Effect of sex on nadir hematocrit and rates of acute kidney injury in coronary artery bypass

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ABSTRACT

Objective: Findings from a large multicenter experience showed that sex influenced the relationship between low nadir hematocrit and increased risk of acute kidney injury after cardiac surgery. We explored whether sex-related differences persisted among patients undergoing isolated coronary artery bypass grafting.

Methods: We undertook a prospective, observational study of 17,363 patients without dialysis (13,137 male: 75.7%; 4226 female: 24.3%) undergoing isolated coronary artery bypass grafting between 2011 and 2016 across 41 institutions in the Perfusion Measures and Outcomes registry. Odds ratios between nadir hematocrit and stage 2 or 3 acute kidney injury were calculated, and the interaction of sex with nadir hematocrit was tested. The multivariable, generalized, linear mixed-effect model adjusted for preoperative and intraoperative factors and institution.

Results: Median nadir hematocrit was 22% among women and 27% among men ($P < .001$). Women were administered a greater median net prime volume indexed to body surface area (407 vs 363 mL/m²) and more red blood cell transfusions (55.5% vs 24.3%; both $P < .001$). Acute kidney injury was higher among women (6.0% vs 4.3%, $P < .001$). There was no effect of sex on the relationship between nadir hematocrit and acute kidney injury ($P = .67$). Low nadir hematocrit was inversely associated with acute kidney injury (adjusted odds ratios per 1-unit increase in nadir hematocrit 0.96; 95% confidence interval, 0.93-0.98); this effect was similar across sexes and independent of red blood cell transfusions.

Conclusions: We found no sex-related differences in the effect of nadir hematocrit on acute kidney injury after isolated coronary artery bypass grafting. However, the strong inverse relationship between anemia and acute kidney injury across sexes suggests the importance of reducing exposure to low nadir hematocrit. (J Thorac Cardiovasc Surg 2019;158:1073-80)

Relationship between nadir Hct during bypass and risk of stage 2 or 3 AKI.

Central Message

Unlike in prior studies, we found no interaction by sex in the relationship between low nadir Hct and AKI. Given its impact on AKI, anemia during isolated CABG should be avoided.

Perspective

Although sex does not modify the relationship between nadir Hct and AKI in an isolated CABG population, nadir Hct continues to confer an increased risk of AKI. These findings persisted after adjusting for baseline risk and RBC transfusions and reinforce the importance of reducing exposure to low nadir Hct on CPB.

See Commentary on page 1081.

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A.A.B. is supported by the National Research Service Award postdoctoral fellowship (No. 5T32HL076123). D.S.L. is supported in part by the Agency for Healthcare Research and Quality under Grants R01HS026003 and R01HS022535. The opinions expressed in this document are those of the authors and do not reflect the official position of the Agency for Healthcare Research and Quality or the US Department of Health and Human Services. Support for the Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative is provided by the

Blue Cross and Blue Shield of Michigan (BCBSM) and Blue Care Network as part of the BCBSM Value Partnerships program. Although the BCBSM and Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative work collaboratively, the opinions, beliefs, and viewpoints expressed by the authors do not necessarily reflect the opinions, beliefs, and viewpoints of BCBSM or any of its employees.

Received for publication Nov 28, 2018; revisions received March 2, 2019; accepted for publication March 9, 2019; available ahead of print April 30, 2019.

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0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2019.03.042>

Abbreviations and Acronyms

AKI	= acute kidney injury
BSA	= body surface area
CABG	= coronary artery bypass grafting
CI	= confidence interval
CPB	= cardiopulmonary bypass
Hct	= hematocrit
HR	= hazard ratio
MSTCVS-QC	= Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative
OR	= odds ratio
PERForm	= Perfusion Measures and Outcomes
RBC	= red blood cell

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Patients undergoing isolated coronary artery bypass grafting (CABG) surgery are at risk for many morbid events, including acute kidney injury (AKI). Prior reports suggest that a spectrum of AKI develops in approximately 30% of patients, with 0.4% to 2% of patients requiring postoperative renal replacement therapy.¹⁻⁴ Emerging literature has documented the risk of further sequelae due to even small increases in creatinine (stage 1 AKI), including an increased risk of mortality (hazard ratio [HR], 1.56; 95% confidence interval [CI], 1.14-2.12), readmission (HR, 1.31; CI, 1.10-1.57) and an approximately 3-fold increased risk of developing end-stage renal disease (HR, 2.92; CI, 1.87-4.55).^{5,6}

