Acute Kidney Injury and Long-term Risk of Cardiovascular Events After Cardiac Surgery: A Population-Based Cohort Study

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Objective: **To examine the impact of postoperative acute kidney injury (AKI) on the long-term risk of myocardial infarction, heart failure, stroke, and all-cause mortality after elective cardiac surgery. The authors investigated whether time of onset of AKI altered the association between AKI and the adverse events.**

Design: **Population-based cohort study in 2006-2011.**

Setting: **Two university hospitals.**

Participants: **Adult elective cardiac surgical patients.**

Interventions: **None.**

Measurements and Main Results: **AKI was defined as an increase in baseline creatinine according to the Kidney Disease Improving Global Outcomes criteria. AKI was defined within 30 days of surgery, and also analyzed as early- or late-onset AKI. The authors followed patients from postoperative day 30 until hospitalization with myocardial infarction, heart failure, stroke, or death. Adjustment for confounding factors was done using propensity scores and standardized-mortality-ratio weights. A total of 1,457 (30.7%) of 4,742 patients developed AKI within 30 days of surgery and 470 (9.9%) patients experienced a composite cardiovascular endpoint. Comparing patients with and without postoperative AKI, weighted hazard ratio (HR) and 95% confidence intervals (CI) of 5-year risk of the composite cardiovascular endpoint was 1.41 (95% CI: 1.11-1.80). For each endpoint separately the weighted HR was similarly increased. Ninety-one days to 5-year weighted HR of all-cause mortality was 1.37 (95% CI: 1.05-1.80). The effect of AKI was similar for early- and late-onset AKI.**

Conclusions: **Early- and late-onset AKI within 30 days of elective cardiac surgery was associated with a similarly increased 5-year risk of myocardial infarction, heart failure, stroke, and increased all-cause mortality.**

KEY WORDS: AKI, cardiac surgery, cardiorenal syndrome, outcome, mortality, stroke

ACUTE KIDNEY INJURY (AKI) is common after cardiac surgery; it occurs in up to 30% of patients and is reported to be associated with increased short- and long-term mortality.[1–5] Coexistence of heart and kidney disease occurs frequently in hospitalized patients and recently has been described under the term "cardiorenal syndrome".[6] The relationship between chronic kidney disease (CKD) and chronic heart failure is well known.[7] However, the clinical effect of AKI on the risk of acute cardiac dysfunction (acute renocardiac syndrome, or cardiorenal syndrome type III) including myocardial infarction, heart failure, arrhythmias, and cardiogenic shock, has been less thoroughly examined.[8] Suggested pathophysiologic mechanisms include: Fluid retention precipitating unstable heart function; renal ischemia causing inflammation and leading to apoptosis and fibrosis at the cardiac level; and activation of the renin-angiotensin-aldosterone system causing water, salt, and vasoconstrictor disturbances.[9] Such mechanisms also may alter the risk of both hemorrhagic and ischemic stroke through changes in blood pressure, altered vascular performance, and cardiac dysfunction, increasing the risk of cardiac embolism.[10]

Recent studies examining the long-term (beyond 90 days) prognosis of AKI after cardiac surgery have found an association with myocardial infarction and heart failure, but not with stroke.[4,5,11–13] The time windows used to define AKI in these studies differ (5, 7, and 30 days), which hampers comparison because the reason for AKI may change during the postoperative period. Early-onset AKI supposedly is related to perioperative stress (including hemodynamics); while late-onset AKI is more likely a consequence of complications, including both cardiac complications and infections/sepsis. Furthermore, previous studies did not adjust for confounding by pre- and perioperative medication use and blood transfusion.

The authors conducted a population-based cohort study of elective cardiac surgical patients with detailed pre-, peri-, and postoperative information examining the impact of early- and late-onset AKI on long-term risk of myocardial infarction, heart failure, stroke, and death.

METHODS

Design and Setting

The authors conducted the study in the Central and North Denmark Regions and included cardiac surgical patients at Aarhus and Aalborg University Hospitals. These hospitals provide cardiac surgery for a mixed rural-urban population constituting 33% of the entire Danish population. The Danish National Health Service provides tax-funded medical care for all Danish residents. The study was approved by the Danish

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Data Protection Agency (record number: 2012-41-0914). According to Danish law, use of Danish register data requires neither informed consent from the participants nor Ethics Committee approval. All patient data were anonymized before analyses and handled with confidentiality.

Elective Cardiac Surgical Patients

All adult (age 15 or older) cardiac surgical patients (except heart transplant patients) were included from Aarhus and Aalborg University Hospitals from April 1, 2006 to December 31, 2011. The patients were identified in the Western Denmark Heart Registry (WDHR), which is a collaborative initiative covering Western Denmark's 3 major cardiac centers and contains information from January 1, 1999 on all invasive cardiac procedures.[14] The registry holds extensive mandatory and prospectively registered information on patient and procedural characteristics. Because of the unique Central Personal Registry number assigned to each Danish citizen at birth and to residents upon immigration, it is possible to make accurate linkage of all registries at an individual level.[15] Patients who were missing baseline plasma creatinine measures within 90 days before surgery (more than 90% had a baseline creatinine measure within 3 days before surgery) or creatinine measures within 30 days of surgery while not receiving dialysis were excluded. Patients undergoing acute surgery, defined as surgery on the same day as admission, were excluded. Patients with previous kidney or heart transplant surgery or requiring dialysis before surgery were excluded. Patients who died within 30 days of surgery, and patients diagnosed with a myocardial infarction, heart failure, or stroke during the same admission as the index surgery, or within 30 days of surgery were excluded. This was to ensure that the development of AKI preceded the specified outcomes (see formation of the study cohort in Fig 1).

