Acute Kidney Injury and Risk of Heart Failure and Atherosclerotic Events

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Abstract

Background and objectives AKI in the hospital is common and is associated with excess mortality. We examined whether AKI is also independently associated with a higher risk of different cardiovascular events in the first year after discharge.

Design, setting, participants, & measurements We conducted a retrospective analysis of a cohort between 2006 and 2013 with follow-up through 2014, within Kaiser Permanente Northern California. We identified all adults admitted to 21 hospitals who had one or more in-hospital serum creatinine test result and survived to discharge. Occurrence of AKI was on the basis of Kidney Disease: Improving Global Outcomes diagnostic criteria. Potential confounders were identified from comprehensive inpatient and outpatient, laboratory, and pharmacy electronic medical records. During the 365 days after discharge, we ascertained occurrence of heart failure, acute coronary syndromes, peripheral artery disease, and ischemic stroke events from electronic medical records.

Results Among a matched cohort of 146,941 hospitalized adults, 31,245 experienced AKI. At 365 days postdischarge, AKI was independently associated with higher rates of the composite outcome of hospitalization for heart failure and atherosclerotic events (adjusted hazard ratio [aHR], 1.18; 95% confidence interval [95% CI], 1.13 to 1.25) even after adjustment for demographics, comorbidities, preadmission eGFR and proteinuria, heart failure and sepsis complicating the hospitalization, intensive care unit (ICU) admission, length of stay, and predicted in-hospital mortality. This was driven by an excess risk of subsequent heart failure (aHR, 1.44; 95% CI, 1.33 to 1.56), whereas there was no significant association with follow-up atherosclerotic events (aHR, 1.05; 95% CI, 0.98 to 1.12).

Conclusions AKI is independently associated with a higher risk of cardiovascular events, especially heart failure, after hospital discharge.

Clin J Am Soc Nephrol 13: 833–841, 2018. doi: https://doi.org/10.2215/CJN.12591117

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Introduction

AKI frequently complicates hospitalizations and has been increasing over time (1,2). AKI contributes to the development and progression of CKD (3–6) and excess mortality (7,8). With cardiovascular disease being a leading cause of death, it is important to evaluate whether AKI contributes to excess cardiovascular events.

AKI leads to acute elevations in inflammatory cytokines (9), endothelial dysfunction (10), and dysregulation in mineral metabolism (11,12), and may contribute to increases in markers of cardiac ischemia (13). However, whether AKI contributes to an excess risk of cardiovascular events remains controversial as previous studies have focused primarily on selected patients such as those with coronary angiography (14), cardiac surgery (15–18), acute myocardial infarction (19), or acute severe hypertension (20), or in populations with limited diversity (21). Furthermore, methodological limitations of existing studies include lack of preadmission kidney function, reliance on administrative codes for AKI, not accounting for relevant confounders (including acute severity of illness) or not using contemporary definitions of AKI (22).

Among a large, contemporary matched cohort of hospitalized adults, we examined the association between AKI and risks of cardiovascular events during the first year after discharge. As seen in other acute medical conditions (23–27) linked to higher risks of cardiovascular events, we hypothesized that AKI would be independently associated with higher risks of post-discharge cardiovascular events.

Materials and Methods

Sample

Kaiser Permanente Northern California is a large integrated health care delivery system caring for more than 4.2 million persons that are highly representative of the local and statewide population (28,29).

We identified adult (≥20 years) members hospitalized at 21 Kaiser Permanente Northern California hospitals between January of 2006 and December of

2013 who had ≥12 months of continuous membership and pharmacy benefit at admission, one or more serum creatinine value during the index hospitalization, and surviving to discharge (Figure 1). Hospitalizations were excluded if the patient had prior ESKD (receipt of chronic dialysis or kidney transplant) identified from a health plan ESKD registry. If a patient had more than one hospitalization during the study period, only the first admission was analyzed.

The study was approved by participating institutions' institutional review boards. Waiver of consent was obtained because of the nature of the study.

AKI

We defined AKI patterned after Kidney Disease: Improving Global Outcomes (KDIGO) criteria demonstrating a difference between serial inpatient serum creatinine concentrations of ≥0.3 mg/dl within 48 hours and/or ≥50% above preadmission baseline serum creatinine concentration (30). Baseline kidney function was defined as the most recent outpatient, nonemergency department serum creatinine concentration between 7 and 365 days before admission (4). All serum creatinine measurements were performed at the regional health plan laboratory using an isotope dilution mass spectrometry-traceable assay. Urine output data were not systematically available. We characterized AKI severity on the basis of serum creatinine-based KDIGO criteria and assigned the highest level of severity that occurred during the index hospitalization (30).

Outcomes

Follow-up occurred through December of 2014 and up to 365 days postdischarge with censoring due to health plan disenrollment, death, or end of follow-up. Death was identified from health system databases, state death certificate files, and Social Security Administration files (31,32). At 365 days postdischarge, 6% of the study cohort were censored because of disenrollment.

