Renal recovery and long-term survival following acute kidney injury after coronary artery surgery: a nationwide study

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Background: Acute kidney injury (AKI) is a relatively common complication following CABG and is associated with adverse outcomes. Nonetheless, we hypothesized that the majority of patients make a good long-term recovery of their renal function. We studied the incidence and risk factors of AKI together with renal recovery and long-term survival in patients who developed AKI following CABG.
Methods: This nationwide study examined AKI among 1754 consecutive patients undergoing CABG in 2001–2013. AKI was defined according to the KDIGO criteria.
Results: Postoperatively 184 (11%) patients developed AKI; 121 (7%), 27 (2%), and 36 (2%) at stages 1, 2, and 3, respectively. AKI was an independent risk factor for chronic kidney disease (CKD) and AKI patients had worse post-operative outcomes. Lower pre-operative glomerular filtration rate, higher EuroSCORE and BMI, diabetes, reoperation, and units of red blood cells transfused were independent risk factors of AKI. At post-operative day 10, renal recovery rates, defined as serum creatinine ratio <1.25 of baseline, were 96 (95% CI 91–99%), 78 (95% CI 53–90%), and 94% (95% CI 77–98%) for AKI stages 1, 2, and 3, respectively. Long-term survival was predicted by AKI with 10-year survival of patients without AKI being 76% and those with AKI stages 1, 2, and 3 being 63%, 56%, and 49%, respectively ($P < 0.001$).
Conclusion: Depending on the severity of the initial AKI, 78–97% of patients made good recovery of their kidney function. However, AKI was significantly linked to progression to CKD and long-term survival remained markedly affected by the severity of the initial kidney injury.

Editorial comment: what this article tells us
In this single-center study, long-term recovery of renal function after acute perioperative kidney injury was examined in a cohort of coronary revascularization subjects. The findings confirmed that perioperative kidney injury in some leads to chronic kidney disease, and the severity of the perioperative injury is associated with less favorable long-term survival.

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Acute kidney injury (AKI) is a severe complication of open heart surgery and a well-established risk factor for worse post-surgical outcome, including infections, prolonged intensive care unit (ICU) stay, and increase in long-term mortality.[1–4] Multiple risk factors for cardiac surgery-associated AKI (CS-AKI) have been reported, such as emergency surgery, chronic kidney disease (CKD), the female sex, age, and diabetes.[4–8] Nonetheless, despite increasing understanding of the pathophysiology of AKI and advances in surgical techniques, anesthesia, and ICU management, effective therapeutic interventions are lacking.[9–12] Therefore, identifying patients at risk and optimization of their overall clinical condition remains important concerning post-operative kidney function.

Most previous studies of CS-AKI have reported on short-term complications and survival, but the focus has been shifting to the impact AKI may have on long-term outcome. Several studies have indicated that early recovery of renal function is associated with better short- and long-term survival following AKI.[13,14] However, no uniform agreement exists on the definition of renal recovery following AKI and existing definitions have their various shortcomings. For example, renal recovery defined as independence from dialysis only involves those with the most severe forms of AKI. As less severe AKI has also been shown to significantly affect morbidity and mortality, definitions that utilize absolute and relative reduction in serum creatinine (SCr), generally to within 1.1- to 1.5-fold the baseline SCr value, have emerged. The main problem with such definitions is that baseline SCr is frequently lacking.

In this study, we sought to test our hypothesis that the majority of patients who experience AKI following CABG recover their renal function. Furthermore we hypothesized that those who survived the first 90 days after the insult would follow the same survival curve as those who did not suffer perioperative AKI. We determined the incidence and risk factors of CS-AKI following CABG and sought to shed light on the association between AKI and post-operative outcomes, especially long-term survival. Furthermore, we aimed to evaluate rates of renal recovery and the effect it has on the development and progression of CKD and the requirement for renal replacement therapy (RRT), even many years after cardiac surgery. We achieved this by using centralized registries representing a large non-selective nationwide cohort of patients, with widely available baseline SCr values, who underwent surgical myocardial revascularization.

Methods

This was a retrospective study of all patients who underwent isolated CABG at the Landspitali University Hospital in Reykjavik from January 1, 2001 to December 31, 2013. The study was approved by the Icelandic National Bioethics Committee (VSN2010010009/03.7) and the Icelandic Data Protection Authority.

