**Small postoperative creatinine increases and clinical outcomes after surgical aortic valve replacement**

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**Abstract**

**Importance:** The impact of small increases in serum creatinine after surgical aortic valve replacement (SAVR) that fails to meet the acute kidney injury stage 1 criteria is unknown.

**Objective:** To investigate prognosis after primary SAVR in patients with small increases in postoperative serum creatinine (5 μmol/L ≤ change in serum creatinine < 26.5 μmol/L).

**Design:** Observational cohort study. Mean (maximum) follow-up time: 5.7 (14.2) years.

**Setting:** Swedish nationwide study.

**Participants:** Adult patients who underwent primary SAVR in Sweden from 2009 to 2022. Patients were excluded if they underwent an emergent operation, had missing pre- or post-operative serum creatinine values, had an estimated glomerular filtration rate < 15 mL/min/1.73 m2, or had preoperative dialysis or preoperative chronic kidney disease. Follow-up data were complete.

**Exposure:** Small increase in postoperative serum creatinine (5–26.5 μmol/L) after SAVR.

**Main Outcomes and Measures:** Long-term all-cause mortality. Secondary outcomes were 30-day mortality, chronic kidney disease, and heart failure.

**Results:** In 16,766 patients, 4,074 (24.2%) had no change in postoperative serum creatinine, 5,764 (34.3%) had a small increase in postoperative serum creatinine and 2,753 (16.4%) satisfied the Kidney Disease Improving Global Outcomes acute kidney injury stage 1 criteria. The mean age was 67 years and 31% of patients were female. No significant difference in long-term all-cause mortality was observed in the small-increase group at 13 years compared with the no-change group (absolute difference: 2%; 95% confidence interval [CI]: −0.4–4.3). A stepwise increase in the risk of 30-day mortality was observed with an increasing change in serum creatinine. At 13 years of follow-up, the estimated cumulative incidence of chronic kidney disease was 10% (95% CI: 8.5–11.8) in the small-increase group compared with 7.2% (95% CI: 5.8–8.9) in the no-change group (absolute difference: 2.8%; 95% CI: 1.1–4.6). At 13 years of follow-up, the estimated cumulative incidence of heart failure was 32 % (95% CI: 30–34) in the small-increase group compared with 29% (95% CI: 27–31) in the no-change group (absolute difference: 3.7%; 95% CI: 1.5–5.9).

**Conclusion and Relevance:** A small increase in postoperative serum creatinine after SAVR was associated with an increased risk of 30-day mortality and a higher risk of long-term chronic kidney disease and heart failure. These negative impacts on the prognosis after SAVR suggest that extending the Kidney Disease Improving Global Outcomes criteria to include a “stage 0” may be prudent and can allow the detection and close monitoring of patients with “subclinical” acute kidney injury.

**Introduction**

Acute kidney injury (AKI) after cardiac surgery is common and affects approximately 12% to 19% of patients who undergo surgical aortic valve replacement (SAVR) [1,2]. AKI is associated with a higher risk of death, chronic kidney disease (CKD), heart failure, and other postoperative complications [3–6]. Compared with many other surgical procedures, cardiopulmonary bypass in cardiac surgery increases the risk of AKI. Aortic cross-clamping, exogenous blood product transfusion, and vasopressors, which are commonly used during cardiopulmonary bypass, contribute to renal vasoconstriction and ischemia, which leads to a higher risk of AKI [7–10]. Established in 2012, the Kidney Disease Improving Global Outcomes (KDIGO) diagnostic criteria categorize AKI into three stages based on changes in serum creatinine and urine output [11,12]. Although AKI stage 1 is the most common postoperative AKI stage, it represents a large reduction in the estimated glomerular filtration rate (eGFR) in healthy individuals and may indicate significant kidney damage [13]. Prior studies have shown that in patients with coronary artery disease, even a minimal increase in serum creatinine that fails to meet the AKI stage 1 criteria results in a higher risk of adverse outcomes after coronary artery bypass grafting (CABG) [14–16]. However, the impact of minimal increases in serum creatinine in patients without coronary artery disease (e.g., after SAVR) is unknown. Knowledge of the impact of small increases in serum creatinine can raise awareness among clinicians and improve patient care and postoperative monitoring. We therefore conducted this nationwide observational cohort study to investigate the risk of long- and short-term all-cause mortality, chronic kidney disease, and heart failure in patients with small postoperative increases in serum creatinine after primary SAVR.

