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

Olsson et al: Kidney Injury, CABG and Heart Failure

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Abstract

**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.

**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 heart failure 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 (HR) with 95% confidence intervals (CI) were calculated for first hospitalization for heart failure 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 (5.5%) cases of incident heart failure. Hazard ratios with 95% CI for heart failure in AKI stage 1, 2 and 3 were 1.60 (1.34 to 1.92), 1.87 (1.54 to 2.27), and 1.98 (1.53 to 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**—Acute kidney injury is associated with increased long-term risk of heart failure after CABG. Patients with AKI after CABG should be followed closely in order to detect early changes in cardiac function.

**Key Words**: acute kidney injury, heart failure, coronary artery bypass grafting
Coronary artery bypass grafting (CABG) is the most common cardiac surgical procedure, and an effective method of relieving angina and improving the prognosis for selected patients with ischemic heart disease.\textsuperscript{1} Despite a gradual decline over the past decade, more than 1000 patients per million population still undergo CABG in the United States each year.\textsuperscript{2} Acute kidney injury (AKI) is a frequent complication after CABG with an incidence between 8 and 15\%\textsuperscript{3,4} and has been associated with an increased risk of postoperative complications as well as increased short- and long-term mortality.\textsuperscript{4-7} A minor elevation of postoperative serum creatinine by 0.5 mg/dL has been found to be associated with an almost threefold increase in 30-day mortality.\textsuperscript{6}

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.\textsuperscript{8} Also, HF is the most common cause of hospital admission in the United States and Europe\textsuperscript{9,10} and HF hospitalization per se is linked to adverse outcome and high treatment costs.\textsuperscript{11} Heart failure 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 co-existence of kidney and heart disease is known as the “cardiorenal syndrome”.\textsuperscript{12} 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.\textsuperscript{12}

While the general relationship between chronic kidney disease (CKD) and chronic HF has received considerable attention in the literature\textsuperscript{13} 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’ previous 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 93-95%. Patients were excluded from the study if they had: undergone previous cardiac surgery; underwent other than isolated CABG during the operation; had missing pre- and/or postoperative creatinine values; died within 30 days of surgery; had a history of previous hospitalization for heart failure; were diagnosed with myocardial infarction (MI) within 14 days before surgery; underwent CABG within 24 hours from decision; had an eGFR <15 mL/min/1.73 m²; or they were diagnosed with heart failure 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 serum creatinine (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. Acute kidney injury was classified into three 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 study5 and is based on AKIN criteria15 and traditional definitions.5

Glomerular filtration rates were estimated using the simplified Modification of Diet in Renal Disease (MDRD) study equation.16 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 prior to surgery and categorized as normal (ejection fraction > 50%), reduced (ejection fraction 30 to 50%) or severely reduced (ejection fraction < 30%).

Outcome
The primary study outcome was 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 1987.17 This register was also used to ascertain information about illnesses prior to surgery. The validity of the diagnosis “heart failure” in this register has been shown to be 95% if it is the principal cause of hospitalization.17,18 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 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 standard deviations for continuous variables. The Kaplan-Meier method was used to calculate the cumulative incidence of first hospitalization for HF and for the composite endpoint 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 to 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 $\geq 0.1$ were included in the multivariable analysis. Age, sex, diabetes mellitus, left ventricular ejection fraction, estimated glomerular filtration rate, 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 three-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 dataset and multiple imputation by chained
equations was used to impute missing values. All multivariable analyses were performed on
the imputed dataset. 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; 8% for left ventricular ejection fraction; and 29% for diabetes mellitus. One
hundred datasets were imputed and estimates from these datasets 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, USA) 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 to 2004 compared with 2004 to
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 cardio-thoracic
surgery was 6, 7, 7 and 9 days for patients with no kidney injury, AKI stage 1, 2, and 3
respectively.
Heart failure hospitalization

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

The hazard ratio for HF increased with the severity of AKI in both unadjusted and multivariably adjusted analyses (Table 2). In crude analysis, hazard ratios with 95% CI for the association between AKI stages 1, 2 and 3 and risk of HF were 2.22 (1.96 to 2.65), 3.10 (2.57 to 3.74) and 3.95 (3.08 to 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, estimated glomerular filtration rate, and myocardial infarction before or after surgery (Table 2). Similar results were found when the primary analysis was performed using the Acute Kidney Injury Network (AKIN) classification of AKI (Table 1, supplemental material).15

The cumulative incidence of the composite endpoint 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. Hazard ratios with 95% CI after adjustment for confounders for the association between AKI and HF or death were 1.31 (1.17 to 1.46), 1.60 (1.42 to 1.80) and 2.13 (1.82 to 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
The hazard ratios for HF hospitalization were similar to the primary analysis; 1.57 (1.27 to 1.95), 1.72 (1.35 to 2.18) and 1.83 (1.33 to 2.51) respectively for stages 1, 2 and 3 of AKI.