Prior studies have documented an inverse relationship between a patient's intraoperative exposure to low nadir hematocrit (Hct) during cardiopulmonary bypass (CPB) and risk of AKI. Although women may be uniquely susceptible to AKI given their increased risk of lower nadir Hct secondary to hemodilution, prior reports have shown conflicting results.⁷⁻⁹ These reports have included a heterogeneous population of cardiac procedures and likely cannot be generalizable to isolated CABG procedures. Thus, efforts aimed at reducing a patient's risk of AKI after isolated CABG requires further investigation into a potential interaction between sex and intraoperative anemia.

In the present analysis, we identified whether sex modifies the relationship between intraoperative anemia and AKI in the setting of isolated CABG (Figure E1). To do so, we conducted an observational study of

nondialysis-dependent patients undergoing isolated CABG across 41 hospitals participating in a multi-institutional quality improvement database.

PATIENTS AND METHODS

This study was approved by the Institutional Review Board of the University of Michigan Health System (HUM00117260, notice of determination of "Not Regulated").

Patient Population

The Perfusion Measures and Outcomes (PERForm) registry is organizationally structured within the Michigan Society of Thoracic and Cardiovascular Surgeons Quality Collaborative (MSTCVS-QC). The MSTCVS-QC began in 2001 as a cardiac surgeon-led quality collaborative embedded in the MSTCVS, and in 2005, it became partially funded by the Blue Cross/Blue Shield of Michigan insurance company. The collaborative meets quarterly to review various processes and outcomes, and to facilitate and evaluate quality improvement studies.

All programs in the MSTCVS-QC use The Society of Thoracic Surgeons data collection forms and submit data on a quarterly basis to the MSTCVS-QC data warehouse. The PERForm registry is the official registry of the American Society of ExtraCorporeal Technology (<http://www.amsect.org>), and the American Society of ExtraCorporeal Technology in turn is the PERForm registry's official societal partner. The PERForm registry contains information related to the care and conduct of cardiovascular perfusion practices. A list of fields and definitions may be found at <http://www.performregistry.org>. Each center's surgical record is merged with a perfusion record from the PERForm registry.¹⁰ Participating centers are routinely audited for data validity and accuracy as part of the MSTCVS-QC audit system.

We included patients who underwent isolated CABG with use of CPB at any of the 41 centers participating in the PERForm registry between July 11, 2011, and September 30, 2016. We excluded patients undergoing dialysis preoperatively or CPB with circulatory arrest, and those with a ventricular assist device.

Measures

The primary outcome for this analysis was stage 2 or 3 AKI, using the Acute Kidney Injury Network creatinine criteria (defined as a 2-fold or greater increase in serum creatinine from baseline, creatinine increase to ≥ 4.0 mg/dL with an acute increase >0.5 mg/dL, or acute dialysis requirement).¹¹ We report crude rates of transfusions, hospital operative mortality, reoperation for bleeding, prolonged ventilation time more than 24 hours, total intensive care unit stay more than 24 hours, need for ultrafiltration or dialysis, low cardiac output, new-onset atrial fibrillation, sepsis, postoperative length of stay, and 30-day readmission.

Statistical Analysis

Categorical variables were presented as percentages and continuous variables as mean (standard deviation) for univariate analyses. Chi-square and Fisher exact tests were used to test statistical significance for categorical variables, and Wilcoxon rank-sum tests were used for continuous variables.

