Associations Between Acute Kidney Injury and Cardiovascular and Renal Outcomes After Coronary Angiography

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Background—Acute kidney injury (AKI) is associated with early mortality after percutaneous coronary revascularization procedures, but its prognostic relevance to long-term clinical outcomes remains controversial.

Methods and Results—We conducted a retrospective study of 14 782 adults who received coronary angiography in the province of Alberta, Canada, between 2004 and 2006. AKI was identified on the basis of changes in serum creatinine concentration within 7 days of the procedure according to AKI Network criteria. The associations between AKI and long-term outcomes, including mortality, end-stage renal disease, and cardiovascular and renal hospitalizations, were studied with the use of Cox regression of multiple failure times. The adjusted risk of death increased with increasing severity of AKI; compared with no AKI, the adjusted hazard ratio for death was 2.00 (95% confidence interval, 1.69 to 2.36) with stage 1 AKI and 3.72 (95% confidence interval, 2.92 to 4.76) with stage 2 or 3 AKI. The adjusted risk of end-stage renal disease requiring renal replacement therapy also increased according to the severity of AKI (hazard ratio, 4.15 [95% confidence interval, 2.32 to 7.42] and 11.74 [95% confidence interval, 6.38 to 21.59], respectively), as did the risks of subsequent hospitalizations for heart failure and acute renal failure.

Conclusions—These findings inform the controversy surrounding AKI after angiography, demonstrating that it is a significant risk factor for long-term mortality, end-stage renal disease, and hospitalization for cardiovascular and renal events after coronary angiography. **(*Circulation*. 2011;123:409-416.)**

Key Words: angiography ■ cohort study ■ contrast- induced nephropathy ■ renal insufficiency

Acute kidney injury (AKI) frequently occurs after percutaneous coronary procedures and is attributed largely to the nephrotoxic effects of iodinated radiocontrast media.[1–3] Although severe AKI that requires acute dialysis is a rare event in this setting,[4] lesser degrees of AKI (represented by small, usually reversible changes in serum creatinine concentration) have been associated with adverse in-hospital outcomes (including myocardial infarction [MI] and target vessel reocclusion),[5,6] prolonged hospital stay,[7,8] and early mortality.[9,10]

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Despite these observations, the true long-term clinical consequences of AKI after coronary angiography have remained controversial in light of observations that death after AKI is often complicated by other acute conditions not mediated by AKI, including cardiogenic shock, sepsis, respiratory failure, and bleeding.[6,11] Conversely, emerging associations between kidney function and cardiovascular disease suggest that it is plausible that kidney injury may contribute to cardiovascular morbidity and mortality in addition to kidney failure after coronary angiography.[5,11,12] Although it is known that patients who develop AKI are at increased risk of death after coronary angiography,[6,13] little is known about the associations between AKI and specific cardiovascular and renal events. These associations are particularly relevant because preexisting kidney disease is common in patients with cardiovascular disease and among patients who develop AKI[14,15] and because subsequent hospitalizations for cardiovascular events and kidney failure lead to adverse health consequences and high costs.

The purpose of this study was to examine the associations between AKI and long-term clinical outcomes (including death, progression to end-stage renal disease [ESRD], and hospitalization for cardiovascular and renal events) after coronary angiography. We hypothesized that

Received June 2, 2010; accepted November 5, 2010.

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The online-only Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.110.970160/DC1.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.110.970160**

AKI would be an independent predictor of these outcomes following hospital discharge after adjustment for important cardiovascular and renal prognostic variables, including anatomic location of coronary disease, ejection fraction, baseline glomerular filtration rate, and proteinuria. Furthermore, we hypothesized that these associations would vary with the severity of AKI in a manner dependent on the outcome of interest.

Methods

Study Population

The study cohort was derived retrospectively from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH). APPROACH prospectively collects data on demographic and clinical characteristics on all patients undergoing coronary angiography in the province of Alberta, Canada.[16] Coronary angiography is performed using nonionic iodinated radiocontrast agents with the choice of low- or iso-osmolar radiocontrast agents and use of prophylaxis strategies, including *N*-acetylcysteine and intravenous fluid, made at the discretion of treating physicians.

The cohort consisted of all Alberta residents ≥18 years of age undergoing coronary angiography from January 1, 2004, to December 31, 2006. Eligible participants required at least 1 outpatient serum creatinine measurement within a 6-month period before coronary angiography and a subsequent measurement (either inpatient or outpatient) within 7 days after the angiogram. Patients with a renal transplant or who were receiving dialysis before coronary angiography were excluded on the basis of the Northern and Southern Alberta Renal Program registries[17] or by a period of continuous physician billing claims for dialysis.[18]

Measurement of Kidney Function

All serum creatinine measurements made in Alberta were obtained from the Alberta Kidney Disease Network repository of laboratory data.[19] Preangiography kidney function was determined with the 4-variable Modification of Diet in Renal Disease Study equation[20] to estimate glomerular filtration rate.[19] AKI was defined on the basis of the change in serum creatinine concentration from the preangiogram level to the peak level observed within 7 days after the coronary angiogram or before coronary artery bypass grafting surgery if the latter was performed within 7 days of angiography. The change in creatinine concentration was calculated using the most recent measurement before the angiogram as the baseline and categorized according to the Acute Kidney Injury Network criteria (AKI stage 1, ≥0.3 mg/dL absolute or 1.5- to 2.0-fold relative increase in serum creatinine; AKI stage 2, >2- to 3-fold increase in serum creatinine; AKI stage 3, >3-fold increase in serum creatinine or serum creatinine ≥4.0 mg/dL with an acute rise of >0.5 mg/dL).[21] Sensitivity analysis was also performed, restricting the analysis to patients with a baseline creatinine measurement within 2 days before the angiogram.