Patients were identified through two separate registries, a computerized surgical registry at Landspitali University Hospital and a centralized cardiac surgery database. A 100% match between databases was confirmed. Pre-operative clinical data were collected from patient medical records and centralized surgical registries and perioperative data were collected from surgical and anesthesiology reports.

All SCr measurements performed at all major clinical laboratories in Iceland were obtained from several electronic databases. Baseline SCr was selected as the closest pre-operative SCr value ≤30 days prior to surgery. Estimated glomerular filtration rate (eGFR) was calculated from standardized SCr measurements using the CKD-EPI equation.[15] CKD was defined as eGFR ≤ 60 ml/min/1.73 m^2 and staged according to the KDOQI classification system.[16]

Patients were categorized as AKI or non-AKI according to the KDIGO criteria.[17] In accordance, severity of AKI was classified as stage 1 (SCr increase of ≥26.5 μmol/l above baseline within 48 h or 1.5–1.9 times baseline ≤7 days), stage 2 (SCr 2.0–2.9 times baseline ≤7 days), and stage 3 (≥3 times baseline ≤7 days, ≥354 μmol/l and a SCr rise of ≥26.5 μmol/l ≤48 h/≥1.5 rise of SCr from baseline ≤7 days or initiation of RRT). Renal recovery following AKI was defined as a reduction in SCr to <1.25 times baseline SCr. Pre-operative anemia was defined as hemoglobin level <120 mg/dl in females and <135 mg/dl in males.

Information on mortality was collected from Statistics Iceland, the Icelandic population registry, which has been shown to be a reliable register, not least due to negligible population migration. Data regarding long-term RRT was obtained from the Icelandic End-Stage Renal Disease Registry. The last survival follow-up date was June 30, 2014 and last follow-up of SCr values was performed on June 15, 2015.

Clinical features were characterized according to the New York Heart Association and Canadian Cardiac Society classification systems and standard European System for Cardiac Operative Risk Evaluation (EuroSCORE) score calculated.[18] Post-operative complications were categorized as minor or major (see Table 2).

Statistical analysis

Data collection was performed using a standardized Excel (Microsoft Corp., Redmond, WA, USA) data sheet. All data analysis was done using the R statistical analysis software, version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria) using the survival, MASS, stargazer, ggplot2, Gmisc, epitools, Greg, epicalc, and pscl packages.

Continuous variables were compared with Welch's *t*-test or Mann–Whitney test based on normality of the data and categorical variables using either Fisher's exact or chi-square tests. Using significant variables from the univariate analysis, a multivariate logistic regression model with backward elimination was constructed to identify independent risk factors for AKI and mortality. Variables with *P*-values <0.1 together with variables judged to be of clinical importance were used as predictor variables. The final model for evaluating pre-operative risk factors of AKI was corrected for age, sex, body mass index (BMI), history of hypertension, diabetes and heart failure, pre-operative eGFR, emergent surgery, and EuroSCORE. The model for evaluation of intra- and post-operative variables was adjusted for total operative time, intraoperative use of inotropes, red blood cell (RBC) transfusions (per unit) intraoperatively and in the first post-operative week, reoperation for bleeding as well as post-operative complications that were significant in univariate analysis (as seen in Table 2). Poisson regression analysis was used to evaluate incidence trends over time. A Cox proportional hazard model was employed to assess the contribution of variables to long-term survival and renal recovery and all variables in the final models met the requirements of proportionality when tested according to the method of Grambsch and Therneau.[19] The final model was corrected for KDIGO stage of AKI, age, sex, EuroSCORE, and major complications. The Kaplan–Meier method was used to graphically illustrate survival and renal recovery. Groups were compared using a Cox proportional hazards model. The level of statistical significance was set at $P < 0.05$.

Results

Incidence of AKI

In total, 1754 patients underwent on-pump CABG or off-pump coronary artery bypass (OPCAB) surgery during the period, 82% of whom were male. The majority [1385 (79%)] underwent CABG and the remainder OPCAB [including 40 patients who were converted to CABG (intention-to-treat)]. Excluded were 35 patients missing baseline SCr, seven patients lacking post-operative values, as well as two patients with ESRD who were receiving hemodialysis pre-operatively.