Missing values of categorical variables with less than 1% missingness were imputed with their lowest risk values. Missing values of continuous variables were imputed to conditional median by sex. The number of missing observations for variables included in the final model and method of imputation are shown in Table E1. Variables were selected using a logistic regression model with the Least Absolute Shrinkage and Selection Operator penalized method. The final model included preoperative and intraoperative factors: surgical year, age, sex, body surface area (BSA), diabetes, peripheral vascular disease, chronic lung disease, preoperative Hct,

TABLE 1. Preoperative patient characteristics

Variable	Female	Male	P value
No. of procedures	4226	13,137	
Age, median [IQR] y	67 [59-74]	65 [58-72]	<.001
<60	25.5	30.2	
60-69	33.8	36.7	
70+	40.7	33.1	
			<.001
BSA, m ²			
<1.60	10.6	0.7	
1.60-1.79	27.1	6.1	
1.80-1.99	33.3	24.1	
≥2.00	28.9	69.2	
			<.001
Risk factors			
Diabetes mellitus, % yes	53.3	44.0	<.001
Vascular disease, % yes	16.8	14.3	<.001
Moderate-severe COPD, % yes	11.8	10.1	.0013
Last preoperative creatinine, mg/dL, median [IQR]	0.93 [0.70-1.04]	1.06 [0.88-1.20]	<.001
Hct, %			
<33	20.6	8.1	
33-36	30.3	14.2	
37-40	31.9	28.1	
41+	17.2	49.6	
			<.001
Hypertension, % yes	91.8	88.8	<.001
EGFR <30 mL/min/1.73 m ² , % yes	3.1	1.3	<.001
EGFR, mL/min/1.73 m ²			
≥90	26.5	30.6	
60-90	42.4	50.7	
30-60	28.0	17.4	
15-30	2.9	1.1	
<15	0.2	0.2	
			<.001
Last WBC count × 10 ⁹ /L, median [IQR]	7.8 [6.3-9.5]	7.5 [6.2-9.2]	<.001
Current smoker within 30 d, %	22.6	22.7	.949
Cardiac history			
CHF, % yes	17.4	12.8	<.001
Prior myocardial infarction, %	54.4	53.2	.15
Prior CABG, %	1.5	2.0	.04
Prior cardiac surgery, %	2.2	2.5	.34
Cardiac anatomy and function			
LVEF, %			
<40	12.9	15.7	
40-49	13.4	15.4	
50-59	32.3	34.7	
60+	41.4	34.1	
			<.001
Left main disease ≥50% stenosis, % yes	34.5	33.9	.44
3+ diseased vessels, % yes	74.3	79.6	<.001
Acuity			
Elective	34.9	41.3	
Urgent	61.1	56.2	
Emergency/salvage	3.9	2.5	

(Continued)

TABLE 1. Continued

Variable	Female	Male	P value
			<.001
STS mortality and morbidity risk score, median % [IQR]	14 [10-21]	10 [7-16]	<.001

IQR, Interquartile range; BSA, body surface area; COPD, chronic obstructive pulmonary disease; Hct, hematocrit; EGFR, estimated glomerular filtration rate; WBC, white blood cell; CHF, congestive heart failure; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; STS, Society of Thoracic Surgeons.

estimated glomerular filtration rate, white blood cell, hypertension, congestive heart failure, New York Heart Association classification, ejection fraction, acuity status, number of diseased vessels, perfusion time, crossclamp time, static volume indexed to BSA, preoperative or intraoperative intra-aortic balloon pump, total volume of fluid in during operation, use of acute normovolemic hemodilution, total cardioplegia volume, lowest temperature during the operation, furosemide use, net prime volume indexed to BSA, and lowest Hct during the operation (and its interaction with sex). The final generalized linear mixed model used a logit link function and included centers as the random effect to account for the clustering of patients within each center.

Sensitivity analyses were performed by analyzing the effect of lowest Hct separately by strata of sex. The effect of nadir Hct on AKI is reported as the odds ratio (OR) per 1-unit increase in nadir Hct. The predicted probability of AKI, fixing the adjusted covariates at the median of the continuous variables or the mode values of the categorical variables (along with 95% CIs), was plotted separately for men and women. Sensitivity analyses were also performed to assess the effect of sex on the relationship between nadir Hct and AKI when stratified by red blood cell (RBC) transfusion status. All statistical calculations used R version 3.4.0 and SAS 9.4 (SAS Institute, Inc, Cary, NC). *P* values of less than .05 (2-tailed) were considered statistically significant.