Acute Kidney Injury

By linkage to the population-based Laboratory Information System (LABKA) the authors obtained pre- and postoperative laboratory measurements. LABKA holds information on all laboratory tests analyzed since the year 2000 in the study area including analysis codes, measurement units, dates of test collection, and results.[16] For each patient, the latest preoperative plasma creatinine, which is equivalent to serum creatinine,[17] sample within 90 days before surgery was used as baseline value. Plasma creatinine from surgery start until postoperative day 30 was compared to baseline plasma creatinine to assign AKI status according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria (Supplementary Table 1).[18]

Because time of onset may reflect different causes of AKI, the authors evaluated both early- and late-onset AKI. The early-onset definition considered plasma creatinine measures from the day of surgery to day 4, and the late-onset definition considered plasma creatinine measures from days 5-30. Patients with early-onset AKI were not considered eligible for late-onset AKI. The term "AKI" included all AKI stages and was further divided into AKI stage 1 and AKI stages 2+3. The urine output criteria were not used.

Study Endpoints

The authors defined a composite cardiovascular endpoint as the occurrence of myocardial infarction, heart failure, or stroke.

For each of the endpoints, composite cardiovascular endpoint, myocardial infarction, heart failure, stroke, and death, the

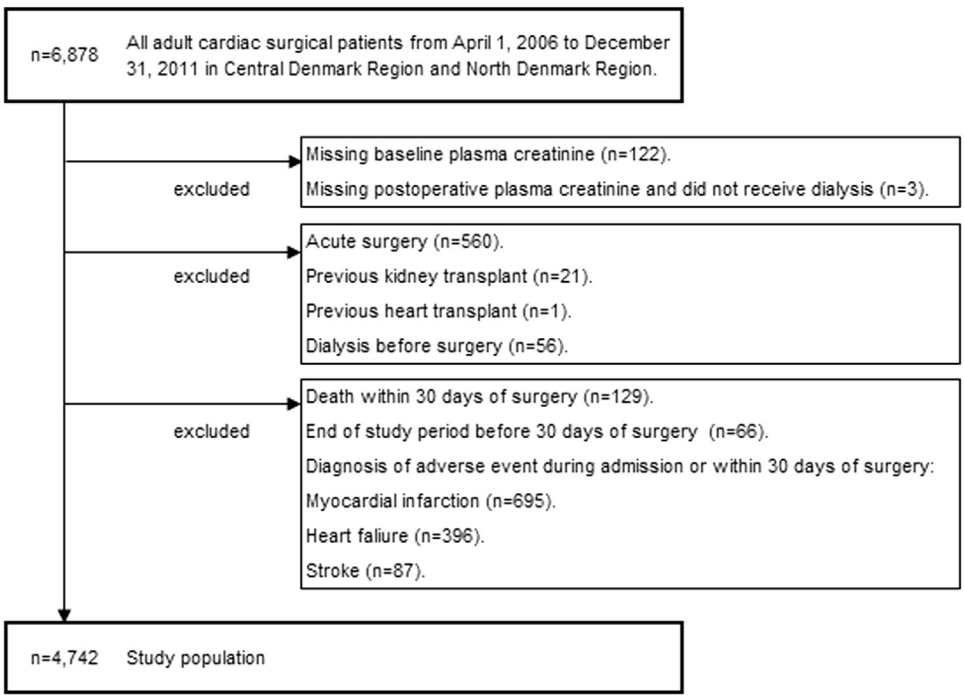

Fig 1. Formation of the study population.

Table 1. Characteristics of Patients Undergoing Adult Elective Cardiac Surgery by AKI Status*