Our primary outcome was the composite of hospitalization for heart failure, acute coronary syndromes (*i.e.*,

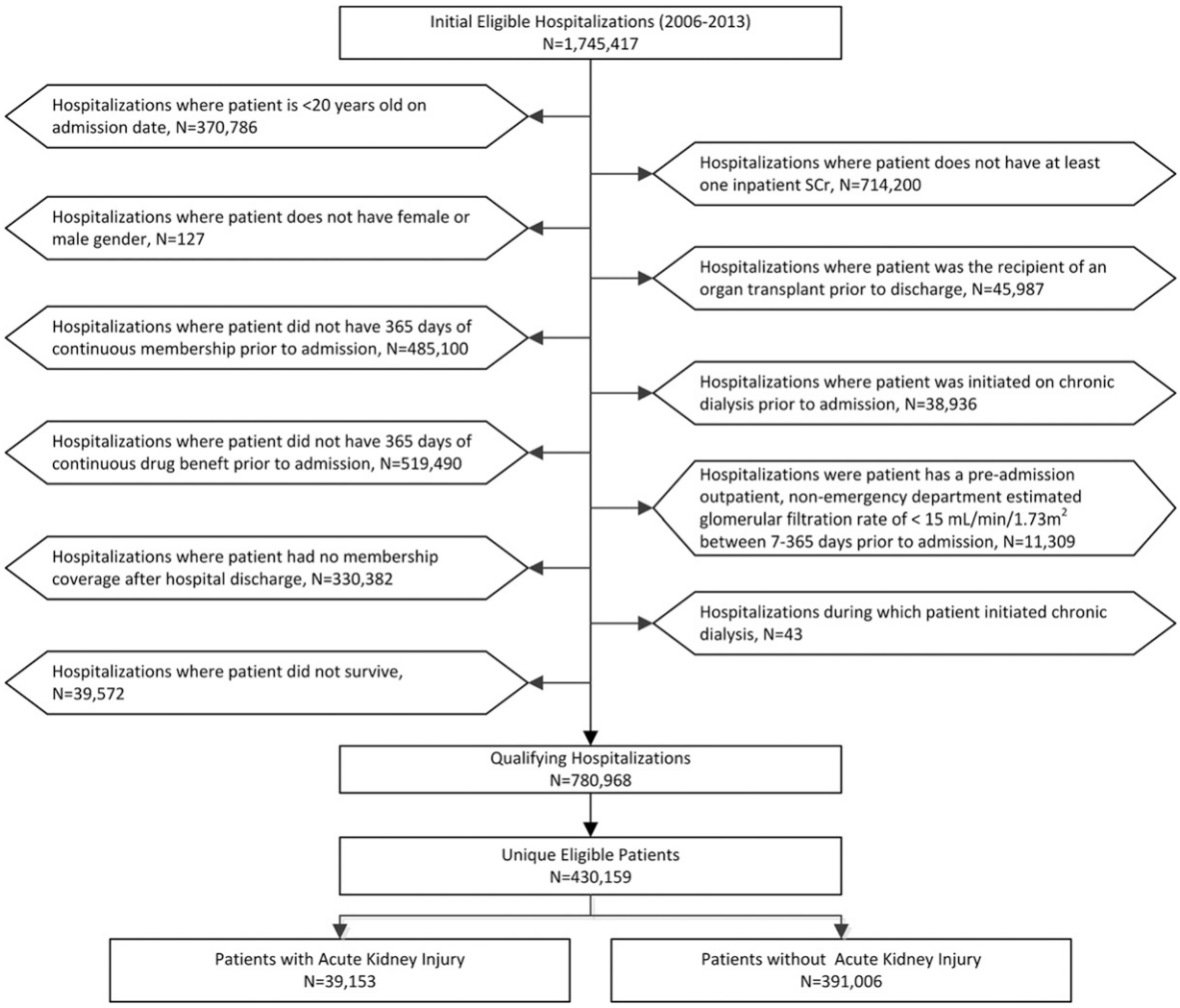

Figure 1. | Cohort assembly of adults hospitalized between January 1, 2006 and December 31, 2013. AKI defined using modified KDIGO criteria: increase in serum creatinine by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 hours or an increase in serum creatinine to ≥1.5 times baseline (defined as the most recent nonemergency department, outpatient value in the 7–365 days before admission). SCr, serum creatinine.

acute myocardial infarction or unstable angina), clinically significant peripheral artery disease (*i.e.,* aortic dissection, rupture or repair, and peripheral artery revascularization), or ischemic stroke. Hospitalizations were ascertained from hospitalization databases using validated algorithms on the basis of International Classification of Diseases, Ninth Edition (ICD-9) discharge codes with high positive predictive values for these outcomes compared against medical record review in our health system (31–33). As a secondary outcome, we assessed a modified composite outcome of atherosclerotic events (acute coronary syndromes, peripheral artery disease, or ischemic stroke). In addition, we separately evaluated individual components of the composite outcome and death.

Covariates

Information on age, sex and self-reported race/ethnicity was obtained from electronic health records. Preadmission eGFR (eGFR in ml/min per 1.73 m^2) was estimated using the CKD Epidemiology Collaboration equation (34) and proteinuria was determined using a urine dipstick result of ≥1+ (31).

