



Heart failure and the risk of acute kidney injury in relation to ejection fraction in patients undergoing coronary artery bypass grafting

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ABSTRACT

Background: We studied the association between heart failure with reduced or preserved ejection fraction (EF) and the risk of acute kidney injury (AKI) in patients undergoing coronary artery bypass surgery (CABG).

Methods: We included all patients who underwent isolated CABG in Sweden 2003 to 2013. AKI was defined according to the Kidney Disease Improving Global Outcomes definition, as an increase in postoperative serum creatinine concentration by $\geq 26 \mu\text{mol/L}$ or $\geq 50\%$, compared to preoperative values. Adjusted odds ratios (OR) for AKI were calculated using logistic regression for patients with and without heart failure, and among patients with heart failure, by EF categories (<30% severely reduced; 30–40% moderately reduced; $\geq 50\%$ preserved).

Results: Included were 36,403 patients of whom 3914 (11%) had heart failure. In patients with heart failure, 26% developed AKI compared with 14% in patients without heart failure. After adjustment for background characteristics, including preoperative kidney function and EF, the OR for AKI was 1.12 (95% CI 1.02–1.23) in patients with heart failure compared with no heart failure. Among patients with heart failure, the adjusted OR for AKI among patients with EF <30% vs. $\geq 50\%$ was 1.32 (95% CI 1.06–1.65) and for 30–49% vs. $\geq 50\%$ 1.06 (95% CI 0.87–1.28), respectively.

Conclusion: Patients with heart failure who underwent CABG had an increased risk for AKI postoperatively even after adjustment for comorbidity such as EF. Among patients with heart failure, having a severely reduced EF was associated with AKI compared to patients with preserved EF.

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1. Introduction

The prevalence of heart failure in the general community is around 2%, and around half of patients with a clinical syndrome of heart failure have a preserved ejection fraction (EF) [1]. Mortality is high in both patients with heart failure and reduced EF and patients with heart failure and preserved EF. Coronary artery disease is the most common cause of heart failure, and heart failure is common in patients undergoing coronary artery bypass grafting (CABG) [2]. Heart failure with preserved EF and reduced EF were both associated with increased short- and long-

term mortality among patients undergoing CABG. After CABG, risk for death was higher in patients with heart failure and reduced EF than in patients with heart failure preserved EF [3]. Yet it was also recently shown that CABG improves outcomes in heart failure with reduced EF [4].

Acute kidney injury (AKI) is a common complication in patients with CABG and is associated with an increased risk of end-stage renal disease, new-onset heart failure, and short- and long-term mortality [5–10]. Heart failure is often regarded as one of the most important risk factors for perioperative AKI [11,12]. However, to the best of our knowledge, there are no studies on heart failure specifically as a risk factor for perioperative AKI, and AKI studies adjusting for heart failure in multivariable models make no distinction between heart failure with preserved EF and heart failure with reduced EF. The study aim was to assess the association between heart failure and the risk of AKI accounting for the EF status in patients undergoing CABG. The study could give new insights

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to the pathophysiologic mechanisms involved in the development of AKI post-CABG and also improve perioperative AKI risk assessment.

2. Methods

In a nationwide population-based observational cohort study we included all patients who underwent a first isolated CABG in Sweden between January 1, 2003 and December 31, 2013. Patients were excluded from the study if they had end-stage renal disease defined as dialysis dependent or having an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m²; if they had missing information on pre- or postoperative serum creatinine samples; or if they had missing information on EF (Fig. 1).

The study population was retrieved from the Swedish Web-system for Enhancement and Development of Evidence based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) register [13,14]. Using the personal identification number assigned to every Swedish resident [15] the Swedish National Board of Wealth and Healthcare linked the cohort with data from the Swedish National Patient Register [16] for additional information on comorbidities and earlier discharge diagnoses, the Swedish National Prescribed Drug Register for information on medication use, and the Longitudinal Integration Database for Health Insurance and Labor Market Studies, from Statistics Sweden, for

