Acute Kidney Injury Following Coronary Artery Bypass Surgery and Long-term Risk of Heart Failure

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Background—Acute kidney injury (AKI) after coronary artery bypass grafting (CABG) is common and increases the risk of postoperative complications and mortality. There is little information on the association between AKI after CABG and long-term risk of incident heart failure (HF).

Methods and Results—All patients (n=24 018) undergoing primary, isolated CABG in Sweden between 2000 and 2008 with complete information on pre- and postoperative serum creatinine values, and no prior hospitalization for HF were included. The postoperative increase in serum creatinine was used to define different stages of AKI: stage 1, 0.3 to 0.5 mg/dL; stage 2, 0.5 to 1 mg/dL; stage 3, >1 mg/dL. Hazard ratios with 95% confidence intervals were calculated for first hospitalization for HF for each stage of AKI using Cox proportional hazards regression. Twelve percent of the study population developed AKI. During a mean follow-up of 4.1 years, there were 1325 cases (5.5%) of incident HF. Hazard ratios with 95% confidence interval for HF in AKI stage 1, 2, and 3 were 1.60 (1.34–1.92), 1.87 (1.54–2.27), and 1.98 (1.53–2.57), respectively, after multivariable adjustment for age, sex, diabetes mellitus, estimated glomerular filtration rate, left ventricular ejection fraction, and myocardial infarction before surgery or during follow-up.

Conclusions—AKI is associated with increased long-term risk of HF after CABG. Patients with AKI after CABG should be followed closely to detect early changes in cardiac function. (Circ Heart Fail. 2013;6:83-90.)

Key Words: acute kidney injury ■ coronary artery bypass grafting ■ heart failure

Clinical Perspective on p 90

Heart failure (HF) is a highly prevalent syndrome with a poor prognosis, resulting in substantial morbidity and reduced quality of life despite recent advances in treatment. Also, HF is the most common cause of hospital admission in the United States and Europe, and HF hospitalization per se is linked to adverse outcome and high-treatment costs. HF is closely interrelated with kidney dysfunction. Both conditions share risk factors, such as hypertension, diabetes mellitus, and ischemic heart disease, and may promote the progression of the other. The coexistence of kidney and heart disease is known as the cardiorenal syndrome. Five different subtypes of cardiorenal syndrome have been described based on the different modes of pathological interaction between the kidney, and heart where acute or chronic dysfunction in one organ results in acute or chronic dysfunction in the other.

Although the general relationship between chronic kidney disease (CKD) and chronic HF has received considerable attention in the literature, studies investigating the impact of AKI on the development of HF are scarce and in the context of cardiac surgery has never been examined. This study aimed to describe the risk of first hospitalization for HF in relation to AKI in a large nationwide cohort of patients who underwent a first isolated CABG.

 Methods

Study Population

All patients who underwent CABG between January 1, 2000 and December 31, 2008 in Sweden were eligible for the study. The patients were identified from the Swedish Web-system
for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) register, where all patients undergoing cardiac surgery in Sweden have been registered since 1992. The register contains information on patients’ medical history and a number of pre, peri- and postoperative variables. The agreement between information contained in medical records and the register has been estimated to 93% to 95%.

Patients were excluded from the study if they had undergone previous cardiac surgery; underwent other than isolated CABG during the operation; had missing pre- or postoperative SCr; died within 30 days of surgery; had a history of previous hospitalization for HF were diagnosed with myocardial infarction within 14 days before surgery; undertook CABG within 24 hours from decision; had an estimated glomerular filtration rate (eGFR) <15 mL/min per 1.73 m²; or they were diagnosed with HF within 30 days of surgery. The numbers of patients excluded are presented in Figure 1. The study complied with the Declaration of Helsinki and was approved by the regional ethics committee in Stockholm, Sweden.

Definitions

Pre- and postoperative SCr values were used to define AKI. The preoperative SCr value was normally taken within 24 hours before surgery. The postoperative SCr value recorded was the highest value observed during the entire postoperative period. AKI was classified into 3 stages according to absolute increases in postoperative SCr values: stage 1, 0.3 to <0.5 mg/dL (26 to <44 µmol/L); stage 2, 0.5 to <1 mg/dL (44 to <88 µmol/L); and stage 3, ≥1 mg/dL (≥88 µmol/L). The reference group was defined as an increase of <0.3 mg/dL (<26 µmol/L) or a decrease in postoperative SCr. The classification has been used in a recently published study and is based on AKI network criteria and traditional definitions.