We identified comorbid conditions up to 5 years before the index hospitalization using inpatient and ambulatory diagnoses and procedures, laboratory results, and drug dispensings from pharmacy databases (codes available upon request). Atrial fibrillation and/or atrial flutter was identified using primary discharge diagnoses. Diabetes mellitus was defined on the basis of one or more primary inpatient discharge diagnosis, two or more outpatient diagnoses, or receipt of an antidiabetic drug (35). Hypertension was defined as two or more outpatient diagnoses or one or more outpatient diagnosis plus receipt of an antihypertensive agent (32). Dyslipidemia was defined on the basis of outpatient diagnoses or receipt of antilipemic medications. Smoking status at the time of admission was ascertained from electronic medical records. Cancer was identified using one or more primary discharge diagnosis or two or more outpatient diagnoses of any malignancy other than nonmelanoma skin cancer. Coronary disease was defined as prior myocardial infarction, unstable angina, or coronary revascularization (31,32). Heart failure was defined as one or more primary discharge diagnosis and/or three or more outpatient visits for heart failure (36,37). Peripheral artery disease was defined as more than one primary hospital discharge or emergency department diagnosis or more than one revascularization procedure. Prior ischemic stroke was defined as one or more primary hospital discharge diagnosis (33).

To address potential confounders occurring during the index hospitalization, we identified occurrence of acute heart failure, sepsis, and coronary revascularization, using diagnosis and procedure codes for the index admission (31,36–38). As one measure of severity of acute illness, we identified patients who received care in the ICU and calculated the length of the stay in the ICU and the overall hospitalization. Finally, to further account for acute severity of illness, we calculated a validated laboratory-based acute physiology score, comorbidity point score, and the predicted mortality score, which are on the basis of automated inpatient, outpatient, and laboratory data (39,40).

We assessed for missingness in potential confounders listed above and found our matched study population had <15% missing data across any variable. For variables with significant missingness, we included a categorical value to reflect this.

Propensity Score and Matching

To control for imbalances in covariates between patients with and without AKI, we performed logistic regression using all variables in Table 1 to calculate the propensity of having AKI during the index hospitalization (model c-index =0.82). We then attempted to match five non-AKIs to each AKI, using age (±5 years), sex, year of index hospitalization, and a ≤0.001 difference in propensity score.

Statistical Methods

Analyses were performed using SAS version 9.3 (Cary, NC). Continuous variables were reported as means with SDs or medians with interquartile ranges; discrete variables were reported as frequencies and proportions. Given the large sample size, for means and proportions, we compared characteristics between those with and without AKI, using Cohen's *D* value, by taking the standardized difference of means or proportions between groups and dividing by the pooled estimate, with a value >0.10 considered significant (41,42). We compared median values using the Wilcoxon rank-sum test, with a *P* value <0.05 considered significant.

Outcomes through 365 days after discharge were reported as proportions with Cohen's *D* value to assess differences between AKI and non-AKI groups, along with cumulative hazards for the primary composite outcome. We applied multivariable stratified Cox regression to assess the association of AKI on outcomes with accounting for matched sets. All variables in Table 1 were included as covariates except for those variables used for matching as well as the laboratory-based acute physiology score and comorbidity point scores, as they were incorporated into the summary predicted mortality score. We adjusted for onset of ESKD (*i.e.,* initiation of RRT) during follow-up; in sensitivity analyses, we censored at ESKD and found that results were unchanged (data not shown), so only the main results are reported.

We assessed for a possible graded relationship between AKI severity with the primary composite outcome. Finally, we performed analyses separately by index age (<65, 65–74, and ≥75 years) and by sex.

Results

Study Population

During the study period, we identified 430,159 eligible adults who were discharged alive, with 39,153 (9%) experiencing AKI (70% stage 1, 14% stage 2, and 16% stage 3) (Figure 1). We successfully matched 31,245 (80%) patients with AKI with up to five patients without AKI on the basis of year of index hospitalization, age, sex, and propensity score, with a median of 5 (interquartile range, 2–5) matched patients without AKI for each patient with AKI. Our matching approach yielded successful balance across most patient characteristics, with the exception of patients with AKI being more likely than matched patients without AKI to have prior heart failure and proteinuria (Table 1).

Table 1. Baseline characteristics for adults hospitalized between 2006 and 2013 before and after propensity matching, stratified by AKI status