Measurement of Covariates

Age, sex, comorbidity, coronary anatomy (based on Duke myocardial jeopardy score[22]), left ventricular systolic ejection fraction, and subsequent receipt of coronary revascularization procedures (none, percutaneous coronary intervention, or coronary artery bypass grafting) were determined from the APPROACH database.[16] Provincial laboratory data were used to obtain all quantitative or semiquantitative outpatient urinary protein or albumin measurements collected within 6 months before angiography.[19] Urine protein was categorized as normal, microalbuminuria/proteinuria, or unmeasured[23] on the basis of the most recent preangiography urine specimen for patients with >1 result available.

Measurement of Outcomes

Participants were followed up for a maximum of 39 months from the date of coronary angiography until death or the study end date (March 31, 2007). Study end points included death resulting from any cause (as recorded by the Alberta Bureau of Vital Statistics, which maintains records of deaths for all residents of the province of Alberta) and progression to ESRD (identified on the basis of date of registration for chronic dialysis or renal transplantation within one of the Alberta renal programs).[17] Participants were also followed up from the date of hospital discharge until the next cardiovascular hospitalization (with a most responsible diagnosis of MI, heart failure, or cerebrovascular accident), hospitalization with acute renal failure, and hospitalization for any other cause. Cause-specific hospitalizations were identified from provincial hospital discharge records with validated *International Classification of Disease*s, 9th and 10th revisions, coding algorithms[24–27] (Table I in the online-only Data Supplement).

Statistical Analysis

Differences in baseline characteristics according to AKI stage were compared by the use of ANOVA and χ^2 tests for continuous and categorical variables, respectively. Pairwise comparisons to the reference group with no AKI were adjusted for multiple comparisons using the Bonferroni correction. Cumulative incidence curves for mortality, ESRD, and first hospitalization for any cause were plotted according to AKI stage. Cox proportional hazards regression was used to model multiple failure times per subject (ie, time to death, ESRD, hospitalization for MI, hospitalization for heart failure, hospitalization for cerebrovascular accident, hospitalization for acute renal failure, and other hospitalizations) as a function of AKI stage, accounting for the correlation in the data through the use of robust variance methods. A competing risk model for correlated unordered events of different type, stratified by outcome type, was fitted under the assumption that the exposure could be associated with repeated events in the same individual. In this model, each outcome can occur once per patient, all patients are at risk for all outcomes, and when a patient experiences 1 outcome, he or she remains at risk for all other outcomes unless death occurs.[28] Participants were censored at the end of follow-up or death. The final model was built looking at single event models to identify stratum-specific effects of exposure and covariates. Covariates considered for adjustment included terms corresponding to the 18 baseline characteristics listed in the Table. Stepwise elimination with backward selection was used to select the most parsimonious set of predictive variables. The proportional hazards assumption for the Cox model was tested and satisfied.

In sensitivity analyses, we repeated models after excluding patients with missing data on proteinuria, severity of coronary artery disease, or left ventricular ejection fraction. All statistical analyses were conducted with STATA (version 11.0; STATA Corp, College Station, TX). The conjoint health research ethics board of the University of Calgary approved the study.

Results

Cohort Formation and Baseline Characteristics

We identified 24 873 Alberta residents ≥18 years of age undergoing coronary angiography during the cohort entry period. We excluded 327 patients receiving renal replacement therapy before study entry, 1105 without a creatinine measurement before coronary angiography, and 8659 patients without a creatinine measurement in the 7 days after coronary angiography (Figure 1). Of the patients without a creatinine measurement within 7 days after angiogram, 8352 (96.4%) were discharged home on the day of the angiogram. The subsequent rates of death, progression to ESRD, and all-cause

Table. Characteristics of Patients Undergoing Coronary Angiography According to AKI Status

	AKI*					
		AKI Stage 1 (n=1099)		AKI Stage 2 or 3 (n=321)		
	No AKI (n=13 362)		P†		P†	Overall P‡
Age, mean (SD), y	62.6 (12.4)	68.0 (12.1)	<0.001	67.4 (12.7)	<0.001	<0.001
Male, n (%)	9564 (71.6)	779 (70.9)	N/A	217 (67.6)	N/A	0.27
Preangiography serum creatinine, mean (SD), mg/dL	1.0 (0.3)	1.2 (0.5)	<0.001	1.6 (1.3)	<0.001	<0.001
Preangiography eGFR, mean (SD) , mL · min^{-1} · 1.73 m^{-2}	75.3 (21.0)	66.6 (12.6)	<0.001	58.5 (31.4)	<0.001	<0.001
Preangiography eGFR, n (%)						
≥60 mL · min^{-1} · 1.73 m^{-2}	10 467 (78.3)	629 (57.2)	<0.001	143 (44.5)	<0.001	<0.001
45–59 mL · min^{-1} · 1.73 m^{-2}	2104 (15.7)	242 (22.0)		71 (22.1)		
30–44 mL · min^{-1} · 1.73 m^{-2}	634 (4.7)	172 (15.7)		46 (14.3)		
<30 mL · min^{-1} · 1.73 m^{-2}	157 (1.2)	56 (5.1)		61 (19.0)		
Proteinuria, n (%)						
Absent	8156 (61.0)	617 (56.1)	<0.001	157 (48.9)	<0.001	<0.001
Microalbuminuria/proteinuria	1512 (11.3)	242 (22.0)		110 (34.3)		
Unmeasured	3694 (27.6)	240 (21.8)		54 (16.8)		
Comorbidities, n (%)						
Diabetes mellitus	3283 (24.6)	365 (33.2)	<0.001	134 (41.7)	<0.001	<0.001
Hypertension	8682 (65.0)	798 (72.6)	<0.001	230 (71.6)	0.039	0.020
Hyperlipidemia	10 096 (75.6)	796 (72.4)	0.063	206 (64.2)	<0.001	<0.001
Heart failure	1799 (13.5)	312 (28.4)	<0.001	142 (44.2)	<0.001	<0.001
Cerebrovascular disease	920 (6.9)	126 (11.5)	<0.001	50 (15.6)	<0.001	<0.001
Peripheral vascular disease	998 (7.5)	126 (11.5)	<0.001	57 (17.8)	<0.001	<0.001
Chronic pulmonary disease	2126 (15.9)	268 (24.4)	<0.001	83 (25.8)	<0.001	<0.001
Liver disease	176 (1.3)	19 (1.7)	0.765	13 (4.0)	<0.001	0.001
Malignancy	548 (4.1)	57 (5.2)	N/A	13 (4.0)	N/A	0.22
Current smoker	4205 (31.5)	278 (25.3)	<0.001	69 (21.5)	<0.001	0.001
Acute coronary syndrome, n (%)	9554 (71.5)	828 (75.3)	0.007	235 (73.2)	0.503	0.021
Coronary vascular disease, n (%)						
Normal	953 (7.1)	57 (5.2)	<0.001	32 (10.0)	<0.001	<0.001
Minimal (<50% stenosis)	1223 (9.2)	64 (5.8)		19 (5.9)		
Low risk (1 or 2 vessels)	6282 (47.0)	392 (35.7)		83 (25.8)		
High risk (3 vessels of proximal LAD)	3844 (28.8)	405 (36.8)		119 (37.1)		
Left main	961 (7.2)	168 (15.3)		62 (19.3)		
Missing	99 (0.7)	13 (1.2)		6 (1.9)		
Left ventricular ejection fraction, n (%)						
>50%	7716 (57.7)	412 (37.5)	<0.001	89 (27.7)	<0.001	<0.001
35–50%	2816 (21.1)	268 (24.4)		73 (22.7)		
20–34%	691 (5.2)	97 (8.8)		33 (10.3)		
<20%	196 (1.5)	29 (2.6)		9 (2.8)		
Unmeasured	1943 (14.5)	293 (26.7)		117 (36.4)		
Procedures, n (%)						
Only coronary angiography	3909 (29.2)	310 (28.2)	<0.001	121 (37.7)	<0.001	0.003
Percutaneous coronary intervention	7398 (55.4)	497 (45.2)		106 (33.0)		
Coronary artery bypass surgery	2055 (15.4)	292 (26.6)		94 (60.4)		

