Renal injury is associated with operative mortality after cardiac surgery for women and men

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Objectives: The purpose of this study was to determine whether acute renal injury develops more frequently in women than in men after cardiac surgery and whether this complication is associated with operative mortality in women.

Methods: Prospectively collected data were evaluated from 9461 patients undergoing coronary artery bypass graft surgery, cardiac valve surgery, or both (3080 women) and not receiving preoperative dialysis. The glomerular filtration rate was estimated by using the Modification of Diet in Renal Disease equations with the last plasma creatinine level before surgical intervention (baseline) and the highest level of the first postoperative week. The primary renal injury outcome was the composite end point of renal injury according to RIFLE criteria (estimated glomerular filtration rate decrease >50% from baseline value) or failure.

Results: Thirty-day operative mortality and renal injury were more common in women than in men (5.9% vs 2.8%, $P = .01$; 5.1% vs 3.6%, $P < .001$, respectively). Nonetheless, patient sex was not independently associated with risk for renal injury when the baseline estimated glomerular filtration rate was included in multivariate modeling. Perioperative complications, intensive care unit length of stay, and mortality were more frequent for patients with than without renal injury (women, 20.6% vs 3.2%, $P < .0001$; men, 18.3% vs 2.2%, $P < .001$). Renal injury was independently associated with 30-day mortality for women (odds ratio, 3.96; 95% confidence interval, 1.86–8.44; $P < .0001$) and men (odds ratio, 4.05; 95% confidence interval, 2.19–7.48; $P < .0001$).

Conclusions: Postoperative renal injury is independently associated with 30-day mortality regardless of patient sex. Higher rates of renal injury in women compared with men might be explained in part by a higher prevalence of low estimated glomerular filtration rate before surgical intervention. (J Thorac Cardiovasc Surg 2010;140:1367-73)

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Women are at higher risk for mortality after cardiac surgery than are men, but an explanation for this higher risk is not completely clear.[1] Understanding the sex-specific causes of operative mortality is fundamental for developing preventative strategies. Acute renal failure develops in 5% to 30% of patients after cardiac surgery when cardiopulmonary bypass (CPB) is used, predisposing affected patients to in-hospital and long-term mortality.[2-6] Even small increases in serum creatinine levels (0.5 mg/dL) after surgical intervention are associated with high mortality, longer length of hospitalization, and higher hospital costs.[4,6] Female sex has been identified as an independent risk factor for postoperative renal failure, although it has not been a consistent finding.[2,5-7] Notably, investigators who have evaluated the role of postoperative renal dysfunction in patient outcomes have not separately considered the effect of female sex.[2-6] This omission is important because women represented a minority (<30%) of patients in these studies, and the small number might limit extrapolation of data derived predominately from men. Furthermore, compared with men, women usually have less muscle mass and are typically older at the time of surgical intervention; both of these factors could affect the levels of serum creatinine.[1,8] Thus the purpose of this study was to evaluate whether acute renal injury that develops after cardiac surgery is more common in women than in men and whether it is associated with operative mortality in women.

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MATERIALS AND METHODS

Study Design and Patient Population

All study procedures were approved by the institutional review board of the Johns Hopkins Medical Institutions, and each patient provided written informed consent for data collection and analysis before surgical intervention. Data were prospectively collected by trained abstractors from an electronic medical records system at the Johns Hopkins Hospital as part of data collection for the Society of Thoracic Surgeons (STS) National Cardiac Surgery Database.[9] Data collected included inpatient medical records, review of outpatient records, letter mailings, and telephone interviews. Patients receiving preoperative dialysis were excluded from the study. We identified 9461 consecutive patients (≥30 years old) who had undergone coronary

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CPB = cardiopulmonary bypass
eGFR = estimated glomerular filtration rate
RIFLE = Risk, Injury, Failure, Loss, and End-Stage Kidney Disease
STS = Society of Thoracic Surgeons

artery bypass grafting (CABG) surgery, cardiac valve surgery, or both between January 1, 1995, and December 31, 2006. Patients' serum creatinine levels were obtained from a system-wide electronic patient record database.