Characteristic	Before Matching			After Matching		
	AKI (*n*=39,153)	No AKI (*n*=391,006)	*D* Value	AKI (*n*=31,245)	No AKI (*n*=115,696)	*D* Value
Age, yr						
Mean (SD)	69 (16)	62 (18)	0.38	69 (15)	69 (16)	0.04
Age group, yr, *n* (%)			0.37			0.03
18–49	4663 (12)	101,428 (26)		3552 (11)	14,205 (12)	
50–59	5463 (14)	64,391 (17)		4218 (14)	15,995 (14)	
60–69	8359 (21)	77,462 (20)		6592 (21)	24,593 (21)	
70–79	10,129 (26)	75,320 (19)		8244 (26)	30,176 (26)	
≥80	10,539 (27)	72,405 (19)		8639 (28)	30,727 (27)	
Sex, *n* (%)			0.17			0.02
Women	19,322 (49)	226,001 (58)		15,686 (50)	59,173 (51)	
Men	19,831 (51)	165,005 (42)		15,559 (50)	56,523 (49)	
Race/ethnicity, *n* (%)			0.05			0.02
White	27,941 (71)	281,584 (72)		22,756 (73)	85,386 (74)	
Black	4506 (12)	33,981 (9)		3287 (11)	11,754 (10)	
Asian/Pacific Islander	4748 (12)	48,634 (12)		3658 (12)	13,093 (11)	
Native American	268 (0.7)	2655 (0.7)		206 (0.7)	699 (0.6)	
Other/unknown	1690 (4)	24,152 (6)		1338 (4)	4764 (4)	
Hispanic ethnicity, *n* (%)	5646 (14)	58,425 (15)	0.01	4462 (14)	15,495 (13)	0.03
Current or former smoker, *n* (%)	20,027 (51)	178,832 (46)	0.13	15,833 (51)	58,126 (50)	0.01
Prior medical history, *n* (%)						
Coronary heart disease	3493 (9)	24,097 (6)	0.24	2690 (9)	9754 (8)	0.01
Chronic heart failure	7643 (20)	28,762 (7)	0.68	4779 (15)	14,401 (12)	0.14
Ischemic stroke	898 (2)	10,118 (3)	0.07	773 (3)	2916 (3)	0.01
Peripheral artery disease	2685 (7)	15,285 (4)	0.36	2071 (7)	6925 (6)	0.07
Atrial fibrillation or flutter	5266 (13)	35,035 (9)	0.28	4217 (13)	14,708 (13)	0.04
Diabetes Mellitus	15,555 (40)	83,724 (21)	0.54	11,256 (36)	38,820 (34)	0.07
Hypertension	30,834 (79)	220,419 (56)	0.64	23,015 (74)	83,170 (72)	0.05
Dyslipidemia	27,273 (70)	207,974 (53)	0.43	21,314 (68)	77,189 (67)	0.04
Cancer	9157 (23)	70,462 (18)	0.20	7498 (24)	27,605 (24)	0.00
Proteinuria	15,101 (39)	77,139 (20)	0.57	10,490 (34)	32,290 (28)	0.16
Preadmission eGFR, ml/min per 1.73 m^2, *n* (%)			0.10			0.08
>150	38 (0.1)	249 (0.1)		32 (0.1)	53 (0.0)	
90–150	6269 (16)	80,484 (21)		5131 (16)	21,095 (18)	
60–89	11,929 (31)	125,959 (32)		10,256 (33)	41,404 (36)	
45–59	6947 (18)	41,133 (11)		5549 (18)	20,342 (18)	
30–44	6030 (15)	21,162 (5)		4301 (14)	13,106 (11)	
15–29	3164 (8)	6297 (2)		1754 (6)	4107 (4)	
Unknown	4776 (12)	115,722 (30)		4222 (14)	15,589 (14)	
Preadmission medication use, *n* (%)						
Angiotensin-converting enzyme inhibitor	16,823 (43)	100,143 (26)	0.47	12,753 (41)	45,526 (39)	0.04
Angiotensin II receptor blocker	4974 (13)	31,458 (8)	0.31	3812 (12)	13,657 (12)	0.02
Diuretic	19,823 (51)	119,145 (31)	0.52	14,998 (48)	52,503 (45)	0.06
β-Blocker	17,353 (44)	112,333 (29)	0.41	13,179 (42)	46,701 (40)	0.05
Calcium channel blocker	9520 (24)	53,340 (14)	0.43	6963 (22)	23,662 (21)	0.07
Statin	19,373 (50)	133,614 (34)	0.38	15,023 (48)	53,697 (46)	0.04
Index hospitalization features, *n* (%)						
Coronary bypass surgery	77 (0.2)	216 (0.1)	0.77	58 (0.2)	130 (0.1)	0.30
Percutaneous coronary intervention	84 (0.2)	842 (0.2)	0.00	69 (0.2)	338 (0.3)	0.17
Sepsis	6945 (18)	22,651 (6)	0.76	3911 (13)	11,130 (10)	0.18
Heart failure	2746 (7)	7972 (2)	0.78	1832 (6)	4793 (4)	0.22
ICU stay, *n* (%)	12,273 (31)	46,576 (12)	0.74	7494 (24)	23,024 (20)	0.14
ICU length of stay, h						
Median (IQR)	68 (35–139)	7 (22–65)	<0.001[a]	53 (29–99)	40 (23–69)	<0.001[a]
Hospital length of stay, d						
Median (IQR)	6 (3–10)	3 (2–5)	<0.001[a]	5 (3–8)	4 (2–6)	<0.001[a]
Laboratory-based acute physiology score						
Median (IQR)	27 (9–44)	6 (0–20)	<0.001[a]	24 (6–41)	16 (1–30)	<0.001[a]
Missing, n (%)	13 (0.0)	179 (0.0)		13 (0.0)	32 (0.0)	