Of the 1710 patients who comprised the study population, 184 (11%) experienced AKI; 121 (7%) patients had stage 1; 27 (2%), stage 2; and 36 (2%), stage 3 AKI. A decrease was seen in incidence over the study period ($P = 0.01$). The median duration of AKI (defined as SCr $\geq$ 1.5 times baseline SCr) was 2 days and the mean duration 8 ± 33 days. The average peak SCr in the first post-operative week was 177 ± 101 μmol/l and occurred 3 ± 2 days following surgery. On average, SCr was measured 6 ± 1 times in the first post-operative week.

Pre-operative characteristics

Pre-operatively, 236 (14%) patients had CKD, of whom 154 (65%) had stage 3A, 62 (26%) stage 3B, 17 (7%) stage 4, and three (1%) had stage 5 CKD. Of the patients who experienced AKI 60 had pre-existing CKD; 32 (53%) had stage 3A, 19 (32%) stage 3B, 8 (13%) stage 4, and one (2%) had stage 5 CKD. As shown in Table 1, patients who experienced AKI were older, had higher pre-operative risk assessment scores, and were 2.5 times more likely to have undergone emergent surgery.

Table 1 Baseline characteristics of patients who did or did not develop AKI according to the KDIGO* criteria.

	Total n = 1710	Non-AKI n = 1526	AKI n = 184
Age, years	66 ± 9	66 ± 9	69 ± 10
Male	1398 (82)	1252 (82)	146 (79)
BMI, kg/m^2	28 ± 4	28 ± 4	29 ± 5
No. of stenotic coronary arteries	3 ± 1	3 ± 1	3 ± 0
Family history of IHD	883 (55)	793 (55)	90 (51)
Smoking	1080 (63)	969 (64)	111 (60)
Hypertension	1108 (65)	984 (64)	124 (69)
Diabetes	270 (16)	225 (15)	45 (25)
Dyslipidemia	966 (58)	858 (58)	108 (60)
Statin use	1283 (78)	1139 (78)	144 (81)
History of MI	383 (23)	331 (22)	52 (29)
History of PCI	357 (21)	314 (21)	42 (23)
Pre-operative CCS score			
0	11 (1)	11 (1)	0 (0)
1	83 (5)	77 (5)	6 (3)
2	324 (19)	302 (20)	22 (12)
3	548 (32)	487 (32)	61 (33)
4	723 (43)	629 (42)	94 (51)
History of HF	158 (9)	136 (9)	22 (12)
Pre-operative LVEF, %	55 ± 10	55 ± 10	55 ± 12
Pre-operative NYHA score			
0	185 (13)	175 (14)	10 (7)
1	98 (7)	90 (7)	8 (5)
2	363 (26)	336 (27)	27 (18)
3	473 (34)	411 (33)	62 (42)
4	289 (21)	249 (20)	40 (27)
History of arrhythmia	174 (10)	155 (10)	19 (10)
Pre-existing CKD	236 (14)	176 (12)	60 (33)
Pre-operative SCr, μmol/l	91 ± 31	90 ± 25	95 ± 39
Pre-operative eGFR, ml/min/1.73 m^2	82 ± 19	83 ± 18	72 ± 23
Pre-operative eGFR, ml/min/1.73 m^2			
≥90	649 (38)	607 (40)	42 (23)
60–89	825 (48)	743 (49)	82 (45)
45–59 (CKD stage 3A)	154 (9)	122 (8)	32 (17)
30–44 (CKD stage 3B)	62 (4)	43 (3)	19 (10)
15–29 (CKD stage 4)	17 (1)	9 (1)	8 (4)
<15 (CKD stage 5)	3 (0)	2 (0)	1 (1)
COPD	120 (7)	106 (7)	14 (8)
Pre-operative hemoglobin (g/mdl)	141 ± 14	142 ± 14	135 ± 16
Emergency surgery	80 (5)	61 (4)	19 (10)
Pre-operative MI	466 (27)	405 (27)	61 (33)
Pre-operative HF	231 (14)	193 (13)	38 (21)
EuroSCORE	5 (±3)	5 (±3)	6 (±4)