The primary endpoint was also analyzed with respect to gender. 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 hazard ratio for men and women increased with the severity of AKI in crude, age-adjusted, and multivariable analysis. Adjusted hazard ratios for men were 1.51 (1.22 to 1.85), 1.79 (1.44 to 2.24) and 1.80 (1.32 to 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 46 respectively, and 220, 36, 30 and 19 for women respectively.

**Presence or absence of chronic kidney disease**

The eGFR-stratified analysis was performed dividing patients into those with eGFR < 60 and those with eGFR ≥ 60 mL/min/1.73m². The results are presented in Table 3. Due to few events in AKI stages 2 and 3 we merged these groups in the analysis. Both patients with and without pre-existing chronic kidney disease 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 pre-existing chronic kidney disease.

**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 etiology 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.

Chronic kidney disease has been widely recognized as an independent risk factor for cardiovascular morbidity and mortality in patients with an established diagnosis of chronic HF. Accumulating evidence also suggests that patients with impaired kidney function are at increased risk of developing HF. The present study expands the understanding of cardio-renal 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 since it reflects disease severity, and is associated with a poor prognosis and causes significant health expenditure. 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 since 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 etiology for HF. It is well known that renal dysfunction is linked
to an increase in cardiovascular events and mortality after cardiac surgery\textsuperscript{13,25,26} and that patients with chronic renal dysfunction have an increased risk of HF.\textsuperscript{13} 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.\textsuperscript{27} 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. While trials using N-acetylcysteine as a protective measure did not change outcome,\textsuperscript{28} a randomized study in patients with left ventricular dysfunction undergoing cardiac surgery has shown potential renoprotective effects with neseritide.\textsuperscript{29}

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.\textsuperscript{12} 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.\textsuperscript{30} One of the most common cardiac complications after AKI is acute decompensated HF.\textsuperscript{30} 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 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.\textsuperscript{31} 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. Acute kidney injury after CABG may cause persistent loss of GFR. A recently published review and meta-analysis suggests an increased risk of developing chronic kidney disease after AKI.\textsuperscript{32} 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.\textsuperscript{33} Therefore, AKI may precipitate or accelerate the course of chronic kidney disease\textsuperscript{32}, which is associated with cardiovascular disease and HF\textsuperscript{13,20,24} Since 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 heart failure during surgery are risk factors for both acquiring AKI and the development of HF in the long-term.\textsuperscript{3,8,34}

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.\textsuperscript{19,20,30,35} Although our study cannot provide novel pathophysiological insight, the independent effect of acute changes in kidney function following 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 pre-existing 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 chronic kidney disease than in patients with pre-existing 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 more than 16,000 patients complete data on all potential confounders for HF was 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 angiotension-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 life style during the nine years of inclusion, which may have affected the risk of developing heart failure.
failure. 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**

Acute kidney injury after coronary artery bypass grafting was associated with increased long-term risk of first hospitalization for HF. This was true for patients with or without pre-existing chronic kidney disease, and for both sexes. Patients with AKI after CABG should be followed closely in order to detect early changes in cardiac function. Our results should be interpreted with caution since we could not control for medication or anemia before or after surgery.

**Acknowledgments**

The authors are thankful to the steering committee of SWEDHEART for making their register available for the purpose of this study.

**Disclosures**

None.

**References**

Table 1. Characteristics of the study population in relation to acute kidney injury classified by absolute increase in postoperative serum creatinine values.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients</th>
<th>No AKI</th>
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<th>3</th>
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<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>24018</td>
<td>21239</td>
<td>1428</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), years</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/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>
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<td>Diabetes mellitus (%)</td>
<td>23</td>
<td>22</td>
<td>27</td>
<td>33</td>
<td>37</td>
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<tr>
<td>Hypertension (%)</td>
<td>57</td>
<td>56</td>
<td>65</td>
<td>72</td>
<td>77</td>
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<td>Hyperlipidemia (%)</td>
<td>61</td>
<td>60</td>
<td>61</td>
<td>62</td>
<td>70</td>
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<td>Peripheral vascular disease (%)</td>
<td>8.9</td>
<td>8.3</td>
<td>13</td>
<td>13</td>
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<td>Current smoking (%)</td>
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<td>15</td>
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<td>COPD (%)</td>
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<td>Prior MI (%)</td>
<td>36</td>
<td>35</td>
<td>40</td>
<td>43</td>
<td>52</td>
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<td>Prior stroke (%)</td>
<td>4.8</td>
<td>4.4</td>
<td>6.9</td>
<td>7.0</td>
<td>12</td>
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<td><strong>Left ventricular function</strong></td>
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<td></td>
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<tr>
<td>Ejection fraction &gt; 50 % (%)</td>
<td>73</td>
<td>74</td>
<td>68</td>
<td>64</td>
<td>61</td>
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<tr>
<td>Ejection fraction 30-50 % (%)</td>
<td>24</td>
<td>23</td>
<td>28</td>
<td>32</td>
<td>33</td>
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<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>
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<td>Internal thoracic artery use (%)</td>
<td>94</td>
<td>94</td>
<td>95</td>
<td>94</td>
<td>93</td>
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<tr>
<td>CABG without cardiopulmonary bypass (%)</td>
<td>5.9</td>
<td>5.6</td>
<td>6.7</td>
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<td>8.7</td>
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<tr>
<td><strong>Year of surgery</strong></td>
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<td></td>
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<tr>
<td>2000-2004 (%)</td>
<td>56</td>
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<td>56</td>
<td>59</td>
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<td>2005-2008 (%)</td>
<td>44</td>
<td>44</td>
<td>44</td>
<td>41</td>
<td>45</td>
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</table>

