Prevalence and prognostic impact of kidney disease on heart failure patients

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ABSTRACT

Objectives: The aim was to determine the prevalence of different degrees of kidney dysfunction and to examine their association with short-term and long-term outcomes in a large unselected contemporary heart failure population and some of its subgroups. We examined to what extent the different cardiac conditions and their severity contribute to the prognostic value of kidney dysfunction in heart failure.

Design: We studied 47,716 patients in the Swedish Heart Failure Registry. Patients were divided into five renal function strata based on estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation. The adjusted association between kidney function and outcome was examined by Cox regression.

Results: 51% of the patients had eGFR <60 mL/min/1.73 m² and 11% had eGFR <30. There was increasing mortality with decreasing kidney function regardless of age, presence of diabetes, New York Heart Association NYHA class, duration of heart failure and haemoglobin levels. The risk HR (95% CI) persisted after adjusting for differences in baseline characteristics, severity of heart disease, and medical treatment: eGFR 60–89: 0.86 (0.79 to 0.95); eGFR 30–59: 1.13 (1.03 to 1.24); eGFR 15–29: 1.85 (1.67 to 2.07); and eGFR <15: 2.96 ([2.53 to –3.47]), compared with eGFR ≥90.

Conclusions: Kidney dysfunction is common and strongly associated with short-term and long-term outcomes in patients with heart failure. This strong association was evident in all age groups, regardless of NYHA class, duration of heart failure, haemoglobin level, and presence/absence of diabetes mellitus. After adjusting for differences in baseline data, aetiology and severity of heart disease and treatment, the strong association remained.

INTRODUCTION

Heart failure is a serious condition with high mortality despite all modern treatment. Many factors contribute to the poor outcome in heart failure. Kidney dysfunction occurs in acute and chronic heart failure, and is associated with reduced survival. Over the years, our knowledge of the interaction between the heart and the kidney has increased, and parts of the pathophysiological background for the cardiorenal syndrome have been established. The heart and kidney function are closely linked together by haemodynamics, neurohormones and the sympathetic nervous system.

The cardiorenal syndrome is complex as heart failure and kidney disease share common risk factors and potentiate each other and other cardiovascular diseases. Most of the previous studies examining the prognostic value of kidney function in heart failure patients have been hampered mainly by inclusion of highly selected randomised controlled trial patients or small sample sizes, and have not been able to examine the whole spectrum of kidney dysfunction. In earlier large studies, the diagnoses of
kidney disease have mainly been based on diagnostic
codes, or defined only by a certain level of
creatinine. Most previous studies have examined
short-term prognosis, whereas long-term follow-up has
been uncommon. Moreover, descriptions of the
prognostic value of kidney dysfunction in important
subgroups have been lacking.

The aim of this study was to determine the preva-
ience of different degrees of kidney dysfunction and to
examine their association with short-term and long-
term outcome in a large unselected contemporary
heart failure population and some of its subgroups. We
also wanted to examine to what extent different
cardiac conditions and their severity contribute to the
prognostic value of kidney dysfunction in heart failure
patients.

METHODS
The Swedish heart failure register (SwedeHF) has been
described in detail elsewhere. SwedeHF has since 2000
included patients with chronic heart failure and offers a
unique possibility to study a large cohort of unselected
heart failure patients.

It is a web-based national quality register including
unselected heart failure patients, of whom 55% are
registered during hospitalisation, while the remaining
are registered in an outpatient setting at the hospital or
in primary care. Inclusion criteria are clinician-judged
heart failure and approximately 80 variables are
recorded at discharge or during visit to a physician or
healthcare team. The patients are informed of their par-
ticipation in the SwedeHF and are allowed to opt out,
but individual patient consent is not required. Uppsala
Clinical Research Center (Uppsala, Sweden) is man-
aging the database. Variables in the registry include
baseline description of the patients, risk factors, history
of heart disease, cardiac interventions, cardiac evalu-
atation (ECG and echocardiogram), medication, and
laboratory tests at discharge or at the outpatient visit.
The protocol, registration form and annual report are
available at http://www.rikssvikt.se