*KDIGO stages: Stage 1 = increase in SCr of ≥26.5 μmol/l within 48 h or 1.5–1.9× baseline ≤7 days; stage 2 = increase in SCr to 2–2.9× baseline ≤7 days; stage 3 = increase in SCr to 3× baseline ≤7 days or ≥354 μmol/l and a SCr rise of ≥26.5 μmol/l ≤48 h/≥1.5 rise of SCr from baseline ≤7 days or initiation of renal replacement therapy. Mean and standard deviations are shown for continuous variables and percentages are shown within parenthesis. AKI, acute kidney injury; BMI, body mass index; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; EuroSCORE, European System for Cardiac Operative Risk Evaluation; HF, heart failure; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SCr, serum creatinine.

Table 2 Perioperative factors and post-operative complications of patients who did or did not develop AKI according to the KDIGO* criteria.

	Total n = 1710	Non-AKI n = 1526	AKI n = 184	P-value
Surgical procedure: CABG vs. OPCAB	1350 (79)	1202 (79)	148 (80)	0.63
CPB time, min	91 ± 34	89 ± 31	104 ± 50	0.0004
Cross-clamp time, min	47 ± 17	47 ± 17	50 ± 23	0.25
Total operative time, min	212 ± 57	211 ± 54	224 ± 74	0.041
Use of IABP	92 (5)	76 (5)	16 (9)	0.054
Use of intraoperative inotropes	885 (53)	776 (52)	109 (60)	0.028
Post-operative bleeding, mL	985 ± 1018	942 ± 636	1341 ± 2478	0.002
§RBC transfusion, units	3 ± 4	2 ± 3	6 ± 7	<0.0001
ICU stay, days	2 ± 3	2 ± 3	3 ± 6	0.0001
Total hospital stay, days	11 ± 8	11 ± 7	14 ± 12	<0.0001
Death < 30 days	40 (2)	24 (2)	16 (9)	<0.0001
RRT for AKI	19 (1)	0 (0)	19 (10)	<0.0001
Post-operative SCr, umol/l	102 ± 55	98 ± 44	137 ± 105	<0.0001
ESRD requiring RRT	5 (0)	4 (0)	1 (1)	0.43
†All major complication	183 (11)	144 (10)	39 (21)	<0.0001
Stroke	9 (1)	8 (1)	1 (1)	1
Mediastinitis	17 (1)	15 (1)	2 (1)	0.7
Myocardial infarction	82 (5)	66 (4)	16 (9)	0.016
Reoperation due to bleeding	118 (7)	95 (6)	23 (13)	0.003
Sternum dehiscence	26 (2)	21 (1)	5 (3)	0.19
ARDS or MOF	53 (3)	35 (2)	18 (10)	<0.0001
‡All minor complication	834 (49)	723 (48)	111 (60)	0.001
Post-operative atrial fibrillation	671 (39)	574 (38)	97 (53)	0.001
Leg wound infection	179 (11)	159 (10)	20 (11)	0.8
Urinary tract infection	59 (4)	50 (3)	9 (5)	0.28
Pleural effusion	191 (11)	160 (11)	31 (17)	0.013
Pneumonia	113 (7)	94 (6)	19 (10)	0.04

*KDIGO stages: Stage 1 = increase in SCr of ≥26.5 μmol/l within 48 h or 1.5–1.9× baseline ≤7 days; stage 2 = increase in SCr to 2–2.9× baseline ≤7 days; stage 3 = increase in SCr to 3× baseline ≤7 days or ≥354 μmol/l and a SCr rise of ≥26.5 μmol/l ≤48 h/≥1.5 rise of SCr from baseline ≤7 days or initiation or initiation of renal replacement therapy. †Stroke, mediastinitis, myocardial infarction (defined as isolated ST segment changes or a new left bundle branch block on electrocardiogram along with an elevation of CK-MB of ≥70 μg/l), reoperation due to bleeding, sternum dehiscence and acute respiratory distress syndrome or multiorgan failure. ‡Atrial fibrillation, leg wound infection, urinary tract infection, pleural effusion and pneumonia. §Units of RBC transfused intraoperatively and during the first post-operative week. Mean and standard deviations are shown for continuous variables and percentages are shown within parenthesis. AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; CABG, coronary artery bypass grafting, CPB, cardiopulmonary bypass; ESRD, end-stage renal disease; IABP, intra-aortic balloon pump; ICU, intensive care unit; MOF, multiorgan failure; OPCAB, off-pump coronary artery bypass; RBC, red blood cell; RRT, renal replacement therapy; SCr, serum creatinine.