Study End Points

Serum creatinine levels were measured as part of clinical care before and after surgical intervention. The testing was carried out at the Clinical Chemistry Laboratory of the Johns Hopkins Hospital with commercial kits (Roche Diagnostics, Indianapolis, Ind) that had a sensitivity of 0.2 mg/dL (1995 to February 2003) or 0.1 mg/dL (February 2003 onward). The last measurement before the day of surgical intervention was considered the baseline value when more than 1 preoperative serum creatinine result was available. In determining the change from baseline values, we considered the maximum serum creatinine level as the highest level obtained during the first 7 days after surgical intervention. The estimated glomerular filtration rate (eGFR) was estimated by using the Modification of Diet in Renal Disease equations: $eGFR = 175 \times (Scr)^{-1.154} \times (Age)^{-0.203}$ in milliliters per minute per 1.73 m^2 of body surface area (the product was multiplied by 0.742 if the subject was female or by 1.212 if the subject was African American).[10,11]

There is no universally accepted definition of renal injury after cardiac surgery. We based our definition of renal injury on the Risk, Injury, Failure, Loss, and End-Stage Kidney Disease (RIFLE) criteria: (1) *risk* when eGFR decreases greater than 25% from baseline value; (2) *injury* when eGFR decreases greater than 50% from baseline value; and (3) *failure* when the plasma creatinine level is 350 μmol/L or greater or when there is an acute increase of 44 μmol/L or greater from the baseline value.[12] We also included new dialysis as an indicator of renal failure. The primary renal outcome of this study was the composite end point of renal injury or failure.

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Statistical Analyses

Relevant clinical, demographic, and outcome variables from files in our STS databases were extracted and merged into a STATA 10.0 data set, which was used for all statistical analyses (StataCorp, College Station, Tex). In initial confirmatory analyses we considered univariate tests of associations between operative mortality and renal injury on sex, clinical measures, and complications from surgical intervention. These analyses consisted of the χ^2 test for categorical variables and the Student's *t* test or, when appropriate, the nonparametric Kruskal–Wallis test for continuous measures. Demographic and operative outcome variables with a *P* value of less than .1 in univariate analyses or those that were deemed to be clinically significant were considered in the multivariable logistic regression model predicting renal injury and operative mortality. Here operative mortality was defined as death from any cause that occurred during hospitalization or after discharge but within 30 days after surgical intervention. We considered spline parameters to account for possible nonlinear associations for continuous variables on renal injury or operative mortality. Definitions for clinical variables were those used by the STS database found at http://www.sts.org/sections/stsnationaldatabase/datamanagers/adultcardiacdb/datacollection/index.html.

RESULTS

Patient characteristics for the 9150 survivors and the 311 patients who experienced operative mortality are listed in Table 1 according to patient sex. Operative mortality was higher for women than for men (4.2% vs 3.0%, $P = .001$). Compared with survivors, women and men who died were older and were more likely than surviving patients of the same sex to have low eGFRs before surgical intervention. Other differences between survivors and nonsurvivors for each sex are noted in Table 1. Comparisons of the frequency of variables that differed between nonsurviving women and men are listed in Table 1. For the most part, variables associated with mortality were similar between women and men, with a few exceptions. Compared with nonsurviving men, women who experienced operative mortality had a higher frequency of diabetes, left ventricular ejection fraction of less than 50%, hypercholesterolemia, hypertension, prior myocardial infarction, and current smoking. Nonsurviving women had a lower frequency of triple-vessel coronary artery disease than did nonsurviving men. Differences in the type of operation between female and male nonsurvivors were noted.

Baseline eGFR, the frequency of different levels of reduced eGFR, and the distribution of RIFLE criteria for renal injury by patient sex are listed in Table 2. Women had a lower eGFR before surgical intervention than did men, and higher frequencies of women had eGFRs of less than 30 mL/min per 1.73 m^2 of body surface area and eGFRs of 30 to 60 mL/min per 1.73 m^2 of body surface area. Forty-four women and 33 men were reported to have new dialysis after surgical intervention but were not listed as having renal injury or failure based on the RIFLE criteria (because of dialysis correction of serum creatinine levels); these patients were included in the renal injury outcome. The primary renal injury outcome occurred in 5.1% of women and 3.6% of men ($P < .001$). The χ^2 value for each category is provided in Table 2 and shows that most of the weighting for the combined *P* value was from the RIFLE categories of ''risk'' or ''injury,'' suggesting that these 2 categories drive the statistical association between sex and RIFLE criteria.