RESULTS

Between July 11, 2011, and September 30, 2016, 17,873 patients underwent isolated CABG at the 41 participating centers. After excluding patients presenting on dialysis (*n* = 443), using a ventricular assist device (*n* = 2), undergoing intraoperative circulatory arrest (*n* = 8), undergoing another cardiac procedure (*n* = 10), or with missing data for AKI staging (*n* = 155), the final study population consisted of 17,363 patients (13,137 male and 4226 female).

Preoperative patient characteristics are listed in detail in Table 1. Women were slightly older and had higher rates of preoperative diabetes, vascular disease, hypertension, and congestive heart failure than men. Additionally, women had lower baseline Hct and estimated glomerular filtration rate, but higher procedural acuity. Smoking history and prevalence of significant left main coronary artery disease were similar between women and men.

Intraoperative characteristics differed between women and men (Table 2). Bypass and crossclamp times were slightly shorter for women compared with men, although women returned to bypass more frequently than men (2.6% vs 1.7%, *P* < .001) and received intra-aortic balloon pumps more commonly in the intraoperative or postoperative period (2.2% vs 1.4%, *P* < .001). Women were administered a greater median net prime volume indexed to BSA, greater total fluid, and a lower median volume of ultrafiltration. Acute normovolemic hemodilution, a

blood conservation strategy, was used less commonly among women (9.0% vs 15.7%). Median nadir Hct was lower among women (22.1% vs 26.9%, *P* < .001). Less than half (48.0%) of women reached a nadir Hct less than 21, compared with only 13.3% of men, whereas women were administered significantly more intraoperative RBC transfusions (33.7% vs 8.1%, *P* < .001).

Initial postoperative Hct was 28.0% in women and 32.0% in men, whereas median postoperative creatinine was 0.9 for women and 1.1 for men (both *P* < .001) (Table 3). Significantly more women exhibited stage 2 or 3 AKI than men (6.0% vs 4.3%, *P* < .001). Women had higher rates for prolonged ventilation, postoperative renal replacement therapy, low cardiac output, RBC transfusion, pneumonia, sepsis, and hospital mortality. Although men were more likely to have new-onset atrial fibrillation, women had longer stays in both the intensive care unit and hospital and were at a higher risk for readmission.

After adjustment, sex did not modify the relationship between nadir Hct and the risk of AKI (*P* = .67, full multivariable table in Table E2). Lower nadir Hct was inversely associated with AKI (adjusted OR per 1-unit increase in nadir Hct 0.96; 95% CI, 0.93-0.98), and this adjusted effect was similar across women (adjusted OR, 0.96; 95% CI, 0.94-0.99) and men (adjusted OR, 0.96; 95% CI, 0.93-0.98) (Figure 1). In sensitivity analyses, the interaction between nadir Hct and sex remained nonsignificant both for patients who received intraoperative RBC transfusion (*P* = .88) and for those who did not (*P* = .32).

Discussion

We used our multi-institutional quality improvement collaborative to investigate whether sex modified the relationship between nadir Hct on CPB and AKI among patients undergoing isolated CABG. Relative to men, women were more likely to be exposed to a lower Hct, to receive RBC transfusions, and to develop postoperative AKI. Women were also at higher risk for nearly every other postoperative complication compared with men, except for new-onset atrial fibrillation. As expected, nadir Hct was inversely associated with AKI. However, in contrast to the prior series evaluating CABG and valve operations,⁹ sex did not modify the relationship between nadir Hct and AKI for patients undergoing isolated CABG, a finding independent of intraoperative RBC transfusions.