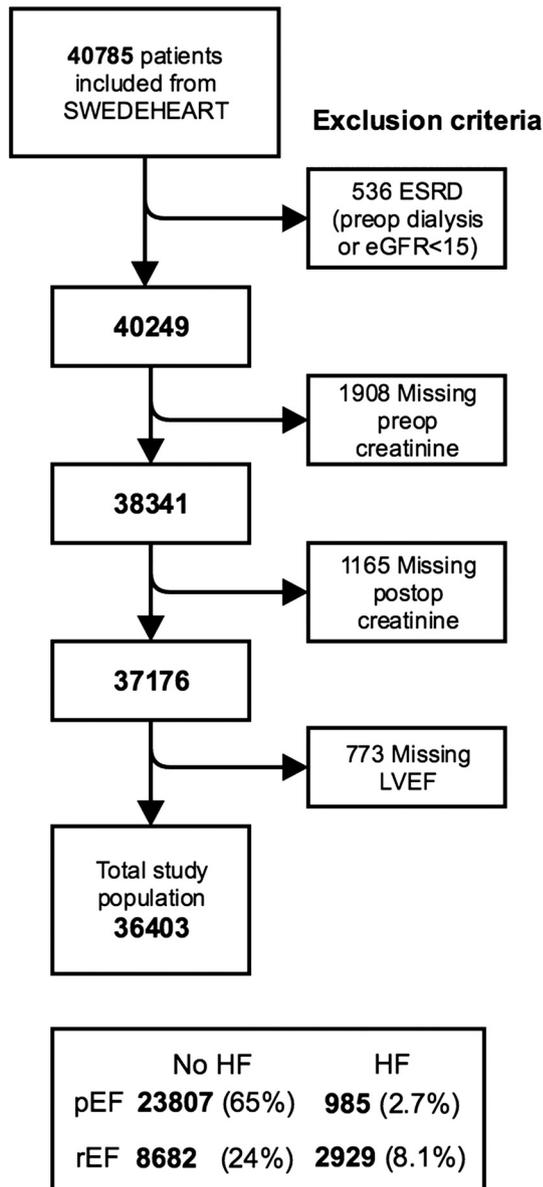


Fig. 1. Exclusion criteria for generating the study population including 36,403 patients undergoing primary isolated coronary artery bypass surgery in Sweden between 2003 and 2013. ESRD, End-stage renal disease; HF, heart failure; LVEF, left ventricular ejection fraction; pEF, preserved ejection fraction; rEF, reduced ejection fraction; SWEDEHEART, Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies.

individual information on educational level, household disposable income, country of birth, and marital status [17]. The investigation conforms to the principles outlined in the Declaration of Helsinki and was approved by the regional ethics committee in Stockholm. The need for informed consent was waived by the committee.

Baseline heart failure was defined as a diagnosis in the Swedish National Patient Register prior to the date of surgery of at least one of the following international classification of disease (ICD) revision 10 codes: I50-I50.9, I42-I43.9, I25.5, I13.0, I13.2, I11.0, and K76.1, or ICD revision 9 codes: 425 and 428. The validity of the heart failure diagnosis in the Swedish National Patient Register has earlier been evaluated; 88–91% of the patients are classified in concordance with the European Society of Cardiology definition [18]. The EF was assessed by echocardiography before surgery and was retrieved from the SWEDEHEART register where it is categorized as $\geq 50\%$, 30%–49%, $<30\%$. A preserved EF was defined as an EF $\geq 50\%$.

The primary outcome AKI was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria as an increase in post- compared with preoperative serum creatinine concentration by ≥ 26 $\mu\text{mol/L}$ or a relative increase of $\geq 50\%$ [12]. The preoperative serum creatinine concentration was in general measured within 24 h before surgery and the postoperative concentration was the highest value during the hospital stay.

Current or prior medical conditions were retrieved from the Swedish National Patient Register where diagnoses are stored as ICD codes. The ICD codes used to define heart failure and co-morbidities are presented in Supplemental Table 1. Glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology collaboration formula [19]. Body mass index was calculated as the weight in kilograms divided by the squared height in meters. Emergent operation was defined as having surgery within 24 h from surgery decision.

