Original Investigation | ASSOCIATION OF VA SURGEONS

# Cardiovascular-Specific Mortality and Kidney Disease in Patients Undergoing Vascular Surgery

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**IMPORTANCE** Acute kidney injury (AKI) affects as many as 40% of patients undergoing surgery and is associated with increased all-cause mortality. Chronic kidney disease (CKD) is a well-known risk factor for cardiovascular mortality.

**OBJECTIVE** To determine the association between kidney disease and long-term cardiovascular-specific mortality after vascular surgery.

**DESIGN, SETTING, AND PARTICIPANTS** A single-center cohort of 3646 patients underwent inpatient vascular surgery from January 1, 2000, to November 30, 2010, at a tertiary care teaching hospital. To determine cause-specific mortality for patients undergoing vascular surgery, a proportional subdistribution hazards regression analysis was used to model long-term cardiovascular-specific mortality while treating any other cause of death as a competing risk. Kidney disease constituted the main covariate after adjusting for baseline patient characteristics, surgery type, and admission hemoglobin level. Final follow-up was completed July 2014 to assess survival through January 31, 2014, and data were analyzed from June 1, 2014, to September 7, 2015.

**MAIN OUTCOMES AND MEASURES** Perioperative AKI, presence of CKD, and overall and cause-specific mortality.

**RESULTS** Among the 3646 patients undergoing vascular surgery, perioperative AKI occurred in 1801 (49.4%) and CKD was present in 496 (13.6%). The top 2 causes among the 1577 deaths in our cohort were cardiovascular disease (845 of 1577 [53.6%]) and cancer (173 of 1577 [11.0%]). Adjusted cardiovascular mortality estimates at 10 years were 17%, 31%, 30%, and 41%, respectively, for patients with no kidney disease, AKI without CKD, CKD without AKI, and AKI with CKD. Adjusted hazard ratios (95% CIs) for cardiovascular mortality were significantly elevated among patients with AKI without CKD (2.07 [1.74-2.45]), CKD without AKI (2.01 [1.46-2.78]), and AKI with CKD (2.99 [2.37-3.78]) and were higher than those for other risk factors, including increasing age (1.03 per 1-year increase; 1.02-1.04), emergent surgery (1.47; 1.27-1.71), and admission hemoglobin levels lower than 10 g/dL (1.39; 1.14-1.69) compared with a hemoglobin level of 12 g/dL or higher.

**CONCLUSIONS AND RELEVANCE** Perioperative AKI is common in patients undergoing vascular surgery and is associated with a high risk for cardiovascular-specific mortality comparable to that seen with CKD. These findings reinforce the importance of preoperative and postoperative risk stratification for kidney disease and the implementation of strategies now available to help prevent perioperative AKI.

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Chronic kidney disease (CKD) is associated with increased cardiovascular-specific mortality in the general population, and this risk increases with progressive decline in the estimated glomerular filtration rate (eGFR) to dialysis dependence and end-stage renal disease (ESRD).[1,2] Chronic kidney disease is also a well-recognized risk factor for adverse short- and long-term outcomes after vascular surgery. Chronic kidney disease is independently associated with excess 30-day mortality, with as much as 4.7 times the risk for postoperative death in patients undergoing thoracoabdominal and abdominal aortic repairs compared with patients with no kidney disease.[3,4] Chronic kidney disease is a risk factor for 1-year mortality after peripheral vascular interventions and abdominal aortic aneurysm repair and for the combined outcome of stroke and all-cause mortality after carotid endarterectomy procedures.[5-7]

Acute kidney injury (AKI) is a common postoperative complication, and Huber et al[8] recently demonstrated that small and often disregarded changes in serum creatinine levels are independently associated with higher hospital and 90-day mortality, increased use of health care resources, and increased hospital cost of care after a broad range of vascular surgical procedures, even after adjusting for preoperative variables and other postoperative complications. Several recent studies using contemporary consensus definitions for AKI have suggested that postoperative AKI is an important risk factor for long-term mortality after major vascular surgery.[9-14] Unfortunately, these studies included only small patient cohorts and selected surgical procedures and largely failed to examine cause-specific mortality. In a large, single-center cohort of patients undergoing major vascular surgery, we examined the associations between cardiovascular-specific mortality and kidney disease while adjusting for demographic variables, comorbidities, hemoglobin levels, and other competing causes of death.

## Methods

### Data Source and Participants

We queried the University of Florida Integrated Data Repository to assemble a single-center cohort of perioperative patients 18 years or older who were admitted to the hospital for longer than 24 hours after any type of major vascular surgery procedure from January 1, 2000, to November 30, 2010.[15] Final follow-up was completed July 2014 to assess survival through January 31, 2014. For patients undergoing multiple operations, we analyzed only the index procedure. We identified study participants as patients in whom the primary admission or discharge service was vascular or cardiothoracic surgery and who received a primary or secondary procedure code from the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) for vascular surgery (eTable 1 in the Supplement).[16] We subdivided procedure codes into categories as described previously[16] and excluded patients receiving dialysis access procedures and other procedures specified in eTable 1 in the Supplement. The final cohort consisted of 3646 patients. The study was approved by the institutional review board and privacy office of the University of Florida, which determined that informed consent was not needed for this study.