Glomerular filtration rates were estimated using the simplified Modification of Diet in Renal Disease study equation. Diagnosis of hypertension, hyperlipidemia, chronic obstructive pulmonary disease, and diabetes mellitus were made on the basis of patients’ ongoing pharmacological treatment for these illnesses. Peripheral vascular disease was defined as previous surgery to the abdominal aorta, iliac artery or carotid artery, or the presence of claudication. Left ventricular function was assessed by echocardiography before surgery and categorized as normal (ejection fraction >50%), reduced (ejection fraction 30%–50%), or severely reduced (ejection fraction <30%).

Outcome

The primary study outcome was a first hospitalization for HF defined as a primary discharge diagnosis of HF in the Swedish National Inpatient Register, where patients hospitalized in Sweden have been registered since 1964. This register covers the whole country since 1987. This register was also used to ascertain information about illnesses before surgery. The validity of the diagnosis HF in this register has been shown to be 95% if it is the principal cause of hospitalization.

A secondary outcome was a composite of first hospitalization for HF or death from any cause. The date of death was obtained from the Swedish Cause-of-Death register, where all deaths of persons residing in Sweden are registered.

Data from SWEDEHEART, the Inpatient Register, and the Cause-of-Death Register were linked by the National Board of Health and Welfare, using the unique personal identification number that is assigned to each permanent resident of Sweden. Follow-up began 30

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**Figure 1.** Selection criteria for the study population consisting of 24,018 patients undergoing primary isolated coronary artery bypass grafting (CABG) between January 1, 2000 and December 31, 2008 in Sweden. GFR indicates glomerular filtration rate.
days postoperatively and ended at first hospitalization for HF, death, or December 31, 2008, whichever came first.

Statistical Analysis
Patient characteristics were described using frequencies and percentages for categorical variables, and means and SDs for continuous variables. The Kaplan–Meier method was used to calculate the cumulative incidence of first hospitalization for HF and for the composite end point of death or first hospitalization for HF. Failure curves were constructed for each level of AKI. Cox proportional hazards regression models were used to study the association between AKI and first hospitalization for HF. Patients who died before December 31, 2008 were censored at the date of death. All patients who were alive, without being hospitalized for HF, were censored on December 31, 2008. The relative risk of hospitalization for HF was estimated for each stage of AKI compared with no AKI and reported with 95% confidence intervals with and without multivariable adjustment. We constructed several multivariable models, considered all baseline characteristics and primary interaction terms, and reached a final parsimonious model by a manual forward and backward stepwise selection procedure. Variables influencing the hazard ratio (HR) ≥1 were included in the multivariable analysis. Age, sex, diabetes mellitus, left ventricular ejection fraction, eGFR, myocardial infarction before surgery or during follow-up were included in the final model. Adding preoperative stroke, hyperlipidemia, hypertension, chronic obstructive pulmonary disease, use of cardiopulmonary bypass, use of the internal thoracic artery, number of obstructed coronary arteries, or history of peripheral vascular disease did not improve the final model.

We also investigated primary interactions. Left ventricular ejection fraction was used as a 3-level categorical variable (normal, reduced, and severely reduced). Age and eGFR were used as continuous variables. All other variables were used as dichotomous variables in the analysis. Some data were missing in the study data set, and multiple imputation by chained equations was used to impute missing values. All multivariable analyses were performed on the imputed data set. We assumed that the missing values were missing at random. The frequency of missing values in the variables included in the final multivariable analysis, with 24,018 patients were none for age, sex, eGFR, and myocardial infarction before surgery or during follow-up; 5% for left ventricular ejection fraction; and 29% for diabetes mellitus. One hundred data sets were imputed, and estimates from these data sets were combined using standard methods. The proportionality assumption of the primary analysis was tested by formal and graphical test and no indication of a violation was found. We also performed a complete-case analysis, where only observations without missing values for model covariates were included (n=16,002). Sex- and eGFR-specific analyses were performed to estimate the risk for incident HF in these subgroups. STATA version 12.1 (StataCorp LP, College Station, TX) was used for data analysis.

