Original Article

Incidence and Predictors of End-Stage Renal Disease in Outpatients With Systolic Heart Failure

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Background—Renal dysfunction is an important prognostic factor in heart failure (HF), but whether this dysfunction progresses to end-stage renal disease (ESRD) is unknown. Therefore, we examined incidence and predictors of ESRD in outpatients with HF.

Methods and Results—Patients with systolic HF were identified in The Danish Heart Failure database and new-onset ESRD from the Danish Registry on Dialysis. Renal function was estimated by The Chronic Kidney Disease Epidemiology Collaboration equation and patients grouped by estimated glomerular filtration rate (eGFR)—group I: ≥60 mL/min per 1.73 m^2, group II: 30 to 59 mL/min per 1.73 m^2, group III: 15 to 29 mL/min per 1.73 m^2, group IV: <15 mL/min per 1.73 m^2. Cox hazard models for time to ESRD, to death, and the composite end point of ESRD or death were constructed and predictors of ESRD identified. A total of 8204 patients were included in the analyses. Median age was 70 years (Q, 61–77), 28% were women, median left ventricular ejection fraction was 30% (Q, 24–40), and median eGFR was 68 (Q, 51–85) mL/min per 1.73 m^2. Forty-one patients developed ESRD (1.3/1000 patient-years). Baseline eGFR group II ($P<0.001$), eGFR group III ($P<0.001$), eGFR group IV ($P<0.001$), uncontrolled hypertension ($P=0.049$), need of diuretics, and age <60 years ($P=0.016$) were associated with time to ESRD.

Conclusions—ESRD is rare in outpatients with systolic HF and is mainly observed in patients with an eGFR <30 mL/min per 1.73 m^2. A low eGFR, age <60 years, need of diuretics, and uncontrolled hypertension identify patients with an increased risk for ESRD. (***Circ Heart Fail***. 2013;6:1124-1131.)

Key Words: heart failure, systolic ◼ kidney failure, chronic ◼ proximal renal tubular dysfunction

Chronic kidney disease (CKD) is a prognostic factor in heart failure (HF) and is associated with an increased mortality risk and increased risk for admission. Furthermore, worsening of renal function during admission and treatment is described in 15% to 20% of patients with HF and is associated with a poor outcome.[1–3]

Clinical Perspective on p 1131

Research on renal dysfunction in HF has focused on risk stratification[4,5] and identification of new renal biomarkers.[6] Little research has focused on pathogenesis of renal dysfunction in HF, despite the fact that approximately half of patients with HF are in CKD stage III to V.[7,8] From post hoc analyses of randomized clinical trials, it is well known that angiotensin-converting

enzyme-inhibitors (ACE-I) and aldosterone receptor antagonists (ARA) increase plasma creatinine concentration, yet still improve survival.[9–11] However, the risk of developing end-stage renal disease (ESRD) requiring dialysis in patients with HF treated with neurohormonal blockade is unknown.[12] In light of the renal side effects of HF therapy, and the prolonged survival in systolic HF, ESRD might be an increasing problem in clinical practice.[13,14] Conversely, it may be speculated that renin–angiotensin–aldosterone system blockade has a reno-protective effect over time, in turn reducing the need for renal replacement therapy. Finally, potential predictors of development of ESRD in systolic HF have not been identified.

Using data from a large cohort followed in The Danish Heart Failure Clinics Network from 2002 to 2009, the aim

of the present study was to identify predictors and describe the incidence of ESRD in outpatients with systolic HF treated according to guideline therapy.

Methods

Registry Data Sources: Study Population, End Points, and Pharmacological Treatment

Study Population

Information about clinical characteristics was obtained from the electronic patient file and research database, Hjerterplus.[15] It was collected from 26 Danish HF clinics, all members of the Danish Heart Failure Clinics Network (DHFCN) between 2002 and 2009, which comprises approximately half of all Danish patients with HF. Patients were referred to the clinics, when diagnosed with systolic HF (left ventricular ejection fraction [LVEF] <45% by echocardiography) for education and uptitration of HF guideline therapy. Patients with HF and preserved LVEF are not referred to the HF clinics in Denmark systematically and were, therefore, excluded. The inclusion ended on December 31, 2009.

End Points: ESRD and Mortality

Information of onset of ESRD, defined as initiation of long-term dialysis, was obtained from the Danish National Registry on Dialysis and Transplantation (NRDT) from 2002 to 2010.[16] This registry contains information on all patients starting long-term hemo- or peritoneal dialysis, defined as a need for therapy of ≥90 days and has been validated and found complete.[16] Primary renal diagnosis, registered as cause for ESRD, was also retrieved from NRDT. Patients with ESRD before referral to a HF clinic were excluded. The end point of death was obtained from the Central Population Registry, in which all deaths are registered within 2 weeks. Immigration is also registered, but no patients in the present cohort immigrated.