Clinical Features	Non-AKI (n = 3,285)	AKI (n = 1,457)	Stage 1 (n = 1,123)	Stages 2+3 (n = 334)
Preoperative characteristics				
Male Sex	2,302 (70.1)	1,040 (71.4)	817 (72.8)	223 (66.8)
Age (yr), median (IQR)	66.9 (58.2-74.2)	73.1 (66.0-78.6)	72.9 (65.9-78.4)	74.3 (66.5-79.1)
Smoker	557 (17.0)	228 (15.7)	179 (15.9)	49 (14.7)
Missing	143 (4.4)	78 (5.4)	56 (5.0)	22 (6.6)
BMI (kg/m^2)				
<25	1,153 (35.1)	472 (32.4)	374 (33.3)	98 (29.3)
25-30	1,402 (42.7)	582 (40.0)	447 (39.8)	135 (40.4)
>30	667 (20.3)	380 (26.1)	288 (25.7)	92 (27.5)
Missing	63 (1.9)	23 (1.6)	14 (1.3)	9 (2.7)
Chronic kidney disease†	314 (9.6)	509 (34.9)	378 (33.7)	131 (39.2)
Diabetes	469 (14.3)	324 (22.2)	237 (21.1)	87 (26.1)
Missing	18 (0.6)	7 (0.5)	6 (0.5)	1 (0.3)
History of myocardial infarction	449 (13.7)	229 (15.7)	180 (16.0)	49 (14.7)
History of heart failure	253 (7.7)	232 (15.9)	173 (15.4)	59 (17.7)
History of stroke	165 (5.0)	117 (8.0)	96 (8.6)	21 (6.3)
History of atrial fibrillation	375 (11.4)	283 (19.4)	211 (18.8)	72 (21.6)
History of malignant tumor	237 (7.2)	153 (10.5)	113 (10.1)	40 (12.0)
Medication use‡				
ACE inhibitor	830 (25.3)	429 (29.4)	337 (30.0)	92 (27.5)
Angiotensin II antagonist	240 (7.3)	155 (10.6)	105 (9.4)	50 (15.0)
Beta-blocker	1,746 (53.2)	863 (59.2)	674 (60.0)	189 (56.7)
Calcium channel blocker	804 (24.5)	459 (31.5)	358 (31.9)	101 (30.2)
Aspirin	1,684 (51.3)	802 (55.0)	639 (56.9)	163 (48.8)
NSAID/COX-2 inhibitor	462 (14.1)	206 (14.1)	165 (14.7)	41 (12.3)
Statin	1,977 (60.2)	858 (58.9)	679 (60.5)	179 (53.6)
Diuretic	1,021 (31.1)	732 (50.2)	549 (48.9)	183 (54.8)
Modified EuroSCORE				
Low risk (score < 2)	2,271 (69.1)	810 (55.6)	644 (57.4)	166 (49.7)
Medium risk (score 2-4)	779 (23.7)	436 (29.9)	330 (29.4)	106 (31.7)
High risk (score > 4)	136 (4.1)	155 (10.6)	107 (9.5)	48 (14.4)
Missing	99 (3.0)	56 (3.8)	42 (3.7)	14 (4.2)
Surgical procedure characteristics				
Type of procedure				
CABG	1,572 (47.9)	563 (38.6)	460 (41.0)	103 (30.8)
CABG and aortic valve	308 (9.4)	208 (14.3)	156 (13.9)	52 (15.6)
Aortic valve	762 (23.2)	377 (25.9)	292 (26.0)	85 (25.5)
Mitral valve	195 (5.9)	51 (3.5)	32 (2.9)	19 (5.7)
Thoracic aortic surgery	121 (3.7)	69 (4.7)	56 (5.0)	13 (3.9)
Single§	145 (4.4)	53 (3.6)	31 (2.8)	22 (6.6)
Complex¶	182 (5.5)	136 (9.3)	96 (8.6)	40 (12.0)
Extracorporeal circulation				
No extracorporeal circulation	445 (13.6)	173 (11.9)	135 (12.0)	38 (11.4)
<120 min	1,862 (56.7)	713 (48.9)	569 (50.7)	144 (43.1)
≥120 min	633 (19.3)	405 (27.8)	294 (26.2)	111 (33.2)
Missing	345 (10.5)	166 (11.4)	125 (11.1)	41 (12.3)
Aprotinin	134 (4.1)	132 (9.1)	91 (8.1)	41 (12.3)
Blood transfusion				
0 mL	2,626 (79.9)	867 (59.5)	714 (63.6)	153 (45.8)
1-500 mL	201 (6.1)	139 (9.5)	112 (10.0)	27 (8.1)
501-1,000 mL	307 (9.3)	236 (16.2)	171 (15.2)	65 (19.5)
>1,000 mL	151 (4.6)	215 (14.8)	126 (11.2)	89 (26.6)

Abbreviations: ACE, angiotensin-converting enzyme; AKI, acute kidney injury; BMI, body mass index; CABG, coronary artery bypass grafting; COX, cyclo oxygenase; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drugs.

*Values are expressed as counts (%) unless otherwise indicated.

†eGFR <60 mL/min per 1.73m^2.

‡Prevalent user: Prescription within 100 days before admission for surgery.

§Single: Procedures including great intrathoracic veins, pulmonary arteries, congenital heart disease, pericardium, atria, atrial septum, pulmonary veins, pulmonary valve surgery, ventricular septum, left and right ventricle, reconstruction of coronary arteries, arrhythmias, and conduction disturbances.

¶Complex: Aortic valve, or mitral valve, or coronary artery bypass grafting, combined with a single procedure.

authors followed patients from day 30 after surgery for up to 5 years or until the specified endpoint occurred: Death, emigration, or administrative censoring on January 1, 2012, whichever came first.

Data regarding hospital admission with myocardial infarction, heart failure, and stroke were obtained from the Danish National Patient Register (DNPR).[19] The DNPR is a nationwide registry established in 1977 and includes civil registration number, admission, and discharge dates, 1 primary diagnosis and up to 19 secondary diagnoses for each hospitalization. Since the year 1994, diagnoses have been coded using the International Classification of Disease 10th revision classification. The authors included the first hospitalization with a primary diagnosis of the specified endpoint occurring after postoperative day 30 (Supplementary Table 2). Date of diagnosis was defined as the date of hospitalization.

Information on all-cause death was obtained from the Danish Civil Registration System.[15] This system includes information on all changes in vital status, migration and date of death for the Danish population since 1968 and is updated electronically daily.