Baseline characteristics were described as raw numbers and percentages for categorical data and means and standard deviations or medians and inter-quartile ranges for continuous data, as appropriate. The association between heart failure and AKI was analyzed using multivariable logistic regression. Odds ratios with 95% confidence intervals were reported. We present the crude analysis and multivariable models adjusted for: a) age, sex, eGFR and EF and b) all variables collected including current and prior medical conditions, ethnicity, social factors and EF. To account for potential nonlinear relationships between the continuous variables age, eGFR, and BMI and the outcome, we flexibly modelled the variables using restricted cubic splines with 4 knots. Family disposable income was categorized into 5 categories. All other variables were dichotomous. Primary interaction between EF and heart failure in the full model was tested. The following variables contained missing data: emergent operation (8.2%), body mass index (6.3%), education (2.5%), marital status (0.2%) and birth region (0.1%). Missing data in education, marital status, and birth region were substituted with the most common category. Missing information on body mass index was substituted as the median value according to sex. Missing information in the emergent operation variable was substituted to become a third category, indicating missing information. To address the potential bias of imputation, we performed a complete case analysis, excluding patients with missing information. As another sensitivity analysis, we excluded all patients undergoing emergent operation. In addition, we calculated the *E*-value that identifies the size of the effect that a potential non-measured confounder must have to reduce all the effect of heart failure on AKI [20]. We also performed a subgroup analysis where we only included patients with heart failure and analyzed the association between EF 30–49% or EF $<30\%$ compared to patients with preserved EF $>50\%$. Data management and statistical analysis was performed using Stata version 14.2 (StataCorp LP, College Station, Tx).

3. Results

A total of 36,403 patients were included of whom 11% ($n = 3914$) had heart failure. Patient characteristics stratified by heart failure and EF are presented in Table 1. Patients with heart failure had lower EF and eGFR, and were more likely to have diabetes, atrial fibrillation, chronic obstructive pulmonary disease, and prior myocardial infarction. Emergent operation was more common in patients with no heart failure with reduced EF. Chronic obstructive pulmonary disease was more common in heart failure and reduced EF patients and hypertension was more common in heart failure with preserved EF patients.

In total 15% ($n = 5432$) developed AKI. Among patients without heart failure, 14% ($n = 4432$) developed AKI compared to 26% ($n = 1000$) among patients with heart failure. Patients with heart failure compared to those without heart failure had an increased risk for AKI in both the unadjusted and multivariable adjusted analyses including adjustment for EF (multivariable adjusted OR 1.12, 95% CI 1.02–1.23) although adjustment reduced the OR considerably (Table 2). There was an interaction between heart failure and EF (*P*-value for interaction <0.001).

The OR for the association between heart failure and AKI in the full multivariable adjusted model including EF was 1.12 (95% CI 1.02–1.23). The *E*-value for the model was 1.31 with a lower CI limit of 1.11. This means that the observed OR of 1.12 could be reduced to 1.00 by an unmeasured confounder that had an association with both heart failure and AKI with an OR of 1.31 and possibly as low as 1.11.

Table 1
Baseline characteristics in 36,403 patients undergoing CABG in Sweden between 2003 and 2013 according to HF status and preserved vs. reduced EF.