TABLE 2. Intraoperative variables

Variable	Female	Male	P value
No. of procedures	4226	13,137	
No. of distal anastomoses			
1	3.2	1.6	
2	20.9	15.0	
3	44.8	41.8	
4+	31.2	41.6	
			<.001
CPB duration, min, median [IQR]	90 [69-117]	93 [73-121]	<.001
Crossclamp duration, min, median [IQR]	68 [52-89]	71 [55-93]	<.001
Returned to bypass, %	2.6	1.7	<.001
IABP, % yes			
Preoperative	7.3	6.7	
Intraoperative	1.7	1.2	
Postoperative	0.5	0.2	
			.0008
Pulsatile perfusion, % yes	0.8	0.8	.80
Strategies to manage hemodilution			
Static prime volume per BSA, mL/m ² , median [IQR]	552 [467-667]	511 [428-604]	<.001
Retrograde autologous priming, % yes	77.9	79.2	.051
Retrograde autologous priming, mL, median [IQR]	550 [400-700]	600 [400-700]	<.001
Net prime volume* per BSA, mL/m ² , median [IQR]	407 [282-566]	363 [251-498]	<.001
Total fluid administration,† mL, median [IQR]	1000 [560-1700]	938 [518-1600]	<.001
Blood management strategies			
Conventional ultrafiltration, % yes	23.1	21.8	.073
Volume if performed, mL, median [IQR]	1200 [700-2050]	1400 [800-2500]	<.001
Cell-saving device, % yes	85.4	85.0	.49
Acute normovolemic hemodilution, % yes	9.0	15.7	<.001
Volume, mL, median [IQR]	450 [400-500]	450 [450-900]	<.001
Cardiotomy suction, % yes	61.5	59.3	.022
Blood-based cardioplegia, % yes	75.9	74.3	.026
Total cardioplegia volume, mL, median [IQR]	2000 [1300-2800]	2136 [1450-3090]	<.001
Lowest core temperature‡			
Severe hypothermia	0.3	0.3	
Moderate hypothermia	4.7	3.4	
Mild hypothermia	67.7	67.7	
Normothermia	27.3	28.6	
			.0013
Furosemide use, % yes	4.5	5.4	.014
Sodium bicarbonate total dose, mg, median [IQR]	50 [40-50]	50 [40-50]	.16
Vasopressin, % yes	9.4	9.2	.75
Nadir Hct			
<19	15.8	3.0	
19-21	32.2	10.3	
22-24	28.3	18.0	
25-27	15.3	25.6	
28+	8.4	43.2	
			<.001

CPB, Cardiopulmonary bypass; IQR, interquartile range; IABP, intra-aortic balloon pump; BSA, body surface area; Hct, hematocrit. *Net prime volume = total prime volume – retrograde autologous prime volume. †Sum: [total volume delivered to patient + 350 × red blood cells given + 250 × fresh frozen plasma + cell saver volume] – [ultrafiltration volume + urine output]. ‡Severe hypothermia less than 28.0°C, moderate hypothermia 28°C to 31.9°C, mild hypothermia 32.0°C to 34.9°C, normothermia ≥35.0°C.

TABLE 3. Postoperative outcomes

Variable	Female	Male	P value
No. of procedures	4226	13,137	
Hct, first in ICU, %, median [IQR]	28.0 [25.0-31.0]	32.0 [28.0-35.0]	<.001
Postoperative creatinine, mg/dL, median [IQR]	0.9 [0.8-1.3]	1.1 [0.9-1.4]	<.001
Outcome, % yes			
Death, in hospital	3.4	1.6	<.001
Reoperation for bleeding	1.4	1.7	.17
Prolonged ventilation	11.1	7.1	<.001
Need for ultrafiltration	0.5	0.3	.006
Need for dialysis	1.8	1.3	.02
AKI, stage 2/3	6.0	4.3	<.001
Low cardiac output*	6.3	4.6	<.001
RBC use			
None	44.5	75.7	
Intraoperative only	17.7	3.6	
Postoperative only	21.8	16.2	
Intraoperative and postoperative	16.0	4.5	
			<.001
Intraoperative RBC units (if transfused), median [IQR]	2 [1-2]	1 [0-2]	<.001
Postoperative RBC units (if transfused), median [IQR]	2 [1-2]	2 [1-3]	.76
Pneumonia	3.0	2.4	.02
New-onset atrial fibrillation	23.1	27.1	<.001
Sepsis	1.3	0.8	.01
Intensive care unit, d			
<1	22.6	28.2	
1-2	23.1	25.9	
2-3	19.4	20.0	
3-4	12.6	10.2	
4+	22.3	15.8	
			<.001
Postoperative hospital d, median [IQR]	6 [5-8]	6 [5-7]	<.001
Readmission, %	5.7	3.6	<.001

Hct, Hematocrit; ICU, intensive care unit; IQR, interquartile range; AKI, acute kidney injury; RBC, red blood cell. *Low cardiac output defined as the return to bypass, ≥ 2 inotropes at 48 hours, or use of an intraoperative or postoperative intra-aortic balloon pump.