Table 1. (Continued)

Characteristic	Before Matching			After Matching		
	AKI (*n*=39,153)	No AKI (*n*=391,006)	*D* Value	AKI (*n*=31,245)	No AKI (*n*=115,696)	*D* Value
Comorbidity point score						
Median (IQR)	77 (46–114)	52 (26–86)	<0.001[a]	75 (44–111)	73 (43–108)	<0.001[a]
Missing, n (%)	415 (1)	4586 (1)		366 (1)	1319 (1)	
Predicted mortality score						
Median (IQR)	3 (1–7)	1 (0–2)	<0.001[a]	2 (1–6)	2 (1–4)	<0.001[a]
Missing, n (%)	1446 (4)	31,026 (8)		1337 (4)	5730 (5)	
Predicted mortality score categorical, *n* (%)			0.42			0.10
<0.1%	1774 (5)	69,083 (18)		1702 (5)	6442 (6)	
0.1%–0.4%	4083 (10)	90,413 (23)		3809 (12)	16,457 (14)	
0.5%–1.9%	9422 (24)	105,600 (27)		8292 (27)	35,639 (31)	
2.0%–4.9%	9452 (24)	53,410 (14)		7503 (24)	27,364 (24)	
5.0%–9.9%	6654 (17)	24,650 (6)		4774 (15)	14,369 (12)	
10.0%–14.9%	2772 (7)	8438 (2)		1826 (6)	4881 (4)	
15.0%–29.9%	2621 (7)	6927 (2)		1590 (5)	4018 (4)	
≥30.0%	929 (2)	1459 (0.4)		412 (1)	796 (0.7)	
Unknown	1446 (4)	31,026 (8)		1337 (4)	5730 (5)	

The *D* value represents the standardized difference in means or proportions with a value >0.10 being significant. ICU, intensive care unit; IQR, interquartile range.
[a]Represents *P* values and not *D* values.

During the index hospitalization, patients with AKI were also more likely to receive coronary revascularization, be diagnosed with sepsis or heart failure, stay in the ICU, and have longer length of stay, but had no material differences in measures of severity of acute illness or predicted short-term mortality (Table 1).

Heart Failure and Atherosclerotic Outcomes

Overall, 10,605 patients experienced the composite outcome of heart failure and atherosclerotic events (4636 heart failure, 2399 acute coronary syndrome, 3042 peripheral artery disease, and 1410 ischemic stroke events) during the first 365 days after discharge (Table 2). Compared with those without AKI, those with AKI had higher crude risks for the primary composite outcome and for heart failure alone, but not for atherosclerotic events alone (Figure 2, Table 2). After adjustment for preadmission patient characteristics and key index hospitalization features (*i.e.*, length of stay, ICU stay, sepsis, heart failure, receipt of coronary revascularization, and predicted mortality score), we found that AKI was associated with an 18% (95% confidence interval [95% CI], 13% to 25%) higher rate of the composite outcome of heart failure and atherosclerotic events (Figure 3). The multivariable association between AKI and the primary composite outcome was similar across age (adjusted hazard ratio [aHR], 1.27; 95% CI, 1.10 to 1.46 for age <65 years, aHR, 1.17; 95% CI, 1.04 to 1.31 for age 65–74 years, and aHR, 1.18; 95% CI, 1.11 to 1.27 for age ≥75 years) and sex (aHR, 1.20; 95% CI, 1.11 to 1.29 for women and aHR, 1.17; 95% CI, 1.09 to 1.25 for men).

Importantly, the adjusted rate of hospitalization for heart failure was 44% higher (95% CI, 33% to 56%) for those with AKI, but there were no significant multivariable associations between AKI and atherosclerotic events (composite or individual atherosclerotic event types) (Figure 3). Results were similar in analyses stratified by age group or sex (data not shown).

Of note, in evaluating the association between AKI severity and the primary outcome at 365 days after discharge, we found that AKI stage 1 was associated with an adjusted 25%

Table 2. Crude risks of the heart failure, atherosclerotic events, and death at 365 days after discharge among hospitalized adults, stratified by AKI status

At 365 d postdischarge, *n* (%)	Overall (*n*=146,941)	AKI (*n*=31,245)	No AKI (*n*=115,696)	*D* Value
Composite of atherosclerotic events and heart failure	10,605 (7)	2765 (9)	7840 (7)	0.18
Composite of atherosclerotic events	6575 (5)	1533 (5)	5042 (4)	0.08
Heart failure	4636 (3)	1423 (5)	3213 (3)	0.31
Acute coronary syndrome	2399 (2)	577 (2)	1822 (2)	0.10
Peripheral artery disease	3042 (2)	725 (2)	2317 (2)	0.09
Ischemic stroke	1410 (1)	307 (1)	1103 (1)	0.02
Death	22,759 (16)	5963 (19)	16,796 (15)	0.20

A *D* value >0.10 is considered statistically significant.