Characteristics for surviving and nonsurviving patients with and without renal injury for each sex are listed in Table 3. Although many univariate predictors of mortality for patients with renal injury were similar for women and men, differences were noted. As in Table 1, the frequency of variables that differed between survivors and nonsurvivors for each sex are listed, and comparisons between nonsurviving women and men are provided for these variables. In contrast to nonsurviving men, women with renal injury who died had a higher frequency of left ventricular ejection fraction of less than 30%, hypercholesterolemia, hypertension, triple-vessel coronary artery disease, and significant left main coronary stenosis. Nonsurviving women with renal injury had

TABLE 1. Patient characteristics of survivors and nonsurvivors based on patient sex

Clinical characteristic	Female survivors (n = 2951)	Female nonsurvivors (n = 129)	Frequency of variable for nonsurvivors	*P* value*	Male survivors (n = 6199)	Male nonsurvivors (n = 182)	Frequency of variable for nonsurvivors	*P* value*	*P* value†
Mean ± SD age (y)	65.9 ± 12.3	71.4 ± 11.5		.0001	63.6 ± 11.7	70.0 ± 11.5		.0001	.8543
African American	492 (16.7%)	23 (17.8%)	4.5%	.730	603 (9.7%)	17 (9.3%)	2.7%	.862	.0117
Mean ± SD body surface area (m^2)	1.80 ± 0.23	1.77 ± 0.23		.1365	2.05 ± 0.22	1.97 ± 0.24		.0001	≤.0001
Chronic lung disease	327 (11.1%)	16 (12.4%)	4.7%	.640	532 (8.6%)	33 (18.1%)	5.8%	≤.0001	.447
Diabetes	917 (31.1%)	49 (38.0%)	5.1%	.098	1553 (25.0%)	53 (29.1%)	3.3%	.213	.026
Left ventricular EF <50%	1489 (50.5%)	92 (71.3%)	5.8%	≤.0001	3578 (57.7%)	123 (67.6%)	3.3%	.008	≤.0001
Left ventricular EF <30%	334 (11.3%)	28 (21.7%)	7.7%	≤.0001	856 (13.8%)	56 (30.8%)	6.1%	≤.0001	.301
Reoperation	119 (4.0%)	13 (10.1%)	9.8%	.001	165 (2.7%)	15 (8.2%)	8.3%	≤.0001	.644
Hypercholesterolemia	1560 (52.9%)	61 (47.3%)	3.8%	.214	3474 (56.0%)	75 (41.2%)	2.1%	≤.0001	.001
Preoperative eGFR									
<30 mL/min per $1.73m^2$	133 (4.5%)	17 (13.2%)	11.3%		144 (2.3%)	16 (8.8%)	10.0%		.704
30-60 mL/min per 1.73 m^2	708 (24.0%)	50 (38.8%)	6.6%	≤.0001	971 (15.7%)	51 (28.0%)	5.0%	≤.0001	.148
>60 mL/min per 1.73 m^2	2110 (71.5%)	62 (48.1%)	2.9%		5084 (82.0%)	115 (63.2%)	2.2%		.100
Hypertension	1997 (67.7%)	92 (71.3%)	4.4%	.386	3982 (64.2%)	120 (65.9%)	2.9%	.638	.002
IABP									
Preoperative	47 (1.5%)	24 (18.6%)	10.1%		96 (1.5%)	29 (15.9%)	8.7%		.636
Intraoperative	9 (0.3%)	6 (4.7%)	33.8%	≤.0001	14 (0.2%)	4 (2.2%)	23.2%	≤.0001	.108
Postoperative	124 (4.2%)	14 (10.9%)	40.0%		231 (3.7%)	22 (12.1%)	22.2%		.448
MI	1194 (40.5%)	70 (54.3%)	5.5%	.002	2849 (46.0%)	94 (51.6%)	3.2%	.129	≤.0001
Emergency PCI	59 (1.9%)	1 (0.8%)	1.7%	.340	111 (1.8%)	4 (2.2%)	3.5%	.768	.662
Peripheral vascular disease	449 (15.2%)	25 (19.4%)	5.3%	.212	740 (11.9%)	39 (21.4%)	5.0%	≤.0001	.835
Cerebral vascular disease	381 (12.9%)	23 (17.8%)	5.7%	.110	599 (9.7%)	34 (18.7%)	5.4%	≤.0001	.825
Cardiac shock	17 (0.6%)	4 (3.1%)	19.0%	.010	39 (0.6%)	4 (2.2%)	9.3%	.033	.422
Current smoking	380 (12.9%)	15 (11.6%)	3.8%	.788	827 (13.3%)	15 (8.2%)	1.8%	.045	.032
Triple-vessel CAD	1253 (42.5%)	59 (45.8%)	4.5%	.659	3531 (57.0%)	87 (47.8%)	2.4%	.118	≤.0001
Left main stenosis >50%	259 (8.8%)	14 (10.8%	5.1%	.525	607 (9.8%)	17 (9.3%)	2.7%	.895	.070
Type of operation									
CABG only									
With CPB	1984 (67.2%)	90 (69.8%)	4.4%	.833	4808 (77.6%)	132 (72.5%)	2.7%	.144	≤.0001
Without CPB	96 (3.3%)	4 (3.1%)	4.0%		214 (3.4%)	5 (2.7%)	2.3%		.469
AVR									
Repair	120 (4.%1)	3 (2.3%)	2.4%	.046	304 (4.9%)	7 (3.8%)	2%	.001	1.00
Replacement	588 (19.9%)	37 (28.7%)	5.9%		981 (15.8%)	48 (26.4%)	4.7%		.262
MVR									
Repair	151 (5.1%)	5 (3.9%)	3.2%	.705	256 (4.1%)	8 (4.4%)	3.0%	.002	1.00
Replacement	486 (16.5%)	24 (18.6%)	4.7%		357 (5.8%)	22 (12.1%)	5.8%		.464
CABG/AVR	247 (8.4)	12 (9.3%)	8.5%	≤.0001	482 (7.8%)	27 (14.8%)	5.3%	.001	.082
CABG/MVR	175 (5.9%)	9 (7.0%)	4.9%	.645	210 (3.4%)	16 (8.8%)	7.1%	≤.0001	.357
Duration of aortic crossclamp (min)‡	72 (55–96)	81 (60–111)		.0331	75 (58–98)	83 (56–124)		.0334	.692
Duration of CPB (min)‡	109 (86–139)	139 (99–173)		.0001	111 (89–138)	136 (100–189)		.0001	.974