Results
The study population consisted of 24,018 patients with a mean age of 66.8±9.2 years, and 21% were women. Patients’ characteristics are presented in Table 1. The overall incidence of AKI was 12% and did not vary significantly between 2000 and 2004 compared with 2004 and 2008. Patients with AKI were more likely to be older; have hypertension, peripheral vascular disease, diabetes mellitus, and a reduced GFR; have had a prior myocardial infarction, a previous stroke or severely reduced left ventricular ejection fraction compared with patients without AKI. The median duration of hospital stay in the department of cardiothoracic surgery was 6, 7, 7, and 9 days for patients with no kidney injury, AKI stage 1, 2, and 3, respectively.

HF Hospitalization
During 99,005 person-years of follow-up (mean 4.1±2.4 years), 1325 patients (5.5%) were hospitalized for new-onset HF. In patients with AKI, 12% were hospitalized for HF during follow-up compared with 5% in patients without AKI. The cumulative incidence of first hospitalization for HF is shown in Figure 2.

The HR for HF increased with the severity of AKI in both unadjusted and multivariable adjusted analyses (Table 2). In crude analysis, HRs with 95% confidence interval for the association between AKI stages 1, 2, and 3 and risk of HF were 2.22 (1.96–2.65), 3.10 (2.57–3.74), and 3.95 (3.08–5.08) compared with patients who did not develop AKI.

In the primary analysis, all stages of AKI remained significantly associated with an increased risk of HF even after adjustment for age, sex, diabetes mellitus, left ventricular ejection fraction, eGFR, and myocardial infarction before or after surgery (Table 2). Similar results were found when the primary analysis was performed using the AKI network classification of AKI (Table 1, online-only Data Supplement).15

The cumulative incidence of the composite end point of death or hospitalization for HF is shown in Figure 3. The overall mortality in the study population during follow-up was 15%. The mortality in patients with no kidney injury, AKI stages 1, 2, and 3 was 14%, 21%, 28%, and 38%, respectively, during follow-up. HRs with 95% confidence interval after adjustment for confounders for the association between AKI and HF or death were 1.31 (1.17–1.46), 1.60 (1.42–1.80), and 2.13 (1.82–2.49) for AKI stages 1, 2, and 3, respectively, compared with the reference group.

To account for the possible impact of missing data, we performed a complete-case analysis, including only those patients with complete information on all confounders (n=16,002). The HRs for HF hospitalization were similar to the primary analysis; 1.57 (1.27–1.95), 1.72 (1.35–2.18), and 1.83 (1.33–2.51), respectively, for stages 1, 2, and 3 of AKI.

The primary end point was also analyzed with respect to sex. Female patients were slightly older and more likely to be treated for diabetes mellitus, hypertension, and, hyperlipidemia, but less likely to have received an internal thoracic artery bypass graft during surgery. The HR for HF in women increased with the severity of AKI in crude, age-adjusted, and multivariable analysis. Adjusted HRs for men were 1.51 (1.22–1.85), 1.79 (1.44–2.24), and 1.80 (1.32–2.45) for AKI stages 1, 2, and 3, respectively. The corresponding values in women were 2.06 (1.44–2.94), 2.14 (1.44–3.19), and 2.85 (1.75–4.63). The number of events for no kidney injury and AKI stages 1, 2, and 3 for men was 777, 105, 92, and 19 for women, respectively.

Presence or Absence of CKD
The eGFR-stratified analysis was performed dividing patients into those with eGFR <60 and those with eGFR ≥60 mL/min per 1.73 m². The results are presented in Table 3. Because of few events in AKI stages 2 and 3, we merged these groups in the analysis. Both patients with and without preexisting CKD had an increased risk of HF during follow-up if they developed AKI postoperatively. Notably, the point estimates
suggested that there might be a stronger association between AKI and risk of HF among patients without preexisting CKD.

**Discussion**

The main finding was that AKI after CABG was associated with an increased long-term risk of new-onset HF. Importantly, AKI remained an independent predictor of hospitalization for HF, even after adjustment for confounders commonly involved in the cause of HF. Notably, even a relatively modest increase in postoperative SCr of 0.3 to 0.5 mg/dL was associated with a significant increase in the risk of new-onset HF.

CKD has been widely recognized as an independent risk factor for cardiovascular morbidity and mortality in patients with an established diagnosis of chronic HF.\(^\text{19-21}\) Accumulating evidence also suggests that patients with impaired kidney function are at increased risk of developing HF.\(^\text{22,23}\) The present study expands the understanding of cardiorenal interaction by demonstrating that an acute injury to kidney function in the setting of cardiac surgery independently adds to patients’ long-term risk of HF.

