Statin Use and Survival After Acute Kidney Injury

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Introduction: The incidence of acute kidney injury (AKI) in hospitalized patients is rising, and survivors are at high risk for cardiovascular events and mortality. Effective strategies that improve long-term outcomes of AKI are unknown.

Methods: A retrospective cohort study was performed between 2008 and 2011. All subjects were followed until 31 March 2013, with a minimum follow-up of 2 years. Participants were adults 18 years of age or older, who developed AKI during a hospitalization and had chronic kidney disease (CKD) following discharge (n = 19,707 mean age 69.9 years, mean postdischarge estimated glomerular filtration rate (eGFR) 43.0 ml/min/1.73 m^2). Exposure to statins was examined prior to the index hospitalization as well as within 2 years following hospital discharge. The primary outcome was mortality; secondary outcomes included all-cause re-hospitalization and cardiovascular events.

Results: Within 2 years of discharge, only 38.3% of the participants were prescribed a statin. After adjustment for comorbidities, statin use prior to admission, demographics, baseline kidney function, and a number of other factors, statin use was associated with lower mortality (hazard ratio, 0.74; 95% confidence interval, 0.69, 0.79) in AKI survivors with CKD. Patients who received a statin also had a lower risk of all cause rehospitalization (adjusted hazard ratio, 0.90; 95% confidence interval, 0.85, 0.94). Statin use was not associated with a reduction in cardiovascular events.

Discussion: Among AKI survivors with CKD, statin use was associated with a lower risk of mortality and rehospitalization rates. This finding suggests that there is an opportunity to improve postdischarge care in AKI survivors.

Acute kidney injury (AKI) is a common complication in hospitalized patients, and has been consistently associated with an increased risk of death, *de novo* or worsening chronic kidney disease (CKD), and end-stage renal disease (ESRD).[1–5] Patients discharged after an episode of AKI have a 40% increased risk of death in the 2 years following hospitalization,[6] and a 50% to 60% increased risk of cardiovascular events, compared to patients who do not develop AKI.[7] There are currently no effective therapies targeting established AKI; however, identifying and treating patients with CKD following an episode of AKI may improve health outcomes. Although recently published data suggested that nephrologist follow-up was associated with a 24% reduction in risk of death after hospitalization with severe AKI requiring dialysis,[8] little is known about processes of care that modify outcomes after episodes of AKI.

Statins are effective for reducing cardiovascular morbidity and mortality in patients with CKD.[8–18] We sought to evaluate whether the use of statins was associated with better outcomes among patients with CKD after AKI.

METHODS

Study Population and Data Sources

We used the Alberta Kidney Disease Network population-based database, which has been described in detail elsewhere.[19] The study cohort[20] included all adults 18 years or older residing in Alberta who were

admitted to the hospital between 1 July 2008 and 31 March 2011 and had an episode of AKI during hospitalization. To be eligible for inclusion, patients had to have at least 1 outpatient serum creatinine (Scr) measurement within 180 days prior to hospitalization to establish baseline kidney function, $\geq$ 1 measurement during the hospitalization to establish AKI, and $\geq$ 1 SCr, urine dipstick (udip), urine albumin to serum creatinine ratio (ACR), or urine protein to serum creatinine ratio (PCR) measurement in the follow-up period after hospital discharge to establish CKD. If participants had more than 1 hospitalization during this period, only the first was considered (index hospitalization). Participants who died or progressed to ESRD (estimated GFR [eGFR] < 15 ml/min per 1.73 m^2, chronic dialysis, prior kidney transplantation) before or during the index hospitalization were excluded. The cohort was restricted to patients who had CKD after an AKI episode. All subjects were followed up from the discharge date of their index hospitalization until 31 March 2013, with a minimum follow-up of 2 years.

The study was reviewed and approved by the institutional review boards at the Universities of Alberta and Calgary.