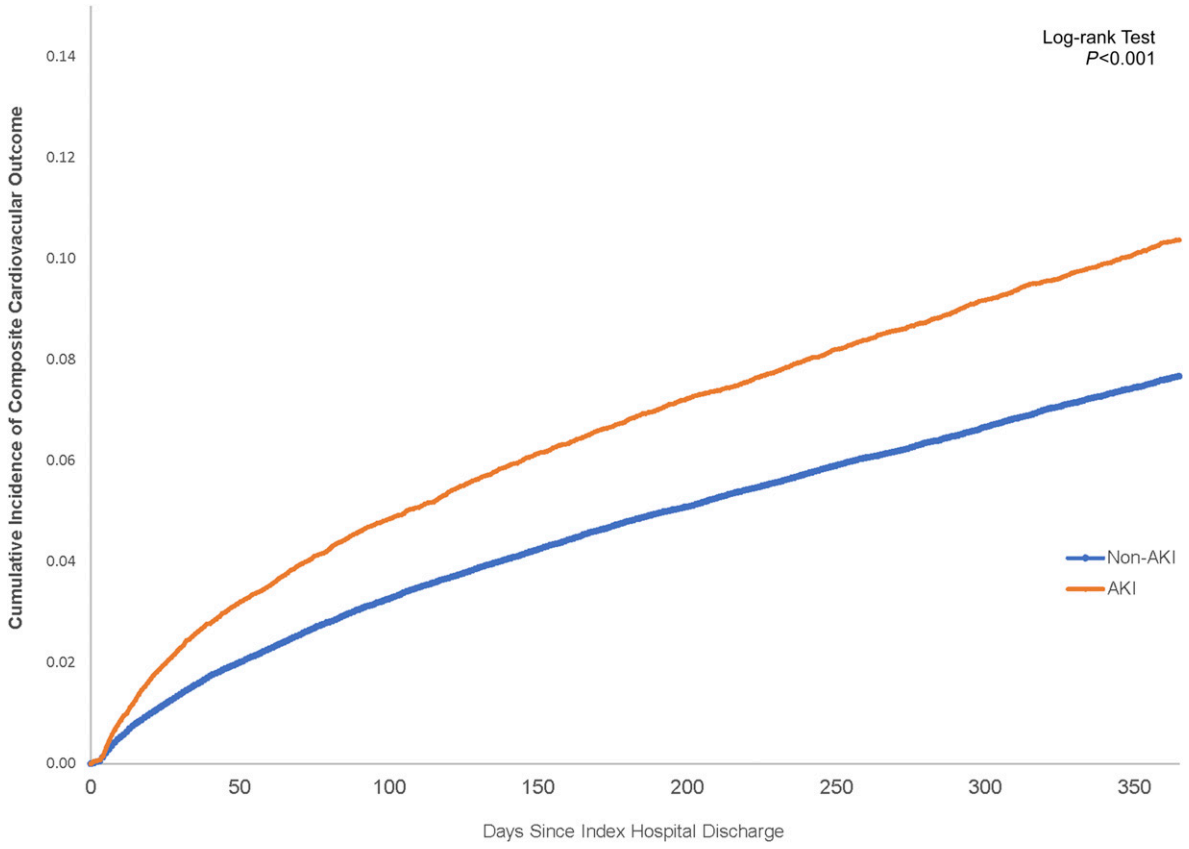

Figure 2. | Cumulative incidence of heart failure or atherosclerotic events at 365 days after discharge higher among hospitalized adults who did or did not experience AKI.

(95% CI, 19% to 33%) higher rate of the composite outcome of heart failure or atherosclerotic events, a 54% (95% CI. 41% to 69%) higher adjusted rate of heart failure, and a 9% (95% CI, 1% to 18%) higher adjusted rate of atherosclerotic events. In contrast, there were no statistically significant multivariable associations for those with stage 2 or stage 3 AKI.

Death

Given the potential concern for competing risk of death associated with AKI in evaluating the strength of association between AKI and cardiovascular events, we separately examined postdischarge rates of death. More patients with AKI died compared with matched patients without AKI during the first 365 days after discharge (19% versus 15%, respectively; *D*-value =0.20) (Table 2). In multivariable analyses, AKI was associated with a higher adjusted rate of all-cause death postdischarge (aHR, 1.20; 95% CI, 1.16 to 1.24) (Figure 3).

Discussion

Within a large, diverse community-based population of hospitalized adults, AKI was associated with significantly higher rates of cardiovascular events during the first 365 days after hospital discharge, even after adjustment for a wide range of characteristics, measures of acute severity of illness, predicted short-term mortality and differences in medical therapy. This excess risk was driven by heart failure events, as AKI was not significantly associated with atherosclerotic events after accounting for potential confounders.