**Methods**

*Study design*

This observational, nationwide, population-based cohort study was approved by the Swedish Ethical Review Authority. Study reporting followed the Strengthening of the Reporting of Observational Studies in Epidemiology and Reporting of Studies Conducted Using Observational Routinely Collected Health Data guidelines [17,18]. The requirement for informed consent was waived.

*Study population and exposure*

All adult patients who underwent primary SAVR with or without concomitant CABG and/or ascending aortic surgery in Sweden between 1 January 2009 and 31 December 2022 were included in the study. In general, preoperative serum creatinine was measured the day before surgery. The peak postoperative serum creatinine concentration during the hospital stay was used. The change in serum creatinine was obtained by subtracting the preoperative serum creatinine from the peak postoperative serum creatinine. The study groups were defined by the interval of postoperative change in serum creatinine after SAVR and were categorized as having a large decrease in serum creatinine (change in [Δ] serum creatinine < −26.5 μmol/L), a small decrease in serum creatinine (−26.5 μmol/L ≤ Δ serum creatinine ≤−5 μmol/L), no change in serum creatinine (−5 μmol/L < Δ serum creatinine < 5 μmol/L), a small increase in serum creatinine (5 μmol/L ≤ Δ serum creatinine < 26.5 μmol/L), AKI stage 1, or AKI stages 2 and 3 (in accordance with the KDIGO criteria). The study groups are further described in Supplemental Table 1 and Supplemental Figure 1.

The AKI stages were defined in accordance with serum creatinine changes in the KDIGO criteria [11,12]. The study’s primary focus was on the following categories: no change in serum creatinine, a small increase in serum creatinine, and AKI stage 1. The exclusion criteria were concomitant surgery on another valve, prior cardiac surgery, emergency surgical treatment (< 24 h from the decision to operate), deep hypothermia and circulatory arrest, missing pre- or post-operative serum creatinine values, eGFR < 15 mL/min/1.73 m2, preoperative dialysis, and preoperative chronic kidney disease. Furthermore, all of the patients from one Swedish center were omitted because of data integrity issues during the period 2009 to 2019 (Supplemental Figure 2).

*Outcomes*

The primary outcome was long-term all-cause mortality, which was obtained from the Swedish Total Population Register [19]. Secondary outcomes were 30-day mortality, the cumulative incidence of chronic kidney disease, and hospitalization from heart failure. The ICD9–10 codes used to ascertain these outcomes were obtained from the National Patient Register [20] and are presented in Supplemental Table 2.

*Data Sources*

The study population was identified using the Swedish Cardiac Surgery register, which is part of the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies registry [21]. All patients who had undergone cardiac surgery in Sweden since 1992 were included in the Swedish Cardiac Surgery register, which also provided information on survival status through linkage with the Total Population Register. The Swedish Cardiac Surgery register has high reliability and validity [22]. Additional baseline characteristics and outcome data were obtained from the Swedish National Patient Register. In external reviews, the heart failure diagnosis in the National Patient Register has been shown to have high reliability and validity [20,23]. The Longitudinal Integrated Database for Health Insurance and Labour Market Studies, which is maintained by Statistics Sweden, was used to obtain data on socioeconomic background characteristics [24]. The Swedish Personal Identity Number allowed the cross-linking of the data at an individual level [25].

*Statistical methods*

Baseline characteristics were shown as numbers and percentages for categorical variables and means and standard deviations for continuous variables. Flexible parametric regression standardization was used to account for baseline differences between groups when estimating the standardized cumulative long-term survival and differences in long-term survival. The resulting survival curve estimated the population outcome if the entire population belonged to each respective study group: no change in serum creatinine, a small increase in serum creatinine, or a change that corresponded to AKI stage 1. This method adjusts for the population distribution of covariates [26,27]. Logistic regression was used to adjust for confounders when estimating the probability of 30-day all-cause mortality. The change in serum creatinine was modeled using restricted cubic splines (degrees of freedom = 4). To adjust for potential confounding while accounting for the competing risk of death, flexible hazard-based regression standardization was used to estimate the cumulative incidence and differences in cumulative incidence in chronic kidney disease and hospitalization from heart failure, using the method previously described by Kipourou et al. [28]. The resulting incidence curves estimated the cumulative incidence of these outcomes had the entire population belonged to each respective study group: no change in serum creatinine, a small increase in serum creatinine, or a change that corresponded to AKI stage 1. Clinical subject matter knowledge and a backward selection strategy aided by the Akaikes information criterion were used during model selection for all outcomes. The Classification And Regression Tree estimation and imputation approach [29] was used to handle missing data. Data were assumed to be missing at random.

