-randomization				<0.001
No Diabetes	2.1±4.2	3.0±4.1	0.81 (0.77 to 0.84)†	
Diabetes	2.2±3.1	3.7±5.6	0.62 (0.58 to 0.66)†	
Intraoperative RBC transfusion (≥1)				0.24
No Diabetes	505/1876 (26.9)	891/1820 (49.0)	0.29 (0.25 to 0.34)	
Diabetes	246/679 (36.2)	436/717 (60.8)	0.23 (0.18 to 0.29)	
Postoperative ICU RBC transfusion (≥1)				0.26
No Diabetes	688/1876 (36.7)	920/1820 (50.5)	0.54 (0.47 to 0.62)	
Diabetes	269/679 (39.6)	407/717 (56.8)	0.45 (0.36 to 0.57)	
Postoperative ward RBC transfusion (≥1)				0.48
No Diabetes	227/1876 (12.1)	166/1820 (9.1)	1.38 (1.12 to 1.71)	
Diabetes	85/679 (12.5)	77/717 (10.7)	1.17 (0.84 to 1.63)	
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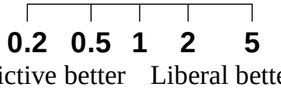
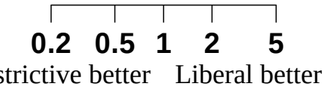
Panel A: Clinical Outcomes at 6 Months

	Restrictive Threshold	Liberal Threshold	Adjusted Odds Ratio (95% Confidence Interval)	P_{int}
Primary Composite Outcome				
No Diabetes	302/1790 (16.9)	293/1747 (16.8)	1.02 (0.85 to 1.22)	
Diabetes	142/644 (22.0)	141/691 (20.4)	1.04 (0.79 to 1.36)	
Death				0.85
No Diabetes	116/1771 (6.5)	116/1728 (6.7)	0.97 (0.74 to 1.27)	
Diabetes	51/635 (8.0)	48/677 (7.1)	1.04 (0.68 to 1.59)	
Stroke				0.92
No Diabetes	64/1696 (3.8)	52/1655 (3.1)	1.24 (0.85 to 1.8)	
Diabetes	26/597 (4.4)	23/643 (3.6)	1.16 (0.65 to 2.07)	
Myocardial Infarction				0.62
No Diabetes	124/1717 (7.2)	118/1665 (7.1)	1.01 (0.78 to 1.32)	
Diabetes	48/608 (7.9)	57/651 (8.8)	0.88 (0.59 to 1.32)	
Dialysis				0.36
No Diabetes	62/1713 (3.6)	68/1667 (4.1)	0.93 (0.65 to 1.35)	
Diabetes	48/613 (7.8)	40/652 (6.1)	1.14 (0.72 to 1.82)	
Expanded Composite Outcome				0.98
No Diabetes	794/1791 (44.3)	749/1748 (42.8)	1.07 (0.94 to 1.23)	
Diabetes	295/644 (45.8)	303/691 (43.8)	1.05 (0.84 to 1.3)	
Revascularization				0.35
No Diabetes	8/1695 (0.5)	13/1649 (0.8)	0.60 (0.25 to 1.45)	
Diabetes	7/598 (1.2)	8/641 (1.2)	0.97 (0.35 to 2.70)	
Healthcare Utilization				0.76
No Diabetes	617/1704 (36.2)	561/1655 (33.9)	1.11 (0.96 to 1.28)	
Diabetes	214/609 (35.1)	215/647 (33.2)	1.07 (0.84 to 1.35)	
ED Visits				0.54
No Diabetes	465/1694 (27.4)	418/1646 (25.4)	1.12 (0.96 to 1.30)	
Diabetes	149/603 (24.7)	163/644 (25.3)	0.95 (0.74 to 1.23)	
Hospital Readmission				0.42
No Diabetes	447/1695 (26.4)	394/1653 (23.8)	1.15 (0.98 to 1.35)	
Diabetes	165/604 (27.3)	154/642 (24.0)	1.17 (0.91 to 1.52)	



