

Supplementary Online Content

Garg AX et al. for the TRICS-III Investigators. Safety of a Restrictive versus Liberal Approach to Red Blood Cell Transfusion on the Outcome of Acute Kidney Injury in Patients Undergoing Cardiac Surgery: A Randomized Clinical Trial

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Supplemental Table 1. TRICS-III patient eligibility criteria

Inclusion criteria
<ul style="list-style-type: none">• Age \geq 18 years• Scheduled to have cardiac surgery with cardiopulmonary bypass• EuroSCORE I^a \geq6
Exclusion criteria
<ul style="list-style-type: none">• Refusal or inability to receive blood products• Involved in a preoperative autologous donation program• Having a heart transplant• Having surgery solely for the insertion of a ventricular assist device• Pregnant or lactating

Abbreviations: EuroSCORE, European System for Cardiac Operative Risk Evaluation.

^a Patients had a moderate-to-high risk for death as defined by a preoperative score of 6 or more on the additive EuroScore I (scores range from 0 to 47 with higher scores indicating a higher risk of death after cardiac surgery).^{1,2}

Supplemental Table 2. Justification of changes made to the published protocol of the kidney substudy

Protocol (<i>Can J Kid Health Dis</i> 2018;5:1)	Change and its justification
Exclusion criteria	
<p>Page 4:</p> <p>(1) Patients with pre-operative end-stage kidney disease, defined as previous chronic dialysis, receipt of a kidney transplant, or an estimated glomerular filtration rate <15 mL/min per 1.73 m².</p> <p>(2) Patients missing a preoperative serum creatinine value or date of surgery (which is needed to define acute kidney injury); less than 1% of randomized patients were excluded for this reason.</p>	<p>Change: (1) Patients with preoperative end-stage kidney disease, defined as previous chronic dialysis, an estimated glomerular filtration rate <15 mL/min per 1.73 m², or anuria or oliguria <10 mL/hour.</p> <p>(2) Patients missing a preoperative serum creatinine value or date of surgery (both are needed to define acute kidney injury).</p> <p>Justification</p> <p>Patients were excluded if they had critical renal failure before surgery; while urine output measurement is often inaccurate, if it was noted that the patient had anuria or oliguria <10 mL/hour before surgery, this was considered good evidence that the patient had some component of acute kidney injury going into the surgery, making the assessment of de novo acute kidney injury after the surgery attributed to the transfusion approach problematic.</p> <p>Two patients who were missing date of surgery were excluded because this information is needed to assess whether acute kidney injury occurred within a specific number of days from surgery.</p> <p>The exclusion of pilot patients was not explicitly stated in the protocol; however, these patients were excluded from the substudy because daily postoperative serum creatinine measurements (which are needed for the assessment of acute kidney injury) were not collected in these patients.</p>
Missing data	
<p>Page 5: We expect that data on postoperative serum creatinine will be missing for <2% of participants due to death and <5% due to missing data. For patients who were randomized but are missing at least 1 postoperative serum creatinine value, we will use recommended model-based multiple imputation methods using all available data to impute acute kidney injury status.</p> <p>Page 14: We will perform several supporting analyses including ... an inverse probability weighted analysis.</p>	<p>Change: A value of 0 (no acute kidney injury) was imputed for 18 patients (0.4%) with no available postoperative serum creatinine measurements.</p> <p>Justification: Only 18 patients (0.4%) had missing outcome data and 16/18 died within one day of surgery, which means the validity of using multiple imputation is questionable. An inverse probability weighted estimating equations method, where the inverse of the conditional probability of missingness is the weight, is not sensible with such a low probability of missingness.</p>

Supplemental Table 3. Prespecified covariates assessed before surgery and used in adjusted analyses

Variable name	Units
Age	Years
Sex	Male; female
Hemoglobin	g/dL
Left ventricular function	(>50%, ≤50%)
Diabetes mellitus	Yes; no
Treated hypertension	Yes; no
Preoperative eGFR category	≥60; <60 mL/min per 1.73m ²

Abbreviations: eGFR, estimated glomerular filtration rate.