The study was approved by the Danish Data Protection Agency and the review board of the DHFCN and the NRDT. Approval by an ethics committee and written informed consent are not required for retrospective registry studies in Denmark.

Pharmacological Treatment

Information on medical products prescribed to and bought by each patient was obtained from The Danish Registry of Medicinal Products Statistics, which keeps records of all drug prescriptions dispensed from Danish pharmacies since 1995.[17] Prescriptions dispensed from pharmacies 90 days after the baseline visit were used for analyses. We included the use of ACE-I or angiotensin receptor blockers (ARB), β-blockers, ARA, acetylsalicylic acid, statins, and diuretics. The use of diuretics was defined as an average daily dose of >80 mg of furosomide (or equivalent), as some patients did not have a daily intake but used diuretics for self-administration when symptomatic.

Patients were linked between the databases by their unique personal registry number, provided to all Danish citizens at birth or at achievement of permanent residency status in Denmark.

Renal Function

Renal function was estimated by the Chronic Kidney Disease Epidemiology Collaboration equation, incorporating age, race, sex, and plasma creatinine concentration.[18] Patients were then divided into 4 estimated glomerular filtration rate (eGFR) groups—group I: ≥60 mL/min per 1.73 m^2, group II: 30 to 59 mL/min per 1.73 m^2, group III: 15 to 29 mL/min per 1.73 m^2, and group IV: <15 mL/min per 1.73 m^2. Intervals for eGFR groups were chosen so they matched CKD stages as specified by the National Kidney Disease Foundation Outcomes Quality Initiative Guidelines.[19] Patients without CKD and CKD stage I+II were placed in eGFR group I, as we did not have information on albuminuria and could not distinguish between patients without renal disease and patients with mild renal disease defined as an eGFR >90 mL/min per 1.73 m^2 and albuminuria. The patients with an eGFR from 60 to 89 mL/min per 1.73 m^2 were also included in

eGFR group I, as they could have decreased renal function according to age or experience mild renal disease.

Statistics

Baseline patient's characteristics in the eGFR groups were compared by χ^2 tests for discrete variables, and by 1-way ANOVA for parametric and trend tests, general linear models, for continuous variables.

Patients registered without information about plasma creatinine concentration were excluded. Baseline variables for included and excluded patients were compared with evaluate selection bias. Crude rates for death and for ESRD were calculated separately in each group as number of events per 1000 person-years of HF (/1000 patient-years), each patient contributed with time calculated in days, from the baseline visit in the HF clinic to an event (=death or initiation of renal replacement therapy) or censoring (=death or end of study).

Because of the competing risk of death to ESRD, end points were evaluated by cumulative incidence functions according to baseline eGFR group and not by Kaplan–Meier estimates and log-rank test.[20] Time-dependent multivariate Cox proportional hazard models were constructed for ESRD, for death and for the composite end point of ESRD or death, adjusted for the clinical relevant explanatory variables chosen from the baseline data: eGFR, sex, age, hypertension, diabetes mellitus, New York Heart Association (NYHA) class, LVEF, use of ACE/ARB, β-blockers, ARA, acetylsalicylic acid, statin, and diuretics. Because of the number of end points in the model including time to ESRD as end point, we created a basic model (model 0) including age, sex, renal function, and uncontrolled hypertension and added in separate model covariates of specific interest: diabetes mellitus, ACE/ARB, and diuretics (model Ia-c).

Model assumptions, the proportional hazards, linearity of continuous variables, and lack of interactions were tested and found valid unless otherwise specified. Because of large differences in the incidence of ESRD between the eGFR groups, we chose to repeat the multivariate Cox models for ESRD stratified by eGFR groups to approach whether there were any differences in significant predictors. A *P* value <0.05 (2-sided) was considered significant.

Results

Study Population

A total of 10 458 patients were registered with a baseline visit in the HF clinics during the period of 7 years (Figure 1). Two-thousand thirty-nine (n=2239) did not have a plasma creatinine concentration registered and 38 patients had ESRD before onset of systolic HF. These patients were excluded. Fifteen (n=15) patients excluded because of missing creatinine, developed ESRD (Table 1; Figure 1).