Only centres using creatinine measurements from
methods that are traceable to isotope dilution mass spec-
troscopy standards were included. Glomerular filtration
rate (eGFR) was estimated with the Chronic Kidney
Disease Epidemiology Collaboration (CKD-EPI)
equation. All patients were divided according to the current
National Kidney Foundation Kidney Disease Outcomes
Quality Initiative (KDIGO) recommendations into five
renal function categories with eGFR (mL/min/1.73 m²):
higher or equal to 90 (eGFR ≥90, normal function),
eGFR higher or equal to 60 but below 90 (eGFR 60–89, mild
dysfunction), eGFR higher or equal to 30 but below 60 (eGFR
30–59, moderate dysfunction), eGFR higher or equal
to 15 but below 30 (eGFR 15–29, severe dysfunction) and
eGFR less than 15 (eGFR <15, end stage renal disease
(ESRD)). Owing to lack of data on albuminuria, these
categories can only be con-
 Considered as renal function strata and not chronic kidney
disease (CKD) stages.

Information about mortality was obtained by linkage
with the Swedish population registry, which includes
the vital status of all Swedish citizens. The registry and
the study conform to the declaration of Helsinki and the
study was approved by the local ethical authority.

Statistics
Continuous variables are presented as median and IQR,
and categorical variables are presented as counts and
proportions (%). p Values for trends were assessed by
Pearson χ² for proportions and Kruskal-Wallis test for
continuous variables. The index date was date of admis-
sion to hospital or date of outpatient visit, respectively.
Crude survival was assessed and illustrated by
Kaplan-Meier analyses. After graphically checking the
model assumption of proportional hazard, univariable
and multivariable Cox proportional hazard regression
was used to examine the association between kidney
function and outcome. In the first model, we adjusted
for baseline variables possibly influencing both kidney
dysfunction and outcome (age, gender, smoking, hyper-
tension and diabetes). In the second model, we added
variables related to the aetiology and severity of heart
failure (heart failure >6 months, ischaemic heart
disease, atrial fibrillation, valvular heart disease, dilated
cardiomyopathy, previous revascularisation, previous
valvular intervention, non-sinus rhythm in the electro-
cardiogram, heart rate, left ventricular ejection fraction
(LVEF), New York Heart Association (NYHA) class, sys-
tolic blood pressure and haemoglobin level). In the
third model, we also adjusted for the given treatment
(ACE inhibitors, angiotensin-receptor blocker (ARB),
β-blockers, aldosterone antagonists, statins and cardiac
resynchronisation therapy (CRT)). To ensure linearity,
the univariable association of different categorisations
of the continuous variables and outcome was examined.
Body mass index and heart rate were divided into quar-
tiles before entry into the models, and age was divided
into age/10 years. Haemoglobin (Hb) and systolic blood
pressure were divided in to four clinically-based categor-
ies: Hb >150 g/L (as reference), Hb 120
–
149 g/L, Hb
110–119 g/L, and Hb <90 g/L; systolic blood pressure
>140 mm Hg (as reference), 110–139 mm Hg, 90–
109 mm Hg, and <90 mm Hg.

RESULTS
From 11 May 2000 to 3 October 2013, a total of 88 317
registrations occurred in SwedeHF. Only the first regis-
tration in the registry were included, and patients who
lacked information on age, creatinine and confirmation
that creatinine had been measured by a standardised
method were excluded. Thus, 47 716 patients were
included in the analyses (figure 1).
Kidney function and heart disease

A total of 24,225 (51%) patients had moderate kidney dysfunction (eGFR <60 mL/min/1.73 m²) and 5,065 (11%) had severe kidney dysfunction (eGFR <30 mL/min/1.73), of which 813 (2%) was classified as ESRD (eGFR <15 mL/min/1.73 m²; table 1).

The median (IQR) age of the population was 77 (67–84) years with higher age in those with worse kidney dysfunction (table 1). Patients with lower kidney function were more often female with more hypertension and diabetes mellitus.

Also, patients with poor kidney function more often had ischaemic heart disease; however, they had a similar rate of previous revascularisation. Atrial fibrillation, stroke and valvular heart disease were more common in those with poor kidney function; however, they less often had dilated cardiomyopathy. Patients with lower kidney function more often had heart failure with a known duration of more than 6 months and were more often hospitalised at inclusion. Mildly symptomatic heart failure was more common in those with preserved kidney function and severe heart failure increased with worsened kidney function. Preserved ejection fraction was more common in those with low eGFR, whereas severe left ventricular systolic dysfunction (LVEF <30%) was more common in those with preserved kidney function.