Confounding Factors

Information on potential confounding factors was collected through the WDHR and included: Gender, age, smoking status, body mass index, diabetes, modified European System for Cardiac Operative Risk Evaluation (EuroSCORE), type of procedure, extracorporeal circulation duration, use of aprotinin, and blood transfusion.[20] To avoid including confounding factors twice (both as single parameters and in the EuroSCORE), the authors excluded some of the parameters (age, sex, recent myocardial infarction, and surgery-related factors), and used a modified version of the EuroSCORE based on the following information: Baseline plasma creatinine, extracardiac arteriopathy, chronic pulmonary disease, neurologic dysfunction, previous cardiac surgery, active endocarditis, critical preoperative state, unstable angina, pulmonary hypertension, and left ventricular dysfunction (Supplementary Table 3). In addition, the authors included information from the DNPR from the 10 years before surgery on any diagnosis of myocardial infarction, heart failure, stroke, atrial fibrillation, or malignant tumor. The authors also included data on medications from the Danish National Database of Reimbursed Prescriptions (DNDRP).[21] The DNDRP holds information on all prescriptions from general practitioners that are reimbursed by the Danish National Health Service. The authors included information on prevalent use defined as a filled prescription within 100 days before admission for surgery for the following drugs: Angiotensin-converting enzyme inhibitors, beta-blockers, angiotensin II antagonists, calcium channel blockers, aspirins, nonsteroidal anti-inflammatory drugs/cyclo oxygenase-2 (COX-2) inhibitors, statins, and diuretics (Supplementary Table 4). Baseline plasma creatinine was used to calculate estimated glomerular filtration rate by the Modification of Diet in Renal Disease equation.[22] CKD was defined as estimated glomerular filtration rate < 60 mL/min per $1.73 m^2$ (stage 3 or higher according to the KDIGO guidelines.[23]

Statistical Analyses

The analyses considered risk of hospitalization with myocardial infarction, heart failure, or stroke, and all-cause mortality. The authors estimated the cumulative incidence as a measure of the absolute risk. Death was considered as a competing risk when estimating the risk of the nonfatal outcomes.[24] For the death endpoint, both short-term (30-90 days) and long-term (91 days to 5 years) cumulative mortality were estimated using the Kaplan-Meier method.

The authors estimated a propensity score—the predicted probability of postoperative AKI conditional on the observed baseline covariates—using multivariate logistic regression. The included covariates are listed in Table 1. Using standardized-mortality-ratio (SMR) weights, in which all AKI patients have weights equal to one (ie, the AKI group is the target population), and the non-AKI patients are weighted with the propensity odds, the authors estimated the effect of AKI in a study population in whom the weighted distribution of covariates was similar to that of the AKI patients.[25] Thus, after applying SMR weights to the study population, covariates were balanced adequately as evidenced by a standardized difference of each covariate to values below 0.1 (Fig 2).[26] The authors computed crude and SMR-weighted hazard ratios (HRs) for the endpoints using Cox proportional hazards regression. In the SMR-weighted model, the authors applied robust variance estimators.[27] In the main analysis, AKI was defined within the day of surgery to postoperative day 30, and the authors stratified by CKD. The assumption of proportional hazards was examined graphically and fulfilled for all Cox proportional regression models.

Missing covariate values were addressed using multiple imputations in the propensity score estimation model. In total, 18.4% had one or more missing values for the covariates included in the propensity score. The frequencies of missing values were 4.7% for smoking status, 1.6% for weight, 1.8% for height, 0.5% for diabetes, 3.5% for modified EuroSCORE, and 10.8% for extracorporeal circulation duration. The authors assumed that missing values were missing at random.[28] Twenty imputed datasets were created using multiple imputations by chained equations.[29] The imputations were done using all covariates listed in Table 1 (except body mass index and modified EuroSCORE), weight, height, covariates included in the modified EuroSCORE, AKI stage, Nelson-Aalen estimate, and event indicators for the studied endpoints.[28] Estimates from the imputed datasets were combined according to the rules of Rubins.[30] The authors repeated the analyses in a complete case scenario in which only observations with no missing values were included.

In subanalyses, the authors stratified by gender, early- and late-onset AKI, and year. For sensitivity analyses, the authors excluded patients who had been admitted with myocardial infarction, heart failure, or stroke within the last 10 years before surgery. To account for the fact that cardiac surgical patients receive fluids during surgery, leading to hemodilution of plasma creatinine, the authors also applied a revised version of the KDIGO criteria, omitting the plasma creatinine measures on the day of surgery and on day 1.