In total, 8204 patients with complete data were included in the final analyses. Median follow-up was 3.7 (quartiles [Q], 2.4–5.1) years. During this period 41 patients developed ESRD (1.3/1000 patient-years), and 2652 patients died (84/1000 patient-years; Table 2). All 41 patients with ESRD were registered with start of dialysis, no patients were registered as recipients of a renal transplant.

Patient characteristics are presented in Table 1 for the entire cohort and according to eGFR groups. Median age was 70 (Q, 61–77) years, 28% were women, median LVEF 30 (Q, 24–40) %, and median eGFR was 68 (Q, 51–85) mL/min per 1.73 m^2. Patients with poorer renal function were older, had a higher NYHA class, more frequently had diabetes mellitus, and had a lower LVEF. Increasing eGFR group was associated with declining use of ACE-I/ARBs, ARAs, and β-blockers while more patients were treated with acetylsalicylic acid. Frequency of uncontrolled hypertension did
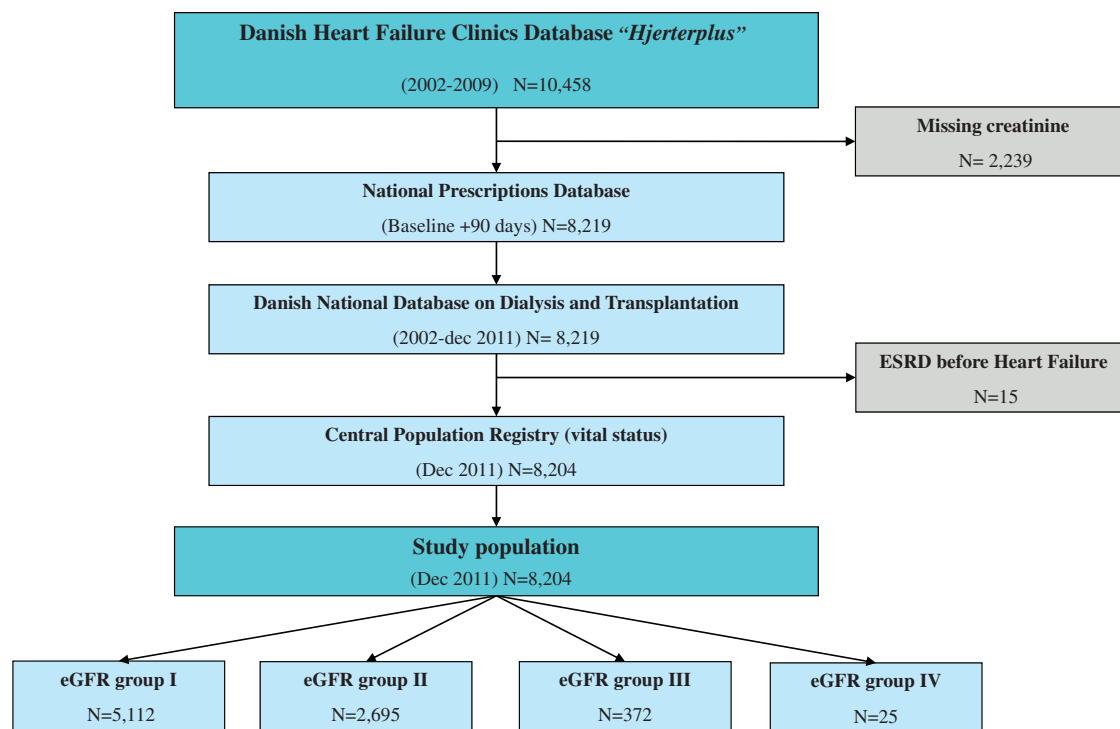
Figure 1. Study population and register flow chart. Study population consisted of patients in Hjerterplus. The Danish Heart Failure Networks Clinics database and information on prescribed medication, end-stage renal disease (ESRD), vital status were added from relevant national registries. The registers were merged and each patient was identified by his/hers unique central personal registry number. eGFR indicates estimated glomerular filtration rate.

not differ between groups. Patients in eGFR group IV were younger than patients in eGFR group III, had a lower LVEF, and fewer had diabetes mellitus.

Incidence of ESRD and Mortality
Of the 25 patients in eGFR group IV at baseline, 5 developed ESRD, resulting in an incident ESRD rate of 106/1000 patient-years, and 18 died leaving the crude mortality rate at 340/1000 patient-years. In eGFR group III, 22 patients of 372 progressed to ESRD and 246 died. Crude ESRD rate was 23.0/1000 patient-years and crude mortality rate 244/1000 patient-years. In eGFR group II, 11 patients of 2695 progressed to ESRD and 1223 died, resulting in an incident ESRD rate of 1.2/1000 patient-years and crude mortality rate of 129/1000 patient-years. In the last eGFR group, 3 developed ESRD and 1165 died, resulting in an incident ESRD rate of 0.10/1000 patient-years and a crude mortality rate of 55.4/1000 patient-years (Table 3; Figure 2).