Values are reported as number of patients, with percentages in parentheses for the variable for each column of survivor or nonsurvivors. A separate column of percentages lists the frequency of the variable for nonsurvivors for each sex. *SD*, Standard deviation; *EF*, ejection fraction; *eGFR*, estimated glomerular filtration rate; *IABP*, intra-aortic balloon pump; *MI*, myocardial infarction; *PCI*, percutaneous coronary artery intervention; *CAD*, coronary artery disease; *CABG*, coronary artery bypass graft; *CPB*, cardiopulmonary bypass; *AVR*, aortic valve replacement; *MVR*, mitral valve replacement. **P* value for comparison between survivors and nonsurvivors of the same sex. †*P* value for comparison of the distribution of the variable between women and men. ‡Values are reported as medians (interquartile ranges).

a lower frequency of left ventricular ejection fraction of less than 50% than did nonsurviving men with renal injury.

Perioperative complications and operative mortality are listed in Table 4 based on the presence or absence of renal injury for both sexes. With the exception of perioperative myocardial infarction, reported complications were more common in patients with renal injury than in those without such injury, irrespective of sex. In addition, duration of mechanical lung ventilation and duration of intensive care unit hospitalization were longer in patients of both sexes with

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TABLE 2. eGFR (in milliliters per minute per 1.73 m^2) and the number and percentage of patients with different levels of decreased eGFR and each RIFLE criterion based on patient sex

Parameter	Women	Men	χ^2 test	P value
Baseline eGFR*	75.3 (57.1–101.5)	81.6 (65.3–101.0)	NA	.0001
eGFR <30	154 (5.0%)	162 (2.5%)		≤.0001
eGFR 30–60	772 (25%)	1039 (16.3%)		
No renal injury	2918 (94.7%)	6119 (95.9%)	0.3	
RIFLE risk	50 (1.6%)	62 (1.0%)	7.5	.001
RIFLE injury	27 (0.9%)	25 (0.4%)	8.9	
RIFLE failure	85 (2.8%)	175 (2.7%)	0.0	

The χ^2 value for each RIFLE category is provided to indicate the relative weighting of each category for the combined *P* value. *eGFR*, Estimated glomerular filtration rate; *NA*, not applicable. *RIFLE*, Risk, Injury, Failure, Loss, and End-Stage Kidney Disease. *Median (interquartile range). RIFLE criteria: risk, eGFR decrease greater than 25% from baseline; injury, eGFR decrease greater than 50% from baseline; and failure, acute plasma creatinine level of 350 μmol/L or greater or acute increase of 44 μmol/L or greater after surgical intervention.

renal injury compared with durations in those without this complication. Operative mortality was markedly higher in both women and men with renal injury than in patients who did not have renal injury.