eGFR indicates estimated glomerular filtration rate; LAD, left anterior descending; and N/A, not assessed.

*Defined according to Acute Kidney Injury Network criteria (AKI stage 1, ≥0.3 mg/dL absolute or 1.5- to 2.0-fold relative increase in serum creatinine; AKI stage 2, >2- to 3-fold increase in serum creatinine; AKI stage 3, >3-fold increase in serum creatinine or serum creatinine ≥4.0 mg/dL with an acute rise of >0.5 mg/dL).

†Pairwise difference for each AKI stage compared with the no AKI group with Bonferroni correction.

‡Overall difference between AKI stages as determined by ANOVA or χ^2 test.

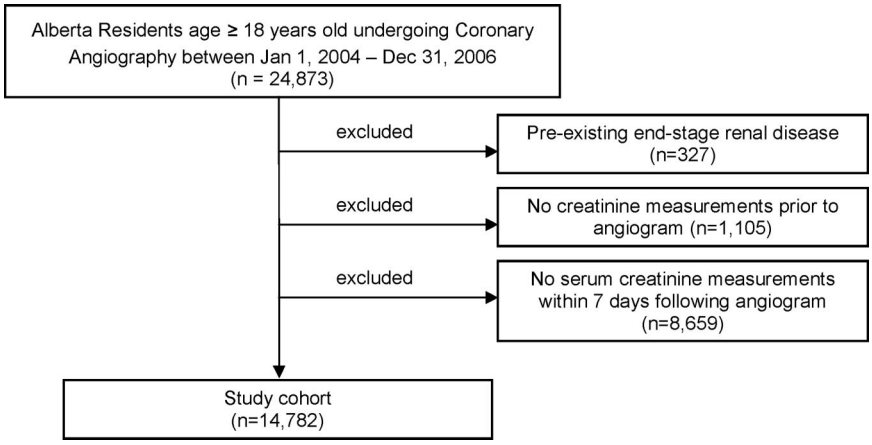

Figure 1. Cohort formation.

hospitalization during long-term follow-up were 3.8%, 0.2%, and 45.9%, respectively, in this subgroup.

Of the 14 782 participants included in the final cohort, 1099 (7.4%) experienced stage 1 AKI and 321 (2.2%) experienced stage 2 or 3 AKI. These participants were older, had lower preangiography estimated glomerular filtration rate, had proteinuria, and were more likely to have certain comorbidities (including diabetes mellitus, hypertension, and heart failure), lower left ventricular ejection fraction, and more severe coronary artery disease (the Table). In addition, participants experiencing AKI were less likely to receive percutaneous coronary intervention and more likely to receive coronary artery bypass grafting as a subsequent revascularization procedure.

Unadjusted Rates of Clinical Outcomes by Severity of AKI

Over a median follow-up after discharge of 19.7 months (interquartile range, 10.8 to 28.8 months), 1103 patients (7.5%) died, 93 (0.6%) progressed to ESRD requiring renal replacement therapy, and 6230 (42.1%) were hospitalized. The unadjusted cumulative incidences of death, ESRD, and all-cause hospitalization according to stage of AKI are shown in Figure 2. The incidence of both mortality and ESRD increased in a graded manner with greater severity of AKI (P for trend <0.001 for both outcomes). The cumulative incidence of all-cause hospitalization exceeded 40% regardless of AKI status and did not increase in a graded manner with greater severity of AKI (P for trend=0.137).