Mortality and Cumulative Incidence of ESRD
The cumulative incidence functions for ESRD and death showed that eGFR groups were associated with both end points, but death occurred much more frequently and the difference in scale on the y-axis should be noted (Figure 3A and 3B).

Cox Multivariate Proportional Hazard Model: ESRD
In model 0, eGFR group at the baseline was closely associated with time to ESRD. For eGFR group II, a hazard ratio (HR) of

13.39 (95% confidence interval [CI], 3.2–48.6; P=0.001); for eGFR group III, a HR of 322.1 (95% CI, 93.3–1122; P<0.001), and for eGFR group IV, a HR of 1586 (95% CI, 365.3–6889; P<0.001) reflect the natural link between decreased renal function and ESRD. Age <60 years (HR, 3.07; 95% CI, 1.24–7.63; P=0.016) and uncontrolled hypertension, that is, systolic arterial blood pressure >140 mm Hg at the baseline visit (HR, 1.9; 95% CI, 1.00–3.59; P=0.049), were also associated with time to ESRD, whereas age 60 to 69 years (HR, 2.89; 95% CI, 1.36–6.16; P=0.057) was not. In model I, diabetes mellitus (HR, 1.87; 95% CI, 0.96–3.72; P=0.072) and ACE/ARB (HR, 0.54; 95% CI, 0.28–1.03; P=0.061) were not associated with time to ESRD, but need for diuretics was (HR, 1.39; 95% CI, 0.90–1.65; P=0.023). All results are presented in Table 2 (model 0+Ia-c).

Five patients (n=5) almost fulfilled the criteria for dialysis at their baseline visit to the HF clinic. This may have weighted our results in favor of the observed close association between eGFR group and ESRD in the whole cohort. Therefore, we performed analyses stratified by eGFR groups, to identify patients with preserved kidney function but at risk. It was not possible to identify any association between the clinical variables and ESRD either in eGFR group I, because of the low number of events (n=3), or in eGFR group IV, because of the low number of patients (n=25). In eGFR groups II and III, we identified age <70 years and uncontrolled hypertension as risk markers for ESRD. Surprisingly, diabetes mellitus was not a risk marker for ESRD in these subgroups (Table I in the online-only Data Supplement).

Table 1. Patient Characteristics

eGFR Groups	All	eGFR I	eGFR II	eGFR III	eGFR IV	*P* Value
N	8204	5112	2695	372	25	
Age, y	70 (46–86)	65 (44–82)	76 (55–87)	78 (61–89)	71 (50–86)	<0.001
Female sex, %	28	25	33	39	26	<0.001
eGFR*	68 (30–103)	80 (62–102)	48 (33–59)	25 (17–30)	12 (9–15)	<0.001
ESRD, n	41	3	11	22	5	<0.001
LVEF, %	30 (45–15)	30 (45–15)	30 (45–15)	30 (45–15)	26 (45–11)	<0.001
IHD, %	51.9	52.0	49.2	64.0	52.8	<0.001
Diabetes mellitus, %	14.4	21.9	27.1	21.5	7.7	<0.001
Atrial fibrillation, %	23.5	12.6	16.5	23.7	18.9	<0.001
NYHA II+III, %	64.4	61.7	69.3	66.6	72.0	<0.001
Hypertension, %	22.5	23	21	24	28	0.367
Sodium, mmol/L	139 (132–146)	139 (132–146)	139 (132–144)	139 (132–144)	137 (132–145)	<0.001
Potassium, mmol/L	4.2 (3.5–4.9)	4.2 (3.5–4.9)	4.3 (3.5–5.1)	4.3 (3.5–5.4)	4.5 (3.3–5.3)	<0.001
ACE-I/ARB, %	89.8	92.6	87.8	66.4	60.0	<0.001
ß-Blocker, %	84.0	85.2	82.3	82.0	72.0	<0.001
Aldo Ant, %	30.0	29.8	31.8	21.0	12.0	<0.001
Diuretics,† %	17.7	13.0	23.3	40.4	32.0	<0.001
Statin, %	51.7	51.7	51.8	51.1	36.0	0.015
ASA, %	53.6	53.1	54.1	57.8	44.0	0.250

ACE-I/ARB indicates angiotensin-converting enzyme inhibitor or angiotensin receptor II blocker; Aldo Ant, aldosterone receptor antagonist; ASA, acetylsalicylic acid; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; hypertension, systolic blood pressure >90 mm Hg at baseline; IHD, ischemic heart disease; LVEF, left ventricle ejection fraction; and NYHA, New York Heart Association functional class.