Variables independently associated with renal injury are listed in Table 5. Factors independently associated with renal injury after correction for baseline eGFR are listed in Table 6. Whereas male sex was independently associated with a reduced risk of renal injury in the first model, after correction for baseline eGFR in the second model, patient sex was no longer significantly related to the risk for renal injury. Because of the nonlinear relationship between eGFR and risk for renal injury, these data were splined at a baseline eGFR of 100 mL/min per 1.73 m^2 of body surface area. A U-shaped relationship between baseline eGFR and risk for renal injury was observed; that is, a reduced risk for renal injury was associated with a baseline eGFR of 100 mL/min per 1.73 m^2. The risk of renal injury was higher above and below a baseline eGFR of 100 mL/min per 1.73 m^2.

Independent predictors of operative mortality based on multivariate logistic regression analysis in a model that included both women and men are listed in Table 7. Multiorgan failure was a strong predictor for operative mortality. Renal injury was associated with risk for operative mortality for women and men after adjustment for other variables associated with death.

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DISCUSSION

The data presented here show that the frequency of renal injury is more common in women than in men after cardiac surgery. This risk, however, might be explained in part by women having a lower baseline eGFR than men. In our study patients with renal injury generally had more predisposing risk factors for morbidity and were more likely to have postoperative complications than were those who did not have renal injury, regardless of sex. Renal injury was independently associated with operative mortality for women and men.

Women have consistently been shown to have higher operative mortality after cardiac surgery than men due in part to a higher prevalence of risk factors for poor outcomes, including advanced age.[1,13-15] Nonetheless, in the large multicenter STS database, female sex was reported to be an independent predictor of operative mortality for all but the highest-risk patients.[1] Our group has reported that a large portion of the excessive risk for operative mortality in women can be explained by a higher prevalence of perioperative stroke in women than in men.[13,14] The results of the current study now show that renal injury is an additional important determinant for operative mortality in women after cardiac surgery.

Renal insufficiency and renal failure after cardiac surgery are known to be associated with risk for adverse operative outcomes, including in-hospital, short-term, and long-term mortality.[2-6] Prior studies have reported that women are at higher risk for renal injury after cardiac surgery, but these findings are inconsistent.[2,7,16] One explanation for why women might have increased susceptibility to postoperative renal injury is that they have a higher prevalence of predisposing risk factors compared with men, including advanced age, diabetes, and hypertension.[1,2,13,15] Another explanation might be related to the modulating effects of sex hormones on renal physiology and responses to ischemia and reperfusion.[17] Studies in whole-animal models have demonstrated greater functional and histologic injury from global renal ischemia in male than in female animals, a finding linked to male and female sex steroids.[17] Whether the absence of estrogens associated with the postmenopausal state modifies these responses is not entirely clear. Nonetheless, in our study we found that after correcting for baseline eGFR, patient sex was no longer significantly associated with renal injury after surgical intervention. Because we found that women had lower eGFRs before surgical intervention than did men, our findings indicate that the higher risk of postoperative renal injury in women is related in part to their lower baseline eGFRs that might, perhaps, contribute to less functional reserve to injury.

Previous investigations that have examined the importance of renal injury on patient outcomes after cardiac surgery have not separately examined whether this risk applies equally to women and men. Rather, most studies have combined data from both sexes, a design that might limit extrapolation of the data to women because they are a minority of cardiac surgical patients.[2-6] Another disadvantage of the previous studies that might limit comparisons is that they have used multiple definitions for renal injury based on changes in serum creatinine levels.[3] Serum creatinine levels are influenced by multiple factors in addition to glomerular filtration.[8] Thus relative, absolute, or both serum creatinine concentrations might poorly predict

TABLE 3. Distribution of risk factors for operative mortality for patients with and without renal injury based on patient sex