Supplemental Table 4. Baseline characteristics of patients in the per-protocol analyses of the TRICS-III main trial (non-pilot patients) (N = 4683) and the kidney substudy (N = 4531)

	Main study (n = 4683)	Kidney substudy (n = 4531)	Excluded from kidney sub-study (n=152)
Preoperative characteristics			
Age, mean (SD), y	72 (10)	72 (10)	67 (12)
Men, No. (%)	3030 (64.7%)	2924 (64.5%)	106 (69.7%)
Body mass index, ^a mean (SD), kg/m ²	28 (5)	28 (5)	28 (6)
Height, ^a mean (SD), cm	168 (10)	168 (10)	168 (11)
Weight, mean (SD), kg	79 (17)	79 (17)	80 (18)
Race/ethnicity, No. (%)			
Caucasian	4219 (90.1%)	4095 (90.4%)	124 (81.6%)
South Asian	165 (3.5%)	158 (3.5%)	7 (4.6%)
East Asian	76 (1.6%)	68 (1.5%)	8 (5.3%)
African descent	33 (0.7%)	31 (0.7%)	2 (1.3%)
Other	190 (4.1%)	179 (4.0%)	11 (7.2%)
Treated hypertension, No. (%)	3460 (73.9%)	3348 (73.9%)	112 (73.7%)
Systolic blood pressure, ^b mean (SD), mm Hg	130 (20)	131 (20)	128 (20)
Diastolic blood pressure, ^b mean (SD), mm Hg	70 (12)	70 (12)	70 (13)
Diabetes, No. (%)	1280 (27.3%)	1213 (26.8%)	67 (44.1%)
Diabetes requiring insulin, No./total, No. (%)	494/1280 (38.6%)	451/1213 (37.2%)	43/67 (64.2%)
Left ventricular function, No./total, No. (%)			
Good	2907/4681 (62.1%)	2829/4529 (62.5%)	78 (51.3%)
Moderate	1380/4681 (29.5%)	1324/4529 (29.2%)	56 (36.8%)
Poor	310/4681 (6.6%)	295/4529 (6.5%)	15 (9.9%)
Very poor	84/4681 (1.8%)	81/4529 (1.8%)	3 (2.0%)
Serum creatinine, ^c mean (SD), μmol/L	102 (70)	95 (33)	347 (278)
eGFR, ^{c,d} mean (SD), mL/min per 1.73 m ²	67 (21)	68 (19)	39 (37)
eGFR categories,^d No. (%)			
eGFR ≥ 60 mL/min per 1.73 m ²	3031/4594 (66.0%)	2989 (66.0%)	42/63 (66.7%)
eGFR 45-59 mL/min per 1.73 m ²	947/4594 (20.6%)	939 (20.7%)	8/63 (12.7%)

	Main study (n = 4683)	Kidney substudy (n = 4531)	Excluded from kidney sub-study (n=152)
eGFR 30-44 mL/min per 1.73 m ²	453/4594 (9.9%)	448 (9.9%)	5/63 (7.9%)
eGFR 15-29 mL/min per 1.73 m ²	163/4594 (3.6%)	155 (3.4%)	8/63 (12.7%)
Hemoglobin, ^e mean (SD, g/dL)	13.1 (1.8)	13.2 (1.7)	117 (20)
Previous cardiac surgery, No. (%)	570 (12.2%)	550 (12.1%)	20 (13.2%)
Aspirin use within 1 week before surgery, No. (%)	2477/4676 (53.0%)	2390/4525 (52.8%)	87/151 (57.6%)
Operative Characteristics			
Type of surgery, No./total, No. (%)			
CABG only	1221/4682 (26.1%)	1160 (25.6%)	61/151 (40.4%)
CABG and valve surgery	892/4682 (19.1%)	865 (19.1%)	27 (17.9%)
CABG and other non-valve surgery	392/4682 (8.4%)	383 (8.5%)	9 (6.0%)
Valve surgery only	1366/4682 (29.2%)	1329 (29.3%)	37 (24.5%)
Non-CABG surgery	811/4682 (17.3%)	794 (17.5%)	17 (11.3%)
Duration of cardiopulmonary bypass, ^f mean (SD), minutes	121 (58)	121 (58)	123 (72)

Abbreviations: eGFR, estimated glomerular filtration rate; CABG, coronary artery bypass graft.