	All patients	No HF			HF		
		All no HF patients	EF ≥ 50%	EF < 50%	All HF patients	EF ≥ 50%	EF < 50%
No. in category, (% of study population)	36,403 (100%)	32,489 (89%)	23,807 (65%)	8682 (24%)	3914 (11%)	985 (2.7%)	2929 (8.0%)
Age, years, mean (SD)	67 (9.2)	67 (9.2)	67 (9.2)	68 (9.2)	70 (9.0)	70 (9.4)	69 (8.9)
Female sex, no. (%)	7520 (21%)	6582 (20%)	5002 (21%)	1580 (18%)	938 (24%)	302 (31%)	636 (22%)
Left ventricular ejection fraction, no. (%)							
≥50%	24,792 (68%)	23,807 (73%)	23,807 (100%)	0 (0.0%)	985 (25%)	985 (100%)	0 (0%)
30–49%	9814 (27%)	7823 (24%)	0 (0%)	7823 (90%)	1991 (51%)	0 (0%)	1991 (68%)
<30%	1797 (4.9%)	859 (2.6%)	0 (0%)	859 (9.9%)	938 (24%)	0 (0%)	938 (32%)
eGFR, mL/min/1.73 m ² , mean (SD)	76 (18)	77 (18)	78 (17)	74 (19)	67 (21)	69 (21)	67 (21)
eGFR categories, no. (%)							
>60 mL/min/1.73 m ²	28,680 (79%)	26,286 (81%)	19,711 (83%)	6575 (76%)	2394 (61%)	632 (64%)	1762 (60%)
45–60 mL/min/1.73 m ²	5369 (15%)	4499 (14%)	3067 (13%)	1432 (17%)	870 (22%)	206 (21%)	664 (23%)
30–45 mL/min/1.73 m ²	1934 (5.3%)	1435 (4.4%)	879 (3.7%)	556 (6.4%)	499 (13%)	112 (11%)	387 (13%)
15–30 mL/min/1.73 m ²	420 (1.2%)	269 (0.8%)	150 (0.6%)	119 (1.4%)	151 (3.9%)	35 (3.6%)	116 (4.0%)
Diabetes mellitus, no. (%)	9369 (26%)	7819 (24%)	5370 (23%)	2449 (28%)	1550 (40%)	368 (37%)	1182 (40%)
Body Mass Index, kg/m ² , mean (SD)	27 (4.1)	27 (4.0)	27 (4.0)	27 (4.1)	28 (4.6)	28 (4.8)	27 (4.5)
Prior myocardial infarction, no. (%)	20,519 (56%)	17,486 (54%)	10,941 (46%)	6545 (75%)	3033 (78%)	704 (72%)	2329 (80%)
Prior PCI, no. (%)	6238 (17%)	5400 (17%)	3815 (16%)	1585 (18%)	838 (21%)	266 (27%)	572 (20%)
Atrial fibrillation, no. (%)	2408 (6.6%)	1665 (5.1%)	1066 (4.5%)	599 (6.9%)	743 (19%)	201 (20%)	542 (19%)
COPD, no. (%)	2909 (8.0%)	2309 (7.1%)	1462 (6.1%)	847 (9.8%)	600 (15%)	113 (12%)	487 (17%)
Hypertension, no. (%)	14,712 (40%)	12,705 (39%)	9409 (40%)	3296 (38%)	2007 (51%)	620 (63%)	1387 (47%)
Hyperlipidemia, no. (%)	9066 (25%)	7900 (24%)	5971 (25%)	1929 (22%)	1166 (30%)	335 (34%)	831 (28%)
Peripheral vascular disease, no. (%)	3863 (11%)	3158 (9.7%)	2008 (8.4%)	1150 (13%)	705 (18%)	170 (17%)	535 (18%)
Stroke, no. (%)	3246 (8.9%)	2675 (8.2%)	1790 (7.5%)	885 (10%)	571 (15%)	165 (17%)	406 (14%)
Cancer, no. (%)	2255 (6.2%)	1976 (6.1%)	1401 (5.9%)	575 (6.6%)	279 (7.1%)	86 (8.7%)	193 (6.6%)
Alcohol dependency, no. (%)	847 (2.3%)	720 (2.2%)	489 (2.1%)	231 (2.7%)	127 (3.2%)	35 (3.6%)	92 (3.1%)
Birth region, no. (%)							
Nordic countries	32,761 (90%)	29,295 (90%)	21,541 (91%)	7754 (90%)	3466 (89%)	873 (89%)	2593 (89%)
Other	3600 (9.9%)	3153 (9.7%)	2244 (9.4%)	909 (11%)	447 (11%)	112 (11%)	335 (11%)
Education, no. (%)							
<10 years	15,432 (44%)	13,597 (43%)	9675 (41%)	3922 (47%)	1835 (49%)	471 (51%)	1364 (49%)
10–12 years	13,819 (39%)	12,468 (39%)	9274 (40%)	3194 (38%)	1351 (36%)	329 (35%)	1022 (37%)
>12 years	6258 (18%)	5730 (18%)	4413 (19%)	1317 (16%)	528 (14%)	129 (14%)	399 (14%)
Marital status, no. (%)							
Married	24,034 (66%)	21,701 (67%)	16,094 (68%)	5607 (65%)	2333 (60%)	596 (61%)	1737 (59%)
Not married	4583 (13%)	3995 (12%)	2815 (12%)	1180 (14%)	588 (15%)	129 (13%)	459 (16%)
Divorced	5666 (16%)	4985 (15%)	3661 (15%)	1324 (15%)	681 (17%)	169 (17%)	512 (18%)
Widowed	2057 (5.7%)	1746 (5.4%)	1200 (5.0%)	546 (6.3%)	311 (7.9%)	91 (9.2%)	220 (7.5%)
Household disposable income, SEK ^a , median (interquartile range)	243,643 (166,950 to 347,500)	248,656 (171,060 to 352,529)	257,320 (176,560 to 361,614)	227,680 (156,667 to 330,300)	202,991 (138,355 to 295,416)	197,830 (136,983 to 300,236)	205,016 (138,589 to 293,640)
Emergent operation, no. (%)	1556 (4.7%)	1412 (4.7%)	705 (3.2%)	707 (8.8%)	144 (4.0%)	28 (3.1%)	116 (4.3%)