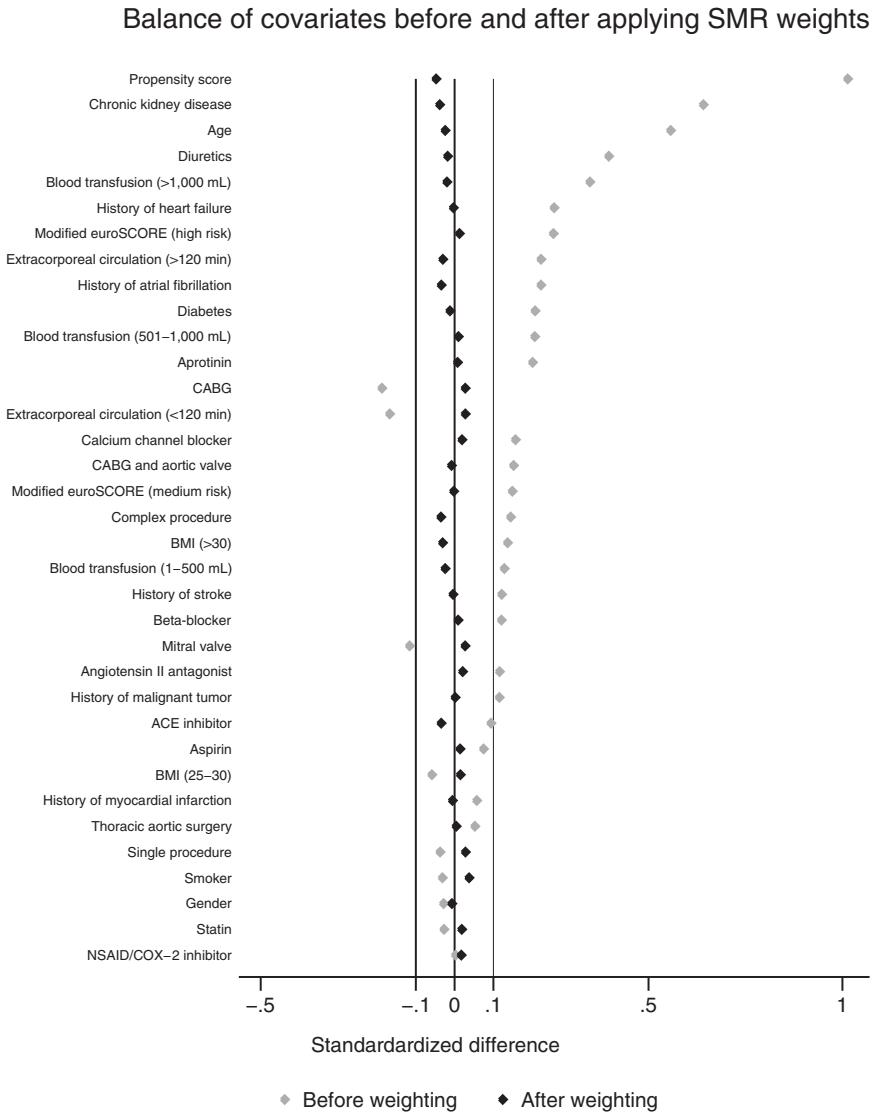

Fig 2. Standardized differences of the covariates included in the propensity score for AKI and non-AKI patients, before and after applying standardized-mortality-ratio weights.

Analyses were performed using the Stata® 12.0 package (StataCorp LP, College Station, TX).

RESULTS

The study population comprised 4,742 elective cardiac surgical patients who survived to postoperative day 30 (Fig 1). A total of 1,457 (30.7%) patients had AKI within 30 days of surgery. Among patients with AKI, 1,123 (77.1%) were in AKI stage 1 and 334 (22.9%) were in AKI stages 2+3. In AKI stages 2+3 a total of 84 (25.1%) patients needed dialysis after surgery. AKI patients were older, had more CKD, and more frequently had a history of heart failure than non-AKI patients. AKI patients used more diuretics, had a higher modified EuroSCORE, had longer extracorporeal circulation duration, and received more blood transfusions. The number of missing covariate values seemed to be unrelated to AKI status (Table 1).

A total of 1,171 (24.7%) patients had early-onset AKI, and 286 (8.0%) patients had late-onset AKI (Supplementary Tables 6-7). Total follow-up time was 12,476 person-years with median duration of 2.7 years (interquartile range [IQR]: 1.2-4.1). Median duration from day of surgery until hospital discharge for non-AKI patients was 8 days (IQR: 6-11) and for AKI patients was 13 days (IQR 9-20), ranging from 11 days (IQR: 8-16) in patients with AKI stage 1 to 21 days (IQR: 12-37) for patients with AKI stages 2+3.

The authors found a cumulative incidence of the composite cardiovascular endpoint of 24.9% (95% CI: 21.5-28.4) for AKI patients and 12.1% (95% CI: 10.4-13.9) for non-AKI patients (Table 2, Fig 3). The weighted HR was 1.41 (95% CI: 1.11-1.80) for AKI patients compared to non-AKI. For AKI stage 1, the weighted HR was 1.31 (1.02-1.67) and for AKI stages 2+3 it was 1.87 (1.30-2.70). Similar results were found for each endpoint separately, although less precise (Table 2, Fig 4).