AKI is a known risk factor for early and late death, but it is unclear whether this may be explained, in part, through an excess risk of cardiovascular events. AKI can lead to higher levels of circulating inflammatory cytokines (9), may contribute to endothelial dysfunction (10), and promote or worsen cardiac ischemia in the short-term (13). AKI may also be associated with acute elevations in certain markers of abnormal mineral metabolism (*e.g.*, fibroblast growth factor 23) which could induce or worsen left ventricular hypertrophy (11,43). However, there have been limited rigorous evaluations of the potential link between AKI and subsequent clinical cardiovascular events. Although there has recently been an increasing number of studies examining the potential cardiovascular-related complications of AKI in various clinical settings or patient populations (14–18,20,44–48), many published studies have focused on selected patients undergoing coronary angiography, with a meta-analysis (combined *n*=70,031) suggesting that AKI complicating coronary angiography is associated with a higher risk of major cardiovascular events (which could include cardiovascular death, myocardial infarction, target vessel reocclusion or need for revascularization, stroke, heart failure, or a composite) (14). However, there was substantial heterogeneity across studies as well as limitations in including "soft" events (*e.g.*, receipt of

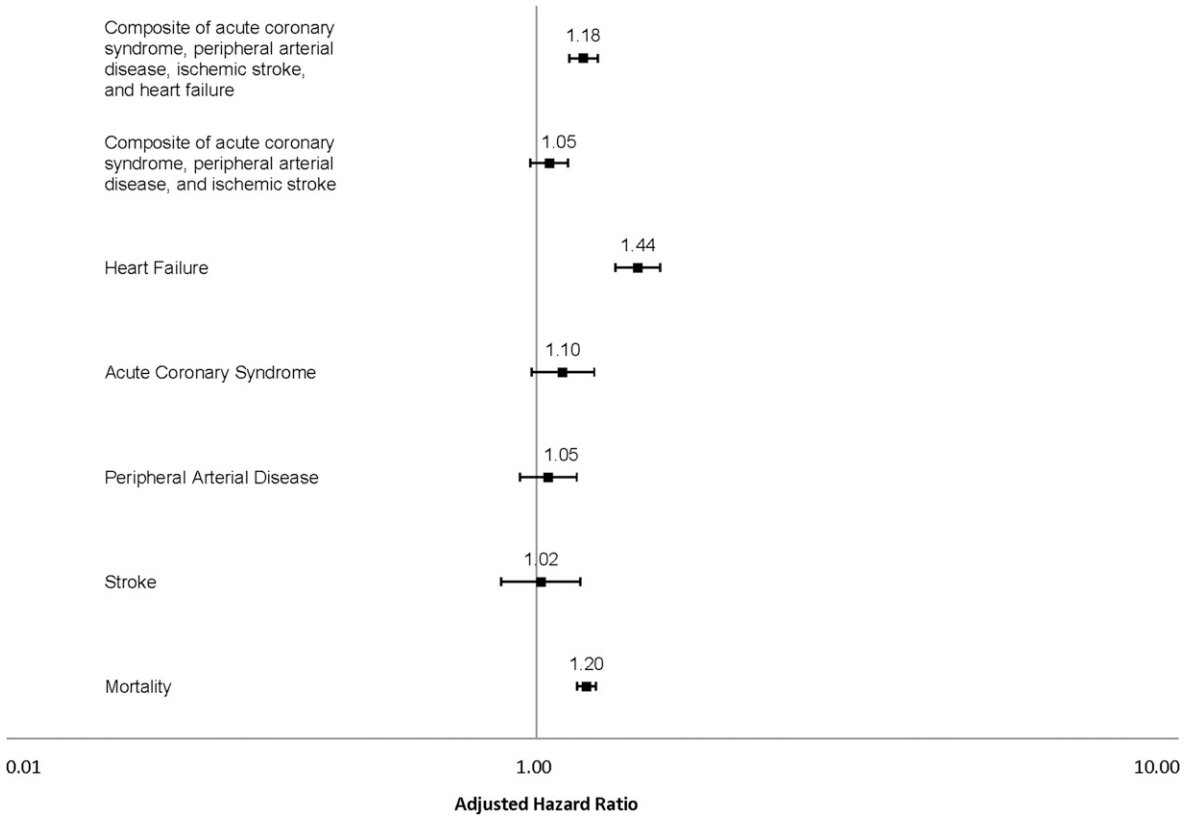

Figure 3. | **AKI is independently associated with all cardiovascular events, heart failure, and death, but not with individual atherosclerotic events at 365 days after discharge among hospitalized adults.** All models adjusted for matching strata, race, prior medical history (coronary heart disease, heart failure, peripheral arterial disease, stroke, atrial fibrillation/flutter, hypertension, diabetes, and cancer), preadmission eGFR and documented proteinuria, diagnosis of selected medical conditions during the hospitalization (heart failure, sepsis), admission to the ICU, length of stay, predicted mortality score, and receipt of dialysis and/or transplant during follow-up.

coronary revascularization) in the analyses that are often the most frequent outcome and most susceptible to subjective clinical decision-making (14). A more recent meta-analysis that focused on cardiovascular death, major adverse cardiovascular events, myocardial infarction, heart failure, and stroke reported a higher risk of these events after AKI, but used varying definitions of AKI, did not incorporate peripheral artery disease events, did not evaluate a specific follow-up period postdischarge, and only adjusted for a modest number of possible confounders (22).