Adjusted Rates of Clinical Outcomes by Severity of AKI

In the adjusted models, AKI remained associated with increases in the risks of death, progression to ESRD, and other cardiovascular and renal-specific hospitalizations (Figure 3). Significant differences were present in the strength of associations between AKI stage and the outcome type (P for interaction by strata <0.001). Compared with those without AKI, the fully adjusted risk of mortality increased 2-fold in those with AKI stage 1 and >3-fold in those with AKI stage 2 or 3. The adjusted risk of ESRD was most substantially increased in those with AKI stage 2 or 3, in whom a >11-fold increase in risk was observed. The adjusted risk of hospitalization for MI was 47% greater among those with AKI stage 1, although this risk was not significantly elevated in those with AKI stage 2 or 3. The adjusted risk of hospitalization for heart failure increased by 48% in those with AKI stage 1 and by >2-fold in those with AKI stage 2 or 3. Hospitalization for cerebrovascular accident was uncommon and was not significantly associated with AKI in adjusted models. Subsequent hospitalizations with AKI were >2- and 3-fold higher in those with stage 1 and stage 2 or 3 AKI, respectively. No significant associations were observed

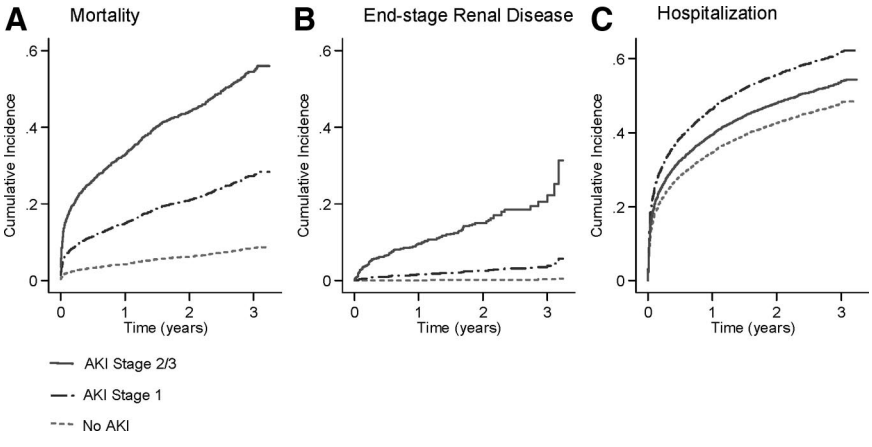

Figure 2. Cumulative incidence of (A) mortality, (B) ESRD, and (C) hospitalization for all causes according to stage of AKI. AKI is defined according to Acute Kidney Injury Network criteria (AKI stage 1, ≥0.3 mg/dL absolute or 1.5- to 2.0-fold relative increase in serum creatinine; AKI stage 2, >2- to 3-fold increase in serum creatinine; AKI stage 3, >3-fold increase in serum creatinine or serum creatinine ≥4.0 mg/dL with an acute rise of >0.5 mg/dL).