### Mortality

The main outcome of the study was cardiovascular-specific mortality, with any other cause of death treated as a competing risk. For the secondary analysis, cancer-specific mortality was treated as the main cause of death in a competing risk model. The date of death was determined using hospital records, the Social Security Death Index, and data from the Florida Bureau of Vital Statistics (detailed in the eMethods in the Supplement). Using the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, we classified the primary cause of death as cardiovascular specific (codes I00-I99, Q20-Q28, E10-E14, N00-N08, N10-N16, and N17-N19), cancer specific (codes C00-C97), and all other causes. We included diabetes mellitus and kidney disease in the expanded cardiovascular disease category to capture additional deaths that were related to CKD but traditionally not classified under cardiovascular diseases, as previously reported by Gansevoort et al.[1] For the sensitivity analysis, we used an alternative approach that was reported for the general population.[17,18]

### Kidney Disease and Other Covariates

The main covariate was the presence of kidney disease during the index hospitalization. For all patients we calculated a preoperative reference eGFR by applying the CKD epidemiology collaboration equation using standardized reference serum creatinine levels, sex, race, and age.[19] For the reference serum creatinine level, we used the minimum of all values available within the 6 months before admission or the minimum and mean of the creatinine values available within the 7 days before admission (used for sensitivity analyses).[20] Patients with CKD who did not require renal replacement therapy and patients with ESRD who required renal replacement therapy before admission were identified by the previously validated combination of *ICD-9-CM* diagnostic and procedure codes (eMethods in the Supplement).[21] Patients with CKD were stratified using reference eGFR levels without criteria for albuminuria as having mild (eGFR, ≥60 mL/min/1.73 $m^2$), moderate (eGFR, 30 to <60 mL/min/1.73 $m^2$), and severe (eGFR, <30 mL/min/1.73 $m^2$) CKD according to guidelines from Kidney Disease: Improving Global Outcomes (KDIGO).[22]

We defined AKI using the consensus KDIGO criteria as at least a 50% and/or a 0.3-mg/dL increase in serum creatinine level (to convert to micromoles per liter, multiply by 88.4) relative to the preoperative reference value.[23] Patients with AKI were stratified according to the maximum change in serum creatinine level during the hospital admission in 3 stages. Stage 1 corresponded to a 50% change in serum creatinine level; stage 2, to a doubling in serum creatinine level; and stage 3, to a tripling or increase in serum creatinine level to 4.0 mg/dL or higher or the initiation of renal replacement therapy.

The presence of underlying comorbidities was identified by *ICD-9-CM* codes based on previously validated criteria,[24] and we calculated the Charlson-Deyo comorbidity index and grouped patients into score categories of 0, 1, 2, and 3 or higher.[25] Aspirin, statins, angiotensin-converting enzyme inhibitors, and

β-blockers dispensed on the day of admission were extracted from the pharmacy database. We stratified hospital admission hemoglobin values into missing and 4 other categories (<8.0, 8.0-9.9, 10.0-11.9, and ≥12 g/dL [to convert to grams per liter, multiply by 10.0]).[26] The thresholds were developed after constructing the spline function of the hemoglobin values and the risk for mortality in univariate analysis and are similar to previously used values in patients with kidney disease.[26] Using primary admission service and primary and secondary procedure codes, we classified all surgical procedures as peripheral vascular procedures (consisting of open carotid, open peripheral, and endovascular peripheral procedures), endovascular thoracic and abdominal aortic procedures, open thoracic and abdominal procedures, and lower extremity amputations.

### Statistical Analysis

Data were analyzed from June 1, 2014, to September 7, 2015. The analytical plan followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations for observational cohort studies.[27] We used Kaplan-Meier estimates to calculate cumulative survival probabilities for all-cause mortality. We used the Fine and Gray proportional subdistribution hazards regression analysis to model cardiovascular- and cancer-specific mortality while treating any other cause of death as a competing risk.[28] We first modeled cardiovascular-specific mortality using the occurrence of kidney disease during the index hospitalization as the primary covariate of interest and adjusted for preoperative covariates, including age, sex, ethnicity, comorbidities via the Charlson-Deyo comorbidity index,[29] admission hemoglobin levels, and emergent surgery status. To better examine the effect of the renal insult on outcomes, we constructed a second model stratifying the AKI covariate into stages 1 through 3 and the CKD covariate into mild, moderate, and severe disease while adjusting for the same covariates as the first model. We developed a third model for cardiovascular-specific mortality that accounted for individual comorbidities; admission medications; surgery type; the preoperative covariates age, sex, ethnicity, and admission hemoglobin level; and emergent surgery status. The occurrence of kidney disease was not stratified according to the severity of the insult in this model. Adjusted hazards ratios (HRs) with 95% CIs were reported for each covariate in the model.

For internal validation and to assess prediction accuracy of competing risk models, we created independent validation data sets using a bootstrap cross-validation method. The prediction models were trained on 100 bootstrap samples that were drawn with replacement from the original data, and the models were assessed in the observations that were not in the bootstrap sample. Discriminative power was compared using the Harrell C index,[30] and sensitivity analyses were performed using alternative classifications for cardiovascular and cancer causes of death and using different methods for missing hemoglobin values and reference serum creatinine level (eMethods in the Supplement). The Bonferroni correction was used whenever more than 2 groups were compared. All significance tests were 2 sided, with $P < .05$ considered statistically significant. Fine and Gray modeling was performed using R, version 3.2.0, with the cmprsk package,[31] and all other statistical analyses were performed with SAS software (version 9.3; SAS Institute Inc).