We acknowledge several limitations to our present study. First, although we adjusted for commonly reported risk factors, we cannot rule out the effect of unmeasured confounding. Second, we acknowledge that a number of potential mechanisms may contribute to the development of AKI (eg, hypotension, preoperative volume status, nephrotoxins); nonetheless, we evaluated the role of a number of factors likely contributing to hemodilution (eg, administration of priming fluid, cardioplegia, total fluid administration). Third, although other studies have evaluated AKI incidence and staging using urine output, we report previously established creatinine-based criteria. Fourth, because of the large size of our dataset, we recognize that some statistically significant differences in sex across many characteristics (eg, prime volume per BSA, retrograde autologous priming volume) are small in absolute magnitude and thus unlikely to be clinically relevant.

Multiple single-center studies have demonstrated an increased risk of AKI associated with a lower intraoperative Hct, including cohorts consisting of cardiac surgery using CPB^{8,12} and those limited to isolated CABG.^{13,14} One multicenter study of patients undergoing isolated CABG not only found nadir Hct to be independently associated with postoperative renal failure and low cardiac output syndrome but also found female sex to be associated with increased mortality on multivariable analysis.¹⁵ Few prior studies have assessed the effect of sex on the well-established relationship between nadir Hct and AKI. The studies exploring the relationship between nadir Hct and AKI have divided patients into 2 of 3 cohorts and established various threshold Hct values that conferred harm, for example, concluding those with Hct less than 21% or greater than 25% have increased risk of dialysis,¹² hemodilution to Hct less than 24% associated with increased

FIGURE 1. Relationship between nadir Hct during CPB and risk of stage 2 or 3 AKI. The predicted probability of AKI is plotted for male patients (solid line) and female patients (dashed line), along with 95% CIs (shaded areas). The model adjusted for preoperative and intraoperative factors, as well as hospital variation.

likelihood of renal injury,¹⁴ and Hct greater than 21% deemed safe for renal function¹⁶ in 3 separate analyses. In contrast to these studies, we evaluate Hct as a continuous variable across the entire range of nadir values, which allows assessment of AKI risk across all Hct and not as a binary variable.

One large single-center study by Mehta and colleagues⁸ examined the effect of sex on the relationship between nadir Hct and AKI among 13,734 cardiac surgical patients. The

authors found that nadir Hct was significantly associated with AKI in both men and women, albeit women had a lower nadir Hct during CPB. The authors further concluded that exposure to Hct 22% or less during CPB was associated with a nonsignificant increased rate of AKI among men, although this relationship did not persist when stratified by transfusion status. Ellis and colleagues⁹ used the PERForm registry to assess the relationship between nadir Hct and AKI among patients undergoing a variety of cardiac surgical procedures. The authors concluded that lower nadir Hct was associated with an increased risk of AKI among both men and women. Additionally, sex modified the relationship between nadir Hct and AKI; the odds of AKI was significantly lower in women than men at a given nadir Hct. In contrast to the study by Mehta and colleagues,⁸ this relationship persisted after adjusting for RBC transfusion. Nonetheless, the majority of men in the series by Ellis and colleagues⁹ underwent isolated CABG (57.1% vs 41.3%), whereas far fewer men underwent isolated valve procedures (22.6% vs 38.1%). The fundamental pathophysiology of coronary disease and valvular dysfunction vastly differs, which may confound the apparent relationship between nadir Hct during CPB and AKI for both men and women. The present analysis furthers our understanding of the relationship between nadir Hct and AKI by assessing whether the demonstrated interaction by sex persists among patients presenting for treatment of their coronary disease. Notably, we conclude that the aforementioned interaction by sex was not significant, and that the inverse relationship between nadir Hct and AKI persisted

FIGURE 2. Visual abstract showing rates of stage 2 or 3 AKI and blood transfusions by sex, interaction of sex on the relationship between nadir Hct and AKI, and study conclusions (right). AKI, Acute kidney injury; Hct, hematocrit; RBC, red blood cell.

across men and women, and independent of RBC transfusions.