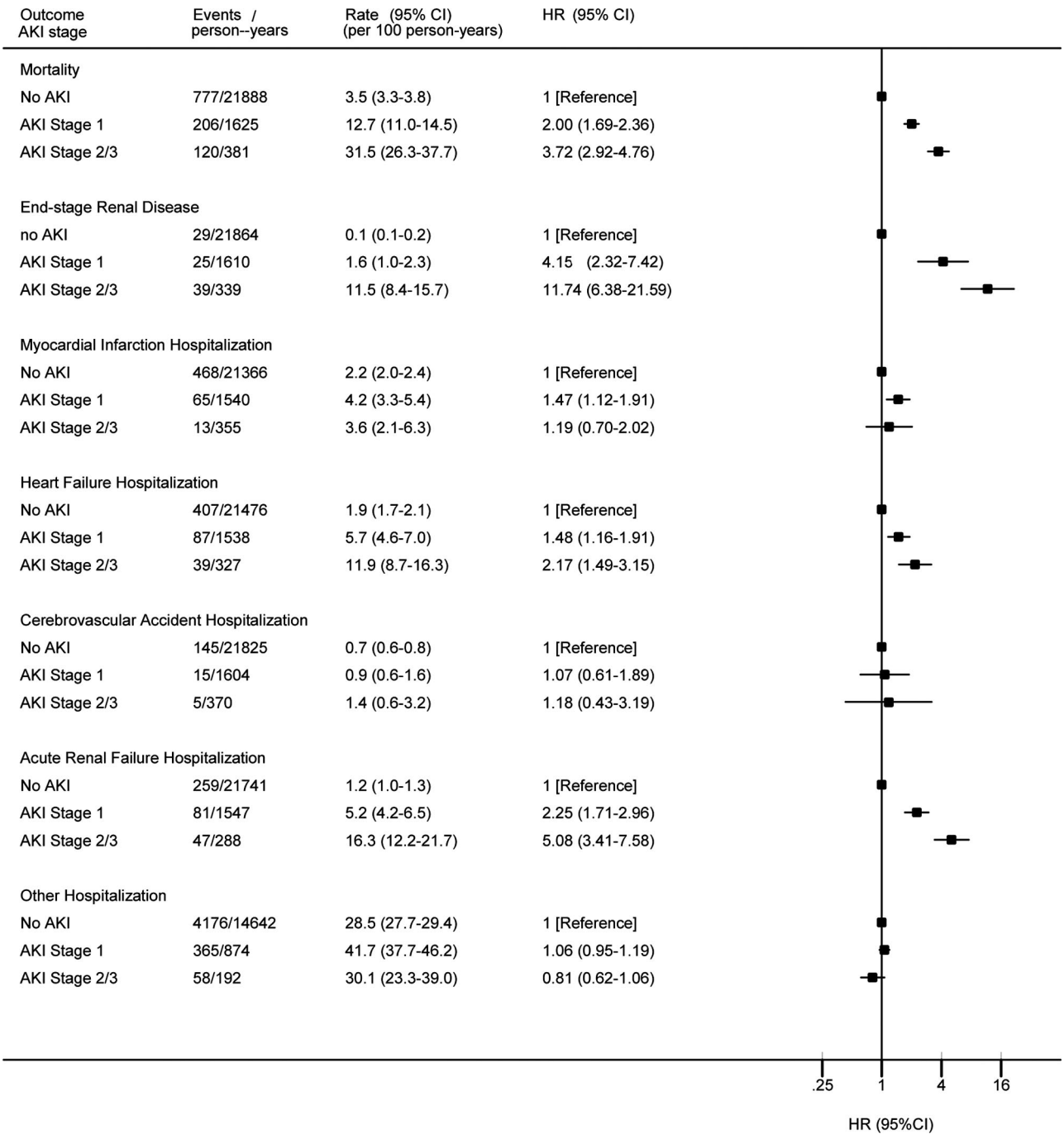

Figure 3. Rates and adjusted hazard ratios for all-cause mortality, ESRD, and hospitalization for cardiovascular, renal, and other events according to stage of AKI. AKI defined according to Acute Kidney Injury Network criteria (AKI stage 1, ≥0.3 mg/dL absolute or 1.5- to 2.0-fold relative increase in serum creatinine; AKI stage 2, >2- to 3-fold increase in serum creatinine; AKI stage 3, >3-fold increase in serum creatinine or serum creatinine ≥4.0 mg/dL with an acute rise of >0.5 mg/dL). Covariates (by stratum) retained in the final model were age (all strata), sex (all strata), diabetes mellitus (all strata), heart failure (all strata), cerebrovascular disease (mortality, MI, cerebrovascular accident, other hospitalization strata), peripheral vascular disease (mortality, MI strata), chronic pulmonary disease (mortality, other hospitalization strata), liver disease (mortality, other hospitalization strata), malignancy (mortality, other hospitalization strata), current smoking (mortality, MI, cerebrovascular accident, other hospitalization strata), acute coronary syndrome (mortality, MI, other hospitalization strata), baseline estimated glomerular filtration rate (all strata), microalbuminuria/proteinuria (all strata), coronary anatomy based on Duke myocardial jeopardy score (mortality, MI, cerebrovascular accident strata), left ventricular ejection fraction (mortality, heart failure, ESRD, acute renal failure, and other hospitalization strata), and coronary revascularization (all strata). HR indicates hazard ratio; CI, confidence interval.

between AKI and the adjusted risk of hospitalization for other causes.

Results were similar when patients without measurements of proteinuria, severity of coronary artery disease, or left ventricular ejection fraction were excluded from the analysis and when the analysis was restricted to patients with a baseline creatinine measurement within 2 days before the angiogram. Rates of adverse outcomes were increased in

those with AKI for participants with chronic kidney disease (preangiography estimated glomerular filtration rate <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) or without chronic kidney disease before coronary angiography (Table II in the online-only Data Supplement).

Discussion

In this population-based cohort undergoing coronary angiography, the risks of death, progression to ESRD, and subsequent hospitalization for cardiovascular and renal events rose with increasing severity of AKI, although the gradient of risk across stages of AKI differed among these events. Death was a common outcome, and a graded increase in the risk of mortality was observed across the categories of AKI. The risk of subsequent hospitalizations for heart failure and acute renal failure also increased progressively with increasing severity of AKI, whereas the risk of progression to ESRD requiring renal replacement therapy was most substantial in those with the most severe episodes of AKI.

The association between even small changes in serum creatinine and adverse short-term clinical outcomes has been documented repeatedly.[6,29,30] Graded increases in mortality within 30 days of coronary angiography and increased length of hospital admission have been shown to correlate with increases in the severity of AKI after coronary angiography.[8] Among patients receiving percutaneous coronary interventions, AKI has been shown to be associated with other early complications, including MI,[5,6] target vessel reocclusion,[5] postprocedural bleeding complications,[6] and the need for mechanical ventilation or circulatory support.[6,7]

The effects of AKI after coronary angiography on long-term adverse cardiovascular and renal events are less clear. Most previous studies of contrast-related AKI have identified events occurring during a short period of follow-up, have not included renal events as outcomes of interest, or were not able to account for important confounders relevant to the risk of future cardiovascular or renal events.[31,32] Other large cohorts of patients hospitalized with MI (only a minority of whom received coronary procedures) have observed that during long-term follow-up, those with small increases in serum creatinine experienced increased rates of death (up to 19.4 to 27.5 deaths per 100 patient-years), comparable to those observed in our study.[33,34] Our findings also further extend knowledge about the prognostic implications of AKI after coronary angiography, including its graded associations with subsequent hospitalizations for heart failure and renal failure and with the risk of future progression to ESRD. Although the risk of MI was higher in patients with mild but not severe episodes of AKI, differences in the presentation of acute coronary syndromes in patients with renal insufficiency[35] and competing risks for death may have contributed to this finding.

The associations between AKI and these long-term risks after AKI have several possible explanations. First, patients who develop AKI have a higher prevalence of comorbidities such as diabetes mellitus, heart failure, and chronic kidney disease, each of which may increase the risk of heart failure, progression to kidney failure, and death.[14,15] However, the strength of the associations that remain after adjustment for important variables related to baseline kidney function and severity of cardiovascular disease suggests that confounding by these characteristics does not completely explain our findings, although we cannot rule out the possibility of residual confounding. Second, AKI may identify patients with impaired cardiac output or renal hemodynamic vulnerability who are at heightened long-term risks for decompensated heart function, loss of kidney function, and death. The long-term risks of adverse outcomes after AKI may be related to long-term effects on kidney function after an episode of AKI. Recent studies suggest that episodes of AKI contribute to persistent loss of kidney function[36,37] and faster subsequent rate of decline in kidney function,[38,39] processes that have been associated with future risks of episodes of heart failure[40] and progression to ESRD.[41] Regardless of causality, the occurrence of AKI does appear to accurately identify a group of patients at higher risk for these adverse events, suggesting that targeting these patients for careful outpatient management has the potential to improve long-term outcomes.