## Results

### Baseline Characteristics and All-Cause Mortality

Baseline characteristics stratified by the occurrence of kidney disease and comorbidities are presented in **Table 1** and eTable 2 in the Supplement. Overall, 2089 of the 3646 patients undergoing major vascular surgery (57.3%) had evidence of kidney disease during hospitalization. At the time of hospitalization, 128 patients (3.5%) had ESRD and 496 (13.6%) had CKD that did not require renal replacement therapy. Among the 496 patients with CKD, 115 (23.2%) presented with severe disease (eGFR, <30 mL/min/1.73 $m^2$). During hospitalization, 1801 patients (49.4%) developed AKI, and 1465 (81.3%) of these did not have underlying CKD. Patients with severe CKD before admission were more likely to develop AKI during hospitalization than patients with mild or moderate CKD. Patients with any form of kidney disease were more likely to be older, be of African American ethnicity, have comorbid congestive heart failure, and have an admission hemoglobin level lower than 10 g/dL. The presence of 3 or more comorbidities at admission was significantly more common in patients with ESRD and CKD regardless of whether their stay was complicated by AKI. Emergent surgery was common (1408 [38.60%] of all patients), which reflected the tertiary care referral patterns at the University of Florida and was associated with AKI and CKD. Patients who underwent open carotid and peripheral vascular procedures were less likely to develop perioperative AKI regardless of underlying comorbid CKD.

Long-term survival rates for patients with any form of acute or chronic kidney disease were significantly lower compared with patients with no known kidney disease after a median follow-up of 7 years ($P < .001$) (**Figure 1** and **Figure 2**). At 10 years of follow-up, unadjusted cumulative survival probability considering all-cause mortality was 59% for patients with no known kidney disease, whereas the survival probability ranged from 13% to 44% for patients with any form of kidney disease. The 10-year cumulative survival for patients with AKI but no CKD was comparable to that for patients with CKD but no AKI. The top 2 causes of death in our cohort were cardiovascular disease (845 of 1577 [53.6%]) and cancer (173 of 1577 [11.0%]). A significantly greater proportion of patients died owing to cardiovascular disease in the group with AKI but no CKD (399 of 693 [57.6%]), AKI with underlying CKD (132 of 215 [61.4%]), CKD without AKI (47 of 76 [61.8%]), and ESRD (68 of 101 [67.3%]) compared with patients with no known kidney disease (199 of 494 [40.4%]). Conversely, the proportion of deaths due to cancer was less in patients with any kidney disease (78 of 1085 [7.2%]) compared with patients with no kidney disease (95 of 492 [19.3%]).

### Competing Risk Models and Cardiovascular-Specific Mortality

Our final competing risk model for cardiovascular-specific mortality included the occurrence of kidney disease as the covariate of interest and was additionally adjusted for individual

Table 1. Clinical Characteristics for All Patients Stratified by Kidney Disease

| Variables | Patient Groups[a] | | | | |
|---|---|---|---|---|---|
| | No Known Kidney Disease (n = 1557) | AKI | | CKD Without AKI (n = 160) | ESRD (n = 128) |
| | | Without CKD (n = 1465) | With CKD (n = 336) | | |
| Age, mean (SD), y | 62 (14) | 66 (14)[b] | 68 (12)[b] | 69 (12)[b] | 64 (12) |
| Age ≥65 y, No. (%) | 741 (47.6) | 895 (61.1)[b] | 234 (69.6)[b] | 112 (70.0)[b] | 62 (48.4) |
| Female, No. (%) | 575 (36.9) | 555 (37.9) | 94 (28.0)[b] | 58 (36.3) | 45 (35.2) |
| African American ethnicity, No. (%) | 116 (7.5) | 157 (10.7)[b] | 53 (15.8)[b] | 25 (15.6)[b] | 33 (25.8)[b] |
| Emergent surgery, No. (%) | 498 (32.0) | 607 (41.4)[b] | 156 (46.4)[b] | 65 (40.6) | 82 (64.1)[b] |
| Weekend admission, No. (%) | 139 (8.9) | 172 (11.7)[b] | 39 (11.6) | 16 (10.0) | 25 (19.5)[b] |
| Charlson-Deyo comorbidity index, No. (%) | | | | | |
| 0 | 86 (5.5) | 55 (3.8) | 1 (0.3)[b] | 3 (1.9) | 0[b] |
| 1 | 591 (38.0) | 540 (36.9) | 56 (16.7)[b] | 19 (11.9)[b] | 1 (0.8)[b] |
| 2 | 484 (31.1) | 458 (31.3) | 54 (16.1)[b] | 26 (16.3)[b] | 8 (6.3)[b] |
| ≥3 | 396 (25.4) | 412 (28.1) | 225 (67.0)[b] | 112 (70.0)[b] | 119 (93.0)[b] |
| Comorbidities, No. (%) | | | | | |
| Myocardial infarction | 205 (13.2) | 208 (14.2) | 62 (18.5)[b] | 28 (17.5) | 15 (11.7) |
| Congestive heart failure | 115 (7.4) | 177 (12.1)[b] | 75 (22.3)[b] | 39 (24.4)[b] | 32 (25.0)[b] |
| Chronic obstructive pulmonary disease | 450 (28.9) | 429 (29.3) | 112 (33.3) | 58 (36.3) | 24 (18.8) |
| Diabetes mellitus | 336 (21.6) | 281 (19.2) | 76 (22.6) | 49 (30.6)[b] | 54 (42.2)[b] |
| Surgery type, No. (%) | | | | | |
| Endovascular thoracic and abdominal | 240 (15.4) | 200 (13.7) | 60 (17.9) | 32 (20.0) | 13 (10.2) |
| Lower extremity amputations | 118 (7.6) | 63 (4.3)[b] | 20 (6.0) | 20 (12.5) | 25 (19.5)[a] |
| Open abdominal | 304 (19.5) | 370 (25.3)[b] | 88 (26.2) | 23 (14.4) | 21 (16.4) |
| Open carotid | 74 (4.8) | 31 (2.1)[b] | 3 (0.9)[b] | 11 (6.9) | 1 (0.8) |
| Endovascular peripheral | 111 (7.1) | 99 (6.8) | 24 (7.1) | 24 (15.0)[b] | 19 (14.8) |
| Open peripheral | 334 (21.5) | 194 (13.2)[b] | 43 (12.8)[b] | 25 (15.6) | 33 (25.8) |
| Open thoracic | 376 (24.1) | 508 (34.7)[b] | 98 (29.2) | 25 (15.6) | 16 (12.5)[b] |
| Admission hemoglobin level, g/dL, No. (%) | | | | | |
| Missing | 318 (20.4) | 215 (14.7) | 53 (15.8) | 27 (16.9) | 26 (20.3) |
| <10 | 249 (16.0) | 299 (20.4)[b] | 76 (22.6)[b] | 34 (21.3) | 35 (27.3)[b] |
| 10-12 | 460 (29.5) | 463 (31.6) | 113 (33.6) | 56 (35.0) | 35 (27.3) |
| ≥12 | 530 (34.0) | 488 (33.3) | 94 (28.0) | 43 (26.9) | 32 (25.0) |
| Admission medications, No. (%) | | | | | |
| Aspirin | 409 (26.3) | 318 (21.7)[b] | 75 (22.3) | 44 (27.5) | 31 (24.2) |
| Statin | 386 (24.8) | 307 (21.0) | 91 (27.1) | 50 (31.3) | 28 (21.9) |
| Angiotensin-converting enzyme inhibitor | 194 (12.5) | 205 (14.0) | 53 (15.8) | 25 (15.6) | 21 (16.4) |
| β-Blocker | 626 (40.2) | 572 (39.0) | 152 (45.2) | 76 (47.5) | 61 (47.7) |
| Chronic kidney disease, No. (%) | | | | | |
| Mild to moderate[c] | NA | NA | 248 (73.8) | 133 (83.1) | NA |
| Severe[d] | NA | NA | 88 (26.2)[e] | 27 (16.9) | NA |
| AKI, No. (%) | | | | | |
| Mild to moderate[f] | NA | 1214 (82.9) | 135 (40.2) | NA | NA |
| Severe[g] | NA | 251 (17.1) | 201 (59.8)[h] | NA | NA |