In this study, incident HF was defined as hospitalization for HF in patients with no prior hospitalization for HF. Hospitalization is recognized as a clinically significant and objective outcome in HF studies because it reflects disease severity and is associated with a poor prognosis and causes significant health expenditure.\(^\text{24}\) Furthermore, the outcome of hospitalization does not depend on whether the underlying mechanism of HF is primarily systolic or diastolic dysfunction. Our data were obtained from nationwide databases in a country where all acute hospital care is provided within the public health care system, suggesting that relatively uniform thresholds for hospitalization were applied and that all patients in need of acute hospital care were captured. However, it is likely that we underestimated the true rate of incident HF because some patients may have developed signs and symptoms of HF without being hospitalized. Furthermore, we cannot specify the proportion of death’s representing fatal HF events. Still, despite these limitations, AKI was significantly associated with first HF hospitalization.

This study evaluated the association between AKI and HF in the context of coronary artery bypass surgery. This is a clinically important given the large number of patients undergoing CABG, the high incidence of AKI as a perioperative complication and also that ischemic heart disease is the leading cause for HF. It is well known that renal dysfunction is linked to an increase in cardiovascular events

### Table 1. Characteristics of the Study Population in Relation to AKI Classified by Absolute Increase in Postoperative Serum Creatinine Values

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients</th>
<th>No AKI</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>24 018</td>
<td>21 239</td>
<td>1426</td>
<td>927</td>
<td>424</td>
</tr>
<tr>
<td>Percent of study population</td>
<td>100</td>
<td>88.3</td>
<td>6.0</td>
<td>3.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Age (SD), y</td>
<td>67 (9)</td>
<td>66 (9)</td>
<td>70 (9)</td>
<td>71 (9)</td>
<td>70 (9)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>5078 (21)</td>
<td>4523 (21)</td>
<td>278 (20)</td>
<td>192 (21)</td>
<td>85 (20)</td>
</tr>
<tr>
<td>eGFR (SD), mL/min per 1.73 m²</td>
<td>77 (21)</td>
<td>78 (20)</td>
<td>73 (23)</td>
<td>68 (26)</td>
<td>58 (25)</td>
</tr>
<tr>
<td>Preop. SCr (SD), μmol/L</td>
<td>92 (26)</td>
<td>90 (22)</td>
<td>98 (33)</td>
<td>107 (40)</td>
<td>131 (64)</td>
</tr>
<tr>
<td>Preop. SCr (SD), mg/dL</td>
<td>1.0 (0.3)</td>
<td>1.0 (0.3)</td>
<td>1.1 (0.4)</td>
<td>1.2 (0.5)</td>
<td>1.5 (0.7)</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>23</td>
<td>22</td>
<td>27</td>
<td>33</td>
<td>37</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>57</td>
<td>56</td>
<td>65</td>
<td>72</td>
<td>77</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>61</td>
<td>60</td>
<td>61</td>
<td>62</td>
<td>70</td>
</tr>
<tr>
<td>Peripheral vascular disease, %</td>
<td>8.9</td>
<td>8.3</td>
<td>13</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>18</td>
<td>18</td>
<td>15</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>COPD, %</td>
<td>5.9</td>
<td>5.8</td>
<td>6.6</td>
<td>6.5</td>
<td>7.8</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>36</td>
<td>35</td>
<td>40</td>
<td>43</td>
<td>52</td>
</tr>
<tr>
<td>Prior stroke, %</td>
<td>4.8</td>
<td>4.4</td>
<td>6.9</td>
<td>7.0</td>
<td>12</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction &gt;50%, %</td>
<td>73</td>
<td>74</td>
<td>68</td>
<td>64</td>
<td>61</td>
</tr>
<tr>
<td>Ejection fraction 30% to 50%, %</td>
<td>24</td>
<td>23</td>
<td>28</td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td>Ejection fraction &lt;30%, %</td>
<td>2.7</td>
<td>2.5</td>
<td>3.7</td>
<td>4.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Internal thoracic artery use, %</td>
<td>94</td>
<td>94</td>
<td>95</td>
<td>94</td>
<td>93</td>
</tr>
<tr>
<td>CABG without cardiopulmonary bypass, %</td>
<td>5.9</td>
<td>5.6</td>
<td>6.7</td>
<td>7.9</td>
<td>8.7</td>
</tr>
<tr>
<td>Year of surgery, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000–2004</td>
<td>56</td>
<td>56</td>
<td>56</td>
<td>59</td>
<td>55</td>
</tr>
<tr>
<td>2005–2008</td>
<td>44</td>
<td>44</td>
<td>44</td>
<td>41</td>
<td>45</td>
</tr>
</tbody>
</table>

Age, GFR, and serum creatinine values are given as means with SDs. AKI indicates acute kidney injury; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; and MI, myocardial infarction.