Physical findings

Regarding heart rate, blood pressure and body mass index, there were no major differences between the eGFR strata (table 2). Presence of left bundle branch block and QRS width did not differ between eGFR strata. The laboratory data showed that patients with low eGFR more often exhibited low haemoglobin and a high potassium level, and a markedly higher level of N-terminal pro-brain natriuretic peptide (NT-proBNP).

Treatment

Patients with low kidney function were less likely to be treated with ACE inhibitor, β-blockers, and aldosterone blockade (table 2). If treated, they were also less likely to receive what was considered by guidelines to be the target dose of ACE inhibitor, ARB and β-blockers. Statins and anticoagulant treatment were used less often whereas aspirin was used more often in those with poor kidney function.

Outcome

Almost one-third of the hospitalised patients in the poorest eGFR strata (eGFR <15) died during the actual hospitalisation. Half of all patients with ESRD (eGFR <15) had died after 6 months and after 1 year, over 40% of those with severe kidney dysfunction (eGFR 15–29) and 60% of the patients with ESRD (eGFR<15) had died (table 3).

There was an increasing mortality with decreasing kidney function regardless of age, presence of diabetes or not, NYHA class, and haemoglobin levels (figure 2A, B).

Although patients with heart failure for more than 6 months had a higher 1-year mortality than patients with heart failure of a shorter duration (25% vs 16%), the prognosis was mainly dependent on the eGFR. One-year mortality in patients with normal kidney function was 7% for heart failure under 6 months versus 8% for heart failure over 6 months; in patients with eGFR<15, the 1-year mortality was 61% versus 63% (see online supplementary table S1).

During long-term follow-up, the cumulative probability of death in 5 years was above 80% in patients with at least severe kidney dysfunction (eGFR <30), and 60% in those with moderate kidney dysfunction (eGFR 30–59; figure 3A). Even in the age group below 65 years, the prognosis was sinister with a 60% probability of death in 5 years for those with severe kidney dysfunction (figure 3B).

When adjusting for baseline variables possibly influencing both kidney dysfunction and outcome (age, gender, smoking, hypertension and diabetes) in model 1, the association between eGFR and mortality was attenuated (table 3). When adding heart failure-related
variables in model 2, the association between eGFR strata and mortality was further somewhat weakened, but still significant. When adjusting for differences in medical treatment in model 3, the association between eGFR strata and mortality remained unchanged.

**DISCUSSION**

The present study has several important findings. First, kidney function is indeed strongly associated with short and long-term mortality in heart failure patients. In hospitalised patients, the inhospital mortality increased from 2% in those with normal kidney function (eGFR >90) to 30% in those with ESRD (eGFR <15). For 5-year mortality, this cumulative probability of death was above 60% in those with moderate kidney dysfunction and above 80% in patients with severe kidney dysfunction. Second, this strong association with outcome was evident in all age groups regardless of NYHA class, duration of heart failure, haemoglobin level and presence or absence of diabetes mellitus. Third, after a stepwise adjustment for differences in baseline data, aetiology, and severity of heart disease and treatment, the strong association remained.

Damman et al has recently, in a meta-analysis including more than 1 million patients, clearly demonstrated the strong association between kidney function and outcome. Our study is so far the largest and most extensively covariate-adjusted cohort study on the association between kidney dysfunction and outcome in an unselected heart failure population. The size of the study and the long-term follow-up allowed us to examine the