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disease; NA, not applicable.

SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10.0.

[a] Percentages have been rounded and may not total 100.

[b] $P < .05$ for comparison with respect to the group with no known kidney disease using Bonferroni adjustment for 4 comparisons.

[c] Indicates estimated glomerular filtration rate (eGFR) of 30 mL/min/1.73 $m^2$ or higher.

[d] Indicates eGFR lower than 30 mL/min/1.73 $m^2$.

[e] $P < .05$ for association between CKD severity (mild to moderate or severe) and 2 renal groups (AKI with CKD and CKD with no AKI).

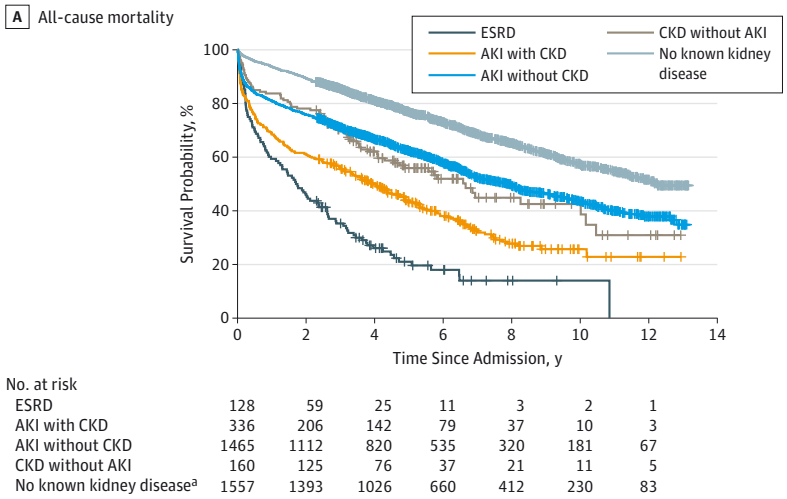
[f] Indicates stage 1 (a 50% change in serum creatinine level) or 2 (a doubling in serum creatinine level).

[g] Indicates stage 3 (a tripling or increase in serum creatinine level to 4.0 mg/dL or higher [to convert to micromoles per liter, multiply by 88.4] or the initiation of renal replacement therapy).

[h] $P < .05$ for association between AKI severity (mild to moderate or severe) and 2 renal groups (AKI with no CKD and AKI with CKD).

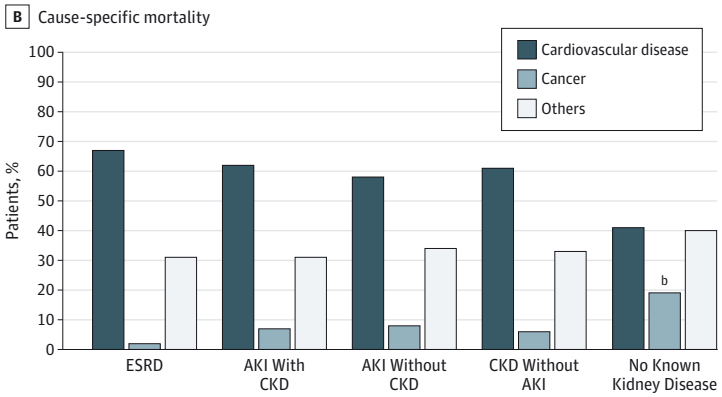
comorbidities, admission medications, surgery type and status, admission hemoglobin levels, and other demographic characteristics (**Table 2** and **Figure 3**). Relative to the reference group with no known kidney disease, the multivariate proportional subdistribution hazards model (HR; 95% CI) showed that AKI with no CKD (2.07; 1.74-2.45), AKI with underlying CKD (2.99; 2.37-3.78), CKD without AKI (2.01; 1.46-2.78), and ESRD (4.90; 3.67-6.53) were independently associated with excess, long-term cardiovascular-specific mortality. Patients with AKI without CKD had an adjusted HR comparable to that of patients with CKD without AKI. Adjusted HRs were significantly elevated for age; the presence of previous myocardial infarction; comor-