*eGFR units: mL/min per 1.73 m².

†Diuretics; use of >80 mg of furosemide daily or equivalent on daily average.

Cox Multivariate Proportional Hazard Model: Mortality

A total of 2652 patients died (84/1000 patient-years). Age >80 years (HR, 1.67; 95% CI, 1.52–2.83; *P*<0.001), eGFR group II (HR, 1.37; 95% CI, 1.26–1.50; *P*<0.001), eGFR group III (HR, 1.83; 95% CI, 1.57–2.12; *P*<0.001), eGFR group IV (HR, 2.75; 95% CI, 1.72–4.42; *P*<0.001), diabetes mellitus (HR, 1.18; 95% CI, 1.07–1.32; *P*=0.002), LVEF <30% (HR, 1.24; 95% CI, 1.15–1.34; *P*<0.001), NYHA class III+IV (HR, 1.32; 95% CI, 1.22–1.44; *P*<0.001), and use of diuretics >80 mg of furosemide, or equivalent, on an averagely daily dose (HR, 1.25; 95% CI, 1.19–1.30; *P*<0.001) were all significantly associated with increased risk of death. Age <60 years (HR, 0.35; 95% CI, 0.29–0.50; *P*<0.001), age 60 to 69 years (HR, 0.62; 95% CI, 0.55–0.69; *P*<0.001), uncontrolled hypertension (HR, 0.81; 95% CI, 0.73–0.89; *P*<0.001), and use of ACE-I/ARB (HR, 0.54; 95% CI, 0.49–0.59; *P*<0.001), β-blocker (HR, 0.54; 95% CI, 0.49–0.57; *P*<0.001), statin (HR, 0.75; 95% CI, 0.69–0.81; *P*<0.001), and acetylsalicylic acid (HR, 0.79; 95% CI, 0.73–0.85; *P*<0.001) were all associated with a decreased mortality risk (Table 2, model II).

Cox Multivariate Proportional Hazard Model: Composite End Point, ESRD, and Death

eGFR group II (HR, 1.39; 95% CI, 1.28–1.52; *P*<0.001), eGFR group III (HR, 1.98; 95% CI, 1.71–2.31; *P*<0.001), eGFR group IV (HR, 3.36; 95% CI, 2.12–5.34; *P*<0.001), NYHA class III+IV (HR, 1.32; 95% CI, 1.22–1.44; *P*<0.001), diabetes mellitus (HR, 1.19; 95% CI, 1.11–1.32; *P*=0.002), and

age ≥80 years (HR, 1.64; 95% CI, 1.40–1.80; *P*<0.001) were all associated with time to death or ESRD. Younger age, <60 years (HR, 0.35; 95% CI, 0.30–0.40; *P*<0.001), 60 to 69 years (HR, 0.63; 95% CI, 0.57–0.70; *P*<0.001), and uncontrolled hypertension (HR, 0.82; 95% CI, 0.74–0.91; *P*<0.001), use of an ACE-I/ARB (HR, 0.54; 95% CI, 0.49–0.59; *P*<0.001), β-blocker (HR, 0.53, 95% CI, 0.49–0.58; *P*<0.001), and statins (HR, 0.75; 95% CI, 0.69–0.82; *P*<0.001) were associated with a decreased risk of death or ESRD (Table 2, model III).

Missing Data Analyses

The included (n=8204) and excluded (n=2239) patients were similar with respect to important clinical variables (missing versus included): female gender (29% versus 28%; *P*=0.434), age (69.8 years versus 70.0 years; *P*=0.418), and diabetes mellitus (14.8% versus 14.6%; *P*=0.771). We observed that excluded patients were less symptomatic (NYHA class I+II; 87.5% versus 77.4%; *P*<0.001), but more had LVEF <30% (56% versus 67%; *P*<0.001). At baseline patients with missing creatinine were treated less frequently with guideline-based therapy. Mortality and ESRD rates did not differ between groups (Table II in the online-only Data Supplement). Age, sex, and incidence rates of death and ESRD did not differ between groups, and the low incidence of ESRD seems not to be explained by selection bias at enrollment because of missing registration of plasma creatinine.