These findings are important because a number of therapeutic interventions have been shown to be of value in improving survival, slowing the progression to ESRD, and preventing hospital admissions in general populations of patients with chronic kidney disease [42] or heart failure.[43,44] Early clinical follow-up, evaluation of volume status, use of diuretics, and inhibitors of the renin-angiotensin system have the potential to improve these outcomes after an episode of AKI; however, further research is needed to evaluate the role of these therapies specifically in survivors of AKI after coronary angiography.

Our study has several strengths, including a source population of all patients undergoing coronary angiography within a defined geographic region in which all residents had access to province-wide funded health care. Our cohort undergoing coronary angiography was well characterized and included detailed information on important prognostic variables related to severity of cardiovascular disease and kidney disease before angiography. We were able to adjust for these important confounders as they related to each of the outcomes of interest in our modeling process.

Our study also has limitations. First, because this study was conducted as a historical cohort study using clinical data, participant selection was limited to patients with clinical concerns or illness that prompted follow-up creatinine measurement within 7 days. Because many patients who were discharged promptly and did not have a follow-up creatinine measurement were excluded, our results may overestimate the overall incidence of these events among all patients undergoing coronary angiography. However, the risks of clinical events in the excluded group without follow-up creatinine measurement were comparable to those in participants without AKI, suggesting that exclusion of these patients is unlikely to have biased estimates of risk relative to the reference group with serum creatinine measurements available but no AKI. Second, episodes of AKI and their severity may have been misclassified owing to our dependence on existing creatinine measurements captured after coronary angiography. However, our approach to identification of AKI is most vulnerable to missing episodes of mild

AKI or underestimating the severity of AKI in those who developed it. If such misclassification occurred, we anticipate that it would have attenuated the relative risk of outcomes associated with the moderate or severe forms of AKI. Finally, despite our attempts to control for important confounding variables, residual confounding resulting from unmeasured variables (volume and type of contrast received, use of prophylactic measures, exposure to other nephrotoxins, and the contribution of atheroembolism) or differences in the severity of chronic kidney disease or other comorbidities between groups remains possible. Observational studies of this nature cannot prove that AKI plays a causal role in these outcomes or that prevention of AKI would improve these long-term outcomes. These results should not be interpreted as evidence that patients at risk for AKI should avoid diagnostic and interventional coronary procedures because several studies have documented that patients with kidney disease who do not receive these procedures have poorer outcomes.[45,46] However, our findings suggest that long-term mortality, ESRD, and cardiovascular and renal hospitalizations would be important outcomes to examine in future randomized trials of interventions targeting postangiography AKI.

Conclusions

Graded increases in the severity of AKI are associated with variation in risks of long-term mortality, progression to ESRD, and hospitalization for cardiovascular and renal events. The presence and severity of AKI after coronary angiography could be used to help identify high-risk patients and to guide further management. Further research focusing on interventions to prevent AKI after coronary angiography should assess the effects on these important clinical outcomes. Strategies to reduce cardiovascular risk and to slow the progression of chronic kidney disease require further study in survivors of radiocontrast-associated AKI.

Sources of Funding

This study was supported by the Kidney Foundation of Canada and the Alberta Kidney Disease Network. The ongoing operation of the APPROACH project has been made possible by operating grants from the Canadian Cardiovascular Outcomes Research Team (a Canadian Institutes of Health Research–funded team grant initiative), the Heart and Stroke Foundation of Alberta, Northwest Territories, and Nunavut. The APPROACH initiative has also received contributions from Alberta Health and Wellness, Merck and Frosst Canada Inc, Monsanto Canada Inc-Searle, Eli Lily Canada Inc, Guidant Corp, Boston Scientific Ltd, Hoffman-LaRoche Ltd, and Johnson&Johnson InCordis to support the basic infrastructure of this cardiac registry initiative. Dr James is supported by a KRESCENT fellowship (Canadian Institutes for Health Research and Kidney Foundation of Canada) and an Alberta Heritage Foundation for Medical Research (AHFMR) Award. Dr Ghali is funded by a Government of Canada Research Chair in Health Services Research and by a Senior Health Scholar Award from the AHFMR. Dr Tonelli is supported by a Health Scholar, and Dr Hemmelgarn is supported by a Population Health Investigator Award from the AHFMR. Drs Tonelli, Manns, and Hemmelgarn are supported by New Investigator Awards from the Canadian Institutes of Health Research.

Disclosures

Dr Knudtson has received honoraria for presentations from the Canadian Cardiovascular Society and Medtronic. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Acute kidney injury (AKI) is a common and potentially serious complication after coronary angiography. Although the incidence of AKI requiring dialysis treatment after percutaneous coronary interventions is low, the presence of even small changes in kidney function has been associated with adverse short-term outcomes, including target vessel reocclusion, prolonged hospital stay, and in-hospital mortality. The long-term clinical consequences of AKI in this setting are less clear. In this retrospective cohort study from Alberta, Canada, that included 14 782 patients who received coronary angiography between 2004 and 2006, AKI was identified on the basis of changes in serum creatinine captured within 7 days after coronary angiography, and patients were followed up for up to 39 months for subsequent cardiovascular and renal outcomes. Stage 1 AKI (according to AKI Network definition) was independently associated with a 2-fold increase in the risk of death, 4-fold increase in the risk of progression to end-stage renal disease, 1.5-fold increase in the risk of hospitalization for heart failure, and 2-fold increase in the risk of hospitalization with acute renal failure. Furthermore, the risk of these outcomes increased in a graded manner with increasing severity of AKI. These results demonstrate that the occurrence of AKI identifies patients at higher risk for subsequent adverse cardiovascular and renal events and suggest that targeting these patients for careful outpatient management after coronary angiography has the potential to improve long-term outcomes. Further research is needed to identify strategies to prevent and reduce the risks and adverse outcomes associated with AKI after these procedures.