^a Data missing in 1 patient.

^b Systolic blood pressure is missing in 6 patients. Diastolic blood pressure is missing in 7 patients.

^c Serum creatinine and eGFR are missing in 21 non-pilot main study patients.

^d eGFR was calculated using the CKD-EPI equation³: $eGFR = 141 * \min(Scr/k, 1)^\alpha * \max(Scr/k, 1)^{-1.209} * 0.993^{Age} * 1.018$ [if female] * 1.159 [if black], where Scr is serum creatinine (mg/dL), $\kappa = 0.7$ for females and 0.9 for males, $\alpha = -0.329$ for females and -0.411 for males.

^e Hemoglobin is missing in 1 non-pilot main study patient.

^f Duration of cardiopulmonary bypass is missing in 2 patients.

Supplemental Table 5. Baseline characteristics of patients in the per-protocol analysis (N = 4531) and the intention-to-treat analysis of the kidney sub-study (N = 4723)

	Group		
	Intention to treat (n = 4723)	Per protocol (n = 4531)	Excluded from per- protocol analysis (n = 192)
Preoperative characteristics			
Age, mean (SD), y	72 (10)	72 (10)	73 (10)
Men, No. (%)	3035 (64.3%)	2924 (64.5%)	111 (57.8%)
Body mass index, ^a mean (SD), kg/m ²	28 (5)	28 (5)	27 (5)
Height, ^a mean (SD), cm	168 (10)	168 (10)	166 (10)
Weight, mean (SD), kg	79 (17)	79 (17)	75 (16)
Race/ethnicity, No. (%)			
Caucasian	4264 (90.3%)	4095 (90.4%)	169 (88.0%)
South Asian	164 (3.5%)	158 (3.5%)	6 (3.1%)
East Asian	75 (1.6%)	68 (1.5%)	7 (3.7%)
African descent	34 (0.7%)	31 (0.7%)	3 (1.6%)
Other	186 (3.9%)	179 (4.0%)	7 (3.7%)
Treated hypertension, No. (%)	3499 (74.1%)	3348 (73.9%)	151 (78.7%)
Systolic blood pressure, ^b mean (SD), mm Hg	130 (20)	131 (20)	129 (19)
Diastolic blood pressure, ^b mean (SD), mm Hg	70 (12)	70 (12)	70 (12)
Diabetes, No. (%)	1266 (26.8%)	1213 (26.8%)	53 (27.6%)
Diabetes requiring insulin, No./total, No. (%)	470/1266 (37.1%)	451/1213 (37.2%)	19/53 (35.9%)
Left ventricular function, No./total, No. (%)			
Good	2941/4721 (62.3%)	2829/4529 (62.5%)	112 (58.3%)
Moderate	1387/4721 (29.4%)	1324/4529 (29.2%)	63 (32.8%)
Poor	308/4721 (6.5%)	295/4529 (6.5%)	13 (6.8%)
Very poor	85/4721 (1.8%)	81/4529 (1.8%)	4 (2.1%)
Serum creatinine, mean (SD), µmol/L	94 (33)	95 (33)	98 (37)
eGFR, ^c mean (SD), mL/min per 1.73 m ²	68 (20)	68 (19)	66 (22)
eGFR categories,^c No. (%)			