Clinical characteristic	Women, no renal injury (n = 2959)	Women, renal injury (n = 160)	Frequency of variable for nonsurvivors	*P* value*	Men, no renal injury (n = 6230)	Men, renal injury (n = 235)	Frequency of variable for nonsurvivors	*P* value*	*P* value†
Mean ± SD age (y)	66.2 ± 12.3	66.6 ± 12.5		.688	63.7 ± 11.7	65.9 ± 12.9		.006	.7120
African American race	488 (16.5%)	39 (24.4%)	7.4%	.010	603 (9.7%)	17 (9.3%)	7.3%	<.0001	.967
Mean ± SD BSA (m^2)	1.8 ± 0.2	1.8 ± 0.2		.148	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	.687	.687
Chronic lung disease	327 (11.0%)	20 (12.5%)	5.8%	.570	532 (8.6%)	33 (18.1%)	6.0%	.002	.885
Diabetes	921 (31.1%)	58 (36.2%)	5.9%	.174	1553 (25.0%)	53 (29.1%)	4.6%	.015	.141
Left ventricular EF <50%	1501 (50.7%)	98 (61.2%)	6.12%	.009	3578 (57.7%)	123 (67.6%)	13.7%	.582	<.0001
Left ventricular EF <30%	333 (11.2%)	33 (20.6%)	9.06%	<.001	856 (13.8%)	56 (30.8%)	5.0%	.018	.006
Reoperation	114 (3.8%)	19 (11.9%)	14.3%	<.001	165 (2.7%)	15 (8.2%)	8.6%	<.0001	.106
Hypercholesterolemia	1567 (53.0%)	77 (48.1%)	4.7%	.233	3474 (56.0%)	75 (41.2%)	2.9%	<.0001	.001
Hypertension	1995 (67.4%)	122 (76.2%)	5.8%	.020	3991 (64.1%)	167 (71.1%)	4.0%	.028	.002
IABP									
Preoperative	125 (4.2%)	13 (8.1%)	9.4%	.017	228 (3.7%)	25 (10.6%)	9.9%	.116	.883
Intraoperative	59 (2.0%)	13 (8.1%)	18.1%		17 (0.3%)	1 (0.4%)	5.6%		.784
Postoperative	10 (0.3%)	5 (3.1%)	33.3%		106 (45.1%)	21 (8.9%)	3.3%		.784
Myocardial infarction	1217 (41.1%)	60 (37.5%)	4.7%	.363	2849 (46.0%)	94 (51.6%)	3.3%	.232	.032
Emergency PCI	58 (2.0%)	2 (1.0%)	3.3%	.320	111 (1.8%)	4 (2.2%)	1.7%	.372	.608
PVD	448 (15.1%)	29 (1.8%)	6.1%	.307	740 (11.9%)	39 (21.4%)	5.0%	.032	.402
Cerebral vascular disease	381 (12.9%)	25 (15.6%)	6.2%	.314	599 (9.7%)	34 (18.7%)	4.4%	.284	.204
Cardiogenic shock	22 (0.7%)	1 (0.6%)	4.3%	.865	39 (0.6%)	4 (2.2%)	13.6%		.408
Current smoker	383 (12.9%)	16 (10.0%)	4.0%	.278	827 (13.3%)	15 (8.2%)	3.5%		.668
Triple-vessel disease	1271 (42.9%)	52 (32.5%)	3.9%	.274	3531 (57.0%)	87 (47.8%)	2.7%		.030
Left main stenosis >50%	261 (8.8%)	14 (8.7%)	5.1%	.524	607 (9.8%)	17 (9.3%)	2.2%		.022
Type of operation									
CABG only				.003					
With CPB	1991 (67.3%)	86 (53.7%)	4.1%	<.0001	4808 (77.6%)	132 (72.5%)	2.9%	<.0001	.008
Without CPB	93 (3.1%)	7 (4.4%)	7.0%		214 (3.4%)	5 (2.7%)	5.9%		
AVR									
Repair	120 (4.0%)	3 (1.9%)	2.4%	<.0001	304 (4.9%)	7 (3.8%)	6.1%	<.0001	.804
Replacement	573 (19.4%)	53 (33.1%)	8.5%		981 (15.8%)	48 (26.4%)	6.0%		
MVR									
Repair	147 (5.0%)	9 (5.6%)	5.8%	.004	256 (4.1%)	8 (4.4%)	3.0%	<.0001	.147
Replacement	462 (15.6%)	49 (30.6%)	9.6%	<.0001	357 (5.8%)	22 (12.1%)	8.7%		
CABG/AVR	247 (8.3%)	24 (15.0%)	8.9%		482 (7.8%)	27 (14.8%)	7.4%	<.001	.057
CABG/MVR	164 (5.5%)	20 (12.5%)	21.9%		210 (3.4%)	16 (8.8%)	4.9%	.345	.169
Duration aortic crossclamp (min)‡	72 (55–96)	85 (62–113)		.0005	75 (58–97)	86 (59–118)		<.0001	.816
Duration of CPB (min)‡	109 (86–139)	138 (104–177)		.0001	111 (89–138)	129 (100–186)		.0001	.461