Assessment of Baseline Kidney Function

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to determine the estimated glomerular filtration rate (eGFR).[21] Baseline kidney function was defined as the mean outpatient Scr in the 180 days prior to the index hospitalization.

Identification of Acute Kidney Injury

AKI was identified by changes between baseline (prehospital) and peak in-hospital Scr. AKI was defined as an increase in serum creatinine by 50% or greater within 7 days or by 26.5 μmol/L within 48 hours and/or requirement for acute dialysis within 7 days of the index hospitalization. AKI severity was determined using the consensus criteria for AKI staging from the recently published Kidney Disease Improving Global Outcomes (KDIGO) AKI guidelines.[22] Requirement for acute dialysis for AKI was determined using a validated approach, based on diagnosis and procedural administrative codes.[23]

Assessment of CKD After AKI

The presence of CKD was assessed using Scr, urine ACR, urine PCR, or udip measured 90 days or more after the AKI episode to allow sufficient time for recovery of renal function (Supplementary Figure S1). A 90-day time frame for recovery was chosen based on the Kidney Disease Outcomes Quality Initiative guidelines,[24] which define CKD as a persistent decline in kidney function lasting >90 days. If subjects had more

than 1 outpatient SCr measurement, the measurement closest to 90 days was considered. Postdischarge CKD was defined as eGFR < 60 ml/min/1.73 m^2, ACR > 30 mg/g, PCR > 150 mg/g, or Udip > trace, consistent with the KDIGO CKD guidelines.[25]

Assessment of Medication Use After Discharge

Prescription drug information was obtained from the Pharmaceutical Information Network (PIN) database. We classified statin exposure into the following groups: no previous prescription, new prescription (defined as at least 1 prescription within 2 years after discharge from the index hospitalization), stopping a previous prescription, and continuing a prescription. Patients were classified in the continuing prescription group if they had at least 1 prescription in the 6 months prior to admission and at least 1 prescription within 2 years postdischarge. High-dose statin was defined as the highest dosage for each statin drug (Supplementary Table S1).

Assessment of Comorbid Conditions

Relevant demographic characteristics, preexisting comorbid conditions (defined using validated algorithms),[20,26] hospitalizations and outpatient physician visits (general practitioner as well as specialist visits), details of the index hospitalization including primary admission diagnosis, and intensive care unit stay were obtained using hospitalization data, claims files, and ambulatory care classification system files. We obtained primary International Classification of Diseases (10th revision) codes and used these to classify primary admission diagnoses using a previously published approach.[26] Resource intensity weight, similar to diagnostic related group weight, was used to categorize acuity and severity of illness.[27,28] Cholesterol level was defined as the mean outpatient total cholesterol in the 1 year prior to the index hospitalization. The cholesterol levels were classified into 5 risk categories according to the Framingham coronary heart disease risk score.[29] Patients who did not have a cholesterol measurement during this time period were classified in an unknown group.

Outcomes

The primary outcome was mortality; secondary outcomes included all-cause re-hospitalization and cardiovascular events. All outcomes were assessed after the discharge date of the index hospitalization. All-cause re-hospitalization was defined as any hospitalization occurring after the index hospitalization. All hospitalizations were identified using AH data. All-cause mortality was identified using administrative data sources. Cardiovascular events were defined as myocardial infarction, stroke, or revascularization procedure, as defined by validated algorithms.[30–32]

Statistical Analysis

Continuous variables were described using the mean and SD or the median with interquartile range as appropriate. Categorical variables were described as proportions of the cohort.

Multivariable Cox proportional hazard models with time-varying covariates were used to estimate the association between use of statin following index hospitalization and all-cause mortality, re-hospitalization, and cardiovascular events. The adjusted models included terms for age, sex, income quintile, aboriginal race, location of residency, health care use preceding the index hospitalization, Canadian Institute for Health Information resource intensity weight, intensive care unit admission during the index hospitalization, primary diagnostic code for hospitalization, procedures associated with AKI (cardiac catheterization, cardiac and abdominal aortic surgery), comorbid conditions, baseline kidney function (based on eGFR), cholesterol level, statin, angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), and β-blocker use in the 6 months preceding admission and following discharge (Supplementary Figure S2). Time of origin was the discharge date for the index hospitalization. The

proportional hazard assumption was evaluated and satisfied by examining plots of the log-negative-log within-group survivorship functions versus log-time.