The time to event was defined as the number of days from the date of surgery until the date of the event or the end of follow-up, whichever came first. The follow-up ended on 31 December 2022. The Kaplan–Meier method was used to calculate the crude cumulative incidence of long-term survival. The Aalen–Johansen estimator was used to estimate the crude cumulative incidence of chronic kidney disease and hospitalization from heart failure while accounting for the competing risk of death. Age- and sex-adjusted incidence rates were estimated using a Poisson model that used restricted cubic splines with four knots to calculate and plot adjusted incidence rates for the time to first event across the spectrum of change in serum creatinine as a continuous variable.

The main analyses were repeated using inverse probability of treatment weighting with optimization-based weights [30] to account for differences in baseline characteristics between the study groups. Sensitivity analysis was performed in the subset of patients who underwent isolated SAVR. We performed subgroup analyses according to preoperative renal function and left ventricular ejection fraction (LVEF). All statistical analyses and data management were performed using the R programming language, version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria) and included the use of the “mexhaz,” “rstpm2,” “rms,” “Hmisc,” “WeightIt,” and “marginaleffects” packages [31–36].

**Results**

We included 16,766 patients who underwent primary SAVR from 2009 to 2022 in Sweden. Of all the patients, 4,074 (24.2%) experienced no change in postoperative serum creatinine, 5,764 (34.3%) had a small increase in postoperative serum creatinine, and 2,753 (16.4%) satisfied the AKI stage 1 criteria. The number of patients in all categories is shown in Supplemental Figure 1. Patients in the no-change group had a mean (SD) age of 65.9 (12.1) years. The mean (SD) ages in the small-increase and AKI stage 1 groups were 67.9 (11.1) years and 71.0 (9.6) years, respectively. Small but potentially important baseline differences were observed between the groups. For example, the percentages of prior heart failure were 14.3%, 16.3,% and 25.5% in the no-change, small-increase, and AKI stage 1 groups, respectively. Data were missing for the following variables: education level (0.8%), body mass index (0.9%), and LVEF (0.1%). The baseline characteristics of the patients across the serum creatinine change categories are presented in Table 1. The baseline characteristics of patients who survived or did not survive 30 days after SAVR are shown in Supplemental Table 3.

*Clinical outcomes*

The regression standardized cumulative incidences and differences of all outcomes at 5, 10, and 13 years after SAVR are shown in Table 2. The crude cumulative incidences for all outcomes at 5, 10, and 13 years are shown in Supplemental Table 4. The crude and age- and sex-adjusted incidence rates for all outcomes are shown in Supplemental Table 5. The proportion of patients in each serum creatinine change category is shown in Supplemental Figure 3.

*Long-term all-cause mortality*

During a mean follow-up of 5.7 (maximum 14.2) years, 3,423 patients (20.4%) died. At 13 years of follow-up, the regression standardized cumulative incidence of all-cause mortality was 41% (95% CI: 39–44) in the no-change group compared with 43% (95% CI: 41–46) in the small-increase group and 50% (95% CI: 47–52) in the AKI stage 1 group. The estimated difference between the no-change and small-increase groups at 13 years was 2% (95% CI: −0.4–4.3) and the estimated difference between the no-change and AKI stage 1 groups was 8% (95% CI: 5.3–10.7). The regression standardized cumulative long-term survival is shown in Figure 1.

*Short-term mortality*

In total, 167 (1.0%) patients died within 30 days of SAVR. The adjusted probabilities of death within 30 days are shown in Figure 2. The adjusted odds ratios of death within 30 days are shown in Supplemental Figure 4.