Intra- and post-operative characteristics

Table 2 shows intra- and post-operative characteristics and complications. Patients who experienced AKI had longer surgical times and were likelier to have received inotropes intraoperatively. No difference was observed between the groups with respect to operation type (on- or off-pump). Patients in the AKI group received on average three times as many units of packed RBCs (6 vs. 2 units; $P < 0.001$) and were twice as likely to undergo reoperation due to bleeding (12 vs. 6%; $P = 0.003$). AKI patients had longer post-operative ICU and in-hospital stays and were 10 times as likely to have required dialysis ≤30 days from surgery ($P < 0.001$), either continuous RRT or intermittent hemodialysis. AKI was independently associated with both minor and major complications with an OR of 1.78 (95% CI 1.29–2.47; $P < 0.001$) and 2.49 (95% CI 1.65–3.76; $P < 0.001$), respectively. Post-operatively, 19 patients (1%) received transient RRT. However, only five of the 1668 patients (0.2%) who were discharged from hospital progressed to end-stage renal disease (ESRD) requiring maintenance dialysis. One of those five patients received RRT in the immediate post-operative period.

Risk factors for AKI

The following independent risk factors for AKI were identified: lower pre-operative eGFR (OR 0.97, 95% CI 0.96–0.98; $P < 0.001$), higher BMI (OR 1.04, 95% CI 1–1.08; $P = 0.037$), diabetes (OR 1.66, 95% CI 1.11–2.47; $P = 0.016$), higher EuroSCORE (OR 1.11, 95% CI 1.06–1.16; $P < 0.001$), number of units of packed RBCs transfused intraoperatively and during the first post-operative week (OR 1.17, 95% CI 1.12–1.24; $P < 0.001$ per unit), and reoperation due to bleeding (OR 0.37, 95% CI 0.15–0.93; $P = 0.024$) (Tables 3 and 4). After excluding those who required reoperation due to bleeding, transfusion continued to be associated with risk of AKI (OR 1.29, 95% CI 1.2–1.39, $P < 0.001$).

Renal recovery and long-term kidney function

Post-operative SCr value follow-up for at least 60 days after surgery was achieved in 1516 (88.7%) of the patients. Of the 194 patients who did not have available follow-up SCr values, 18 had died during the period and 13 were lost to long-term follow-up. Out of the 163 remaining patients who had follow-up data for survival analysis, but not SCr values for evaluation of kidney function, 23 had been diagnosed with AKI (9, 8 and 6 patients with AKI stage 1, 2 and 3, respectively), leaving 87.5% of the 184 patients who developed post-operative AKI, available for follow-up of kidney function.

At post-operative day 10 renal recovery rates, defined as SCr ratio <1.25 of baseline, were 96 (95% CI 91–99%), 78 (95% CI 53–90%), and 94% (95% CI 77–98%) for AKI stages 1, 2, and 3, respectively (Fig. 1). At 20 days, the recovery rates in stages 2 and 3 rose further to 96% (95% CI 70–99%) and 94% (95% CI 77–98%), respectively. Mean follow-up time for evaluation of kidney function was 62 ± 47 months. A total of 348 incident cases of CKD (4/100 patients years)

Table 3 Multivariate logistic regression analysis for pre-operative risk factors of AKI after CABG ($r^2 = 0.516$).

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P*-value
BMI (kg/m^2)	1.04 (1.01–1.08)	1.04 (1–1.08)	0.037
Diabetes	1.94 (1.34–2.82)	1.66 (1.11–2.47)	0.016
Pre-operative mean eGFR, ml/min/ 1.73 m^2	0.97 (0.96–0.98)	0.97 (0.96–0.98)	<0.001
EuroSCORE	1.08 (1.01–1.15)	1.11 (1.06–1.16)	<0.001

AKI, acute kidney injury; BMI, body mass index; eGFR, estimated glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation.