Associations Between Acute Kidney Injury and Cardiovascular and Renal Outcomes After Coronary Angiography

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Circulation. 2011;123:409-416; originally published online January 17, 2011;
doi: 10.1161/CIRCULATIONAHA.110.970160
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Supplemental Material

Supplementary Table 1 - Identification of study outcomes

Outcome	Criteria
Mortality	Alberta Vital Statistics record
End-stage renal disease	Registry for dialysis or kidney transplantation in Northern or Southern Alberta Renal Program
Hospitalization for myocardial infarction	ICD-9: 410
	ICD-10: I21, I22
Hospitalization for heart failure	ICD-9: 428
	ICD-10: I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43, I50, P29.0
Hospitalization for cerebrovascular accident	ICD-9: 362.3, 430, 431, 433, 434, 435, 436
	ICD-10: H341,I60, I61, I63, I64, G45
Hospitalization for acute renal failure	ICD-9: 584.5, 584.6, 585.7, 584.8, 584.9
	ICD-10: N17.0, N17.1, N17.2, N17.8, N17.9

Abbreviations: ICD = International Classification of Diseases

Supplementary Table 2 – Rates of mortality, end-stage renal disease, and cardiovascular and renal hospitalizations stratified by acute kidney injury (AKI) status and pre-angiography eGFR.

	Rate (95% CI) per 100 person years	
	Pre-angiography eGFR ≥ 60 mL/min/1.73m^2	Pre-angiography eGFR < 60 mL/min/1.73m^2
Death		
No AKI	2.5 (2.3-2.8)	7.4 (6.6-8.2)
AKI Stage 1	8.5 (6.9-10.6)	19.2 (16.3-22.9)
AKI Stage 2/3	27.9 (21.0-37.2)	34.3 (27.3-43.2)
End-stage Renal Disease		
No AKI	0.2 (0.1-0.6)	0.5 (0.4-0.8)
AKI Stage 1	0.4 (0.2-1.1)	3.4 (0.4-0.8)
AKI Stage 2/3	0.6 (0.1-4.3)	22.0 (16.0-30.3)
Myocardial Infarction Hospitalization		
No AKI	2.0 (1.8-2.3)	2.8 (2.3-3.3)
AKI Stage 1	3.8 (2.7-5.2)	4.9 (3.4-7.0)
AKI Stage 2/3	1.2 (0.3-5.0)	5.7 (3.1-10.2)
Heart Failure Hospitalization		
No AKI	1.3 (1.1-1.5)	4.2 (3.6-4.8)
AKI Stage 1	2.9 (2.0-4.2)	10.0 (7.8-13.0)
AKI Stage 2/3	11.8 (7.3-19.0)	12.0 (7.9-13.0)
Cerebrovascular Accident Hospitalization		
No AKI	0.5 (0.4-0.6)	1.3 (1.0-1.6)
AKI Stage 1	0.9 (0.5-1.8)	0.9 (0.4-2.1)
AKI Stage 2/3	1.2 (0.3-4.9)	1.4 (0.5-4.5)
Acute Renal Failure Hospitalization		
No AKI	0.6 (0.5-0.7)	3.4 (3.0-4.0)
AKI Stage 1	2.4 (1.6-3.6)	9.9 (7.7-12.9)
AKI Stage 2/3	11.6 (7.2-18.6)	21.2 (1.5-3.0)
Other Hospitalization		
No AKI	27.7 (25.8-27.6)	36.6 (34.4-38.9)
AKI Stage 1	40.7 (35.7-46.4)	43.5 (36.9-51.3)
AKI Stage 2/3	35.6 (25.1-50.7)	25.6 (17.5-37.3)

Abbreviations: AKI = Acute Kidney Injury SD = Standard Deviation, eGFR = estimated Glomerular Filtration Rate

AKI defined according to Acute Kidney Injury Network Criteria (AKI stage 1 ≥0.3 mg/dl absolute or 1.5-2.0 fold relative increase in serum creatinine; AKI stage 2 >2-3 fold increase in serum creatinine; AKI stage 3 > 3 fold increase in serum creatinine or serum creatinine ≥4.0 mg/dl with an acute rise of >0.5 mg/dL)

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관상동맥 조영술 후 급성 신기능 저하가 발생하면 장기 예후가 나쁘다.

조 상 호 교수 한림대학교 성심병원 순환기내과

Summary

배경

관상동맥 중재술 후의 급성 콩팥손상(acute kidney injury, AKI)은 조기 사망과 관련성이 있으나, 장기 예후에 미치는 영향에 대해서는 논란이 있다.

방법 및 결과

2004-2006년까지 캐나다의 앨버타 주에서 관상동맥 조영술을 시행 받은 14,782명의 환자를 대상으로 후향적 연구를 시행하였다. AKI는 AKI 네트워크의 기준에 따라, 시술 7일 이내의 혈청 크레아티닌 변화에 근거하여 정의하였다. AKI와 사망, 말기 신부전, 심혈관계-신장 질환에 의한 입원을 포함한 장기 심혈관계 사건의 관련성은 Cox regression을 이용하였다. AKI가 심해질수록 AKI가 없는 환자에 비해서 사망률은 증가하였다. Stage 1의 AKI는 보정 위험도(adjusted hazard ratio)가 2.0(95% CI, 1.69-2.36)이었고, stage 2, 3의 AKI는 3.72(95% CI, 2.92-4.76)였다. 신대체요법이 필요한 말기 신부전의 위험도 역시 AKI의 정도가 심해질수록 증가하였다. 즉, 위험도가 각각 4.15(95% CI, 2.32-7.42)와 11.74(95% CI, 6.38-21.59)였다. 또한, 심부전이나 신부전으로 인한 입원도 유사한 결과를 보였다.