A number of reasons might help explain why our present findings differ from those reported by Ellis and colleagues.⁹ The difference in outcome in the effect of sex on the relationship between nadir Hct and AKI may be due to the difference in surgical procedures, involved centers, and time period. Specifically, Ellis and colleagues⁹ included 15,221 patients across 26 centers who underwent a variety of surgical procedures (ie, CABG, valve, or CABG/valve) between 2010 and 2014, whereas the present analysis examined 17,363 patients undergoing isolated CABG across 41 centers between 2011 and 2016. Additionally, the effect demonstrated in the analysis by Ellis and colleagues⁹ did not persist among those patients who did not receive intraoperative RBC transfusion ($P = .16$). The effect of sex in our analysis was nonsignificant for patients who received intraoperative RBC transfusion ($P = .88$) and patients who did not ($P = .32$).

Although one may expect women to reach a lower nadir Hct intraoperatively because they began with lower Hct preoperatively, our data showing increased risk of AKI with lower nadir Hct across sexes should prompt enhanced fluid restrictive management strategies for women, because they did not appear to have sex-related renal protective mechanisms during CABG and may enter the operation at increased risk for postoperative AKI. In contrast, the administered net prime volume adjusted for BSA was higher for women than men (407 vs 363 mL/m², $P < .001$). Additionally, only 9% of women underwent acute normovolemic hemodilution, despite approximately 80% of women presenting with an Hct greater than 33%. Our data show that teams were less willing to attempt blood conservation techniques and more likely to transfuse RBCs in women than in men. The preoperative risk factors carried by women were compounded by intraoperative management strategies and resulted in a higher rate of AKI in women (6.0% vs 4.3%, $P < .001$).

This multicenter observational study reinforces the potential harmful associated sequelae due to low nadir Hct during CPB. We found that women were administered more net prime volume per BSA intraoperatively, reached lower nadir Hct, and had higher rates of stage 2 and 3 AKI postoperatively, in addition to being at higher risk for nearly every postoperative complication.

CONCLUSIONS

We report that in an isolated CABG population, no effect of sex was found on the established inverse relationship between nadir Hct and AKI, a finding that persisted after adjustment for RBC transfusions (Figure 2). These data indicate that the same deleterious effects of low Hct persist

across sexes and reinforce the importance of reducing exposure to low nadir Hct on CPB.

Conflict of Interest Statement

H.J.P. is a consultant for WL Gore, Medtronic, and Terumo. All other authors have nothing to disclose with regard to commercial support.

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Key Words: nadir hematocrit, acute kidney injury, coronary artery bypass grafting, cardiopulmonary bypass, blood conservation, blood transfusion

FIGURE E1. Conceptual model showing the research question of whether sex functions as an effect modifier on the known strong inverse relationship between nadir Hct on CPB and postoperative AKI. *GFR*, Glomerular filtration rate; *NYHA*, New York Heart Association; *ANH*, acute normovolemic hemodilution; *BSA*, body surface area; *Hct*, hematocrit; *AKI*, acute kidney injury.

TABLE E1. Missing observations for variables included in the final model, stratified by sex and with imputation methods listed, if applicable

Variable	Female missing observations, total n = 4226 (%)	Male missing observations, total n = 13,137 (%)	Method of imputation, if performed
Nadir Hct, median	47 (1.1)	95 (0.7)	Median by sex
Vascular disease, %	2 (0.05)	2 (0.02)	No imputation
Moderate to severe COPD, %	74 (1.8)	198 (1.5)	No imputation
Preoperative Hct, median	28 (0.7)	62 (0.5)	Median by sex
WBC count, mean	32 (0.8)	71 (0.5)	Median by sex
CPB duration, median	5 (0.1)	4 (0.03)	Median by sex
Crossclamp duration, median	88 (2.1)	175 (1.3)	Median by sex
Static volume, median mL	75 (1.8)	180 (1.4)	Median by sex
Total fluid administration, median mL	315 (7.5)	904 (6.9)	Median by sex
Acute normovolemic hemodilution, %	245 (5.8)	622 (4.7)	Missing imputed as “no”
Total cardioplegia volume, median mL	187 (4.4)	462 (3.5)	Median by sex
Lowest core temperature, median °F	50 (1.2)	93 (0.7)	Mode ($\geq 35^{\circ}\text{F}$) imputed
Total prime volume, median mL	96 (2.3)	221 (1.7)	Median by sex

Hct, Hematocrit; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; CPB, cardiopulmonary bypass.