Table 4 Multivariate logistic regression analysis for intra- and post-operative risk factors of AKI after CABG ($r^2 = 0.42$).

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P*-value
*RBC transfusions, units	1.19 (1.13–1.25)	1.23 (1.16–1.31)	<0.001
Reoperation due to bleeding	2.07 (1.09–3.94)	0.37 (0.15–0.93)	0.024

*Units of RBC transfused intraoperatively and during the first post-operative week. CABG, coronary artery bypass grafting; RBC, red blood cell.

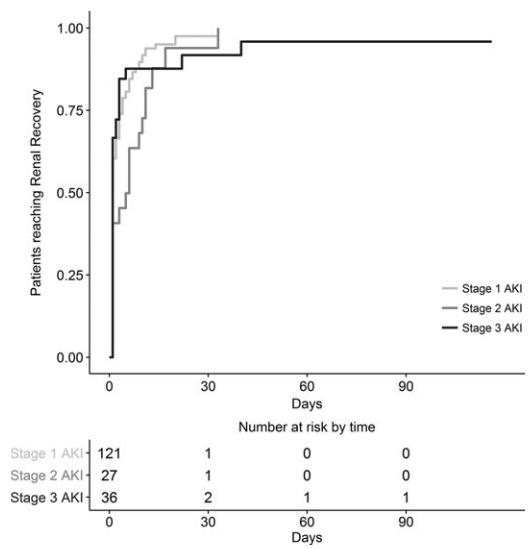

Fig. 1. Post-operative follow-up of kidney function in patients who experienced AKI. Shown is the proportion of patients who recovered renal function (defined as reduction in serum creatinine <1.25 baseline) in the post-operative period, divided for AKI stages 1–3.

were noted during follow-up and in the AKI group 60 patients (33%) developed CKD compared with 288 (19%) in the non-AKI group ($P < 0.001$). AKI was found to be a significant risk factor for development of CKD (HR 2.08, 95% CI 1.49–2.9; $P < 0.001$) but not ESRD (HR 2.74, 95% CI 0.28–26.46; $P = 0.427$). Regression analysis showed that when patients who achieved reduction to SCr to <1.25 times baseline were compared with those who did not, the aforementioned group had a higher probability of long-term survival (OR 0.38, 95% CI 0.2–0.73; $P = 0.004$ vs. OR 0.16, 95% CI 0.06–0.39; $P < 0.001$, respectively).

Survival

Thirteen patients were lost to long-term follow-up and 40 patients died ≤30 days of surgery. Death ≤30 days was significantly higher in the AKI group compared the non-AKI group, 8.7% (16/184) vs. 1.6% (24/1526) ($P < 0.001$) (Table 2). Furthermore, mortality rates ≤30 days increased with severity of AKI, being 6.6% (8/121), 11.1% (3/27), and 13.4% (5/36) for stages 1, 2, and 3, respectively ($P < 0.001$).

Mean follow-up time of survival was 75 ± 43 months and a Kaplan–Meier survival curve is seen in Fig. 2. Survival was inversely related to the severity of AKI and the 10-year survival of patients without AKI was 76% and those with AKI stages 1, 2, and 3 was 63%, 56%, and 49%, respectively ($P < 0.001$). When the sub-classifications of AKI were analyzed only the difference in stage 3 AKI was significant ($P < 0.001$). When patients without AKI were excluded from analysis the difference between stage 1 and stage 3 remained significant ($P = 0.003$).

Patients with AKI had more than twofold higher risk of death as compared with patients with normal post-operative kidney function (unadjusted HR 2.23, 95% CI 1.69–2.96; $P < 0.001$) and the risk correlated with severity of AKI (unadjusted HR 1.81, 95% CI 1.26–2.59; $P = 0.001$, unadjusted HR 2.03, 95% CI 1.05–3.96; $P = 0.037$ and unadjusted HR 4.44, 95% CI 2.74–7.17; $P < 0.001$, for AKI stages 1, 2, and 3, respectively). As shown in Table 5, stage 3 AKI was an independent risk factor for mortality (HR 2.02, 95% CI 1.22–3.33; $P < 0.001$).