Figure 1. Unadjusted Survival Probability




No. at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ESRD | 128 | 59 | 25 | 11 | 3 | 2 | 1 |
| AKI with CKD | 336 | 206 | 142 | 79 | 37 | 10 | 3 |
| AKI without CKD | 1465 | 1112 | 820 | 535 | 320 | 181 | 67 |
| CKD without AKI | 160 | 125 | 76 | 37 | 21 | 11 | 5 |
| No known kidney disease[a] | 1557 | 1393 | 1026 | 660 | 412 | 230 | 83 |

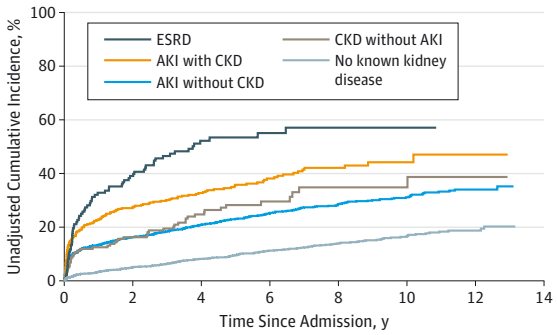



Kaplan-Meier survival curves and cumulative survival probabilities are given for patients stratified by kidney disease for all-cause mortality and cause-specific mortality. AKI indicates acute kidney injury; CKD, chronic kidney disease; and ESRD, end-stage renal disease.

[a] Log-rank $P < .001$ for comparison of groups with respect to the group with no known kidney disease using Bonferroni adjustment.

[b] Log-rank $P < .05$ for comparison with respect to the group with no known kidney disease using Bonferroni adjustment.

Figure 2. Unadjusted Cumulative Incidence Curves for Cardiovascular-Specific Mortality by Kidney Disease Status




No. at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ESRD[a] | 128 | 59 | 25 | 11 | 3 | 2 | 1 |
| AKI with CKD[a] | 336 | 206 | 142 | 79 | 37 | 10 | 3 |
| AKI without CKD[a] | 1465 | 1112 | 820 | 535 | 320 | 181 | 67 |
| CKD without AKI[a] | 160 | 125 | 76 | 37 | 21 | 11 | 5 |
| No known kidney disease | 1557 | 1393 | 1026 | 660 | 412 | 230 | 83 |

AKI indicates acute kidney injury; CKD, chronic kidney disease; and ESRD, end-stage renal disease.

[a] Log-rank $P < .001$ for comparison of groups with respect to the group with no known kidney disease using Bonferroni adjustment.

bid congestive heart failure, chronic obstructive pulmonary disease, and diabetes mellitus; and emergent surgery status. With an admission hemoglobin level of 12 g/dL or higher as the reference group, hemoglobin levels lower than 10 and 10 to 12 g/dL were also significantly associated with cardiovascular-specific mortality. Peripheral vascular procedures and lower extremity amputations were additionally associated with excess long-term mortality when endovascular thoracic and abdominal procedures were treated as the reference group. As in the unadjusted results, the cancer-specific mortality was less

Table 2. Adjusted HRs for Cardiovascular-Specific Mortality Using Multivariable Subdistributional Hazards Models