Acute kidney injury classified according to absolute raise in serum creatinine values. Stage 1, 0.3 to 0.5 mg/dL; stage 2, 0.5 to 1 mg/dL; stage 3, >1 mg/dL.
and mortality after cardiac surgery, and that patients with chronic renal dysfunction have an increased risk of HF. Our study adds to this knowledge by emphasizing the independent contribution of acute renal injury to the long-term risk of developing HF. This finding is consistent with a recent report in patients undergoing coronary angiography, showing that AKI is a significant risk factor for long-term mortality and cardiovascular events, including hospitalization for HF. Thus, our data highlight the role of AKI as an important marker of increased risk of cardiovascular events in general and HF in particular and suggest that patients with AKI should be subject to particularly close follow-up. Furthermore, the results direct attention toward a clinical need of developing strategies to prevent AKI. Although trials using N-acetylcysteine as a protective measure did not change outcome, a randomized study in patients with left ventricular dysfunction undergoing cardiac surgery has shown potential renoprotective effects with neseritide.

Our findings suggest a harmful effect of AKI on the heart, which is consistent with cardiorenal syndrome type 3. This syndrome describes the connection between acute impairment of renal function and injury to or dysfunction of the heart. Several mechanisms have been proposed to mediate the harmful effects of AKI on the heart, including the release of inflammatory mediators, and hemodynamic and electrolyte disturbances. One of the most common cardiac complications after AKI is acute decompensated HF. This complication could explain why the greatest increase in the cumulative incidence of HF in our study occurred within the first year. Patients who develop HF after AKI might have early signs of

Table 2. Hazard Ratios of First Hospitalization for Heart Failure with 95% Confidence Intervals in Relation to Acute Kidney Injury Stage Defined by Absolute Increase in Postoperative Serum Creatinine Values*

<table>
<thead>
<tr>
<th>Acute Kidney Injury</th>
<th>No Kidney Injury</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients, %</td>
<td>21 239 (88.4)</td>
<td>1428 (5.6)</td>
<td>927 (3.9)</td>
<td>424 (1.8)</td>
</tr>
<tr>
<td>No. of events, %</td>
<td>997 (4.7)</td>
<td>141 (9.9)</td>
<td>122 (13.2)</td>
<td>65 (15.3)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>2.22 (1.86–2.65)</td>
<td>3.10 (2.57–3.74)</td>
<td>3.95 (3.08–5.08)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
<td>1.87 (1.57–2.23)</td>
<td>2.48 (2.05–2.99)</td>
<td>3.29 (2.56–4.23)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
<td>1.60 (1.34–1.92)</td>
<td>1.87 (1.54–2.27)</td>
<td>1.98 (1.53–2.57)</td>
</tr>
</tbody>
</table>

Total number of patients n=24 018. HR indicates hazard ratio; and CI, confidence interval.

*Acute kidney injury classified according to absolute increase in serum creatinine values. Stage 1, 0.3 to 0.5 mg/dL; stage 2, 0.5 to 1 mg/dL; and stage 3, >1 mg/dL.

†Multivariable adjustment was made for age, sex, diabetes mellitus, left ventricular ejection fraction, estimated glomerular filtration rate, pre- and postoperative myocardial infarction.
decreased left ventricular systolic and diastolic dysfunction. This concurs with the findings of an earlier animal study in which left ventricular dilatation was detected within 48 hours of induced renal ischemia. To our knowledge, no studies have been published that have examined the acute effect of AKI on left ventricular function measured by echocardiography in humans.