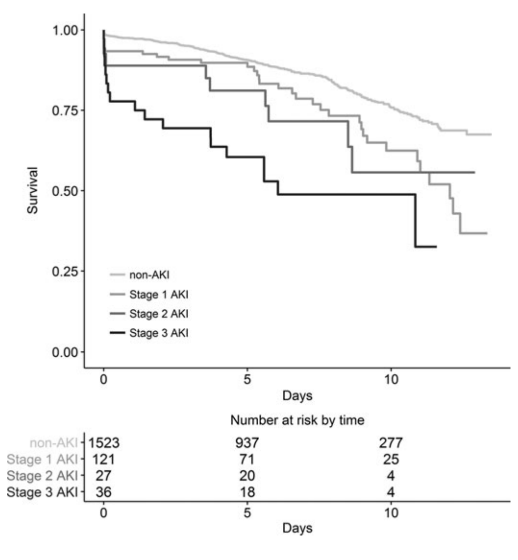

Fig. 2. Kaplan–Meier survival curves comparing survival of patients with normal postoperative kidney function and AKI stages 1–3.

Discussion

In the present study, approximately one in every 10 patients developed AKI following CABG. However, the majority recovered their renal function within a few days and those patients that did recover renal function had better long-term survival. At post-operative day 10, renal recovery rates were 96%, 78%, and 94% AKI stages 1, 2, and 3, respectively. We found AKI to be an independent risk factor for incident chronic kidney disease but no significant effect was seen with regard to progression to ESRD.

Table 5 Multivariate Cox regression analysis of risk factors associated with long-term mortality after CABG ($r^2 = 0.133$).

	HR (95% CI)	*P*-value
AKI		
Stage 1	1.42 (0.99–2.04)	0.059
Stage 2	1.65 (0.84–3.22)	0.143
Stage 3	2.02 (1.22–3.33)	<0.001
Age (per year)	1.02 (1.01–1.04)	<0.001
EuroSCORE	1.22 (1.18–1.26)	<0.001
Major complication	1.86 (1.40–2.48)	<0.001

AKI, acute kidney injury; CABG, coronary artery bypass grafting; EuroSCORE, European System for Cardiac Operative Risk Evaluation.

Long-term survival was predicted by, and inversely related to, the severity of AKI.

Independent risk factors for AKI were pre-operative eGFR, EuroSCORE, BMI, diabetes, reoperation due to bleeding, and units of RBC transfused. Patients who developed AKI had more pronounced comorbidities and were likelier to be unstable at the time of surgery. However, even after correcting for pre-operative clinical characteristics, patients that suffered AKI remained likelier to experience post-operative complications, had longer hospital and ICU stay, and higher 30-day mortality.

The reported incidence of AKI in our study was in the lower range of previously reported rates of AKI following CABG, which for the most part range from approximately 20–45%.[20,21] As Landspitali University Hospital is the sole institution performing open heart surgery in Iceland, the study represents a cohort of over 300,000 individuals for 13 years which may be considered, from most aspects of healthcare, similar to the majority of other Western countries. However, age, female sex, and diabetes are known independent risk factors of AKI and, thus, the relatively low average age, high proportion of male patients and low prevalence of diabetes in our study may contribute to the low incidence of AKI. Furthermore, it should be noted that detailed information on urine output was not available for a significant number of patients. Therefore the diagnosis and staging of AKI was solely based on the SCr component of the KDIGO criteria. A recent publication by Kellum et al. suggests that this might lead to underestimation of the incidence of AKI. However, in that study, patients diagnosed with AKI based only on urine output had a milder disease and proved to have the same mortality as those not diagnosed with AKI.[22]

An overall decreasing trend of AKI incidence was seen during the period. The reason behind this is not clear and possibly multifactorial, e.g. improved perioperative care, implementation of lung-protective ventilation strategies in the operating room, more aggressive treatment of patients with sign of infection, and increased awareness of AKI following the publication of consensus criteria for the definition of AKI.