Renal Diagnosis

The most common diagnosis registered as cause of ESRD was CKD of unknown pathogenesis (34%), the main part (32%)

Table 2.   Cox Multivariate Proportional Hazard Models: ESRD, Mortality Risk, and Composite End Point

	Hazard Ratio	95% Confidence Interval	P Value
ESRD: model 0			
eGFR			
Group I (ref)	1.00	.	.
Group II	13.39	3.62–48.6	<0.001
Group III	322.13	93.3–1112.1	<0.001
Group IV	1586	365.3–6889.5	<0.001
Age, y			
≥70 and <80 (ref)	1.00		
<60	3.07	1.24–7.63	0.016
60–69	2.89	1.36–6.16	0.057
≥80	0.47	0.17–1.34	0.157
Uncontrolled hypertension	1.9	1.00–3.59	0.049
ESRD: model la-c: model 0 + in separate models:			
Diabetes mellitus	1.83	0.94–3.44	0.073
ACE-I/ARB	0.54	0.28–1.03	0.061
High-dose diuretics*	1.39	0.90–1.65	0.023
Mortality risk: model II			
eGFR			
Group I (ref)	1.00		
Group II	1.37	1.26–1.50	<0.001
Group III	1.83	1.57–2.12	<0.001
Group IV	2.75	1.72–4.42	<0.001
Age, y			
≥70 and <80 (ref)	1.00		
<60	0.35	0.29–0.39	<0.001
60–69	0.62	0.55–0.69	<0.001
≥80	1.67	1.52–1.83	<0.001
Uncontrolled hypertension	0.81	0.73–0.89	<0.001
Diabetes mellitus	1.18	1.07–1.32	0.002
LVEF <30%	1.24	1.15–1.34	<0.001
NYHA class III+IV	1.32	1.22–1.44	<0.001
High-dose diuretics*	1.25	1.19–1.30	<0.001
ACE-I/ARB	0.54	0.49–0.59	<0.001
ß-Blocker	0.53	0.49–0.57	<0.001
Aldosterone antagonist	1.07	0.97–1.17	0.166
Statin	0.75	0.69–0.81	<0.001
acetylsalicylic acid	0.73	0.73–0.85	<0.001
Composite end point: model III			
eGFR			
Group I (ref)	1.00		
Group II	1.39	1.28–1.52	<0.001
Group III	1.98	1.71–2.31	<0.001
Group IV	3.36	2.12–5.34	<0.001
Age, y			
≥70 and <80 (ref)	1.00		
<60	0.38	0.30–0.40	<0.001

(Continued)

Table 2.   Continued

	Hazard Ratio	95% Confidence Interval	P Value
60–69	0.63	0.57–0.70	<0.001
≥80	1.64	1.50–1.80	<0.001
Uncontrolled hypertension	0.82	0.74–0.91	<0.001
Diabetes mellitus	1.86	1.07–1.32	0.002
LVEF <30%	1.24	1.14–1.34	<0.001
NYHA class III+IV	1.32	1.22–1.44	<0.001
High-dose diuretics*	1.25	1.19–1.30	<0.001
ACE-I/ARB	0.54	0.49–0.59	<0.001
ß-Blocker	0.53	0.49–0.57	<0.001
Aldosterone antagonist	1.06	0.97–1.16	0.176
Statin	0.75	0.69–0.82	<0.001
Acetylsalicylic acid	0.79	0.73–0.86	<0.001

ACE-I/ARB indicates angiotensin-converting enzyme inhibitor or angiotensin receptor II blocker; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; LVEF, left ventricle ejection fraction; and NYHA Class: New York Heart Association functional class.

*Diuretics; use of >80 mg of furosemide or equivalent on average daily.

being chronic. Diabetic kidney disease (30%) and hypertensive and vascular disease (21%) were also dominating. Five percent were registered with a primary parenchymal renal disease (ie, glomerulonephritis). Ten percent had cancer, polycystic kidney disease, or renal infarction.

Discussion

In a large cohort with a long follow-up period, we observed a low incidence of ESRD in outpatients with systolic HF. A low eGFR, age <60 years, uncontrolled hypertension, and need for diuretics were important risk markers for the development of ESRD.

Despite a high proportion of patients in eGFR groups II to IV, we observed a low incidence of ESRD. This may be explained by several factors, including competing mortality risk, contradictions to start of dialysis, and selection bias of the cohort, as discussed below.

Mortality rates were 80× higher than ESRD rates and competing risk likely explains the low incidence of ESRD. To avoid underestimation of the incidence of ESRD because of competing risk, we calculated cumulative incidence function and not Kaplan–Meier estimates and observed that the incidence of ESRD could be stratified by eGFR.[20] This was also the case for the incidence of death.