First use of statin was used to update the exposure status during the course of the follow-up (i.e., a person on a statin would contribute person time to the "no statin use" before the first statin was prescribed and contribute person time to the "statin use" group after the first statin was prescribed). Patients were censored if they moved out of the province or reached the end of the study date (31 March 2013) for all outcomes. For the secondary outcomes, patients were censored if they died.

Analyses were repeated after further categorizing statin users into the following groups: new prescription postdischarge, continuing a previous prescription within 2 years postdischarge, and stopping use of a pre-hospital admission prescription. In the sensitivity analysis, we excluded patients who required acute dialysis to determine whether associations were similar in patients with less severe AKI. We also performed a sensitivity analysis excluding patients with proteinuria at any time during the study period to assess whether associations were similar in patients with non-proteinuric CKD. We repeated analyses after excluding
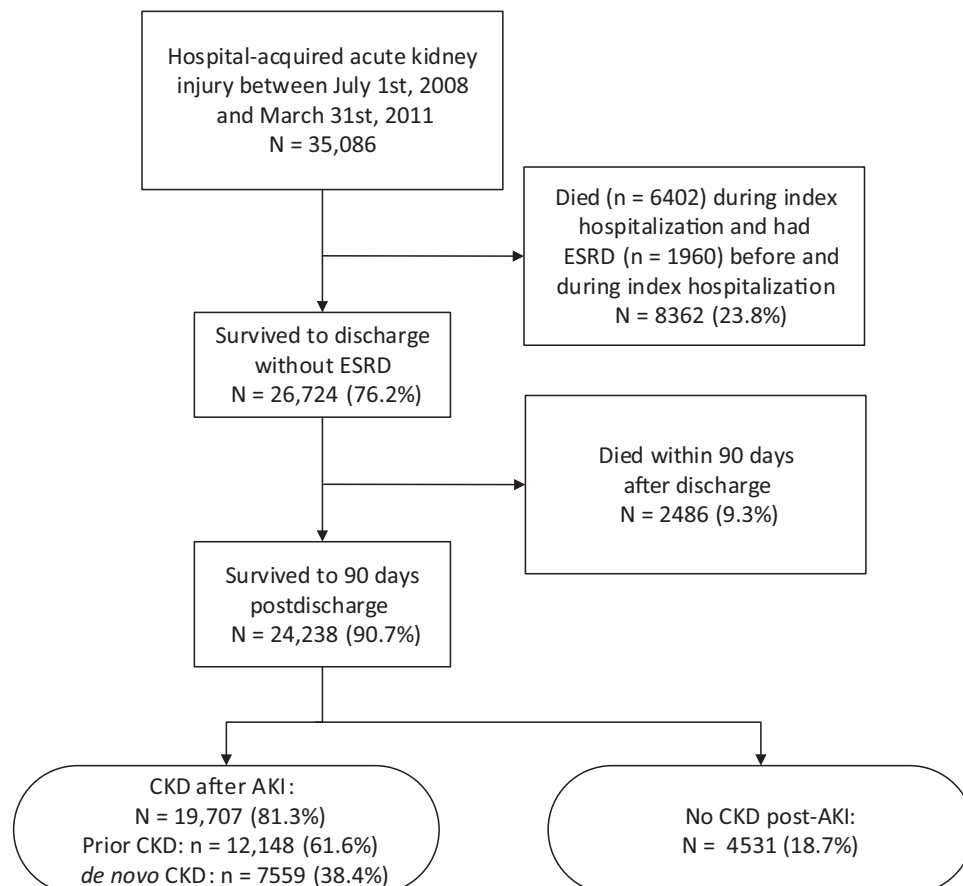