Values are reported as numbers of patients, with percentages in parentheses for the variable for each column of survivors or nonsurvivors. A separate column of percentages lists the frequency of the variable for patients without renal injury for each sex. *SD*, Standard deviation; *BSA*, body surface area; *EF*, ejection fraction; *IABP*, intra-aortic balloon pump; *PCI*, percutaneous coronary artery intervention; *PVD*, peripheral vascular disease; *CABG*, coronary artery bypass graft; *CPB*, cardiopulmonary bypass; *AVR*, aortic valve replacement; *MVR*, mitral valve replacement. **P* value for comparison between survivors and nonsurvivors of the same sex. †*P* value for comparison of the distribution of the variable between women and men. ‡Values are reported as medians (interquartile ranges).

renal function in elderly women. In this study we estimated eGFR with the Modification of Diet in Renal Disease equations, which take into account age, sex, and race.[10,11] Furthermore, we used RIFLE criteria for defining grades of renal injury.[12] Regardless, the frequency of renal injury and the associated mortality in our study were similar to those of other studies.[2-6,18-20]

Renal injury associated with cardiac surgery likely results from hypotension, embolism, or exposure to nephrotoxins, including radiocontrast dye used before surgical intervention.[4,21,22] Patients with renal injury are more likely than others to have postoperative complications. The development of complications, such as sepsis and other organ injury, might predispose them to hemodynamic instability and renal ischemia, as well as to exposure to nephrotoxic antibiotics. Nonsurgical patients with renal injury have prothrombotic tendency, endothelial dysfunction, and other abnormalities that predispose them to cardiovascular disease.[23] Perhaps these variables contribute to the poorer outcomes seen in patients with renal injury after cardiac surgery. In our study we

TABLE 4. Variables independently associated with renal injury based on multivariate logistic regression analysis

Variable	Odds ratio (95% CI)	*P* value
Multiorgan failure	14.44 (8.57–24.33)	≤.0001
African American race	1.83 (1.39–2.42)	≤.0001
Duration of cardiopulmonary bypass	1.01 (1.01–1.02)	≤.0001
Male sex	0.68 (0.54–0.85)	.001
Hypertension	1.50 (1.17–1.93)	.002
Left ventricular ejection fraction <30%	1.48 (1.11–1.96)	.007
Hypercholesterolemia	0.77 (0.61–0.96)	.021

CI, Confidence interval.

TABLE 5. Variables independently associated with renal injury

Variable	Odds ratio (95% CI)	*P* value
Multiorgan failure	12.65 (7.00–22.87)	≤.0001
African American race	1.80 (1.32–2.44)	≤.0001
Duration of cardiopulmonary bypass	1.01 (1.005–1.01)	≤.0001
Baseline eGFR <100 mL/min per 1.73 m^2*	0.94 (0.94–0.95)	≤.0001
Baseline eGFR ≥100 mL/min per 1.73 m^2†	1.08 (1.07–1.10)	≤.0001

Calculations are based on multivariate logistic regression analysis after adjusting for baseline estimated glomerular filtration rate with a linear spline at 100 mL/min per 1.73 m^2. *CI*, Confidence interval; *eGFR*, estimated glomerular filtration rate. *The risk for each 1-unit increase in eGFR when baseline eGFR is less than 100 mL/min per 1.73 m^2 of body surface area. †The risk for a 1-unit increase in eGFR when baseline eGFR is greater than 100 mL/min per 1.73 m^2 of body surface area.

observed an apparent U-shaped relationship between baseline eGFR values and risk for renal injury after surgical intervention. At less than a baseline of 100 mL/min per 1.73 m^2 of body surface area, each unit increase in eGFR reduced the risk for renal injury. In contrast, for patients with baseline eGFRs of greater than 100 mL/min per 1.73 m^2 of body surface area, each unit increase in eGFR increased the risk for renal injury. Reasons for the latter observation are not clear other than the potential for higher renal embolic load during surgical intervention for patients with high baseline eGFRs. Importantly, our observations suggest that optimizing the eGFR before surgical intervention in patients with a baseline eGFR of up to 100 mL/min per 1.73 m^2 of body surface area might provide a strategy for reducing the risk for renal injury, particularly in women. One potential strategy would be to allow recovery of renal function from radiocontrast dye exposure before subjecting patients to the added risk of renal injury for surgical perturbations.