Although our results are consistent with cardiorenal syndrome type 3, several other explanations are possible. AKI after CABG may cause persistent loss of GFR. A recently published review and meta-analysis suggests an increased risk of developing CKD after AKI. The cause of worsening renal function is unclear, but one animal study has shown long-term development of renal fibrosis after induced ischemia to the kidney. Therefore, AKI may precipitate or accelerate the course of CKD, which is associated with cardiovascular disease and HF. Because we had no information about SCr values after discharge, we could not control for persisting loss of renal function and subsequent worsening of kidney function. Other factors could also explain the connection between AKI after CABG and an increased long-term risk of developing HF. Cardiovascular disease, reduced kidney function before surgery, hemodynamic alterations, or acute HF during surgery are risk factors for both acquiring AKI and the development of HF in the long term.

Several explanations have been proposed to elucidate the prognostic value of kidney function in HF, including impairment of hemodynamic status, neurohormonal activation, and inflammatory processes that promote atherosclerosis, general vascular disease, and other factors. Although our

### Table 3. HRs of Hospitalization for HF Stratified by eGFR With 95% CIs in Relation to AKI*

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>No Kidney Injury</th>
<th>AKI 1</th>
<th>AKI 2 and 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients, %</td>
<td>24 018 (100)</td>
<td>21 239 (100)</td>
<td>1428 (100)</td>
<td>1351 (100)</td>
</tr>
<tr>
<td>No. of events, %</td>
<td>1325 (5.5)</td>
<td>997 (4.7)</td>
<td>141 (9.9)</td>
<td>187 (14)</td>
</tr>
<tr>
<td>Age groups†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR ≥60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients, %</td>
<td>19 430 (81)</td>
<td>17 684 (83)</td>
<td>1018 (71)</td>
<td>728 (54)</td>
</tr>
<tr>
<td>No. of events, %</td>
<td>806 (4.1)</td>
<td>656 (3.7)</td>
<td>67 (6.6)</td>
<td>83 (11)</td>
</tr>
<tr>
<td>Risk of HF hospitalization (HR; 95% CI)</td>
<td>1.00</td>
<td>1.41 (1.10–1.82)</td>
<td>2.24 (1.78–2.83)</td>
<td></td>
</tr>
<tr>
<td>eGFR &lt;60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients, %</td>
<td>4588 (19)</td>
<td>3555 (17)</td>
<td>410 (29)</td>
<td>623 (46)</td>
</tr>
<tr>
<td>No. of patients hospitalized for HF, %</td>
<td>519 (11)</td>
<td>341 (9.6)</td>
<td>74 (18)</td>
<td>104 (17)</td>
</tr>
<tr>
<td>Risk of HF hospitalization (HR; 95% CI)</td>
<td>1.00</td>
<td>1.82 (1.41–2.34)</td>
<td>1.70 (1.35–2.12)</td>
<td></td>
</tr>
</tbody>
</table>

Total number of patients n=24 018. AKI indicates acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; and HR, hazard ratio.

*AKI classified according to absolute raise in serum creatinine values. Stage 1, 0.3–0.5 mg/dL; stage 2 and 3, >0.5 mg/dL.
†Multivariable adjustment was made for age, sex, diabetes mellitus, left ventricular ejection fraction, pre- and postoperative myocardial infarction.
study cannot provide novel pathophysiological insight, the independent effect of acute changes in kidney function after cardiac surgery seem to be a valuable marker of increased risk for developing cardiovascular events in general and HF in particular.

The risk of HF associated with AKI was increased independently of preexisting kidney disease in the analysis stratified for baseline GFR. Interestingly, our results suggest that the risk related to severe AKI may be greater in patients without CKD than in patients with preexisting kidney disease.

Women with AKI had a higher relative risk for HF in all stages of AKI than men, suggesting that the impact of AKI may be more substantial in women. The evidence of differences in postoperative risks between men and women is not uniform. A recent study showed that female sex is an independent risk factor for mortality and morbidity after cardiac surgery, although another study found that the difference in mortality was largely explained by preoperative risk factors.

The main strength of our study was the size of the study population and length of follow-up. Also, our study population was recruited from a nationwide register and may, therefore, be generalizable to other countries with a similar level of healthcare. The registers used for follow-up were virtually complete, and no patients were lost to follow-up. Also, the outcome studied has been found to have a high validity in the register used.