Table 2. Cumulative Incidence and Hazard Ratio of Hospitalization With Myocardial Infarction, Heart Failure, and Stroke By AKI Status and Stratified By CKD*

				Hazard Ratio	
	Number at Period Start	Events	Cumulative Incidence	Crude	Weighted
AKI Status	n	n	% (95% CI)	(95% CI)	(95% CI)
Composite cardiovascular endpoint					
All patients					
Non-AKI	3,285	242	12.1 (10.4-13.9)	1.0 (reference)	1.0 (reference)
AKI	1,457	228	24.9 (21.5-28.4)	2.45 (2.05-2.94)	1.41 (1.11-1.80)
Stage 1	1,123	164	23.8 (20.2-27.7)	2.21 (1.81-2.69)	1.31 (1.02-1.67)
Stages 2+3	334	64	31.4 (23.0-40.2)	3.44 (2.61-4.54)	1.87 (1.30-2.70)
No CKD					
Non-AKI	2,971	198	11.4 (9.6-13.4)	1.0 (reference)	1.0 (reference)
AKI	948	122	21.8 (17.7-26.2)	2.19 (1.75-2.74)	1.55 (1.20-2.01)
CKD					
Non-AKI	314	44	18.11 (13.3-23.6)	1.0 (reference)	1.0 (reference)
AKI	509	106	31.7 (26.0-37.5)	1.78 (1.25-2.53)	1.49 (0.98-2.27)
Myocardial infarction					
All patients					
Non-AKI	3,285	54	2.7 (1.8-3.7)	1.0 (reference)	1.0 (reference)
AKI	1,457	44	6.0 (4.2-8.1)	2.08 (1.39-3.08)	1.55 (0.88-2.71)
Stage 1	1,123	30	5.4 (3.5-7.9)	1.77 (1.13-2.76)	1.32 (0.74-2.34)
Stages 2+3	334	14	7.9 (4.2-13.0)	3.26 (1.81-5.87)	2.76 (1.30-5.82)
No CKD					
Non-AKI	2,971	50	2.7 (1.8-3.9)	1.0 (reference)	1.0 (reference)
AKI	948	24	5.4 (3.4-8.2)	1.65 (1.02-2.69)	1.30 (0.74-2.26)
CKD					
Non-AKI	314	4	2.0 (0.6-4.8)	1.0 (reference)	1.0 (reference)
AKI	509	20	6.9 (4.1-10.7)	3.78 (1.29-11.07)	1.72 (0.47-6.37)
Heart failure					
All patients					
Non-AKI	3,285	130	6.3 (5.1-7.6)	1.0 (reference)	1.0 (reference)
AKI	1,457	148	15.5 (12.9-18.2)	2.9 (2.30-3.69)	1.36 (0.99-1.87)
Stage 1	1,122	111	15.7 (12.8-18.9)	2.75 (2.13-3.54)	1.34 (0.97-1.86)
Stages 2+3	334	37	14.3 (10.0-19.4)	3.55 (2.46-5.12)	1.46 (0.91-2.35)
No CKD					
Non-AKI	2,971	99	5.6 (4.3-7.0)	1.0 (reference)	1.0 (reference)
AKI	947	82	13.5 (10.5-16.9)	2.91 (2.17-3.90)	1.91 (1.35-2.70)
CKD					
Non-AKI	314	31	12.6 (8.6-17.4)	1.0 (reference)	1.0 (reference)
AKI	509	66	18.8 (14.5-23.6)	1.53 (1.00-2.35)	1.22 (0.74-2.02)
Stroke					
All patients					
Non-AKI	3,285	79	4.2 (3.2-5.4)	1.0 (reference)	1.0 (reference)
AKI	1,457	61	7.6 (5.6-9.9)	1.96 (1.40-2.74)	1.37 (0.92-2.04)
Stage 1	1,123	42	6.4 (4.5-8.8)	1.60 (1.16-2.46)	1.20 (0.79-1.84)
Stages 2+3	334	19	12.1 (6.2-20.0)	3.00 (1.81-4.96)	2.22 (1.22-4.02)
No CKD					
Non-AKI	2,971	67	4.1 (3.1-5.5)	1.0 (reference)	1.0 (reference)
AKI	948	33	6.5 (4.2-9.5)	1.70 (1.12-2.59)	1.20 (0.76-1.89)
CKD					
Non-AKI	314	12	4.9 (2.6-8.4)	1.0 (reference)	1.0 (reference)
AKI	509	28	9.4 (6.0-13.7)	1.70 (0.87-3.35)	1.66 (0.79-3.50)

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
*eGFR $<$ 60 mL/min per 1.73 m^2.

The weighted HR for 30-90 day mortality was 3.40 (95% CI: 1.41-8.20) comparing patients with AKI to patients without AKI. The cumulative incidence of death was 2.6% (95% CI: 1.9-3.9) for AKI patients (Table 3). In patients who survived the first 90 days of surgery, cumulative incidence of all-cause mortality was 21.6% (95% CI: 18.3-25.4) for AKI patients and 9.2% (95% CI: 7.8-10.8) for non-AKI patients Fig 4. The authors found a weighted HR of death 1.37 (95% CI: 1.05-1.80) (Table 3). Of 129 patients who died within 30 days of surgery, 106 (82.2%) had AKI.

The results were similar when stratified by gender (Supplementary Table 5), for early- and late-onset AKI

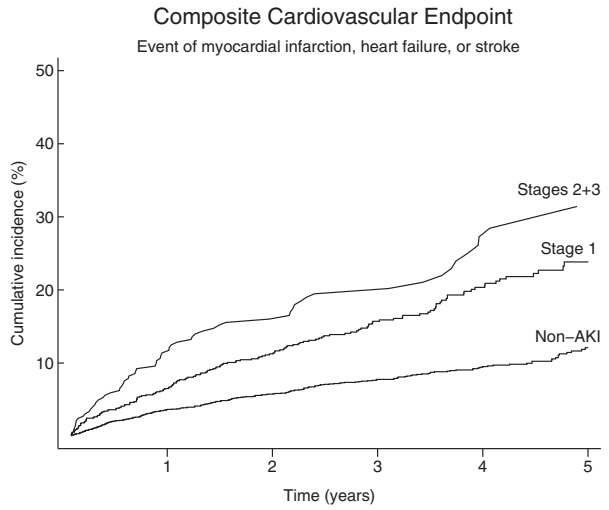

Fig 3. Cumulative incidence of the composite cardiovascular endpoint by AKI status after elective cardiac surgery.