A large Veterans Affairs-based study focused on AKI in the setting of myocardial infarction demonstrated that compared with those who had myocardial infarction alone, those with AKI and myocardial infarction had a higher subsequent rate of a composite cardiovascular end point (49). However, that study did not examine individual types of cardiovascular outcomes or address peripheral artery disease events, and we found that the associations differed by type of outcome. A retrospective study using only inpatient claims data from Taiwan between 1999 and 2008 compared 4869 patients who recovered from dialysis-requiring AKI and survived ≥30 days postdischarge and had no readmission or reinitiation of dialysis with a group of 4869 patients without dialysis-requiring AKI matched on age, sex, calendar year, and propensity-matched on claims-based comorbidities (21). During mean follow-up of 3.4 years, dialysis-requiring AKI was associated with a higher adjusted rate (hazard ratio, 1.67; 95% CI, 1.36 to 2.04) of a composite of "coronary events" defined as nonfatal myocardial infarction, coronary bypass surgery, or diagnostic coronary angiography (21). This study was limited by only studying the most severe AKI, limited control for relevant confounders, inclusion of coronary angiography and bypass surgery as part of their primary outcome, and concerns about generalizability to other populations.

In a prospective cohort of 968 older adults undergoing cardiac surgery, Parikh *et al.* (18) studied the association of AKI with a composite end point of death or hospitalization for acute coronary syndrome, myocardial infarction, heart failure, or coronary revascularization. AKI Network stage 1 and stages 2 and 3 were associated with higher adjusted rates of the composite end point (hazard ratio, 1.99; 95% CI, 1.46 to 2.71 and hazard ratio, 3.52; 95% CI, 2.17 to 5.71, respectively), but this study was also limited by inclusion of coronary revascularization procedures and all-cause mortality as part of their primary outcome in addition to focusing only on selected cardiac surgery patients and adjustment for a limited number of potential confounding factors (18).

Our study materially expands on existing literature by examining a larger, contemporary, multicenter, and carefully matched population with a wide range of AKI severity, and clarifies the association between an AKI episode and

primarily the risk of subsequent hospitalization for heart failure during the first year after discharge. The higher risk was present despite excess mortality from any cause after discharge associated with AKI. The reasons for why AKI was more strongly associated with subsequent heart failure than atherosclerotic events are not clear, but if the association is proven to be causal, it may be related to differential effects of aberrations in inflammatory, endothelial dysfunction, and other pathways associated with AKI or possible differences in therapy (*e.g.*, use or dosage of renin-angiotensin system inhibitors or diuretics) after an AKI episode. Our population had broad demographic diversity with comprehensive ascertainment of AKI on the basis of recommended KDIGO criteria (rather than reliance on administrative diagnostic codes) as well as postdischarge, clinically important "hard" cardiovascular events (*i.e.*, heart failure, acute coronary syndromes, peripheral artery disease, and ischemic stroke). Compared with previous studies, we were also able to carefully account for a much wider set of potential confounders, including relevant preadmission patient features, factors during the index hospitalization, longitudinal treatment, as well as a validated measure of acute illness severity (39).

Our study also had several limitations. Even though we carefully matched patients and further adjusted for a wide range of confounders, we cannot confirm a causal association. We conducted this study in a large, community-based population with comprehensive longitudinal follow-up, which should enhance generalizability, but our results may not be fully applicable to uninsured patients or to all settings. Although we defined AKI on the basis of recommended KDIGO criteria using changes in serum creatinine concentration, additional diagnostic information on the basis of urine output was unavailable. Given the known difficulty in determining cause(s) of an AKI episode, we were unable to evaluate potential differences in cardiovascular risk by AKI etiology. Information on potential specific pathways that may mediate the association between AKI and subsequent cardiovascular events was unavailable. Also, because there was no systematic follow-up testing within the index hospitalization and postdischarge in this clinical database study, we were unable to address the rates of AKI recovery and the potential mediating effect on subsequent outcomes. Finally, although we relied on validated algorithms to detect the occurrence of heart failure and atherosclerotic events in our health system, we were unable to address the negative predictive value of these algorithms on the basis of hospitalization records, as well as potentially missed cardiovascular events among observed deaths as the underlying cause was unavailable.

In conclusion, an episode of AKI complicating a hospitalization was independently associated with a higher risk of subsequent heart failure but not atherosclerotic events. If these associations are confirmed, additional research is needed to delineate underlying mechanisms driving the excess risk of heart failure events, to clarify longer-term risks, and to determine whether prevention of AKI or more aggressive screening and risk reduction measures after AKI improves overall outcomes.

Acknowledgments

This study was supported by research grants R01DK098233, U01DK082223, and R01DK067126 from the National Institute of Diabetes, Digestive and Kidney Disease, National Institutes of Health.

The funders had no role in the design or conduct of the study, collection, management, analysis or interpretation of the data, or preparation, review, or approval of the manuscript.

Disclosures

A.S.G. has received a research grant through his institution from Astra-Zeneca. None of the other authors have any relevant disclosures.

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Received: November 10, 2017 **Accepted:** February 22, 2018

Published online ahead of print. Publication date available at www.cjasn.org.

See related editorial, "Ptolemy and Copernicus Revisited: The Complex Interplay between the Kidneys and Heart Failure," on pages 825–828.