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

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.
Table 2. Hazard ratios of first hospitalization for heart failure with 95 percent confidence intervals in relation to acute kidney injury stage defined by absolute increase in postoperative serum creatinine values*. 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>21239 (88.4)</td>
<td>1428 (5.6)</td>
<td>927 (3.9)</td>
<td>424 (1.8)</td>
</tr>
<tr>
<td>Number 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>Crude</td>
<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>
</tr>
<tr>
<td>Adjustment for age and sex</td>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>1.87 (1.57-2.23)</td>
<td>2.48 (2.05-2.99)</td>
</tr>
<tr>
<td>Multivariable adjustment†</td>
<td>HR (95% CI)</td>
<td>1.00</td>
<td>1.60 (1.34-1.92)</td>
<td>1.87 (1.54-2.27)</td>
</tr>
</tbody>
</table>

* 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, stage 3; >1 mg/dL. 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 postoperative myocardial infarction.
Table 3. Hazard ratios of hospitalization for heart failure stratified by estimated glomerular filtration rate with 95 percent confidence intervals in relation to acute kidney injury*. Total number of patients n = 24 018.

<table>
<thead>
<tr>
<th>Age groups†</th>
<th>eGFR ≥60</th>
<th>eGFR &lt;60</th>
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<tr>
<td></td>
<td>Number of patients (%)</td>
<td>24 018 (100)</td>
</tr>
<tr>
<td></td>
<td>Number of events (%)</td>
<td>1325 (5.5)</td>
</tr>
<tr>
<td>Risk of HF hospitalization (HR; 95% CI)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

| Number of patients (%) | 21 239 (100) | 17 684 (83) |
| Number of events (%) | 997 (4.7) | 656 (3.7) |
| Risk of HF hospitalization (HR; 95% CI) | 1.00 | 1.00 |

| Number of patients (%) | 1428 (100) | 1018 (71) |
| Number of events (%) | 141 (9.9) | 67 (6.6) |
| Risk of HF hospitalization (HR; 95% CI) | 2.24 (1.78-2.83) | 2.24 (1.78-2.83) |

| Number of patients (%) | 1351 (100) | 728 (54) |
| Number of events (%) | 187 (14) | 83 (11) |
| Risk of HF hospitalization (HR; 95% CI) | 1.70 (1.35-2.12) | 1.70 (1.35-2.12) |

* AKI; Acute kidney injury classified according to absolute raise in serum creatinine values. Stage 1; 0.3-0.5 mg/dL, stage 2&3; > 0.5 mg/dL. CI; confidence interval, HF; heart failure, HR; hazard ratio. † Multivariable adjustment was made for; age, sex, diabetes mellitus, left ventricular ejection fraction, pre- and postoperative myocardial infarction.
Figure Legends

Figure 1. Selection criteria for the study population consisting of 24,018 patients undergoing primary isolated coronary artery bypass grafting between January 1, 2000 and December 31, 2008 in Sweden.

Figure 2. Cumulative incidence for first hospitalization of heart failure. The curves represent no kidney injury, and different stages of acute kidney injury. The inset shows the same data on an enlarged y-axis.

Figure 3. Cumulative incidence of the composite endpoint of first hospitalization for heart failure or death. The curves represent no kidney injury, and different stages of acute kidney injury. The inset shows the same data on an enlarged y-axis.
<table>
<thead>
<tr>
<th>Event Description</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Had undergone previous cardiac surgery.</td>
<td>1027</td>
</tr>
<tr>
<td>Underwent surgery other than isolated CABG.</td>
<td>7059</td>
</tr>
<tr>
<td>Had missing pre- or post-operative serum creatinine.</td>
<td>10605</td>
</tr>
<tr>
<td>Died within 30 days after surgery.</td>
<td>402</td>
</tr>
<tr>
<td>Diagnosed with heart failure before surgery.</td>
<td>1149</td>
</tr>
<tr>
<td>Myocardial infarction within 14 days before surgery.</td>
<td>4724</td>
</tr>
<tr>
<td>Underwent surgery &lt;24 hours from decision.</td>
<td>766</td>
</tr>
<tr>
<td>Preoperative estimated GFR &lt;15 ml/min/1.73m².</td>
<td>125</td>
</tr>
<tr>
<td>Diagnosed with heart failure within 30 days after surgery.</td>
<td>369</td>
</tr>
</tbody>
</table>
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>HR (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></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.