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics</th>
<th>eGFR ≥90 n=5251</th>
<th>eGFR 60–89 n=18 240</th>
<th>eGFR 30–59 n=19 160</th>
<th>eGFR 15–29 n=4252</th>
<th>eGFR &lt;15 n=813</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
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</tr>
<tr>
<td>Age (years) (n=47 716)</td>
<td>60 (51–66)</td>
<td>74 (65–81)</td>
<td>81 (74–86)</td>
<td>83 (78–88)</td>
<td>81 (73–87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female (n=47 716)</td>
<td>27%</td>
<td>35%</td>
<td>44%</td>
<td>50%</td>
<td>42%</td>
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<td><strong>Risk factors</strong></td>
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</tr>
<tr>
<td>Hypertension (n=47 702)</td>
<td>36%</td>
<td>45%</td>
<td>52%</td>
<td>57%</td>
<td>62%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus (n=47 704)</td>
<td>21%</td>
<td>21%</td>
<td>26%</td>
<td>35%</td>
<td>36%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (n=47 711)</td>
<td>24%</td>
<td>11%</td>
<td>6%</td>
<td>5%</td>
<td>8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol overconsumption (n=47 703)</td>
<td>6%</td>
<td>3%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Heart disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction (n=18 285)</td>
<td>24%</td>
<td>29%</td>
<td>37%</td>
<td>41%</td>
<td>37%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischaemic heart disease (n=47 698)</td>
<td>33%</td>
<td>41%</td>
<td>50%</td>
<td>56%</td>
<td>54%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter (n=47 702)</td>
<td>32%</td>
<td>48%</td>
<td>54%</td>
<td>52%</td>
<td>42%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valvular heart disease (n=47 699)</td>
<td>14%</td>
<td>19%</td>
<td>23%</td>
<td>24%</td>
<td>19%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dilated cardiomyopathy (n=47 698)</td>
<td>22%</td>
<td>12%</td>
<td>7%</td>
<td>5%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy (n=29 648)</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>0.672</td>
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<tr>
<td><strong>Comorbidity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Previous stroke (n=18 281)</td>
<td>7%</td>
<td>12%</td>
<td>15%</td>
<td>17%</td>
<td>19%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary disease (n=47 704)</td>
<td>17%</td>
<td>17%</td>
<td>18%</td>
<td>19%</td>
<td>18%</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Previous procedures</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Revascularisation (n=47 675)</td>
<td>23%</td>
<td>24%</td>
<td>25%</td>
<td>23%</td>
<td>23%</td>
<td>0.113</td>
</tr>
<tr>
<td>Valve intervention (n=47 703)</td>
<td>5%</td>
<td>5%</td>
<td>6%</td>
<td>6%</td>
<td>3%</td>
<td>0.372</td>
</tr>
<tr>
<td>CRT (n=47 700)</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>0.710</td>
</tr>
<tr>
<td>Hospitalisation at inclusion (n=47 713)</td>
<td>48%</td>
<td>61%</td>
<td>70%</td>
<td>83%</td>
<td>90%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New heart failure (n=18 279)</td>
<td>53%</td>
<td>43%</td>
<td>29%</td>
<td>20%</td>
<td>20%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart failure &gt;6 month (n=47 254)</td>
<td>32%</td>
<td>40%</td>
<td>55%</td>
<td>65%</td>
<td>59%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA class (n=32 848)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA I (n=3753)</td>
<td>20%</td>
<td>14%</td>
<td>8%</td>
<td>5%</td>
<td>6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA II (n=14 844)</td>
<td>51%</td>
<td>50%</td>
<td>42%</td>
<td>32%</td>
<td>28%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA III (n=12 582)</td>
<td>27%</td>
<td>33%</td>
<td>44%</td>
<td>50%</td>
<td>42%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA IV (n=1669)</td>
<td>2%</td>
<td>3%</td>
<td>6%</td>
<td>13%</td>
<td>24%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (n=41 369)</td>
<td>&gt;50%</td>
<td>20%</td>
<td>25%</td>
<td>28%</td>
<td>26%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>40–49% (n=8566)</td>
<td>20%</td>
<td>21%</td>
<td>20%</td>
<td>20%</td>
<td>21%</td>
<td>0.508</td>
</tr>
<tr>
<td>30–39% (n=11 323)</td>
<td>29%</td>
<td>28%</td>
<td>26%</td>
<td>25%</td>
<td>27%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;30% (n=12 314)</td>
<td>36%</td>
<td>31%</td>
<td>28%</td>
<td>28%</td>
<td>26%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are proportion or median and IQR. CRT, cardiac resynchronisation therapy; NYHA, New York Heart Association.
Table 2  Physical signs, laboratory results and medical treatment