^a 1 SEK = 0.10 Euro = 0.09 British Pound = 0.12 USD (12Jan2018). CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; EF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; PCI, percutaneous coronary intervention; SD, standard deviation; SEK, Swedish krona.

In the analysis investigating the association between preoperative EF categories and the risk for AKI among patients with heart failure, there was an increased risk for AKI in patients with heart failure and EF <30% compared to patients with heart failure and preserved EF ≥50% (OR 1.32, 95% CI 1.06–1.65). No association with AKI was found when comparing patients with heart failure and EF 30–49% compared

to patients with heart failure and preserved EF >50% (OR 1.06, 95% CI 0.87–1.28) (Table 3).

The sensitivity analyses; (1) complete case analysis and (2) analysis excluding patients undergoing emergent operation, showed similar results as the primary analysis. The results are presented in the Supplemental material.

Table 2
Association between a preoperative diagnosis of HF and AKI in 36,403 patients who underwent primary isolated CABG.

	No HF	HF	
Number events/Number of patients (%)	4432/32489 (14%)	1000/3914 (26%)	
Crude	1.00	OR (95% CI)	AIC
Adjusted for age, sex, eGFR, EF ^a	1.00	2.17 (2.01–2.35)	30,340
Multivariable adjusted ^{a, b}	1.00	1.24 (1.14–1.36)	28,326
		1.12 (1.02–1.23)	27,534

AIC, Akaike information criterion; AKI, acute kidney injury; CABG, coronary artery bypass grafting; CI, confidence interval; EF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; OR, odds ratio.

^a EF was defined according to three categories: ≥50%, 30–49%, <30%.

^b Multivariable adjustment was made for all variables in Table 1 including EF.

Table 3
Association between preoperative EF and AKI among patients with heart failure who underwent primary isolated CABG.

	EF		
	≥50% ^a	30 to 49%	<30%
Number events/Number of patients (%)	233/985 (24)	508/1991 (26)	259/938 (28)
Crude, OR (95% CI)	1.00	1.11 (0.93–1.32)	1.23 (1.00–1.51)
Multivariable adjusted ^b , OR (95% CI)	1.00	1.06 (0.87–1.28)	1.32 (1.06–1.65)

AKI, acute kidney injury; CABG, coronary artery bypass grafting; CI, confidence interval; EF, left ventricular ejection fraction.

^a Reference category.

^b Multivariable adjustment was made for all variables in Table 1 except EF.

The 30-day mortality among patients with no heart failure was 1.1% ($n = 346$) and in patient with heart failure 3.1% ($n = 120$). The 30-day mortality according to EF categories in patients with no heart failure was 0.7% ($n = 155$), 1.6% ($n = 125$), 7.7% ($n = 66$) in patients with EF $\geq 50\%$, EF 30 to 49%, and $< 30\%$, respectively. The 30-day mortality according to EF categories in patients with heart failure was 2.0% ($n = 20$), 2.4% ($n = 48$), 5.5% ($n = 52$) in patients with EF $\geq 50\%$, EF 30 to 49%, and $< 30\%$, respectively. The Kaplan-Meier estimated 5-year survival was among patients with no heart failure 91% (95% CI, 90–91%) and among patient with heart failure 73% (95% CI, 72–75%).