Figure 1. Selection of study population after episode of hospital-acquired acute kidney injury (AKI). CKD, chronic kidney disease; ESRD, end-stage renal disease.

patients who had any pre-existing cardiovascular disease, to examine findings in patients less likely to have pre-existing established cardiovascular disease. We compared the effect of statin use after stratifying the cohort according to whether patients had pre-existing CKD or *de novo* CKD (post-AKI) patients. We also compared outcomes in patients on high-dose versus low-dose statins.

Table 1. Characteristics of statin users and non−statin users

	All subjects	Statin users	Non−statin users	*P* value
Number of subjects (%)	19,707	7539 (38.3)	12,168 (61.7)	
Age, yr, mean (SD)	69.9 (14.9)	70.7 (12)	69.3 (16.5)	<0.01
Sex, male (%)	52.5	57.6	49.4	<0.01
Aboriginal (%)	3.8	3.2	4.2	<0.01
Income quintile				0.59
Lowest (level = 1) (%)	24.9	24.6	25.1	
Highest (level = 5) (%)	15.9	15.6	16.0	
Urban location (%)	83.7	84.3	83.2	0.04
Healthcare access 3-year preceding hospital admission, mean (median, IQR)				
Number of hospitalizations	1.7 (1, 0–2)	1.7 (1, 0–2)	1.8 (1, 0–2)	0.02
Number of GP visits	50.8 (36, 21–64)	48.2 (37, 22–61)	52.4 (36, 20–66)	<0.01
Number of nephrologist visits	1.1 (0, 0–0)	1.2 (0, 0–0)	1 (0, 0–0)	<0.01
Number of cardiology visits	3.1 (0, 0–2)	4.6 (0, 0–5)	2.2 (0, 0–1)	<0.01
Number of internist visits	7.2 (3, 0–8)	7.7 (3, 1–9)	6.9 (2, 0–8)	<0.01
Number of emergency visits	5.8 (3, 1–6)	5.5 (3, 1–6)	6 (3, 1–7)	<0.01
CIHI resource intensity weight, mean (SD)	3.1 (6.3)	2.7 (4.4)	3.4 (7.2)	<0.01
Intensive care unit during hospitalization (%)	18.9	24.8	15.3	<0.01
Primary diagnostic code for hospitalization (%)				
Cardiovascular	18.4	26.0	13.6	<0.01
Respiratory	9.1	8.9	9.3	0.245
Gastrointestinal	10.3	8.4	11.4	<0.01
Infectious disease	4.6	3.8	5.1	<0.01
Cancer	7.6	5.4	9.0	<0.01
Orthopedic	4.6	4.9	4.4	0.09
Hematologic	5.8	6.2	5.5	0.04
Genitourinary	11.1	10.4	11.5	0.02
Injury/poisoning	5.1	4.5	5.4	<0.01
Other disease	23.5	21.4	24.7	<0.01
Procedure or condition during index hospitalization (%)				
Sepsis	4.8	3.8	5.4	<0.01
Cardiac surgery	2.7	4.7	1.5	<0.01
Cardiac catheterization	3.7	6.5	1.9	<0.01
Abdominal aortic aneurysm repair	0.5	0.8	0.3	<0.01
Pneumonia	10.7	10.0	11.2	0.01
Liver failure	0.7	0.2	1.0	<0.01
Acute myocardial infraction	10.1	16.3	6.3	<0.01
Noncardiac surgery	17.0	15.3	18.1	<0.01
Comorbid disease (%)				
Diabetes	42.6	55.7	34.5	<0.01
Hypertension	80.9	90.5	74.9	<0.01
Myocardial infarction	13.0	19.8	8.8	<0.01
Chronic heart failure	33.4	38.3	30.4	<0.01
Stroke or TIA	23.1	25.9	21.4	<0.01
Cancer	9.0	7.8	9.6	<0.01
Liver disease	2.4	1.0	3.2	<0.01
Peripheral vascular disease	7.2	10.0	5.4	<0.01
Kidney function				
Baseline eGFR, ml/min/1.73 m^2, mean (SD)	62.3 (25.8)	58.8 (23.1)	64.4 (27.1)	<0.01
Prior CKD (%)	61.6	66.2	58.8	<0.01
Prior CKD defined by eGFR	33.3	34.0	32.9	<0.01
Prio CKD defined by proteinuria	11.6	11.8	11.5	0.02
Prior CKD defined by eGFR and proteinuria	16.7	20.3	14.5	<0.01