<table>
<thead>
<tr>
<th>Physical signs</th>
<th>eGFR≥90 (n=5251)</th>
<th>eGFR 60–89 (n=18240)</th>
<th>eGFR 30–59 (n=19160)</th>
<th>eGFR 15–29 (n=4252)</th>
<th>eGFR&lt;15 (n=813)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>72 (64–84)</td>
<td>72 (63–83)</td>
<td>72 (64–83)</td>
<td>74 (64–84)</td>
<td>76 (67–90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood pressure systolic</td>
<td>120 (110–140)</td>
<td>128 (112–140)</td>
<td>125 (110–140)</td>
<td>124 (110–140)</td>
<td>130 (110–150)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Blood pressure diastolic</td>
<td>75 (68–80)</td>
<td>74 (66–80)</td>
<td>70 (61–80)</td>
<td>70 (60–80)</td>
<td>70 (60–80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>27 (24–31)</td>
<td>26 (23–30)</td>
<td>26 (23–29)</td>
<td>26 (23–29)</td>
<td>26 (23–29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non-sinus rhythm</td>
<td>29%</td>
<td>45%</td>
<td>54%</td>
<td>52%</td>
<td>42%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left bundle branch block</td>
<td>15%</td>
<td>16%</td>
<td>17%</td>
<td>17%</td>
<td>14%</td>
<td>0.006</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>139 (127–150)</td>
<td>135 (123–147)</td>
<td>129 (117–141)</td>
<td>120 (110–131)</td>
<td>112 (103–123)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>67 (58–75)</td>
<td>83 (72–93)</td>
<td>116 (102–133)</td>
<td>191 (163–220)</td>
<td>382 (325–492)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Potassium</td>
<td>4,1 (3,8–4,4)</td>
<td>4,1 (3,8–4,4)</td>
<td>4,2 (3,9–4,6)</td>
<td>4,2 (3,9–4,6)</td>
<td>4,5 (4,0–5,0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>1390 (494–3366)</td>
<td>2320 (1090–4800)</td>
<td>3800 (1780–7826)</td>
<td>7880 (3357–16862)</td>
<td>21 000 (1260–35000)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACEI</td>
<td>76%</td>
<td>69%</td>
<td>58%</td>
<td>38%</td>
<td>20%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;50% of target dose</td>
<td>80%</td>
<td>77%</td>
<td>72%</td>
<td>55%</td>
<td>49%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ARB</td>
<td>16%</td>
<td>29%</td>
<td>22%</td>
<td>20%</td>
<td>16%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;50% of target dose</td>
<td>63%</td>
<td>56%</td>
<td>46%</td>
<td>29%</td>
<td>36%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-blocker</td>
<td>89%</td>
<td>85%</td>
<td>84%</td>
<td>81%</td>
<td>77%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;50% of target dose</td>
<td>66%</td>
<td>64%</td>
<td>62%</td>
<td>59%</td>
<td>58%</td>
<td>&lt;0.001</td>
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<tr>
<td>Aldosteronblocker</td>
<td>28%</td>
<td>29%</td>
<td>30%</td>
<td>22%</td>
<td>11%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Digitalis</td>
<td>16%</td>
<td>19%</td>
<td>17%</td>
<td>10%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statins</td>
<td>44%</td>
<td>44%</td>
<td>42%</td>
<td>37%</td>
<td>35%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nitrates</td>
<td>6%</td>
<td>13%</td>
<td>21%</td>
<td>27%</td>
<td>25%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>39%</td>
<td>39%</td>
<td>38%</td>
<td>29%</td>
<td>17%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin</td>
<td>45%</td>
<td>49%</td>
<td>52%</td>
<td>56%</td>
<td>57%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are proportion or median and IQR.
ARBo angiotensin-receptor blocker; BMI, body mass index; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide.
whole spectrum of kidney disease and its association with subsequent mortality. It was also possible to examine the prognostic influence of different degrees of kidney dysfunction in important subgroups and it provides us with important findings regarding these patients’ risk profile.

In our registry, half of the patients had at least a moderate kidney dysfunction (eGFR <60 mL/min), which is in line with earlier observations. For lower kidney function, the patients were older and more often had hypertension, diabetes mellitus and other cardiovascular disease as seen in other studies. They also more often had a long duration of disease and more severe NYHA class, in line with other previous studies.