TABLE E2. Multivariable generalized linear mixed effect model output

Variable	Estimate	Standard error	t value	P value
Year				
2011	0.2877	0.1945	1.48	.1391
2012	0.1769	0.146	1.21	.2258
2013	−0.00635	0.1366	−0.05	.9629
2014	−0.00303	0.1244	−0.02	.9806
2015	0.2209	0.1136	1.94	.0518
2016	0			
Age, median y	0.01823	0.004384	4.16	<.0001
BSA (m ²)	1.0744	0.2017	5.33	<.0001
Diabetes	0.293	0.08165	3.59	.0003
Peripheral vascular disease	0.1552	0.09572	1.62	.105
Chronic lung disease	0.4771	0.1018	4.69	<.0001
Preoperative Hct, median %	−0.04097	0.008797	−4.66	<.0001
Hypertension	0.1487	0.1533	0.97	.3322
EGFR, mL/min/1.73 m ²				
≥90	−2.5981	0.3843	−6.76	<.0001
60-90	−2.9167	0.3806	−7.66	<.0001
30-60	−2.5684	0.3816	−6.73	<.0001
15-30	−1.1354	0.4031	−2.82	.0049
<15	0			
Last white blood cell count × 10 ⁹ /L, median				
<4.5	−0.2796	0.2253	−1.24	.2146
≥4.5 and ≤10	−0.1732	0.09652	−1.79	.0728
>10	0			
CHF	0.278	0.1507	1.84	.0652
NYHA class III-IV	0.09068	0.165	0.55	.5826
Left ventricle ejection fraction, %				
<40	0.3685	0.1192	3.09	.002
40-49	0.2886	0.1172	2.46	.0138
50-59	0.07976	0.1003	0.8	.4264
≥60	0			
Acuity				
Elective	−0.4597	0.2011	−2.29	.0223
Urgent	−0.4052	0.1881	−2.15	.0312
Emergency/salvage	0			
3+ diseased vessels	0.03741	0.1004	0.37	.7096
Perfusion time, min, median	0.009287	0.001678	5.53	<.0001
Crossclamp time, min, median	−0.00627	0.002316	−2.71	.0068
Static volume per BSA, mL/m ² , median	0.0002	0.000498	0.4	.6878
Intra-aortic balloon pump	0.4528	0.1199	3.78	.0002
Total fluid administration, mL, median	−0.00006	0.000037	−1.64	.1015
Acute normovolemic hemodilution, % yes	−0.1429	0.1573	−0.91	.3637
Total cardioplegia volume, mL, median	0.000033	0.000022	1.53	.1257
Lowest temperature on bypass, °C				
Severe hypothermia (<28)	0.7353	0.4883	1.51	.1321
Moderate hypothermia (≥28 and <32)	0.06801	0.2085	0.33	.7443
Mild hypothermia (≥32 and <35)	−0.04016	0.09781	−0.41	.6814

(Continued)

TABLE E2. Continued

Variable	Estimate	Standard error	t value	P value
Normothermia (≥ 35)	0	.	.	.
Furosemide use	0.5675	0.1623	3.5	.0005
Net prime volume by BSA, mL/m ² , median	0.000285	0.000244	1.17	.2427
Nadir Hct	−0.03727	0.02163	−1.72	.0848
Male sex	0.06987	0.5031	0.14	.8896
Nadir Hct and sex interaction term	−0.00944	0.02217	−0.43	.6704
Nadir Hct given female	−0.0327	0.967829		
Nadir Hct given male	−0.04671	0.954364		
Model intercept	−2.2147	0.9288	−2.38	.0221

BSA, Body surface area; Hct, hematocrit; EGFR, estimated glomerular filtration rate; CHF, congestive heart failure; NYHA, New York Heart Association.