Panel B: Clinical Outcomes at 28 Days

	Restrictive Threshold	Liberal Threshold	Adjusted Odds Ratio (95% Confidence Interval)	P_{int}
Duration of Mechanical Ventilation (days)				0.26
No Diabetes	0.4 (0.2 to 0.8)	0.3 (0.2 to 0.7)	0.92 (0.86 to 0.98)†	
Diabetes	0.4 (0.2 to 0.8)	0.4 (0.2 to 0.8)	0.99 (0.89 to 1.10)†	
ICU Length of Stay (days)				0.61
No Diabetes	2.1 (1.0 to 4.0)	1.9 (1.0 to 3.9)	0.90 (0.84 to 0.96)†	
Diabetes	2.2 (1.0 to 4.6)	1.9 (1.0 to 4.0)	0.92 (0.82 to 1.02)†	
Hospital Length of Stay (days)				0.85
No Diabetes	8.0 (7.0 to 12.0)	8.0 (6.0 to 12.0)	0.93 (0.88 to 1.00)†	
Diabetes	9.0 (7.0 to 14.0)	9.0 (7.0 to 13.0)	0.95 (0.86 to 1.06)†	
Prolonged Low Output State				0.21
No Diabetes	788/1875 (42.0)	737/1820 (40.5)	1.04 (0.91 to 1.19)	
Diabetes	269/679 (39.6)	303/717 (42.3)	0.89 (0.71 to 1.11)	
Infection				0.99
No Diabetes	92/1875 (4.9)	74/1819 (4.1)	1.23 (0.89 to 1.69)	
Diabetes	47/678 (6.9)	43/717 (6.0)	1.10 (0.71 to 1.71)	
Gut Infarction				0.6
No Diabetes	9/1875 (0.5)	4/1819 (0.2)	2.10 (0.68 to 7.78)	
Diabetes	2/678 (0.3)	2/717 (0.3)	1.09 (0.13 to 9.13)	
Seizure				0.7
No Diabetes	37/1875 (2.0)	33/1819 (1.8)	1.13 (0.70 to 1.82)	
Diabetes	16/678 (2.4)	10/717 (1.4)	1.53 (0.69 to 3.55)	
Acute Kidney Injury				0.33
No Diabetes	585/1797 (32.6)	580/1750 (33.1)	0.98 (0.85 to 1.12)	
Diabetes	267/650 (41.1)	253/687 (36.8)	1.17 (0.94 to 1.47)	
Encephalopathy				0.71
No Diabetes	21/1875 (1.1)	16/1819 (0.9)	1.31 (0.68 to 2.58)	
Diabetes	8/678 (1.2)	8/717 (1.1)	0.92 (0.33 to 2.55)	
Delirium				0.28
No Diabetes	227/1875 (12.1)	191/1819 (10.5)	1.17 (0.96 to 1.44)	
Diabetes	107/678 (15.8)	85/717 (11.9)	1.39 (1.02 to 1.90)	



	Restrictive Threshold	Liberal Threshold	Adjusted Odds Ratio (95% Confidence Interval)	P_{int}
Primary Composite				0.25
No Symptomatic Coronary Disease	32/185 (17.3)	41/199 (20.6)	0.75 (0.44 to 1.27)	
Symptomatic Coronary Disease	104/448 (23.2)	92/478 (19.2)	1.22 (0.88 to 1.70)	
Death				0.64
No Symptomatic Coronary Disease	14/185 (7.6)	12/199 (6.0)	1.21 (0.54 to 2.72)	
Symptomatic Coronary Disease	37/445 (8.3)	36/471 (7.6)	1.03 (0.63 to 1.68)	
Stroke				0.5
No Symptomatic Coronary Disease	5/174 (2.9)	7/190 (3.7)	0.75 (0.23 to 2.44)	
Symptomatic Coronary Disease	21/418 (5.0)	15/446 (3.4)	1.47 (0.74 to 2.92)	
Myocardial Infarction				0.42
No Symptomatic Coronary Disease	11/175 (6.3)	18/189 (9.5)	0.62 (0.28 to 1.37)	
Symptomatic Coronary Disease	31/422 (7.3)	33/449 (7.3)	1.02 (0.61 to 1.70)	
Dialysis				0.08
No Symptomatic Coronary Disease	7/176 (4.0)	11/192 (5.7)	0.56 (0.20 to 1.57)	
Symptomatic Coronary Disease	41/432 (9.5)	27/451 (6.0)	1.51 (0.87 to 2.62)	
Expanded Composite				0.61
No Symptomatic Coronary Disease	82/185 (44.3)	86/199 (43.2)	1.02 (0.68 to 1.55)	
Symptomatic Coronary Disease	205/448 (45.8)	208/478 (43.5)	1.06 (0.81 to 1.38)	
Revascularization				0.8
No Symptomatic Coronary Disease	2/174 (1.1)	3/190 (1.6)	0.72 (0.12 to 4.45)	
Symptomatic Coronary Disease	5/419 (1.2)	5/444 (1.1)	1.08 (0.31 to 3.79)	
Healthcare Utilization				0.54
No Symptomatic Coronary Disease	69/180 (38.3)	59/192 (30.7)	1.41 (0.91 to 2.19)	
Symptomatic Coronary Disease	143/424 (33.7)	154/448 (34.4)	0.95 (0.71 to 1.26)	
ED Visits				0.93
No Symptomatic Coronary Disease	48/178 (27.0)	48/192 (25.0)	1.13 (0.70 to 1.8)	
Symptomatic Coronary Disease	100/420 (23.8)	113/445 (25.4)	0.91 (0.66 to 1.24)	
Hospital Readmission				0.38
No Symptomatic Coronary Disease	53/178 (29.8)	39/192 (20.3)	1.66 (1.02 to 2.68)	
Symptomatic Coronary Disease	111/421 (26.4)	114/443 (25.7)	1.01 (0.74 to 1.38)