The higher mortality in patients with kidney dysfunction seen in the present study, compared to several previous studies, is probably explained by the unselected nature of the material. Since this is registry data collected from the clinical routine, patients were considerably older (median age of 77 years) than in the other studies. However, even though the mortality was lower in patients under 65 years of age, there was still a high 5-year mortality, well in line with earlier results in more selected population.

The associations between kidney function and outcome was similar regardless of age, NYHA class and degree of heart failure. Though, even after adjustments for age, hypertension and diabetes, impaired kidney function remained strongly associated with mortality (figure 2). Furthermore, in patients with at least severe kidney dysfunction, the mortality was very high and the additive prognostic value of NYHA class and haemoglobin level limited. There are several possible reasons for the present finding. The worse prognosis can at least partially be explained by residual confounding that arises from unmeasured or dichotomised variables. However, it may also indicate that factors that are strongly related to kidney dysfunction, such as activation of neurohumoral systems (RAAS), inflammation and sympathectomy, are of crucial importance for outcome as these affect vital organs.

### Table 3: Mortality and unadjusted and adjusted mortality risk in relation to eGFR

<table>
<thead>
<tr>
<th>eGFR</th>
<th>All patients</th>
<th>At 6 months</th>
<th>At 1 year</th>
<th>Long-term (HR) unadjusted</th>
<th>Model 1 (HR)</th>
<th>Model 2 (HR)</th>
<th>Model 3 (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥90</td>
<td>n=5251</td>
<td>n=18 240</td>
<td>n=19 016</td>
<td>n=4252</td>
<td>n=813</td>
<td>p Value</td>
<td></td>
</tr>
<tr>
<td>n=82 108</td>
<td>2%</td>
<td>2%</td>
<td>4%</td>
<td>12%</td>
<td>30%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>60–89</td>
<td>5%</td>
<td>8%</td>
<td>16%</td>
<td>35%</td>
<td>53%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>30–59</td>
<td>7%</td>
<td>13%</td>
<td>23%</td>
<td>46%</td>
<td>62%</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>15–29</td>
<td>n=47 636</td>
<td>1.85 (1.73 to 1.97)</td>
<td>3.57 (3.35 to 3.80)</td>
<td>7.72 (7.20 to 8.28)</td>
<td>11.71 (10.62 to 12.90)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>eGFR &lt;15</td>
<td>n=47 636</td>
<td>0.83 (0.77 to 0.89)</td>
<td>1.13 (1.05 to 1.21)</td>
<td>2.12 (1.96 to 2.29)</td>
<td>4.19 (3.79 to 4.64)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>At 6 months (%)</td>
<td>n=18 240</td>
<td>0.84 (0.74 to 0.92)</td>
<td>1.10 (1.00 to 1.20)</td>
<td>1.87 (1.68 to 2.08)</td>
<td>3.26 (2.79 to 3.80)</td>
<td>&lt;0.01 for all comparisons with eGFR ≥90</td>
<td></td>
</tr>
<tr>
<td>At 1 year (%)</td>
<td>n=19 016</td>
<td>0.86 (0.79 to 0.95)</td>
<td>1.13 (1.03 to 1.24)</td>
<td>1.86 (1.67 to 2.07)</td>
<td>2.96 (2.53 to 3.47)</td>
<td>&lt;0.01 for all comparisons with eGFR ≥90</td>
<td></td>
</tr>
<tr>
<td>Long-term (HR)</td>
<td>n=27 302</td>
<td>1</td>
<td>1.85 (1.73 to 1.97)</td>
<td>3.57 (3.35 to 3.80)</td>
<td>7.72 (7.20 to 8.28)</td>
<td>11.71 (10.62 to 12.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 1 (HR)</td>
<td>n=47 545</td>
<td>0.86 (0.79 to 0.95)</td>
<td>1.13 (1.03 to 1.24)</td>
<td>1.86 (1.67 to 2.07)</td>
<td>2.96 (2.53 to 3.47)</td>
<td>&lt;0.01 for all comparisons with eGFR ≥90</td>
<td></td>
</tr>
<tr>
<td>Model 2 (HR)</td>
<td>n=27 304</td>
<td>1</td>
<td>1.85 (1.73 to 1.97)</td>
<td>3.57 (3.35 to 3.80)</td>
<td>7.72 (7.20 to 8.28)</td>
<td>11.71 (10.62 to 12.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 3 (HR)</td>
<td>n=27 302</td>
<td>1</td>
<td>1.85 (1.73 to 1.97)</td>
<td>3.57 (3.35 to 3.80)</td>
<td>7.72 (7.20 to 8.28)</td>
<td>11.71 (10.62 to 12.90)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are proportion and HR based on Cox regression analysis (95% CI). Model 1: adjustment for baseline variables possibly influencing both kidney dysfunction and outcome (age, gender, smoking, hypertension and diabetes). Model 2: adjustment for variables related to the aetiology and severity of heart failure (heart failure >6 months, ischaemic heart disease, atrial fibrillation, valvular heart disease, dilated cardiomyopathy, previous revascularisation, previous valvular intervention, non-sinus rhythm in the electrocardiogram, heart rate, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class, systolic blood pressure and haemoglobin level). Model 3: adjustment for given treatment (ACE inhibitors, ARB, β-blockers, aldosterone antagonists, statins and cardiac resynchronisation therapy (CRT)). eGFR, estimated glomerular filtration rate.
Several studies have shown that patients with cardiovascular disease and CKD receive less of guideline recommended treatments, partly due to lack of evidence from clinical trials and concerns regarding drug toxicity. In the present study, differences between eGFR strata regarding the use of antithrombotic treatment, statins and β-blockers were rather small despite the large differences in age distributions. Patients with low eGFR were less often treated with ACE inhibitors and less often reached target doses of RAAS blockade. However, though these drugs are believed to be beneficial even with severely depressed kidney function caution is recommended when treating patients with CKD.