결론

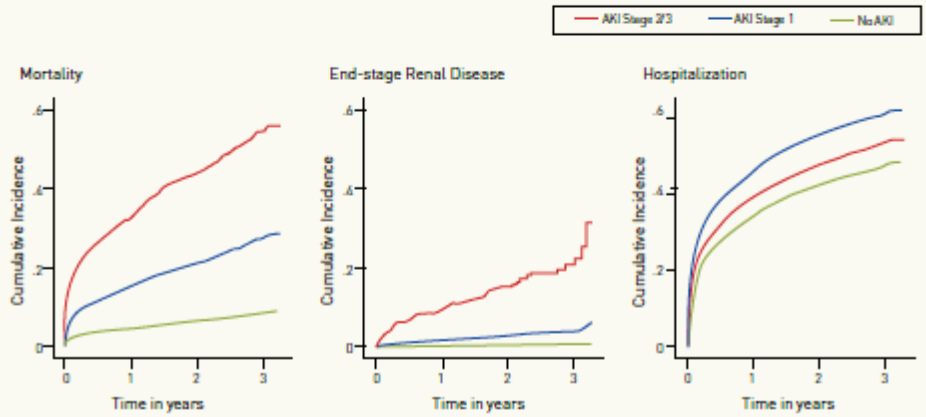
관상동맥 조영술 후의 AKI는 장기적 사망, 말기 신부전, 심혈관에 의한 입원, 신장 질환에 의한 입원의 중요한 위험인자이다.

혈관 조영제를 사용한 검사, 시술 후에 발생하는 조영제 유발 신기능 저하(contrast-induced nephropathy, CIN)는 입원 환자에서 발생하는 신부전의 세 번째 원인을 차지하며, 약 3-50%의 발생률을 보고하고 있다. 발생률의 보고가 다양한 이유는 대상 환자의 위험도나 사용하는 조영제의 종류, 시술의 종류, CIN의 진단 기준이 다양하기 때문이다. CIN은 대체로 기저 신기능이 저하된 환자, 당뇨병 환자, 쇼크 환자, 노인 환자에서 더욱 잘 발생하며, 발생 시 입원 중 예후가 불량하다고 보고되고 있다. 즉, 환자의 사망, 심근경색, 재입원, 투석, 혈관중재술의 재시행 및 장기적 신부전을 유발한다는 다수의 보고가 있었다. 그러나 입원 중의 사망은 대체로 심인성 쇼크, 패혈증, 호흡부전, 출혈 등의 다른 동반 질환에 의해 발생하는 경우가 많았기 때문에, 신부전 자체의 역할에 대해서는 논란이 있다. 또한, 대개 입원 중이나 1년 이내의 데이터들이 제시되고 있어서 과연 3년 이상의 장기 예후에 어떠한 영향을 미치는가에 대한 연구는 많지 않다. 또한, 조영제 투여 후 일시적으로 혈청 크레아티닌이 상승했다가 이후에 정상으로 회복되는 경미한 환자의 경우에도 과연 장기적 관점에서 임상적으로 불리할지에 대한 연구 역시 적다.

본 연구에서는 AKI stage 1 환자, 즉 크레아티닌이 절대적으로 0.3mg/dL 이상 증가하거나, 상대적으로 기저의 1.5-2배 상승한 경우에 사망률이 2배 오르고 말기 신부전으로의 진행은 4배, 심부전에 의한 입원, 급성 신부전에 의한 입원은 2배로 증가하며, AKI의 정도가 심할수록 위험도가 더욱 증가함을 잘 보여주고 있다(Figure 1). AKI stage 1 중에 좀 더 경미한 크레아티닌의 상승인 0.3mg/dL 이상 혹은 상대적으로 25% 이상의 상승(일반적인 CIN의 정의에 따라)이 어떤 영향을 미칠 것인가에 대한 분석이 없는 점은 아쉽다.

AKI stage 1 조차도 장기 예후에 큰 영향을 끼치므로, 이에 대한 철저한 예방은 중요하다. 구체적 방법으로는 우선 기전 신장 기능이 저하된 환자, 고령의 환자, 당뇨병 환자와 같은 조영제 유발 신기능 저하의 위험성이 높은 경우에 불필요한 조영제 투여 검사/시술을 삼가해야 하

Figure 1. Cumulative incidence of (A) mortality, (B) ESRD, and (C) hospitalization for all causes according to stage of AKI



AKI is defined according to Acute Kidney Injury Network criteria(AKI stage 1, ≥0.3mg/dL absolute or 1.5- to 2.0- fold relative increase in serum creatinine; AKI stage 2, >2- to 3-fold increase in serum creatinine; AKI stage 3, >3-fold increase in serum creatinine or serum creatinine ≥4.0mg/dL with an acute rise of >0.5mg/dL)

겠다. 또한, 검사 전 신독성이 있는 약제들을 미리 중단하며 되도록 최소한의 조영제를 사용하여야 한다. 되도록 혈장과 삼투압이 같은 등장성(iso-osmolar) 조영제나 저장성(low-osmolar) 조영제를 사용하여야 하겠고 예방적 약물요법으로는 충분한 수액 공급이 가장 중요하다. 즉, 심부전이 없다면 검사 12시간 전, 후로 1mL/kg/hr의 속도로 0.9% saline을 정맥으로 투여한다. 저렴하고 쉽게 구할 수 있으며 부작용이 거의 없는 항산화제인 N-acetylcysteine(NAC) 1,200mg po bid를 검사 전후로 각각 2회씩, 총 4회 경구 투여하는 것도 고려해 볼 수 있다.

비록, 본 연구는 후향적 코호트 연구라는 단점이 있지만, 약 15,000명의 대규모 환자를 대상으로 3년간 관찰하였다는 데에 큰 의미가 있다. 조영제에 의한 신기능 부전이 총 사망은 물론, 투석이 필요한 말기 신부전으로의 악화와 반복되는 입원의 독립적 위험인자라는 것을 밝힌 매우 의미 있는 연구이다. 향후, 대규모 전향적 연구가 나온다면 보다 명확한 결론에 도달할 수 있을 것이다.