4. Discussion

The primary finding of this study was that there was an association between heart failure and an increased risk of AKI after CABG regardless of preoperative EF and background characteristics. Second, among patients with heart failure compared to those with EF $\geq 50\%$, patients with EF 30–49% did not have a higher risk for AKI, but patients with EF $< 30\%$ did.

The cornerstone contributors to perioperative AKI can be divided into decreased perfusion, venous congestion, inflammation, and nephrotoxic medications [21]. Reported risk factors for developing perioperative AKI are age, female sex, chronic kidney disease, diabetes, chronic obstructive pulmonary disease, peripheral vascular disease, high body mass index and heart failure [11,12,22,23]. In this study, we were able to account for all these risk factors. Preoperative conditions such as dehydration, anemia, and acute decompensated heart failure are also reported to be associated with AKI [11]. Perioperative risk factors for AKI include hypotension, hypovolemia, blood loss, anemia, blood transfusions, and cardiopulmonary bypass [24]. Many preoperative conditions and perioperative risk factors may cause hemodynamic alterations. To maintain the kidneys' glomerular filtration capacity, the glomeruli need a high blood flow. On the other hand, a low blood flow is necessary in the renal medulla to maintain a high osmotic gradient enabling fluid reabsorption [25]. The renal medulla is therefore very sensitive to disturbances in renal perfusion and oxygen delivery. AKI is very common in patients with acute decompensated heart failure and this association have been presumed to be a truth in the perioperative setting [26]. Since the kidneys are very sensitive to hemodynamic alterations, this assumption is very reasonable. However, to our knowledge, heart failure as a risk factor for perioperative AKI have not been studied specifically.

The association found between heart failure and AKI even after multivariable adjustment including preoperative EF suggests that heart failure is a relevant risk factor for perioperative AKI. Heart failure should be taken in account when assessing perioperative AKI risk and planning the design of AKI studies.

In the primary analysis we found an interaction between heart failure and EF and the risk for AKI. This is in line with the analysis including only patients with heart failure where patients with heart failure and EF 30–49% compared to patients with heart failure and EF $\geq 50\%$ did not have a higher risk for AKI, but patients with heart failure and EF $< 30\%$ did. This suggests that the risk for AKI in patients with heart failure with preserved EF and patients with heart failure and EF 30–49% is comparable but having heart failure and EF $< 30\%$ further increases the risk for AKI. It may be surprising that EF 30–49% was not associated with increased risk compared to $\geq 50\%$. But it is becoming increasingly well described that the mid-range and preserved EF groups have distinctly lower risk of cardiovascular events compared to severely reduced EF in heart failure and our findings suggest that this applies also to renal outcomes [27,28]. The observation is also reasonable given that a low EF reflects disease severity in heart failure. The result is also in line with Dalén et al.'s study on patients undergoing CABG showing higher mortality in patients with heart failure and reduced EF than in patient with heart failure and preserved EF [3]. The results suggest that taking

into account EF can improve AKI risk assessment and the design of AKI studies.

A strength of the study was the large nationwide study population including all patients who underwent cardiac surgery during the study period. The study has thereby high generalizability due to the nationwide complete coverage. The quality of the heart failure diagnosis have earlier been evaluated and is considered as good [16]. In addition, the heart failure diagnosis might be even more valid in this cohort than the general population since we may assume all patients were evaluated by cardiologists before undergoing the CABG [17]. However, there is a risk of misclassification of exposure since some patients might have been classified as not having heart failure due to a normal EF, even though fulfilling the criteria for heart failure with preserved EF. There is also a risk that patients were diagnosed with heart failure only on the basis of a reduced EF, or that patients with a reduced EF had signs, and symptoms of heart failure, but never needed hospitalization, and were not labeled as having heart failure in the registry. Although there was an increased risk for AKI in patients with heart failure that continued after multivariable adjustment, there may be residual confounding due to factors that we were not able to measure, for example medical treatment. Also, we had no information on severity of symptoms as New York Heart Association class. Information about EF was only available in categories because in SWEDHEART it is reported as $\geq 50\%$, 30% to 49%, and $< 30\%$. We had no information on perioperative information such as time under cardiopulmonary bypass or amount of intravenous fluid and transfusions given, or vasoactive therapies. However, many perioperative risk factors for AKI are associated with preoperative heart failure and can be on the causal pathway between heart failure and AKI. Adjustment for them may bias estimates of the association between the exposure and the outcome. We had no information on natriuretic peptide concentrations, atrial enlargement, left ventricular hypertrophy, or left ventricular relaxation or filling, to further support the heart failure with preserved EF diagnosis.