(Supplementary Tables 6-7), after excluding patients with previous diagnosis of myocardial infarction, heart failure, or stroke (Supplementary Table 8), when using the revised KDIGO definition (Supplementary Table 9), and when conducting a complete case analysis (Supplementary Table 10, Supplementary Figure 1). When stratifying by year, an attenuated effect of AKI in the last part of the study period (Supplementary Table 11) was seen.

DISCUSSION

The authors found that almost one third of adult elective cardiac surgical patients had AKI within 30 days of surgery. The 5-year risk of myocardial infarction, heart failure, and stroke was increased in patients with AKI compared to non-AKI patients for both early- and late-onset AKI. Furthermore, AKI was associated with an increase in both short- and long-term mortality. For every endpoint the risk increased with advancing AKI stage.

This study is supported by other clinical studies investigating the renocardiac syndrome.[4,5,11–13] In a previous, smaller study, the authors found indication of an increased 5-year risk of myocardial infarction, and this association is now supported by the findings in the present population-based study.[4] Tsai et al found an adjusted 1-year HR of 2.6 (95% CI: 1.0-6.3) for myocardial infarction after aortic dissection comparing AKI patients with non-AKI patients.[13] The finding of a dose-dependent relationship between AKI stage and HR of specifically heart failure by Olsson et al supports the authors' finding, although much more attenuated in this study (Table 2).[11] This Swedish cohort study of patients undergoing first-time isolated CABG had a multivariate-adjusted HR of 1.60 (95% CI: 1.34-1.92) for AKI stage 1, 1.87 (95% CI: 1.54-2.27) for AKI stage 2, and 1.98 (95% CI: 1.53-2.57) for AKI stage 3.[11] In another study, Holzmann et al found an increased risk of stroke in AKI patients after first-time CABG, with a multivariable-adjusted HR of 1.12 (95% CI: 1.04-1.66) and 1.31 (95% CI: 0.92-1.87) for AKI stage 1 and AKI stage 3, respectively.[12] The association was attenuated and became non-significant after applying a subdistributional HR to account for the competing risk of death, and they concluded that AKI was not a long-term predictor of stroke. However, the interpretation of subdistributional hazards is not straightforward, and great precaution must be taken when using this method. In the presence of an etiologic prognostic study, describing the association between AKI and the endpoints and controlling for potential shared risk factors, the authors believe the cause-specific hazard model is the most appropriate.[24] The results did not reveal whether the presence of pre-existing CKD modified the effect of AKI.

In a meta-analysis, Coca et al investigated the impact of AKI on long-term mortality in various settings and found a pooled-adjusted HR of 2.0 (95% CI: 1.3-3.1). AKI was defined in the majority of studies as severe AKI, and this agreed with the finding for AKI stages 2+3.[31] The authors did not include data on initiation of renal replacement therapy in this study. However, research shows that early initiation compared to late initiation of renal replacement therapy in severe AKI after cardiac surgery diminished short-term mortality, odds ratio 0.29 (95% CI: 0.16-0.52).[32] This warrants further investigation with regard to cardiovascular events.

Strengths and Limitations

The strengths of this study included the population-based nature of the cohort within a uniform healthcare system with equal access to healthcare, which reduces selection bias. Furthermore, the restriction to elective surgery patients ensured a more homogenous cohort and thus strengthened internal validity. Accurate linkage through registries was ensured by the unique personal identification number. Furthermore, the authors collected highly relevant, pre-, peri-, and postoperative clinical characteristics.

This study may have been limited by factors of unmeasured confounding and data quality, common to many database studies. The authors only lacked baseline plasma creatinine or postoperative plasma creatinine for a small number of patients and excluded these. This may have been due to lack

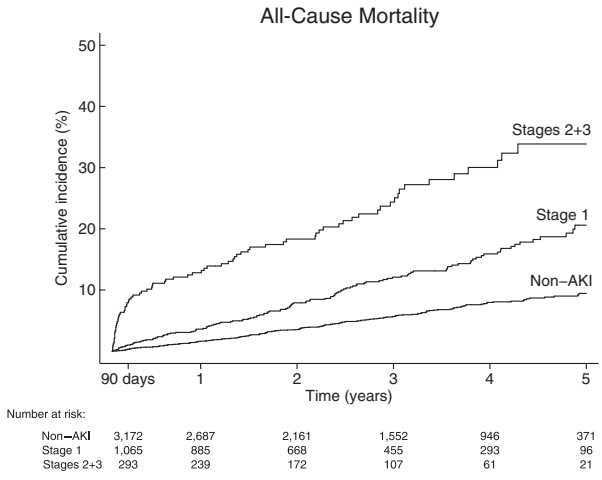

Fig 4. Cumulative incidence of all-cause mortality by AKI stage after elective cardiac surgery. A Kaplan-Meier plot.