	Group		
	Intention to treat (n = 4723)	Per protocol (n = 4531)	Excluded from per- protocol analysis (n = 192)
eGFR ≥ 60 mL/min per 1.73 m ²	3105 (65.7%)	2989 (66.0%)	116 (60.4%)
eGFR 45-59 mL/min per 1.73 m ²	972 (20.6%)	939 (20.7%)	33 (17.2%)
eGFR 30-44 mL/min per 1.73 m ²	480 (10.2%)	448 (9.9%)	32 (16.7%)
eGFR 15-29 mL/min per 1.73 m ²	166 (3.5%)	155 (3.4%)	11 (5.7%)
Hemoglobin, mean (SD, g/dL)	13.1 (1.7)	13.2 (1.7)	12.4 (1.8)
Previous cardiac surgery, No. (%)	580 (12.3%)	550 (12.1%)	30 (15.6%)
Aspirin use within 1 week before surgery, No. (%)	2490/4717 (52.8%)	2390/4525 (52.8%)	100 (52.1%)
Operative Characteristics			
Type of surgery, No./total, No. (%)			
CABG only	1193 (25.3%)	1160 (25.6%)	33 (17.2%)
CABG and valve surgery	910 (19.3%)	865 (19.1%)	45 (23.4%)
CABG and other non-valve surgery	409 (8.7%)	383 (8.5%)	26 (13.5%)
Valve surgery only	1380 (29.2%)	1329 (29.3%)	51 (26.6%)
Non-CABG surgery	831 (17.6%)	794 (17.5%)	37 (19.3%)
Duration of cardiopulmonary bypass, ^d mean (SD), minutes	122 (59)	121 (58)	151 (83)

Abbreviations: eGFR, estimated glomerular filtration rate; CABG, coronary artery bypass graft.

^a Data missing in 1 patient.

^b Systolic blood pressure is missing in 6 patients. Diastolic blood pressure is missing in 7 patients.

^c eGFR was calculated using the CKD-EPI equation³: $eGFR = 141 * \min(Scr/\kappa, 1)^\alpha * \max(Scr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018$ [if female] * 1.159 [if black], where Scr is serum creatinine (mg/dL), $\kappa = 0.7$ for females and 0.9 for males, $\alpha = -0.329$ for females and -0.411 for males.

^d Duration of cardiopulmonary bypass is missing in 1 patient.

Supplemental Table 6. Number of units of red blood cells transfused (N = 4531)

No. of units of red blood cells transfused	Treatment Group	
	Restrictive (n = 2251)	Liberal (n = 2280)
0	1111 (49.4%)	642 (28.2%)
1	356 (15.8%)	360 (15.8%)
2	253 (11.2%)	346 (15.2%)
3	166 (7.4%)	255 (11.2%)
4	124 (5.5%)	205 (9.0%)
≥5	241 (10.7%)	472 (20.7%)

Supplemental Table 7. Number of units of red blood cells transfused among patients with chronic kidney disease (N = 1542)

No. of units of red blood cells transfused	Treatment Group	
	Restrictive (n = 767)	Liberal (n = 775)
0	309 (40.3%)	174 (22.5%)
1	127 (16.6%)	111 (14.3%)
2	97 (12.7%)	113 (14.6%)
3	71 (9.3%)	91 (11.7%)
4	61 (8.0%)	83 (10.7%)
≥5	102 (13.3%)	203 (26.2%)

Supplemental Table 8. Prespecified supporting analysis: Complete-case analysis. Effect of a restrictive versus liberal approach to red blood cell transfusion on acute kidney injury in patients undergoing cardiac surgery

	Number of Events (%) ^a		Risk Difference ^b (95% CI)
	Restrictive	Liberal	
Primary definition			
Acute kidney injury ^c	624/2246 (27.8%)	636/2267 (28.1%)	-0.3% (-2.9%, 2.3%)
Secondary definitions			
Acute kidney injury or death ^d	636/2250 (28.3%)	662/2279 (29.1%)	-0.8% (-3.4%, 1.9%)
Acute kidney injury for at least 2 days ^{a,e}	363/2246 (16.2%)	354/2267 (15.6%)	0.5% (-1.6%, 2.7%)
Stage 2 (or higher) acute kidney injury ^{a,f}	166/2246 (7.4%)	150/2267 (6.6%)	0.8% (-0.7%, 2.3%)
Stage 3 acute kidney injury ^{a,g}	75/2246 (3.3%)	84/2267 (3.7%)	-0.4% (-1.4%, 0.7%)
Acute dialysis within 30 days of surgery ^h	54/2250 (2.4%)	66/2279 (2.9%)	-0.5% (-1.4%, 0.4%)

^a At least one postoperative serum creatinine assessment was available for 99.6% of 4531 patients; the 18 patients with no available assessments were excluded from the complete-case analysis; 16 of the 18 died within one day of surgery; none had dialysis within 30 days of surgery.