Table 1. (Continued)

	All subjects	Statin users	Non−statin users	P value
AKI stage (%)				<0.01
AKI stage 1	75.9	77.9	74.6	<0.01
AKI stage 2	14.8	13.5	15.6	<0.01
AKI stage 3 (no dialysis)	7.1	6.2	7.6	<0.01
Dialysis	2.3	2.4	2.2	0.37
Baseline total cholesterol, mmol/l				<0.01
<4.1	29.7	40.6	23.0	<0.01
4.15−5.17	18.7	20.6	17.5	<0.01
5.18−6.21	10.2	10.1	10.3	0.67
6.22−7.24	3.3	3.6	3.1	0.05
≥7.25	1.3	1.9	1.0	<0.01
Unknown	37	23	45	<0.01

AKI, acute kidney injury; CIHI, Canadian Institute for Health Information; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; TIA, transient ischemic attack.

RESULTS

Patient Characteristics

Between 1 July 2008 and 31 March 2011, there were 35,086 patients 18 years of age or older residing in Alberta with hospital-acquired AKI (Figure 1). Of these participants, 26,724 (76.2%) survived to 90 days after their AKI episode. The study cohort included 19,707 patients with CKD after the AKI episode: 12,148 (61.6%) had prior CKD and 7,559 (38.4%) had *de novo* CKD (Figure 1). The mean patient age was 69.9 years, 52.5% were men, and 83.7% lived in an urban location (Table 1). The mean number of hospitalizations during the 3 years preceding the index hospitalization was 1.7 (interquartile range [IQR] 0−2), and 18.4% of the cohort had a cardiovascular diagnostic code as the diagnosis most responsible for the index hospitalization. The majority of participants (80.9%) had hypertension, and a large number of patients had diabetes (42.6%), chronic heart failure (33.4%), and history of stroke or TIA (23.1%).

Primary Outcomes

More than one-half (54.4%) of the cohort were never prescribed a statin, 12.0% received a new prescription, and 26.3% were continued on a statin within 2 years after hospital discharge. Only 7.3% of previous statin prescriptions were not restarted after hospital discharge (Table 2).

Over a total of 53,700 person-years of follow up, the adjusted hazard ratio for mortality associated with statin use after hospital discharge, compared with no statin use, was 0.74 (95% confidence interval [CI], 0.69, 0.79). Statin use after hospitalization was also associated with a lower risk of all cause re-hospitalization (hazard ratio [HR], 0.90; 95% CI, 0.85, 0.94) (Table 3).

Both a new statin prescription (HR, 0.73; 95% CI, 0.66, 0.80) and continuing a previous prescription (HR, 0.76; 95% CI, 0.71, 0.81) after hospital discharge was associated with better survival compared to no statin use. There was also lower all-cause re-hospitalization in both patients who were given a new statin prescription or continued on a previous statin prescription after hospital discharge, compared to no statin use (Table 4).