*Chronic kidney disease*

During a mean follow-up of 5.5 (maximum 14.0) years, 798 (4.8%) patients developed chronic kidney disease. At 13 years of follow-up, the regression standardized cumulative incidence of chronic kidney disease was 7.2% (95% CI: 5.8–8.9) in the no-change group compared with 10% (95% CI: 8.5–11.8) in the small-increase group and 16.3% (95% CI: 14.1–18.9) in the AKI stage 1 group. The estimated difference between the no-change and small-increase groups at 13 years was 2.8% (95% CI: 1.1–4.6) and the estimated difference between the no-change and AKI stage 1 groups was 9.2% (95% CI: 6.9–11.5). The regression standardized cumulative incidence of chronic kidney disease is shown in Figure 3.

*Heart failure*

During a mean follow-up of 5.0 (maximum 14.0) years, 3,101 (18.5%) patients were hospitalized for heart failure. At 13 years of follow-up, the regression standardized cumulative incidence of heart failure was 29% (95% CI: 27–31) in the no-change group compared with 32% (95% CI: 30–34) in the small-increase group and 38% (95% CI: 36–40) in the AKI stage 1 group. The estimated difference between the no-change and small-increase groups at 13 years was 3.7% (95% CI: 1.5–5.9), and the estimated difference between the no-change and AKI stage 1 groups was 9.3% (95% CI: 6.7–11.9). The regression standardized cumulative incidence of heart failure is shown in Figure 4.

*Sensitivity and subgroup analyses*

The results of sensitivity analyses conducted in the subset of patients who underwent isolated SAVR were consistent with those of the main analyses (Supplemental Figures 5–7). Similar results were obtained when the main analyses were repeated using inverse probability of treatment weighting with optimization-based weights (Supplemental Figures 9–11) and crude analyses (Supplemental Figures 12–14). Poisson regression with change in serum creatinine as a continuous independent variable (Supplemental Figures 15–17) was performed and yielded similar results. When the clinical outcomes were reassessed after stratification according to eGFR ≥ 60 mL/min/1.73 m2 or eGFR <60 mL/min/1.73 m2 (Supplemental Figures 18–20), the results were consistent with the findings in the total study population, with minimal differences in heart failure and chronic kidney disease between the no-change and small-increase groups. The clinical outcomes were also assessed after stratification according to LVEF > 50% or LVEF ≤ 50% (Supplemental Figures 21–23); results were similar to those in the total study population, although a minimal difference in heart failure and chronic kidney disease was observed between the no-change and small-increase groups.

**Discussion**

In this nationwide population-based cohort study, we observed that a small increase in serum creatinine after SAVR was not significantly associated with long-term all-cause mortality. Both decreases and increases in serum creatinine after SAVR resulted in a stepwise increase in the risk of 30-day all-cause mortality. A small increase in postoperative serum creatinine was associated with a higher risk of long-term chronic kidney disease and heart failure. However, patients with a small increase in serum creatinine did not have as high a risk of long-term all-cause mortality, chronic kidney disease, and heart failure as patients with AKI stage 1.

*All-cause mortality*

In a single-center cohort study of 4,118 patients conducted between 1 January and 31 December 2001, Lassnigg et al. investigated the impact of postoperative serum creatinine changes on long-term and 30-day all-cause mortality after all types of cardiac surgery [14]. The inclusion of all types of cardiac surgery makes a comparison with our results difficult because a different pathophysiology may underlie the postoperative serum creatinine increases of these patients compared with that of patients who underwent SAVR. Nonetheless, in concordance with our results, the authors did not find any association between late mortality and minimal changes in postoperative serum creatinine. The authors also observed that a small increase in serum creatinine (0–0.5 mg/dL) was associated with a threefold increase in 30-day all-cause mortality. However, 5.2% of all patients in Lassnigg et al .’s study died within 30 days of surgery, compared with 1% of patients in our study.

A previous study by Liotta and colleagues included 25,686 patients who underwent elective primary isolated CABG in Sweden from 2000 to 2008 [15]. The authors observed that small increases in serum creatinine (< 26.5 μmol/L) were associated with a significant increase in long-term all-cause mortality. Our findings are consistent with these results. However, our study adds important and novel information about the SAVR population because patients with coronary artery disease often have more general atherosclerosis and thus renal vasculature that is more affected than that of patients who undergo SAVR. In addition, coronary artery disease is associated with an increased risk of insufficient oxygen supply and myocardial injury [37]. Furthermore, patients with coronary artery disease are more frequently affected by peripheral artery disease, which can increase postoperative ischemic complications.