^b The unadjusted absolute risk difference was calculated as the proportion of patients with acute kidney injury in the restrictive group minus the proportion in the liberal group. A 2-sided 95% CI for the risk difference was calculated using the normal approximation for the difference in proportions. Noninferiority is accepted if the upper limit of the 2-sided 95% CI is less than the noninferiority margin of 3.5%.

^c Defined as a postoperative increase in the serum creatinine concentration (from the preoperative value) of 0.3 mg/dL or more (≥ 26.5 $\mu\text{mol/L}$) within 48 hours of surgery, or 50% or more within 7 days of surgery.

^d Met the primary definition of acute kidney injury or died within 5 days of surgery. The two participants who did not die within 30 days of surgery and did not provide a postoperative serum creatinine measurement were excluded from this analysis.

^e Defined as an increase in postoperative serum creatinine (from the preoperative value) of 0.3 mg/dL or more (≥ 26.5 $\mu\text{mol/L}$) within 48 hours of surgery, or 50% or more within 7 days of surgery—on at least 2 days (not necessarily consecutive). This definition was examined because a longer duration of acute kidney injury is associated with worse outcomes.

^f Defined as an increase in postoperative serum creatinine of 100% or more from the preoperative value or an increase to an absolute value of 4.0 mg/dL or more (≥ 353.6 $\mu\text{mol/L}$) within 7 days of surgery, or receipt of dialysis within 30 days of surgery.

^g Defined as an increase in postoperative serum creatinine of 200% or more from the preoperative value or an increase to an absolute value of 4.0 mg/dL or more (≥ 353.6 $\mu\text{mol/L}$) within 7 days of surgery, or receipt of dialysis within 30 days of surgery.

^h This definition was examined as an indication of severe acute kidney injury. In patients who received dialysis, the median increase in the serum creatinine concentration from the preoperative value to the peak postoperative value was 1.1 mg/dL (IQR, 0.6-1.9) (99 $\mu\text{mol/L}$ [IQR, 52-169]). Two patients missing data on postoperative dialysis status (1 [0.04%] in each group) were excluded from this complete-case analysis.

Supplemental Table 9. Prespecified supporting analysis: Adjusted analysis. Effect of a restrictive versus liberal approach to red blood cell transfusion on acute kidney injury in patients undergoing cardiac surgery (N = 4531)

	Number of Events (%) ^a		Adjusted Risk Difference ^b (95% CI)
	Restrictive (n = 2251)	Liberal (n = 2280)	
Primary definition			
Acute kidney injury ^c	624 (27.7%)	636 (27.9%)	0.0% (-2.7%, 2.6%)
Secondary definitions			
Acute kidney injury or death ^d	636 (28.3%)	662 (29.0%)	-0.6% (-3.3%, 2.0%)
Acute kidney injury for at least 2 days ^e	363 (16.1%)	354 (15.5%)	0.8% (-1.3%, 2.9%)
Stage 2 (or higher) acute kidney injury ^f	166 (7.4%)	150 (6.6%)	0.8% (-0.6%, 2.2%)
Stage 3 acute kidney injury ^g	75 (3.3%)	84 (3.7%)	-0.2% (-1.2%, 0.7%)
Acute dialysis within 30 days of surgery ^h	54 (2.4%)	66 (2.9%)	-0.4% (-1.1%, 0.4%)

^a At least one postoperative serum creatinine assessment was available for 99.6% of patients. Acute kidney injury was considered absent in the 18 patients with no available assessments (5 in the restrictive group and 13 in the liberal group); 16 of these 18 patients died within one day of surgery; none had dialysis within 30 days of surgery.