5. Conclusions

Patients with heart failure who underwent CABG had an increased risk for AKI postoperatively even after adjustment for comorbidity such as ejection fraction. Among patients with heart failure, having a severely reduced ejection fraction, was associated with AKI compared to patients with preserved ejection fraction.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2018.09.092>.

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None.

References

- [1] R.S. Bhatia, J.V. Tu, D.S. Lee, P.C. Austin, J. Fang, A. Haouzi, Y. Gong, P.P. Liu, Outcome of heart failure with preserved ejection fraction in a population-based study, *N. Engl. J. Med.* 355 (2006) 260–269.
- [2] D.M. Lloyd-Jones, M.G. Larson, E.P. Leip, A. Beiser, R.B. D'Agostino, W.B. Kannel, J.M. Murabito, R.S. Vasan, E.J. Benjamin, D. Levy, Framingham Heart Study, Lifetime risk for developing congestive heart failure: the Framingham heart study, *Circulation* 106 (2002) 3068–3072.
- [3] M. Dalén, L.H. Lund, T. Ivert, M.J. Holzmann, U. Sartipy, Survival after coronary artery bypass grafting in patients with preoperative heart failure and preserved vs reduced ejection fraction, *JAMA Cardiol* 1 (2016) 530–538.
- [4] M.C. Petrie, P.S. Jhund, L. She, C. Adlbrecht, T. Doenst, J.A. Panza, J.A. Hill, K.L. Lee, J.L. Rouleau, D.L. Prior, I.S. Ali, J. Maddury, K.S. Golba, H.D. White, P. Carson, L. Chrzanowski, A. Romanov, A.B. Miller, E.J. Velazquez, S.T.I.C.H. Trial Investigators, Ten-year outcomes after coronary artery bypass grafting according to age in patients with heart failure and left ventricular systolic dysfunction: an analysis of the extended follow-up of the STICH trial (surgical treatment for ischemic heart failure), *Circulation* 134 (2016) 1314–1324.
- [5] D. Olsson, U. Sartipy, F. Braunschweig, M.J. Holzmann, Acute kidney injury following coronary artery bypass surgery and long-term risk of heart failure, *Circ Heart Fail* 6 (2013) 83–90.
- [6] M. Liotta, D. Olsson, U. Sartipy, M.J. Holzmann, Minimal changes in postoperative creatinine values and early and late mortality and cardiovascular events after coronary artery bypass grafting, *Am. J. Cardiol.* 113 (2014) 70–75.
- [7] L. Rydén, S. Ahnve, M. Bell, N. Hammar, T. Ivert, U. Sartipy, M.J. Holzmann, Acute kidney injury after coronary artery bypass grafting and long-term risk of myocardial infarction and death, *Int. J. Cardiol.* 172 (2014) 190–195.
- [8] L. Rydén, U. Sartipy, M. Evans, M.J. Holzmann, Acute kidney injury after coronary artery bypass grafting and long-term risk of end-stage renal disease, *Circulation* 130 (2014) 2005–2011.
- [9] L. Rydén, S. Ahnve, M. Bell, N. Hammar, T. Ivert, M.J. Holzmann, Acute kidney injury following coronary artery bypass grafting: early mortality and postoperative complications, *Scand. Cardiovasc. J.* 46 (2012) 114–120.
- [10] J.W. Pickering, M.T. James, S.C. Palmer, Acute kidney injury and prognosis after cardiopulmonary bypass: a meta-analysis of cohort studies, *Am. J. Kidney Dis.* 65 (2015) 283–293.
- [11] C.V. Thakar, Perioperative acute kidney injury, *Adv. Chronic Kidney Dis.* 20 (2013) 67–75.
- [12] J.A. Kellum, N. Lameire, A.K.I. Kdigo, Guideline work group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (part 1), *Crit. Care* 17 (2013) 204.