Table 3. Cumulative Incidence and Hazard Ratio of All-Cause Mortality by AKI Status and Stratified by CKD*

				Hazard Ratio	
	Number at Period Start	Events	Cumulative Incidence	Crude	Weighted
AKI Status	n	n	% (95% CI)	(95% CI)	(95% CI)
Death (30-90 days)					
All patients					
Non-AKI	3,285	10	0.3 (0.2-0.6)	1.0 (reference)	1.0 (reference)
AKI	1,457	37	2.6 (1.9-3.6)	8.50 (4.23-17.09)	3.40 (1.41-8.20)
Stage 1	1,123	11	1.0 (0.6-1.8)	3.25 (1.38-7.64)	1.39 (0.52-3.69)
Stages 2+3	334	26	7.9 (5.5-11.4)	26.96 (13.09-55.91)	9.39 (3.36-26.21)
No CKD					
Non-AKI	2,971	8	0.3 (0.1-0.6)	1.0 (reference)	1.0 (reference)
AKI	948	17	1.8 (1.1-2.9)	6.76 (2.92-15.67)	2.64 (0.98-7.12)
CKD					
Non-AKI	314	2	0.7 (0.2-2.6)	1.0 (reference)	1.0 (reference)
AKI	509	20	4.0 (2.6-6.1)	6.33 (1.48-27.07)	2.10 (0.33-13.47)
Death (91 days-5 years)					
All patients					
Non-AKI	3,172	169	9.2 (7.8-10.8)	1.0 (reference)	1.0 (reference)
AKI	1,358	164	21.6 (18.3-25.4)	2.45 (1.99-3.06)	1.37 (1.05-1.80)
Stage 1	1,065	114	19.8 (16.2-24.1)	2.16 (1.70-2.73)	1.26 (0.95-1.67)
Stages 2+3	293	50	28.2 (21.3-36.8)	3.71 (2.70-5.08)	1.81 (1.22-2.68)
No CKD					
Non-AKI	2,869	142	8.7 (7.2-10.4)	1.0 (reference)	1.0 (reference)
AKI	890	80	18.1 (14.1-23.0)	1.95 (1.48-2.56)	1.09 (0.80-1.48)
CKD					
Non-AKI	303	27	13.2 (8.9-19.5)	1.0 (reference)	1.0 (reference)
AKI	468	84	28.3 (22.9-34.7)	2.30 (1.49-3.55)	1.78 (1.04-3.05)

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
*eGFR < 60 mL/min per 1.73 m^2.

of completeness in the laboratory register and, thus, presumably non-differential, hence not introducing bias.

The authors acknowledge that the number of postoperative plasma creatinine measures might be affected by preexisting CKD or whether the patient is making a good clinical recovery. This may influence the status and staging of AKI, in particular late-onset.

Date of dialysis treatment is not recorded in the WDHR. However, the study population only comprised 84 patients receiving dialysis and the median length of admission was less than 30 days, thus the impact of the potential bias due to misclassification of AKI was expected to be limited.

The outcome ascertainment relies on diagnostic coding. The positive predictive value was above 92% for myocardial infarction, 81% for heart failure, and 80% for stroke.[33–35] The false positive events would presumably be non-differential and, thus, bias the association towards unity.

The diagnosis of heart failure in the DNPR has a sensitivity of only 29% and a specificity of 99%.[34] This suggests severely underreporting and affects the number of observed events, hence lowering the absolute risk estimates. However, when specificity is perfect, the relative measures of effect still can be unbiased.[36]

Information on covariates from the WDHR was missing for 18.4% of the study population. However, using multiple imputations is a reasonable way to handle this drawback.[28] The findings of the complete case scenario supported the main analysis.

Confounding was adjusted for using propensity score-based SMR weights. As evidenced by the adequate balance of covariates in the weighted cohort, the authors achieved exchangeability among the exposure groups. However, residual confounding by unknown or immeasurable confounding factors could not be ruled out despite the large number of potential confounding factors included in the study.

The authors aimed to study causality of AKI and the specified outcomes. The finding of an association for both early- and late-onset AKI suggested a causal relationship between AKI and the studied endpoints.

The study is most likely generalizable throughout the setting of elective cardiac surgery. The authors excluded patients diagnosed with myocardial infarction, heart failure, and stroke during admission or within 30 days of surgery; thus, the results may not be generalizable to these patients. This was a trade-off to ensure that AKI preceded the endpoint.

CONCLUSION

The authors found that AKI within 30 days of surgery occurred in almost one-third of adult elective cardiac surgical patients. AKI was associated with a significantly increased 5-year risk of the composite cardiovascular endpoint of myocardial infarction, heart failure, and stroke. Analyzing the endpoints separately showed a similar 5-year risk for AKI patients compared to non-AKI patients. Both short-and long-term all-cause mortality were increased. Furthermore, the effect of AKI was the same regardless of early- or late-postsurgical onset.

This study suggested that patients experiencing AKI may expect higher long-term morbidity, specifically myocardial infarction, heart failure, and stroke, and mortality. This was

regardless of time of onset of AKI. Whether more awareness and earlier intervention against AKI may change the course for the patient still is unknown.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version at doi:10.1053/j.jvca.2014.08.020.

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