^b The adjusted absolute risk difference was computed using the marginal predicted probability of acute kidney injury for the restrictive-threshold group vs the liberal-threshold group using mixed effects logistic regression with a random intercept to account for randomization at the center-level. 95% CIs were computed using Stata's margins procedure with the predict (mu fixed) statement.⁴ Models included center (randomization stratum) and the following pre-specified covariates measured before surgery: age (per year), sex, hemoglobin (per 10 g/L), left ventricular systolic ejection fraction categories, diabetes mellitus, treated hypertension, and eGFR (above or below 60 mL/min per 1.73m²).

^c Defined as a postoperative increase in the serum creatinine concentration (from the preoperative value) of 0.3 mg/dL or more (≥ 26.5 $\mu\text{mol/L}$) within 48 hours of surgery, or 50% or more within 7 days of surgery.

^d Met the primary definition of acute kidney injury or died within 5 days of surgery.

^e Defined as an increase in postoperative serum creatinine (from the preoperative value) of 0.3 mg/dL or more (≥ 26.5 $\mu\text{mol/L}$) within 48 hours of surgery, or 50% or more within 7 days of surgery—on at least 2 days (not necessarily consecutive). This definition was examined because a longer duration of acute kidney injury is associated with worse outcomes.

^f Defined as an increase in postoperative serum creatinine of 100% or more from the preoperative value or an increase to an absolute value of 4.0 mg/dL or more (≥ 353.6 $\mu\text{mol/L}$) within 7 days of surgery, or receipt of dialysis within 30 days of surgery.

^g Defined as an increase in postoperative serum creatinine of 200% or more from the preoperative value or an increase to an absolute value of 4.0 mg/dL or more (≥ 353.6 $\mu\text{mol/L}$) within 7 days of surgery, or receipt of dialysis within 30 days of surgery.

^h This definition was examined as an indication of severe acute kidney injury. In patients who received dialysis, the median increase in the serum creatinine concentration from the preoperative value to the peak postoperative value was 1.1 mg/dL (IQR, 0.6-1.9) (99 $\mu\text{mol/L}$ [IQR, 52-169]).

Supplemental Table 10. Prespecified supporting analysis: Intention-to-treat noninferiority analysis. Effect of a restrictive versus liberal approach to red blood cell transfusion on acute kidney injury in patients undergoing cardiac surgery (N = 4723)

	Number of Events (%) ^a		Risk Difference ^b (95% CI)	P value (superiority) ^c
	Restrictive (n = 2361)	Liberal (n = 2362)		
Primary definition				
Acute kidney injury ^d	675 (28.6%)	666 (28.2%)	0.4% (-2.2%, 3.0%)	.76
Secondary definitions				
Acute kidney injury or death ^e	689 (29.2%)	696 (29.5%)	-0.3% (-2.9%, 2.3%)	.83
Acute kidney injury for at least 2 days ^f	404 (17.1%)	375 (15.9%)	1.2% (-0.9%, 3.4%)	.25
Stage 2 (or higher) acute kidney injury ^g	200 (8.5%)	164 (6.9%)	1.5% (0.0%, 3.1%)	.05
Stage 3 acute kidney injury ^h	101 (4.3%)	92 (3.9%)	0.4% (-0.8%, 1.5%)	.51
Acute dialysis within 30 days of surgery ⁱ	76 (3.2%)	73 (3.1%)	0.1% (-0.9%, 1.1%)	.80

^a At least one postoperative serum creatinine assessment was available for 99.6% of patients. Acute kidney injury was considered absent in the 20 patients with no available assessments (5 in the restrictive group and 15 in the liberal group); 18 of these 20 patients died within one day of surgery; none had dialysis within 30 days of surgery.

^b The unadjusted absolute risk difference was calculated as the proportion of patients with acute kidney injury in the restrictive group minus the proportion in the liberal group. A 2-sided 95% CI for the risk difference was calculated using the normal approximation for the difference in proportions. Noninferiority is accepted if the upper limit of the 2-sided 95% CI is less than the noninferiority margin of 3.5%.

^c P values for superiority tests (two-sided; alpha=0.05) were calculated when noninferiority was shown as prespecified in the protocol.