In another study of 9,047 patients who underwent primary isolated SAVR between 1999 and 2013, Rydén et al. investigated the association between AKI after SAVR and all-cause mortality [37]. The Cox regression-adjusted hazard ratio for long-term mortality in the study was 1.27 (95% CI: 1.12–1.44) among patients with AKI stage 1 at 15 years of follow-up. Our results (43% adjusted cumulative incidence of all-cause mortality at 13 years) are aligned with this finding.

The lack of association between a small increase in serum creatinine and long-term survival may be attributable to the typically early death (i.e., within the first 30 postoperative days) of many high-risk patients, yielding a remaining population with a relatively low-risk profile. Serum creatinine values tend to peak on the second postoperative day and return to baseline by day 5 [14,38]. Therefore, patients who survived the first 30 days after surgery may have had sufficient renal function recovery to achieve a long-term survival prognosis similar to that of patients without impaired postoperative renal function.

*Chronic kidney disease*

In a cohort study conducted by Ishani and colleagues that investigated the association between serum creatinine increases after cardiac surgery and the risk of chronic kidney disease, the authors included 20,263 patients without baseline chronic kidney disease who underwent cardiac surgery between 1999 and 2005 [39]. At 5 years of follow-up, the authors observed an adjusted hazard ratio of 1.4 and a 1%–24% increase from baseline in postoperative serum creatinine. Although our study showed an association between a small increase in serum creatinine and the risk of chronic kidney disease, the regression standardized cumulative incidence of chronic kidney disease was only 2.9% with a small postoperative increase in serum creatinine at 5 years of follow-up.

Proposed mechanisms in which postoperative AKI increases the risk of chronic kidney disease include renal fibrosis, loss of renal vascular support for tubular regeneration, and the stimulation of persistent interstitial inflammation [40]. Similar mechanisms may be involved in patients who develop chronic kidney disease following small increases in postoperative serum creatinine.

*Heart failure*

Olsson et al. analyzed the association between AKI and the risk of hospitalization from heart failure in 24,018 patients who underwent primary isolated CABG in Sweden between 2000 and 2008 [4]. After multivariable adjustment, the authors reported that patients with AKI stage 1 had a higher risk of first-time hospitalization from heart failure than patients with no kidney injury (hazard ratio: 1.60, 95% CI: 1.34–1.92). Our findings are consistent with these results: both an increase in postoperative serum creatinine and the presence of AKI stage 1 increased the risk of heart failure. The cardio-renal syndrome type 3 mechanism is often used to explain the association between AKI and cardiac dysfunction [4,41]. Briefly, this mechanism involves the release of inflammatory mediators that cause hemodynamic and electrolyte disturbances that contribute to a higher risk of heart failure.

The KDIGO AKI criteria specify an absolute serum creatinine increase of 26.5 μmol/L; this increase often indicates a substantial reduction in glomerular filtration rate. Furthermore, the increase in serum creatinine appears late in the clinical course of the syndrome [42]. Ronco et al. presented the term “subclinical” AKI as a condition that fails to meet the AKI stage 1 criteria but includes tubular kidney damage and must instead be identified with new AKI biomarkers. Patients with subclinical AKI may exhibit a small increase in serum creatinine but have no significant glomerular function loss [42]. The adverse outcomes associated with the small increases in serum creatinine that were observed in our study support this suggestion. Additionally, detecting subclinical AKI in the population that undergoes SAVR is arguably especially important because these patients are less likely to receive medication that prevents the deterioration of renal function than patients who undergo CABG, who often receive guideline-recommended secondary prevention medication such as aspirin, beta-blockers, and angiotensin-converting enzyme inhibitors [43].

*Strengths and limitations*

The specific strength of our study was the inclusion of all cardiac centers in Sweden, which resulted in a large study population with a high degree of generalizability. The accuracy of Swedish national registries and complete nationwide health data registers provided our study with high-quality data, and follow-up data were complete for all of the patients.

This study also had limitations. First, given the nature of observational studies, residual confounding may have been introduced. Despite a granular characterization of the study population, potentially important baseline patient characteristics such as frailty, urine output, and the use of medications were missing. Other factors that may have affected postoperative serum creatinine levels (e.g., the amount of fluid given, anemia, and duration of CPB) were unavailable. Second, chronic kidney disease and hospitalization from heart failure that occurred outside of Sweden could not be ascertained; however, out-of-country outcomes likely accounted for a minimal number of patients given the universal tax-financed health care coverage in Sweden.