Sensitivity Analysis

In the sensitivity analysis excluding patients with cardiovascular disease (n = 15,116), those who used

Table 2. Number of patients (%) who were using statin before and after index hospitalization

	Within 6 months before admission			2 yr After discharge
Statin	6620 (33.6%)			7539 (38.3%)
	Never prescribed	New prescription	Stopping previous prescription	Continuing prescription
Statin	10,729 (54.4%)	2358 (12.0%)	1439 (7.3%)	5181 (26.3%)

Table 3. Hazard ratios of statin use after hospital discharge

Outcome	Adjusted hazard ratio (95% CI)	Number of events	Follow-up time in person-yr	Crude hazard ratio (95% CI)
Survival	0.74 (0.69–0.79)	6758	53700.94	0.75 (0.71–0.79)
All cause re-hospitalization	0.90 (0.85–0.94)	15,256	25144.77	0.94 (0.9–0.97)
Cardiovascular event	0.95 (0.87–1.04)	3493	48764.46	1.54 (1.43–1.65)

CI, confidence interval.
Adjusted factors: Angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB), β-blocker, and statin use within 6 months before admission, ACEI/ARB and β-blocker after discharge, age, sex, income quintile, urban location, health care use 3 years before hospital admission, Canadian Institute for Health Information resource intensity weight, intensive care unit, primary diagnostic code for hospitalization, procedure or condition during index hospitalization, comorbid disease, baseline kidney function (estimated glomerular filtration rate), and total cholesterol risk categories.
Separate Cox proportional hazard models with medication use as time-varying covariates were fit for the outcome of all-cause mortality, all-cause re-hospitalization, and cardiovascular events. All patients were followed up for at least 2 years starting at the date of hospital discharge, with further censoring for death, outmigration from Alberta, and the end of study (31 March 2013) in the model fit of all-cause re-hospitalization and cardiovascular events, and for outmigration from Alberta and end of study in the model fit for mortality.

Table 4. Hazard ratios of statin use for never prescribed, new prescription, stopping previous prescription, or continuing previous prescription

Outcome	Statin use	Hazard ratio (95% CI)
Survival	Never prescribed	1
	New prescription	0.73 (0.66–0.80)
	Stopping previous prescription	1.00 (0.91–1.09)
	Continuing prescription	0.76 (0.71–0.81)
All cause re-hospitalization	Never prescribed	1
	New prescription	0.85 (0.79–0.91)
	Stopping previous prescription	0.98 (0.93–1.03)
	Continuing prescription	0.91 (0.87–0.95)
Cardiovascular event	Never prescribed	1
	New prescription	0.92 (0.81–1.05)
	Stopping previous prescription	1.01 (0.90–1.13)
	Continuing prescription	1.00 (0.92–1.10)

Prescription	6 mo Before admission	2 yr After discharge
Never prescribed	No prescription	No prescription
New prescription	No prescription	At least 1 prescription
Stopping previous prescription	At least 1 prescription	No prescription
Continuing prescription	At least 1 prescription	At least 1 prescription

CI, confidence interval.
Adjusted factors: Angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB), β-blocker and statin use within 6 months before admission, ACEI/ARB and β-blocker after discharge, age, sex, income quintile, urban location, health care use 3 years before hospital admission, Canadian Institute for Health Information resource intensity weight, intensive care unit, primary diagnostic code for hospitalization, procedure or condition during index hospitalization, comorbid disease, baseline kidney function (estimated glomerular filtration rate), and total cholesterol risk categories.
Separate Cox proportional hazard models with medication use as time-varying covariates were fit for the outcomes of all-cause mortality, all-cause re-hospitalization, and cardiovascular events. All patients were followed up for at least 2 years starting at the date of hospital discharge, with further censoring for death, outmigration from Alberta, and the end of study (31 March 2013) in the model fit of all-cause re-hospitalization and cardiovascular events, and for outmigration from Alberta and end of study in the model fit for mortality.

a statin after hospital discharge had lower mortality (HR, 0.70; 95% CI, 0.64, 0.76), and all-cause re-hospitalization (HR, 0.90; 95% CI, 0.85, 0.95) (Table 5). Exclusion of patients with the most severe AKI requiring dialysis (n = 19,250) and proteinuria before or after the index hospitalization (n = 15,792) did not change results for survival, re-hospitalization rates, or cardiovascular events (Table 5).