When adjusting for treatment in our study, the association between kidney function and outcome remained unchanged. This may indicate that under treatment is not an important cause of the association between kidney dysfunction and outcome.

There are limitations to this study. This is a registry that reflects clinical practice. There may be a certain selection of patients, as some patients may not have been included in the register because of frailty, comorbidity, or other reasons. This may affect the generalisability of our study. However, compared to many other studies, our study sample should be considered as fairly unselective, closely reflecting the everyday clinical practice. Patients are included according to clinician-judged heart failure, which due to the heterogeneity of the disease and difficulty in establishing the correct diagnoses is likely to contain a certain degree of...

Figure 2  (A) 1-year mortality in relation to estimated glomerular filtration rate (eGFR), age (n=47,636) and presence of diabetes mellitus (n=47,624). (B) 1-year mortality in relation to eGFR and New York Heart Association class (n=32,811) and haemoglobin level (n=47,626).

DM, diabetes mellitus; y, years.
The authors would like to thank the steering group of the Swedish Heart Failure Registry, and all the hospitals and outpatient clinics that report to the registry.

Contributors IL, KS and TJ have worked with all parts of the study. LHL, IH and UD were involved with the planning of the study, analysing and interpretation of the data, and the revising of the manuscript. All authors have approved the manuscript and its submission. There has been no relationship with the industry.

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Competing interests UD reports grants from Astra Zeneca Inc, other from Novartis Inc, outside the submitted work. LHL has received grants to his institution from Boston Scientific and Astra Zeneca, and honorary for lecturing from Novartis. TJ has received honorary from Astra Zeneca for lecturing and consulting. KS has received lecture honorary from Astra Zeneca and Aspen.

Ethics approval Ethics Committee of Stockholm.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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REFERENCES


Figure 3  (A) Mortality in patients with heart failure and different estimated glomerular filtration rate (eGFR) strata, crude survival assessed by Kaplan-Meier analysis, log rank p<0.001. (B) Mortality in patients under 65 years with heart failure and different GFR strata, crude survival assessed by Kaplan-Meier analysis, log rank p<0.001.

misclassification. The register has no information of creatinine over time and no data regarding blood urea nitrogen. Dialysis status was not collected as part of the SwedishHF and hence this cannot be reported; however, in an earlier SwedishHF study with linkage to the Swedish Patient Registry, dialysis was used in about 1% of the patients. In spite of adjusting for a large number of confounders, residual confounding may still exist due to unmeasured factors that could not be adjusted for.

In conclusion, this large and extensively covariate-adjusted study from a nationwide and generalisable registry shows that kidney dysfunction is strongly associated with short-term and long-term outcome in patients with heart failure. These findings emphasise the importance of close follow-up and kidney preservation in patients with heart failure and kidney disease.
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