| Variables | Adjusted HR (95% CI) | | |
|---|---|---|---|
| | Model 1[a] | Model 2[b] | Model 3[c] |
| Kidney disease | | | |
| No known kidney disease | 1 [Reference] | NA | 1 [Reference] |
| AKI without CKD | 2.05 (1.73-2.43)[d] | NA | 2.07 (1.74-2.45)[d] |
| AKI with CKD | 2.73 (2.16-3.45)[d] | NA | 2.99 (2.37-3.78)[d] |
| CKD without AKI | 1.86 (1.35-2.58)[d] | NA | 2.01 (1.46-2.78)[d] |
| ESRD | 3.99 (2.95-5.40)[d] | NA | 4.90 (3.67-6.53)[d] |
| Kidney disease stratified by severity stages[e] | | | |
| No known kidney disease | NA | 1 [Reference] | NA |
| ACI | | | |
| Stage 1 | NA | 1.43 (1.17-1.75)[d] | NA |
| Stage 2 | NA | 2.08 (1.67-2.60)[d] | NA |
| Stage 3 | NA | 4.17 (3.40-5.12)[d] | NA |
| Mild CKD | NA | 1.33 (0.70-2.55) | NA |
| Moderate CKD | NA | 2.04 (1.35-3.06)[d] | NA |
| Severe CKD | NA | 2.49 (1.32-4.69)[d] | NA |
| ESRD | NA | 4.25 (3.14-5.76)[d] | NA |
| Age per 1-y increase | 1.03 (1.02-1.04)[d] | 1.03 (1.02-1.04)[d] | 1.03 (1.02-1.04)[d] |
| Male (vs female) | 1.01 (0.87-1.16) | 1.01 (0.87-1.16) | 1.03 (0.89-1.19) |
| African American vs other ethnicities | 1.08 (0.87-1.33) | 1.08 (0.87-1.34) | 1.06 (0.86-1.32) |
| Charlson-Deyo comorbidity index | | | |
| 0 | 1 [Reference] | 1 [Reference] | NA |
| 1 | 0.99 (0.59-1.66) | 0.97 (0.57-1.65) | NA |
| 2 | 1.75 (1.05-2.94)[d] | 1.68 (0.996-2.85) | NA |
| ≥3 | 1.93 (1.15-3.22)[d] | 1.79 (1.06-3.03)[a] | NA |
| Comorbidities | | | |
| Myocardial infarction (yes vs no) | NA | NA | 1.32 (1.11-1.58)[d] |
| Congestive heart failure (yes vs no) | NA | NA | 1.42 (1.18-1.71)[d] |
| Chronic obstructive pulmonary disease (yes vs no) | NA | NA | 1.28 (1.10-1.49)[d] |
| Diabetes mellitus (yes vs no) | NA | NA | 1.20 (1.02-1.41)[d] |
| Admission medications | | | |
| Aspirin (yes vs no) | NA | NA | 1.01 (0.85-1.19) |
| Statin (yes vs no) | NA | NA | 0.83 (0.69-0.99)[d] |
| Angiotensin-converting enzyme inhibitor (yes vs no) | NA | NA | 0.86 (0.70-1.05) |
| β-Blocker (yes vs no) | NA | NA | 0.97 (0.83-1.12) |
| Surgery type | | | |
| Endovascular thoracic and abdominal | NA | NA | 1 [Reference] |
| Peripheral vascular[f] | NA | NA | 1.40 (1.10-1.78)[d] |
| Open thoracic and abdominal | NA | NA | 1.24 (0.99-1.57) |
| Lower extremity amputations | NA | NA | 1.43 (1.02-1.99)[d] |
| Emergent surgery (vs elective) | 1.54 (1.34-1.78)[d] | 1.41 (1.22-1.63)[d] | 1.47 (1.27-1.71)[d] |
| Admission hemoglobin level, g/dL | | | |
| ≥12 | 1 [Reference] | 1 [Reference] | 1 [Reference] |
| <10 | 1.36 (1.12-1.66)[d] | 1.32 (1.09-1.61)[d] | 1.39 (1.14-1.69)[d] |
| 10-12 | 1.20 (1.01-1.44)[d] | 1.20 (1.01-1.44)[d] | 1.24 (1.04-1.48)[d] |
| Missing | 1.10 (0.89-1.37) | 1.12 (0.91-1.39) | 1.10 (0.89-1.37) |

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disease; HR, hazard ratio; NA, not applicable.

SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10.0.

[a] Adjusted for Charlson-Deyo comorbidity index.

[b] Adjusted for Charlson-Deyo comorbidity index and kidney disease severity.

[c] Adjusted for individual comorbidities, admission medications, and surgery type.

[d] $P < .05$.

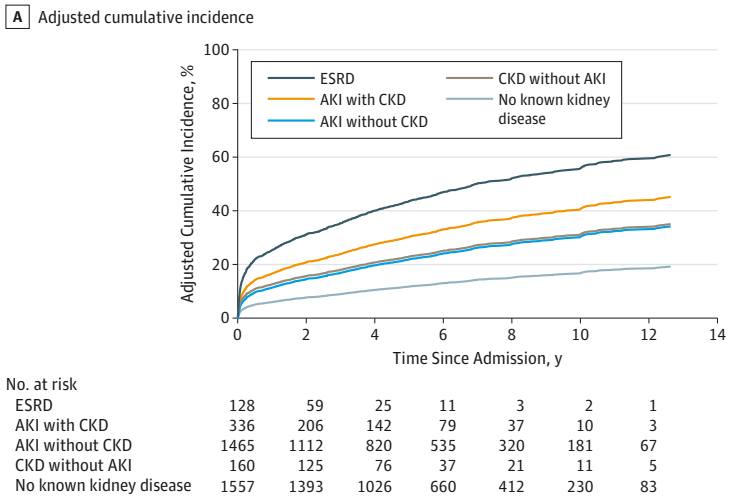
[e] Stages of AKI and severity of CKD are described in Table 1.

[f] Includes open carotid, open peripheral, and endovascular peripheral procedures.

in patients with any kidney disease compared with the cardiovascular-specific mortality.

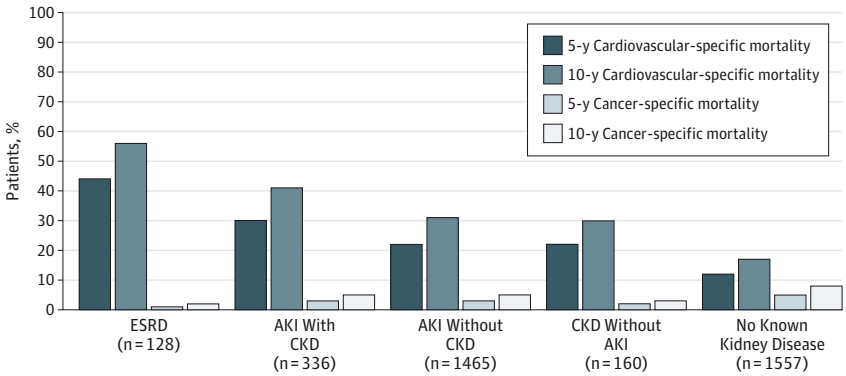
Compared with patients with no known disease, the risk for cardiovascular-specific mortality was proportional to the severity of the kidney disease. Among patients who developed AKI, the adjusted HRs (95% CIs) were 1.43 (1.17-1.75), 2.08 (1.67-2.60), and 4.17 (3.40-5.12) for patients with stages 1, 2, and 3 kidney injury, respectively. Patients with mild CKD