Statin use was associated with lower mortality and all cause re-hospitalization in both patients with pre-existing CKD and *de novo* CKD. Statin use was not

Table 5. Hazard ratios of statin use for patients not requiring dialysis, with no proteinuria and no pre-existing cardiovascular disease

	Hazard ratio (95% CI)		
	Excluding dialysis patients	Excluding patients with proteinuria	Patients without pre-existing CVD[a]
Number of subjects	19,250	15,792	15,116
Survival	0.74 (0.69–0.79)	0.74 (0.69–0.80)	0.70 (0.64–0.76)
All-cause rehospitalization	0.89 (0.85–0.94)	0.89 (0.84–0.93)	0.90 (0.85–0.95)
Cardiovascular events	0.96 (0.87–1.05)	0.95 (0.86–1.04)	0.92 (0.81–1.05)

CI, confidence interval; CVD, cardiovascular disease.
[a]Pre-existing CVD includes acute myocardial infarction, coronary artery bypass grafting, cardiac catherization, congestive heart failure, cerebrovascular accident (including all stroke-related events), and percutaneous coronary interventions in the 3 years before admission and during the index hospitalization.

associated with lower risk of cardiovascular events in patients with pre-existing or *de novo* CKD (Table 6).

Low-dose and high-dose statin had similar effects on mortality, all-cause re-hospitalization, and cardiovascular events (Table 7).

DISCUSSION

Using a large population-based cohort we characterized statin use in patients with CKD after an episode of AKI in the hospital. Over a follow-up period of at least 2 years after discharge, AKI survivors who were dispensed a statin after the index hospitalization had a lower risk of death compared to those with no statin use. Statin use was also associated with a decreased risk of all-cause re-hospitalization.

The risks of developing CKD following an episode of AKI are well documented in both pediatric[33] and adult[34] cohort studies. Recent work from our group confirms that failure to recover renal function to within 25% of baseline SCr within 90 days after moderate to severe AKI is associated with an increased risk of long-term mortality (adjusted HR, 1.26; 95% CI, 1.10, 1.43).[35] Management of CKD after AKI may mitigate the risks of progressive CKD and increased mortality. A recently published systematic review of randomized controlled trials confirmed the importance of ACEi, ARB, β-blocker, and statin use as effective therapies for the treatment of CKD stages 1 to 3.[36] Statins showed reduced mortality and cardiovascular events versus placebo or control in patients with impaired eGFR. To date no studies have examined the effect of statin use in AKI survivors.

Conservative population based estimates of AKI incidence in hospitalized adults are in the range of 3,000 per 100,000 person years,[37] and the majority of these patients will survive hospital discharge. Recent KDIGO guidelines recommended that patients be followed up 3 months after an AKI episode to assess for CKD; however, there has been a lack of information to guide the care that these patients should receive. Based on our results, AKI survivors may benefit from statin therapy post-discharge, an intervention that does not require specialized care and could be readily implemented. In our study, only 39.1% of the cohort who had CKD after AKI were dispensed a statin within 2 years of their index hospitalization, despite their high risk profile for

Table 6. Hazard ratios of statin use after hospital discharge for patients with prior chronic kidney disease (CKD) and *de novo* CKD

	Hazard ratio (95% CI)	
Outcome	Prior CKD	*De novo* CKD
Number of subjects	12,148	7559
Survival	0.76 (0.70–0.83)	0.67 (0.59–0.77)
All cause rehospitalization	0.90 (0.85–0.96)	0.86 (0.79–0.94)
Cardiovascular events	0.96 (0.87–1.07)	0.92 (0.77–1.10)