Some previously identified risk factors, such as age and emergent surgery, did not emerge as independent risk factors in the present study, possibly due to inadequate power or variable confounding. However, in line with numerous other studies, we found a significant relationship between the number of units RBC transfused and risk of AKI.[23,24] The reasons for this relationship are believed to be complex but the pro-inflammatory effect of transfusions and promotion of oxidative stress have been suggested.[25,26] Although the observational nature of our study precludes the determination of a causal relationship these findings might suggest that CABG patients' kidney function could benefit from a more restrictive blood transfusion strategy. Nonetheless, in light of the prospective study by Murphy et al., it should also be kept in mind that higher transfusion rates in the group with AKI might be associated with a higher pre-operative comorbidity burden, rather than transfusions directly contributing to risk of AKI.[27]

There remains a paucity of studies exploring the impact of recovery of renal function following an episode of AKI, as data on the subject is often missing in previous publications. Furthermore, comparison of studies examining the effect of renal recovery on long-term outcomes of patients has been complex, as highly variable definitions of renal recovery have been used. These including different SCr cut-off values, 24 h urinary creatinine clearance assessment and freedom from dialysis.[28–30] As less severe AKI also has a significant effect on morbidity and mortality, we chose to define renal recovery as a relative reduction in serum creatinine (SCr). This was possible due to the fact that cohort baseline SCr values were available for 97.5% of patients. Furthermore, follow-up of kidney function was possible in almost 90% of the total study population and in 87.5% of the group who suffered AKI. This was possible due to centralized nationwide databases recording SCr and hemodialysis need. Nonetheless, as mentioned earlier, limited power could have affected some of the findings in the present study, with the risk of type II error. For instance, recovery after stage 2 AKI appeared to be poorer than after grade 1 and 3. However, it may also be speculated that patients classified into stage 3 AKI due to dialysis treatment or relatively little "extra" kidney dysfunction (i.e., increase of SCr to ≥354 μmol/l in patients with CKD) would not subsequently need to drastically improve their kidney function to near normalize to pre-operative SCr levels.

Regression analysis showed that patients that achieved renal recovery had a higher probability of long-term survival as compared to those who did not. To our knowledge, the present study is the first to examine the effect of renal recovery on long-tem survival in a nationwide cohort with such extensive follow-up. However, prospective studies are warranted to better characterize the impact of post-operative AKI and renal recovery on the development of incident CKD and survival.

Severe AKI requiring RRT following cardiac surgery is associated with poor outcome.[31] In our study, 19 patients (1%) needed dialysis in the post-operative period and five patients (0.3%) progressed to ESRD requiring a maintenance dialysis, which is a relatively low proportion when compared with various other studies.[31–33] Only one of these five aforementioned patients had experienced post-operative AKI and the numbers of patients is too small to draw conclusions regarding the effect of AKI on the development to ESRD requiring hemodialysis.

Our study showed a 10-year survival of 76% in patients who did not suffer AKI and 63%, 56%, and 49% in patients with post-operative AKI stages 1, 2, and 3, respectively. Stage 3 AKI was an independent risk factor of mortality but stages 1 and 2 were not found to be independent predictors of long-term mortality, possibly due to lack of statistical power. This variability in survival might also result from a stronger effect of other variables in our multivariate regression model than milder forms of kidney dysfunction.

Although our study shows a clear association between AKI and adverse outcomes causality cannot be determined based on our outcomes. The development of AKI may indeed be a surrogate marker of low physiological reserve that identifies patients who are at higher risk of morbidity and mortality. Nonetheless, AKI remains a costly complication linked to inferior long-term outcomes and our results further highlight the need for better interventions to prevent or ameliorate this disorder.[34]

The main limitation of this study was the retrospective observational design. As mentioned previously, the strength of our study is the availability of all SCr measurements from hospitals and private clinics in Iceland, including baseline SCr values. Another strength is the comprehensive follow-up data, both regarding survival and kidney function. In addition, all patients underwent CABG surgery in a single center, decreasing the risk of referral bias. What is more the size and nationwide nature of our study, as well as large number of recorded variables helps to reduce confounding.

In summary, the majority of patients in our study had nearly recovered their kidney function at 10 days after CABG. Nonetheless, acute kidney injury remained a significant risk factor for chronic kidney disease. However, only five patients progressed to end-stage renal disease requiring hemodialysis during long-term follow-up.

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