Many of the variables that we identified to be independently associated with mortality are widely recognized.[1] Women are likely to be older than men at the time of surgical intervention and are more likely to have hypertension, fewer coronary artery stenoses, and preserved left ventricular function.[1] Thus differences in preoperative comorbidities between patient sexes might confound our examination of the importance of renal injury for operative mortality. Nonetheless, most of these risk factors for mortality were similar between patient sexes based on univariate analysis, although several variables did differ between survivors and nonsurvivors in analysis within each sex. However, our use of multivariate logistic regression analysis to adjust for other potential confounding factors between the sexes suggests that a higher comorbidity rate in women with renal injury is an unlikely explanation for the link between this outcome and operative mortality. We observed that hypercholesterolemia was associated with lower mortality risk in men. This finding might represent an epiphenomenon that identifies patients receiving statin drugs, which have been shown to be associated with a decreased risk for mortality after cardiac surgery.[24] However, whether preoperative statin therapy decreases the risk of postoperative acute kidney injury is not conclusive.[24,25]

In addition to the retrospective nature of this analysis, several limitations are associated with this study. Our analysis included a heterogeneous population of patients undergoing CABG surgery, valvular surgery, or both. Serum creatinine levels, which were used in the definition of renal injury, might have been influenced by nonrenal factors, including

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TABLE 6. Postoperative complications and outcomes

	Women			Men		
Clinical characteristic	No renal injury (n = 2920)	Renal Injury (n = 160)	*P* value	No renal Injury (n = 6146)	Renal Injury (n = 235)	*P* value
Reoperation for bleeding	41 (1.4%)	9 (5.6%)	<.0001	91 (1.5%)	17 (7.2%)	<.0001
Stroke	158 (5.3%)	23 (14.4%)	<.0001	212 (3.4%)	24 (10.2%)	<.0001
Perioperative MI	10 (0.3%)	0	.453	19 (0.3%)	2 (0.8%)	.160
Pneumonia	77 (2.6%)	12 (7.5%)	<.0001	170 (2.7%)	29 (12.3%)	<.0001
Sepsis	43 (1.4%)	28 (17.5%)	<.0001	72 (1.1%)	38 (16.2%)	<.0001
Multiorgan failure	17 (0.6%)	10 (6.2%)	<.0001	28 (0.4%)	25 (11.9%)	<.0001
Duration in the ICU (h)	48 (24–96)	191 (84–456)	.0001	36 (22–69)	165 (73–449)	.0001
Duration of lung ventilation (h)	13 (9–22)	110 (30–268)	.0001	10 (7–16)	63 (14–281)	<.0001
Operative mortality	96 (3.2%)	33 (20.6%)	<.0001	139 (2.2%)	43 (18.3%)	<.0001

MI, Myocardial infarction; *ICU*, intensive care unit.

TABLE 7. Variables independently associated with mortality after cardiac surgery based on multivariate logistic regression analysis

Variable	Odds ratio (95% CI)	*P* value
Multiorgan failure	31.57 (16.23–63.39)	≤.0001
Reoperation for bleeding	3.98 (2.22–7.13)	≤.0001
Male subject with renal injury	3.72 (2.21–6.23)	≤.0001
Female subjects with renal injury	3.77 (2.18–6.54)	≤.0001
Stroke	3.60 (2.49–5.22)	≤.0001
Left ventricular ejection fraction <30%	2.05 (1.50–2.82)	≤.0001
Duration of cardiopulmonary bypass	1.01 (1.01–1.02)	≤.0001
Duration of aortic crossclamping	0.99 (0.98–0.99)	≤.0001
Hypercholesterolemia	0.75 (0.57–0.94)	.042

CI, Confidence interval.

body weight, ethnicity, sex, and nutrition.[1,8] Cystatin C is an endogenous marker of renal function that is more sensitive than creatinine for identifying mild and moderate decrements in eGFR.[26] Although use of the latter marker might have provided a more accurate detection of mild renal injury, it was not widely available or routinely measured during the period of this study. Likewise, aprotinin use, a variable found in retrospective studies to be associated with renal injury, was not recorded in our database.[27] Antifibrinolytic drugs consisted of aminocaproic acid; aprotinin was mostly restricted to reoperative surgery. Whether inclusion of aprotonin in our multivariate models of operative mortality would have modified our finding that renal injury is independently associated with operative mortality in women and men is not known but unlikely because only a minority of patients received the drug.

In summary, we have shown that the occurrence of renal injury after cardiac surgery is independently associated with an increased risk of postoperative mortality. Furthermore, the incidence of renal injury after cardiac surgery appears to be higher in women than in men. However, this discrepancy could be caused in part by women having a lower baseline eGFR than men. Optimizing eGFR before surgical intervention in patients with a baseline eGFR of less than 100 mL/min per 1.73 m^2 of body surface area and allowing patients time to recover renal function after exposure to renal toxins, such as radiocontrast dye, might provide strategies for reducing the risk of renal injury after cardiac surgery.

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