^d The primary outcome of the TRICS-III kidney substudy is perioperative acute kidney injury, defined as a postoperative increase in the serum creatinine concentration (from the preoperative value) of 0.3 mg/dL or more (≥ 26.5 $\mu\text{mol/L}$) within 48 hours of surgery, or 50% or more within 7 days of surgery.

^e Met the primary definition of acute kidney injury or died within 5 days of surgery. This accounts for the potential effect of early deaths (47/2361 [2.0%] in the restrictive group and 58/2362 [2.5%] in the liberal group) on the ascertainment of acute kidney injury.

^f Defined as an increase in postoperative serum creatinine (from the preoperative value) of 0.3 mg/dL or more (≥ 26.5 $\mu\text{mol/L}$) within 48 hours of surgery, or 50% or more within 7 days of surgery—on at least 2 days (not necessarily consecutive). This definition was examined because a longer duration of acute kidney injury is associated with worse outcomes.

^g Defined as an increase in postoperative serum creatinine of 100% or more from the preoperative value or an increase to an absolute value of 4.0 mg/dL or more (≥ 353.6 $\mu\text{mol/L}$) within 7 days of surgery, or receipt of dialysis within 30 days of surgery.

^h Defined as an increase in postoperative serum creatinine of 200% or more from the preoperative value or an increase to an absolute value of 4.0 mg/dL or more (≥ 353.6 $\mu\text{mol/L}$) within 7 days of surgery, or receipt of dialysis within 30 days of surgery.

ⁱ This definition was examined as an indication of severe acute kidney injury. In patients who received dialysis, the median increase in the serum creatinine concentration from the preoperative value to the peak postoperative value was 1.1 mg/dL (IQR, 0.6-2.0) (101 $\mu\text{mol/L}$ [IQR, 53-173]).

Supplemental Table 11. Post-hoc subgroup analyses

Subgroup	No. patients	Restrictive Threshold	Liberal Threshold	Unadjusted Risk Difference (95% CI)	<i>P</i> Value for Interaction
Age					
≥ 75 years	2170	298/1074 (27.8%)	308/1096 (28.1%)	-0.4% (-4.1 to 3.4%)	.23
< 75 years	2361	326/1177 (27.7%)	328/1184 (27.7%)	0.0% (-3.6 to 3.6%)	
CPB time					
≥ 107 ^a minutes	2270	369/1147 (32.2%)	367/1123 (32.7%)	-0.5% (-4.4 to 3.3%)	.91
< 107 minutes	2261	255/1104 (23.1%)	269/1157 (23.3%)	-0.2% (-3.6 to 3.3%)	
Surgery type					
CABG only	1160	142/570 (24.9%)	136/590 (23.1%)	1.9% (-3.1 to 6.8%)	.22
Non-CABG	2123	289/1063 (27.2%)	278/1060 (26.2%)	1.0% (-2.8 to 4.7%)	
CABG plus other	1248	193/618 (31.2%)	222/630 (35.2%)	-4.0% (-9.2 to 1.2%)	
EuroSCORE I					
≥ 8	2150	335/1088 (30.8%)	331/1062 (31.2%)	-0.4% (-4.3 to 3.5%)	.94
< 8	2376	289/1161 (24.9%)	304/1215 (25.0%)	-0.1% (-3.6 to 3.4%)	
Wijeysundera score					
0	471	50/233 (21.5%)	46/238 (19.3%)	2.1% (-5.2 to 9.4%)	.64
1	2009	252/989 (25.5%)	258/1020 (25.3%)	0.2% (-3.6 to 4.0%)	
2	1619	241/822 (29.3%)	252/797 (31.6%)	-2.3% (-6.8 to 2.2%)	
3	374	68/179 (38.0%)	70/195 (35.9%)	2.1% (-7.7 to 11.9%)	
≥ 4	58	13/28 (46.4%)	10/30 (33.3%)	13.1% (-11.9 to 38.1%)	

Abbreviations: CPB, cardiopulmonary bypass; CABG, coronary artery bypass graft; EuroSCORE, European System for Cardiac Operative Risk Evaluation.

^aThe median duration of cardiopulmonary bypass was 107 minutes.