Selection bias could cause underestimation because it may be speculated that patients with systolic HF is not offered dialysis in clinical practice because of low systolic blood pressure and poor prognosis. It should be noted, however, that HF is not considered a contraindication to dialysis in Denmark. At baseline, 25 patients had eGFR <15 mL/min per 1.73 m^2 and 5 of those started dialysis, based on these small numbers the true incidence of ESRD might be ≤5× higher. However, not all patients with an eGFR of 15 mL/min per 1.73 require dialysis and it does not change the fact that mortality risk is a much larger clinical problem. It should also be noted that the present cohort consists of patients referred to a HF clinic and considered eligible for education and uptitration of guideline-recommended therapy. They

Table 3.   Crude Rates for the End Points: End-Stage Renal Disease and Death

	N	ESRD, n	ESRD Rate *(95% CI)	Death, n	Death rate *(95% CI)
All	8204	41	1.3 (0.9–1.7)	2652	84.0 (81.0–87.1)
eGFR					
Group I	5112	3	0.1 (0.0–0.3)	1165	55.4 (52.3–58.5)
Group II	2695	11	1.2 (0.5–1.8)	1223	129 (122–135)
Group III	372	22	23.0 (13.5–32.5)	246	244 (217–270)
Group IV	25	5	106 (18.2–194)	18	340 (212–467)

CI indicates confidence interval; eGFR, estimated glomerular filtration rate; and ESRD, end-stage renal disease.

*Rates: number of events per 1000 patient-years.

represent a selected group, possibly in better clinical condition than the total HF population, and this could lead to underestimation of the true ESRD rate for the population.

Previous studies of incidence of ESRD in HF do not exist, but our results can be compared with those found in patients with vascular disease, hypertension, and diabetes mellitus.[21] Compared with these patients the observed incidence of ESRD is a little lower, which may be explained by a higher mortality in patients with systolic HF and by the definition of ESRD as start of dialysis, a renal transplant, or death in the mentioned study.

We observed a low rate of progression of ESRD in the present systolic HF cohort, but our data also underscore that the prevalence of patients with systolic HF requiring dialysis is low.

Despite these reservations our, data clearly demonstrate that mortality risk is still a much larger problem than ESRD, and that progression of CKD to ESRD is rare in outpatients with systolic HF.

Young age, uncontrolled hypertension, need for diuretics, and eGFR group II, III, and IV were associated with ESRD, but diabetes mellitus was not (Table 2). However, one third of all patients who started dialysis had a diagnosis of diabetic nephropathy. Young age and uncontrolled hypertension were also associated with a decreased mortality risk, whereas eGFR groups II to IV and diabetes mellitus were associated with an increased mortality risk.

Our data indicate that HF clinics should focus on blood pressure if it is not well treated after uptitration in neurohormonal blockade and monitor eGFR closely because ESRD may develop in patients with a good long term-outcome.
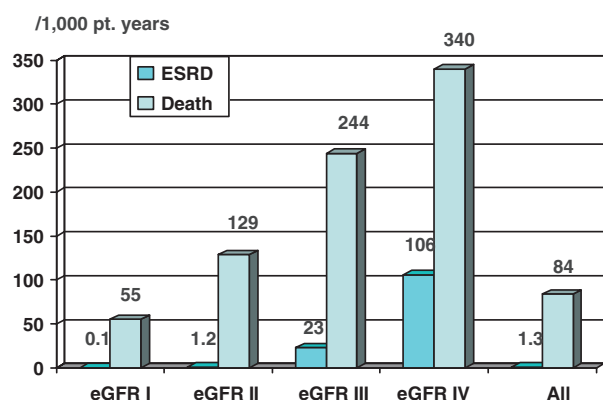

Figure 2. Incidence of end-stage renal disease (ESRD) and death. Incidence of end-stage renal disease according to estimated glomerular filtration rate (eGFR)-group and for the entire cohort, shown as numbers per 1000 patient-years.

Young age was also associated with time to ESRD in a recently large published meta-analysis[21] and may be explained by the lack of competing risk and selection bias for start of dialysis. In a study by van Pottelbergh et al[22] in older patients, where ESRD was defined as development of eGFR <15 mL/min per 1.73 m² and not as dialysis, it was also observed that older age was associated with a lower risk for ESRD. Furthermore, lower ESRD risk at any given level of eGFR at old age has been reported in other patient groups.[23,24] The association between young age and time to ESRD in the present study is, therefore, biologically plausible and may reflect a natural progressive history of CKD in systolic HF. eGFR groups II, III, and IV were all associated with an increased risk of ESRD and death, which clearly indicates that eGFR should be used in clinical practice as a predictor for both survival and a renal end point.