Figure 3. Model-Based Adjusted Cumulative Incidence and Mortality




No. at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ESRD | 128 | 59 | 25 | 11 | 3 | 2 | 1 |
| AKI with CKD | 336 | 206 | 142 | 79 | 37 | 10 | 3 |
| AKI without CKD | 1465 | 1112 | 820 | 535 | 320 | 181 | 67 |
| CKD without AKI | 160 | 125 | 76 | 37 | 21 | 11 | 5 |
| No known kidney disease | 1557 | 1393 | 1026 | 660 | 412 | 230 | 83 |




Cumulative incidence curves are given for cardiovascular-specific mortality by kidney disease status. Covariates are adjusted for age, sex, ethnicity, comorbidities, admission medications, emergent surgery status, surgery type, and admission hemoglobin level. All groups with acute kidney injury (AKI) or chronic kidney disease (CKD) have significantly higher hazards ratios compared with the group with no known kidney disease ($P < .001$). The bar graph shows adjusted 5- and 10-year cumulative cardiovascular and cancer-specific mortality rates for each group.

before the index hospital admission had an insignificant increase in the HR (95% CI) for cardiovascular-specific mortality (1.33; 0.70-2.55), whereas those for cardiovascular-specific mortality were significantly increased for patients with moderate (2.04; 1.35-3.06) or severe (2.49; 1.32-4.69) CKD before the index hospital admission.

For internal validation of the study, we compared the performance of models in the training and validation cohort from multiple iterations. The C index values for our final multivariable competing risk model from training cohorts were 0.76, 0.72, and 0.70 at 1, 5, and 10 years, respectively. This model performed well, with C index values (95% CI) of 0.75 (0.71-0.77), 0.71 (0.69-0.73), and 0.69 (0.67-0.70) at 1, 5, and 10 years, respectively, simultaneously in the validation data set. Similar performances were observed for the other models, and no significant differences were found in the C index values of competing risk models applied to training and validation cohorts ($P > .05$ for all).

The unadjusted and adjusted cumulative incidence of cardiovascular-specific mortality was lower for patients with no known kidney disease relative to patients with AKI or CKD (Figure 2 and Figure 3). Ten-year, adjusted, cardiovascular-specific mortality estimates were 17%, 31%, 30%, 41%, and 56% for patients with no known kidney disease, AKI without CKD, CKD without AKI, AKI with CKD, and ESRD, respectively ($P < .001$) (Figure 3). Patients with AKI without CKD had a 10-year estimate of cardiovascular-specific mortality comparable to that of patients with CKD but no AKI. In contrast, 10-year adjusted cancer-specific mortality estimates were highest for patients with no known kidney disease at 8% and ranged from 2% for patients with ESRD to 5% for patients with AKI without CKD and AKI with CKD (Figure 3). Similar results were obtained in adjusted and unadjusted analyses when comparing patients grouped by sex, age, and type of procedure (eFigures 1-4 in the Supplement).

## Discussion

In a cohort of patients undergoing major vascular surgery, AKI and CKD were associated with significant increases in long-term cardiovascular-specific mortality compared with patients with no kidney disease. This association was proportional to the severity of kidney disease independent of the patients' age, sex, comorbidity burden at admission, or the type of operation in the cohort that included open and

endovascular surgery. Postoperative AKI, with or without underlying CKD, was independently associated with cardiovascular-specific mortality. Even patients with stage 1 AKI, who in clinical practice are often not even considered to have true organ damage, had a 43% increase in the adjusted HR for cardiovascular-specific mortality compared with patients with no kidney disease. The incidence of AKI alone was more than 3 times that of CKD alone, and patients with AKI alone had a cardiovascular-specific mortality comparable to that seen in patients with CKD alone for all periods. Patients with AKI superimposed on underlying CKD constituted a smaller proportion of patients with AKI but had an even higher cardiovascular-specific mortality.

Declining eGFR and the development of albuminuria, the clinical manifestations of CKD, are both important determinants of longevity in the general population.[32] Chronic kidney disease is a well-known risk factor for cardiovascular disease, and the absolute risk for death increases exponentially with decreasing renal function, even among patients without manifest cardiovascular disease.[33,34] Individuals with lesser stages of CKD are more likely to die of cardiovascular disease than to develop kidney failure requiring dialysis, whereas those with ESRD have as much as 30 times the cardiovascular mortality of the general population.[1-3,35] Recent studies suggest that AKI might also be a risk factor for cardiovascular disease through the progression to CKD or through independent mechanisms.[36-40] Patients with AKI have an increased risk for coronary angiography, coronary artery bypass grafting surgery, myocardial infarction, congestive heart failure, and stroke regardless of any progression to CKD.[41-43]

Major open vascular surgery, with the risk for intraoperative hypotension and the frequent need to cross-clamp the aorta, has long had an association with renal failure.[44] Modern vascular surgery relies heavily on preoperative and, especially with endovascular procedures, intraoperative contrast-enhanced imaging and thus carries an increased risk for contrast-induced AKI. The use of nephrotoxic broad-spectrum antibiotics can increase the risk for AKI in the perioperative period for patients undergoing major vascular surgery.[45] The novel finding in this study is that major vascular surgery has high cardiovascular-specific mortality associated with AKI and CKD. This finding has important implications for the preoperative and perioperative management of the patient undergoing major vascular surgery.