- [13] T. Jernberg, M.F. Attebring, K. Hambræus, T. Ivert, S. James, A. Jeppsson, B. Lagerqvist, B. Lindahl, U. Stenstrand, L. Wallentin, The Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART), *Heart* 96 (2010) 1617–1621.
- [14] P. Vihholm, T. Ivert, J. Nilsson, A. Holmgren, W. Freter, L. Ternström, H. Ghaidan, U. Sartipy, C. Olsson, H. Granfeldt, S. Ragnarsson, Ö. Friberg, Validity of the Swedish Cardiac Surgery Registry, *Interact. Cardiovasc. Thorac. Surg.* 27 (2018) 67–74.
- [15] J.F. Ludvigsson, P. Otterblad-Olausson, B.U. Pettersson, A. Ekblom, The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research, *Eur. J. Epidemiol.* 24 (2009) 659–667.
- [16] J.F. Ludvigsson, E. Andersson, A. Ekblom, M. Feychting, J.-L. Kim, C. Reuterwall, M. Heurgren, P.O. Olausson, External review and validation of the Swedish national inpatient register, *BMC Public Health* 11 (2011) 450.
- [17] L. Emilsson, B. Lindahl, M. Köster, M. Lambe, J.F. Ludvigsson, Review of 103 Swedish healthcare quality registries, *J. Intern. Med.* 277 (2015) 94–136.
- [18] E. Ingelsson, J. Arnlöv, J. Sundström, L. Lind, The validity of a diagnosis of heart failure in a hospital discharge register, *Eur. J. Heart Fail.* 7 (2005) 787–791.
- [19] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, CKD-EPI (chronic kidney disease epidemiology collaboration). A new equation to estimate glomerular filtration rate. *Ann. Intern. Med.* 2009;150:604–612.
- [20] T.J. Vanderweele, P. Ding, Sensitivity analysis in observational research: introducing the E-value, *Ann. Intern. Med.* 167 (2017) 268–274.
- [21] M. Legrand, D. Payen, Case scenario: hemodynamic management of postoperative acute kidney injury, *Anesthesiology* 118 (2013) 1446–1454.
- [22] K.E. O'Sullivan, J.S. Byrne, A. Hudson, A.M. Murphy, D.M. Sadlier, J.P. Hurley, The effect of obesity on acute kidney injury after cardiac surgery, *J. Thorac. Cardiovasc. Surg.* 150 (2015) 1622–1628.
- [23] M.E. Grams, B.C. Astor, L.D. Bash, K. Matsushita, Y. Wang, J. Coresh, Albuminuria and estimated glomerular filtration rate independently associate with acute kidney injury, *J. Am. Soc. Nephrol.* 21 (2010) 1757–1764.
- [24] M. Haase, A. Shaw, Acute kidney injury and cardiopulmonary bypass: special situation or same old problem? *Contrib. Nephrol.* 165 (2010) 33–38.
- [25] W.F. Boron, E.L. Boulpaep, Eds. *Medical Physiology: A Cellular and Molecular Approach*. 2nd Ed., International Ed, Saunders/Elsevier, Philadelphia, PA, 2009.
- [26] P. Susantitaphong, D.N. Cruz, J. Cerda, M. Abulfaraj, F. Alqahtani, I. Koulouridis, B.L. Jaber, Acute Kidney Injury Advisory Group of the American Society of Nephrology, World incidence of AKI: a meta-analysis, *Clin. J. Am. Soc. Nephrol.* 8 (2013) 1482–1493.
- [27] L.H. Lund, B. Claggett, J. Liu, C.S. Lam, P.S. Jhund, G.M. Rosano, K. Swedberg, S. Yusuf, C.B. Granger, M.A. Pfeffer, J.J.V. McMurray, S.D. Solomon, Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum, *Eur. J. Heart Fail.* 20 (2018) 1230–1239.
- [28] O. Vedin, C.S.P. Lam, A.S. Koh, L. Benson, T.H.K. Teng, W.T. Tay, O.Ö. Braun, G. Savarese, U. Dahlström, L.H. Lund, Significance of ischemic heart disease in patients with heart failure and preserved, midrange, and reduced ejection fraction: a Nationwide cohort study, *Circ Heart Fail* 10 (2017).