*Conclusions*

We observed no association between a small increase in postoperative serum creatinine and long-term survival after SAVR. Small increases in postoperative serum creatinine were associated with a stepwise increased risk of 30-day all-cause mortality after SAVR and a higher risk of long-term chronic kidney disease and heart failure. Patients who experience small increases in postoperative serum creatinine after SAVR should be monitored closely to detect any early changes in renal and cardiac functions. These negative impacts suggest that extending the KDIGO criteria to include a “ stage 0” (i.e., patients with “subclinical” AKI) may be prudent.

**Data sharing statement**

No data are available.

**Acknowledgments**

We thank the steering committee of the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies for providing data for this study. We also thank Anahid Pinchis from Edanz ([www.edanz.com/ac](https://www.edanz.com/ac)) for editing a draft of this manuscript.

**Contributor statement**

Michael Dismorr and Ulrik Sartipy had full access to all of the study data and are responsible for data integrity and the accuracy of the data analysis.

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Lu, Dismorr.

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**Funding**

This work was supported by the Swedish Heart-Lung Foundation (grant number 20190533 to US and grant number 20220364 and 20190570 to NG), Region Stockholm (ALF Project; grant number FoUI-962048 to US and grant number FoUI-961871 to NG), Region Stockholm clinical postdoctoral appointment (FoUI-955489 to NG), the Swedish Society of Medicine (grant number SLS-934749 to NG), the Eva and Oscar Ahrén Research Foundation (to NG), the Seraphim Hospital Foundation (to NG), the Magnus Bergvall Foundation (grant number 2021-04333 and grant number 2022-117 to NG), the Mats Kleberg Foundation (grant number 2022-119 to NG), the Karolinska Institutet Foundations and Funds (grant number 2022-01575 to NG), donations from the Schörling Foundation, and Mr. Fredrik Lundberg.

**Disclosures**

The authors have no conflicts of interest to disclose.

**References**

**Figure Legends**

**Figure 1. Regression standardized survival and difference in survival.**

*Upper panel:*The curves represent the estimated survival and 95% CIs had the population had no change or a small change in serum creatinine or AKI stage 1. For example, if the entire population had a small increase in serum creatinine, the estimated population survival at 13 years would be 57%.

*Lower left panel:*Estimated difference in survival (95% CI) between the no-change and small-increase serum creatinine groups.

*Lower right panel:*Estimated difference in survival (95% CI) between the no change in serum creatinine and AKI stage 1 groups. CI = confidence interval.

**Figure 2. Number of patients and mortality within 30 days.**

*Upper panel:*Number of patients per serum creatinine change category after surgical aortic valve replacement in Sweden from 2009 to 2022.

*Lower panel:* Mortality within 30 days (%) based on continuous serum creatinine changes.

**Figure 3. Regression standardized chronic kidney disease and difference in chronic kidney disease.**

*Upper panel:*The curves represent the estimated chronic kidney disease and 95% CI had the population had no change or a small change in serum creatinine or AKI stage 1. For example, if the entire population had a small increase in serum creatinine, the estimated population with chronic kidney disease at 13 years would be 10%.

*Lower left panel:*Estimated difference in chronic kidney disease (95% CI) between the no-change and small-increase serum creatinine groups.

*Lower right panel:*Estimated difference in chronic kidney disease (95% CI) between the no change in serum creatinine and AKI stage 1 groups.

CI = confidence interval.

**Figure 4. Regression standardized hospitalization from heart failure and difference in hospitalization from heart failure.**

*Upper panel:*The curves represent the estimated cumulative incidence of hospitalization from heart failure and 95% CI had the population had no change or a small change in creatinine or AKI stage 1. For example, if the entire population had a small increase in serum creatinine, the estimated hospitalization from heart failure at 13 years would be 32%.

*Lower left panel:*Estimated difference in heart failure (95% CI) between the no-change and small-increase serum creatinine groups.

*Lower right panel:*Estimated difference in heart failure (95% CI) between the no change in serum creatinine and AKI stage 1 groups.

CI = confidence interval.