Efforts must then focus on AKI prevention in vascular surgery, mitigation of further injury when AKI has already occurred, and facilitation of renal recovery in patients with established AKI. More tools are available toward these goals than are commonly recognized. Goal-directed intraoperative management to reduce the risk for postoperative AKI through optimizing renal perfusion is feasible and underused.[46] The emergence of new biomarkers and imaging techniques has provided new tools for early risk stratification and diagnosis in the perioperative period.[47,48] Standardized follow-up is important after an episode of AKI and can help to prevent the development of CKD.[49] This area can be addressed quickly and relatively easily because less than 50% of patients with the most severe AKI will have a follow-up creatinine level measured within the first 3 months of hospitalization, and follow-up is even less likely to be obtained after less severe AKI.[50]

We acknowledge the limitations of all retrospective studies. With the use of multivariable adjustments and the evaluation of model discrimination on validation data sets, we have attempted to increase the internal validity of the competing risk models. Although our study used patients from a single center, which may limit our ability to generalize the findings, the study site is a large tertiary care center that receives a large number of referrals from all over the state and hence has a very heterogeneous patient profile with a wide range of procedures. To our knowledge, no prospective surgical cohort of this size and heterogeneity had concomitant data for kidney disease and cardiovascular mortality. We had only limited data concerning urine output or concerning AKI and preoperative albuminuria among patients with CKD; if available, those data could have strengthened our analysis. We used a combination of *ICD-9-CM* administrative codes and eGFR on admission to define CKD status. A recent systematic review demonstrated that, although sensitivity for coded CKD covariates was highly variable, specificity was high, with all studies reporting values of 0.90 or higher.[51] We have not attempted to link progression to ESRD among patients with AKI as a main determinant of cardiovascular mortality, although the evidence from patients with mild CKD suggests that death from cardiovascular disease is more likely than progression to dialysis.[1-3] Several traditional Framingham risk factors for cardiovascular disease were not recorded in our administrative database—including systolic blood pressure, total and high-density lipoprotein cholesterol levels, smoking history, and current use of antihypertensives—and thus could not be included as covariates.[52] Patient cardiovascular comorbidity information, however, was available for previous myocardial infarctions, congestive heart failure, peripheral vascular disease, cerebrovascular disease, diabetes mellitus without complications, and diabetes mellitus with complications, and each patient's Charlson-Deyo comorbidity index was calculated and included as a model covariate.

## Conclusions

To the best of our knowledge, this study is the first to demonstrate that the deleterious effects of AKI and CKD on long-term survival after major vascular surgery are comparable and are primarily owing to the increase in cardiovascular-specific mortality. Both AKI and CKD were common in patients undergoing major vascular surgical procedures and were associated with as much as a 4-fold increase in long-term cardiovascular-specific mortality compared with patients with no kidney disease. This association was proportional to the severity of kidney disease and was unaffected by sex and markedly more pronounced in older patients. These findings reinforce the importance of preoperative CKD risk stratification through the application of consensus staging criteria for CKD using eGFR and albuminuria for all patients undergoing major vascular surgery. Preoperative and postoperative risk stratification for AKI using clinical scores and urinary biomarkers similarly can help

to direct the implementation of simple and inexpensive preventive strategies in the perioperative period that could prevent or mitigate further decline in kidney function. The appropriate transition of patients undergoing surgery to follow-up in the outpatient setting with an emphasis on the prevention of kidney disease progression and mitigation of cardiovascular risk can be an important factor in improving the care of the patient undergoing vascular surgery who has AKI and/or CKD. Our findings present compelling evidence that such efforts are warranted and justifiable.

## ARTICLE INFORMATION

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*Study concept and design:* Ozrazgat-Baslanti, Bihorac.
*Acquisition, analysis, or interpretation of data:* All authors.
*Drafting of the manuscript:* Huber, Ozrazgat-Baslanti, Bihorac, Hobson.
*Critical revision of the manuscript for important intellectual content:* All authors.
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Invited Commentary

# Transient Acute Kidney Injury in the Postoperative Period
## It Is Time to Pay Closer Attention

Christian de Virgilio, MD; Dennis Yong Kim, MD

**Many of us** have had the unsettling experience of watching the serum creatinine level rise or the urine output dwindle following a complex vascular operation. As kidney function deteriorates, we steel ourselves for the inevitable need for dialysis. The second guessing begins. Was it the contrast? The brief intraoperative hypotension? Or, perhaps a nephrotoxic drug? As the creatinine level ebbs, we breathe a sigh of relief. However, a growing body of literature indicates that we are lulled by a false sense of security. As highlighted in the article by Huber et al,[1] transient acute kidney injury (AKI) in the postoperative period has lasting, long-term, mortal consequences on the heart.

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On first pass, it seems counterintuitive that a brief period of AKI would have lasting effects, particularly in a patient with normal kidney function at baseline. One must not forget, however, that an extreme loss of renal function is required to develop AKI in such patients. Alarmingly, nearly half of the patients in the study by Huber and colleagues developed AKI, and even transient AKI was associated with a 31% increase in 10-year adjusted cardiovascular mortality. This begs the question: what are the potential links between transient postoperative AKI and long-term cardiovascular death? The answer may lie in the concept of organ cross talk, which refers to the mechanism whereby injury of one organ affects the function of distant organs. The ischemia-reperfusion associated with AKI leads to an initial insult of the renal tubule and renal vascular endothelium.[2] This appears to trigger a proinflammatory cascade, with the release of cellular and soluble mediators that lead to remote cardiac injury by various mechanisms including neutrophil infiltration, maladaptive neurohumoral responses, and cardiac myocyte apoptosis.[3] An imbalance in cardiac homeostasis ensues, with the potential for long-term myocardial dysfunction.

The results of the study by Huber and colleagues should prompt a call to action in terms of earlier diagnosis, treatment, and prevention of postoperative AKI. Recently, urinary markers of cell cycle arrest have been validated for the early identification of AKI far in advance of clinical manifestations