Table 7. Hazard ratios of high- and low-dose statin use

Outcome	Hazard ratio (95% CI)	Number of subjects
Survival		
Low-dose	0.74 (0.69–0.79)	6651
High-dose	0.71 (0.62–0.82)	888
No statin	1.00 [reference]	12,168
High-dose versus low-dose	0.97 (0.84–1.11)	–
All-cause rehospitalization		
Low-dose	0.89 (0.85–0.94)	4993
High-dose	0.91 (0.82–1.00)	679
No statin	1.00 [reference]	14,035
High-dose versus low-dose	1.01 (0.92–1.12)	–
Cardiovascular events		
Low-dose	0.94 (0.85–1.03)	6310
High-dose	1.10 (0.94–1.29)	815
No statin	1.00 [reference]	12,582
High-dose versus low-dose	1.18 (1.02–1.37)	–

CI, confidence interval.
A total of 888 patients used high-dose statin before death occurred or the end of the follow-up period; 679 patients used high-dose statin before re-hospitalization after discharge from the index hospitalization or the end of the follow-up period; and 815 patients used high-dose statin before a cardiovascular event occurred or the end of the follow-up period.

cardiovascular disease, and despite recently released international guidelines for lipid management in CKD, which recommends that adults >50 years of age with eGFR < 60 ml/min/1.73 m^2 should be treated with a statin.[38] Furthermore, 5.8% of statin prescriptions were not restarted postdischarge. We also observed better survival in the subgroup of patients who were given a new statin prescription compared to those who did not receive a statin. These findings suggest that there is an opportunity to improve postdischarge care in AKI survivors with CKD.

Several recent studies have suggested that AKI is a risk factor for cardiovascular disease and future cardiovascular events.[39] Our results showed a trend toward a reduction in cardiovascular events in patients who received a statin, although it was not significant. This may be explained by the fact that patients who develop AKI and progress to CKD likely have undetected or early cardiovascular disease.

Despite reporting outcomes adjusted for many important confounders, there are some limitations to our analysis, related primarily to the retrospective use of administrative and laboratory data and observational design. First, entry into the cohort was limited to subjects who had ≥1 outpatient SCr measurement within 180 days prior to hospitalization and >1 inpatient SCr measurement performed as part of hospital care in Alberta. However, repeated measurements of SCr are common in patients hospitalized for acute medical and surgical problems, and based on prior work, patients who do not have SCr drawn after hospitalization have outcomes similar to those who do not have AKI; therefore, it is likely that we were able to

capture all AKI patients at high risk for poor outcomes after discharge. Second, we were unable to obtain measures of some potentially important covariates such as blood pressure, urine output, nutritional status, and deconditioning after hospitalization with AKI. Third, as patients were not randomized to different processes of care, there is potential for treatment-by-indication bias, whereby certain patient characteristics prompt differences in prescription of a statin, thereby introducing confounding. However, because we expect that patients at higher cardiovascular risk are more likely to receive a statin, we expect that the direction of bias in our study is toward the null, and thus the strength of any observed associations between medications and outcomes is likely conservative. It is also possible that statin use was a marker of better follow-up care. Finally, our exposure was defined as a dispensed prescription, and the rate of compliance among patients in the statin group is likely not 100%.

CONCLUSIONS

The use of a statin in AKI survivors who progress to CKD after hospital discharge is associated with lower mortality and re-hospitalization. This observation requires further evaluation in prospective studies evaluating postdischarge care strategies for AKI survivors. In particular, our results suggest a need for a trial to evaluate treatment with statin in survivors of AKI, to determine whether this intervention improves long-term outcomes in high-risk patients.

DISCLOSURE

This study is based in part on data provided by Alberta Health and Alberta Health Services. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta or Alberta Health Services. Neither the Government of Alberta nor, Alberta Health or Alberta Health Services express any opinion in relation to this study. All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Table S1. Drug identification numbers for the group of medications known as statins.
Figure S1. Distribution of the first abnormal laboratory test results (SCr/udip/umcr/pcr) after AKI episode.

Figure S2. Cumulative proportion of subjects who used angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, statin, and β-blocker postdischarge.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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