However, the present study also has several limitations. Information for some of the traditional risk factors for cardiovascular disease was missing for a part of the study population, but in a subset of >16,000 patients complete data on all potential confounders for HF were available, and in this subset a similar association between AKI and HF was found as in the total study population. Hypertension and smoking, which are common cardiovascular risk factors, did not change point estimates significantly and were therefore not used in the final statistical model. Another limitation is that we did not have information if medication that may mitigate the development of HF was stopped postoperatively in patients with AKI more frequently than among those without AKI. Also, we did not have information on some preoperative risk factors for HF as presence of anemia or if patients were treated with angiotensin-converting-enzyme inhibitors, angiotensin-receptor-blockers, betablockers or aldosterone antagonists before surgery. Another limitation was the lack of information regarding proteinuria at baseline. Also, we did not have information on changes in lifestyle during the 9 years of inclusion, which may have affected the risk of developing HF. Even though we could adjust for left ventricular systolic dysfunction, we did not have information about diastolic function. Thus, there may have been residual confounding that we could not control for which may have affected our results.

Conclusions

AKI after CABG was associated with increased long-term risk of first hospitalization for HF. This was true for patients with or without preexisting CKD, and for both sexes. Patients with AKI after CABG should be followed closely to detect early changes in cardiac function. Our results should be interpreted with caution because we could not control for medication or anemia before or after surgery.

Acknowledgments

We are thankful to the steering committee of Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies for making their register available for the purpose of this study.

Disclosures

None.

References

the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation. 2003;108:2154–2169.


**CLINICAL PERSPECTIVE**

Acute kidney injury (AKI) is common after coronary artery bypass grafting (CABG) and has been associated with early and long-term mortality. It has been proposed that AKI can lead to changes in cardiac structure and function. To better understand the association between AKI after CABG and new-onset heart failure (HF), we followed all 24 018 patients without previous HF who underwent CABG in Sweden during 9 years. During a mean follow-up of 4 years, there were 1325 incident cases of HF (5.5%). After adjustment for a number of confounders, AKI was still strongly associated with new-onset HF. Patients in AKI stage 1 had 60% increased risk; in stage 2, 87% increased risk; and in stage 3, 98% increased risk to develop HF during follow-up compared with patients without AKI. The impact of AKI on risk for HF seemed to be similar for both men and women. Also, there were no major differences in relative risks for patients without preexisting chronic kidney disease compared with those with chronic kidney disease. A large proportion of the HF events came within the first few months after CABG. This may be because of acute changes in the myocardium associated with AKI. Our results suggest that AKI is an independent risk factor for new-onset HF after CABG in the long term. It may be wise to follow patients with AKI after CABG more closely to introduce measures to prevent new-onset HF.
Acute Kidney Injury Following Coronary Artery Bypass Surgery and Long-term Risk of Heart Failure
Daniel Olsson, Ulrik Sartipy, Frieder Braunschweig and Martin J. Holzmann

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**Supplemental Material**

**Supplemental Table 1.** Hazard Ratios of first hospitalization for heart failure with 95 percent confidence intervals in relation to acute kidney injury stage defined by the AKIN classification*. Total number of patients n = 24 018.

<table>
<thead>
<tr>
<th>Acute kidney injury</th>
<th>No kidney injury</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td>21 230 (88)</td>
<td>2452 (10)</td>
<td>278 (1.2)</td>
<td>58 (0.2)</td>
</tr>
<tr>
<td>Number of events (%)</td>
<td>997 (4.7)</td>
<td>282 (12)</td>
<td>40 (14)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Crude</td>
<td>1.00</td>
<td>2.72 (2.66-2.78)</td>
<td>2.90 (2.74-3.08)</td>
<td>2.40 (2.09-2.75)</td>
</tr>
<tr>
<td>Adjustment for age and sex</td>
<td>1.00</td>
<td>2.31 (2.26-2.37)</td>
<td>2.44 (2.30-2.58)</td>
<td>2.22 (1.93-2.54)</td>
</tr>
<tr>
<td>Multivariable adjustment†</td>
<td>1.00</td>
<td>1.69 (1.48-1.94)</td>
<td>2.33 (1.69-3.22)</td>
<td>1.87 (0.84-4.20)</td>
</tr>
</tbody>
</table>

* Acute kidney injury classified according to the Acute Kidney Injury Network classification. Stage 1; > 0.3 mg/dL or 50-100% increase, stage 2; 100-200% increase, stage 3; > 200% increase of postoperative creatinine values. HR; Hazard Ratio. CI; confidence Interval. † Multivariable adjustment was made for: age, sex, diabetes mellitus, left ventricular ejection fraction, estimated glomerular filtration rate, pre- and post-operative myocardial infarction.