^bPreoperative risk of renal replacement therapy after cardiac surgery.⁵

Supplemental Table 12. Number of daily postoperative serum creatinine measurements and day of measurement during the hospital stay in the per-protocol intervention groups (N = 4531)

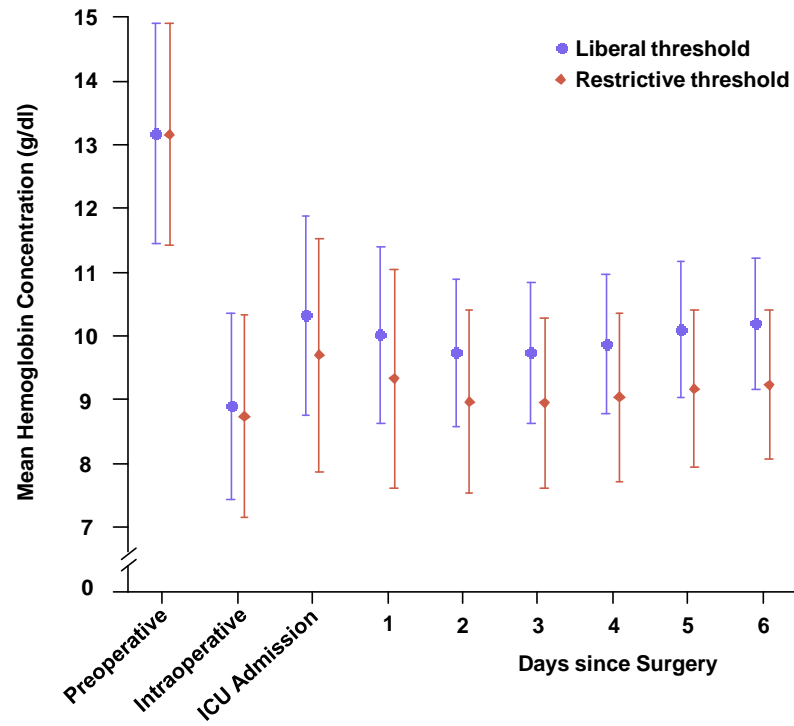
	Restrictive Threshold n = 2251	Liberal Threshold n = 2280
Postoperative measurement day^a		
Day 0	1974 (87.7%)	1979 (86.8%)
Day 1	2204/2247 (98.1%)	2215/2264 (97.8%)
Day 2	2202/2232 (98.7%)	2210/2245 (98.4%)
Day 3	2152/2222 (96.8%)	2152/2235 (96.2%)
Day 4	1782/2212 (80.6%)	1801/2226 (80.9%)
Day 5	1895/2140 (88.6%)	1898/2171 (87.4%)
Day 6	1154/1878 (61.4%)	1129/1893 (59.6%)
Day 7	980/1553 (63.1%)	933/1522 (61.3%)
Number of postoperative serum creatinine measurements^b		
0 ^c	5 (0.2%)	13 (0.6%)
1	6 (0.3%)	9 (0.4%)
2	14 (0.6%)	20 (0.9%)
3	26 (1.2%)	26 (1.1%)
4	164 (7.3%)	161 (7.1%)
5	356 (15.8%)	403 (17.7%)
6	572 (25.4%)	576 (25.3%)
7	500 (22.2%)	498 (21.8%)
8	608 (27.0%)	574 (25.2%)

^a Excludes patients who died or were discharged before the postoperative measurement day. For example, patients who were discharged or died on day 0 or day 1 are excluded from the calculation on day 2; patients who were discharged or died on day 2 or later are included.

^b Number of postoperative serum creatinine measurements in the 7-day period after surgery.

^c Of the 18 patients with no available serum creatinine assessments, 16 died within one day of surgery (4 in the restrictive group and 12 in the liberal group); no patients had dialysis within 30 days of surgery.

Supplemental Figure 1. Mean nadir hemoglobin concentration from baseline to postoperative day 7 (N = 4531)



No. of observations	
Liberal threshold	2280 2273 2266 2208 2197 2179 2117 1912 1448 1090
Restrictive threshold	2251 2247 2244 2190 2189 2171 2081 1890 1487 1128

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