Finally, despite the application of cumulative incidence functions, we cannot exclude that patients with a poor renal function who died would have progressed to ESRD because of the fact that eGFR is a strong prognostic factor in HF.

We did not observe that renin–angiotensin–aldosterone system blockade was reno-protective (Table 2, model I). Treatment was associated with an improved outcome (Table 2, model II) after adjustment for eGFR group. The lack of reno-protective effect may be explained by the nonrandomized design of our study, by an increased mortality risk in untreated patients, a too short follow-up period or a type II error.

However, several attempts to up-titrate the patients with CKD should be done in the HF clinics because of the high mortality risk of patients with systolic HF and CKD. Because of declining tolerance of drugs, according to renal function, our data also indicate a potential role for a renal sparring ARA and K+-binding polymer in patients with systolic HF and CKD, but the potential effect remains to be examined.[25,26]

A need of diuretics, defined as an average daily dose of >80 mg of furosomide (or equivalent), was associated with time to ESRD independently of eGFR levels. Whether this association reflects confounding by indication, for example, patients with HF who need high doses of diuretics have impaired renal blood flow and increased tubular reabsorption of sodium and water, or a true association between doses of diuretics and time to ESRD cannot be deduced from our results.

Strengths and Limitations

Some methodological strengths and limitations should be discussed. First, the generalizability of our data is limited to patients with systolic HF and mild and moderate symptoms
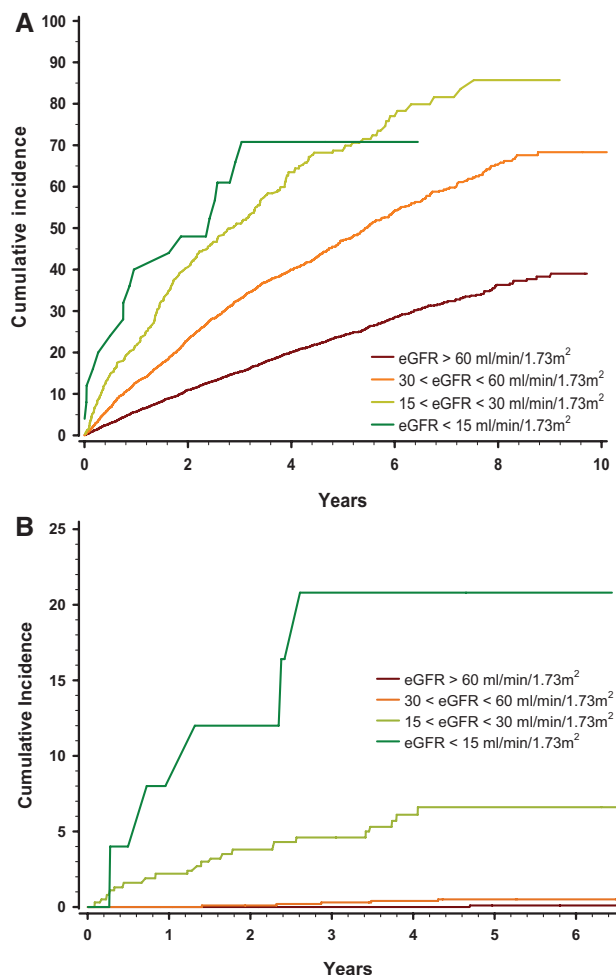
Figure 3. Cumulative incidence of death and end-stage renal disease. Cumulative incidence curves for the end point of death (**A**) and end-stage renal disease (**B**). The much larger scale for the end point death reflects the competing risk of death to development of end-stage renal disease. eGFR indicates estimated glomerular filtration rate.

considered eligible for uptitration in neurohormonal blockade. The results should not be extrapolated to patients with acute, advanced or terminal HF[27] nor to patients with HF with preserved EF. It may be speculated that the incidence of ESRD is higher in patients with preserved EF because of a better long-term outcome and in acute and patients with advanced HF because of hemodynamic instability. The majority of patients had an eGFR ≥30 mL/min per 1.73 m² and more data on patients with systolic HF who were not considered eligible for uptitration of guideline-recommended therapy with an eGFR <30 mL/min per 1.73 m² are needed. The present cohort consists of whites and our results should, therefore, be extrapolated to other ethnic and racial groups with caution.

The number of renal end points (n=41) should be noted and the lack of association between drug therapy and time to ESRD may reflect lack of power.

We have only 1 measurement of serum creatinine concentration at the baseline visit in HF clinic, and it may be argued that it has resulted in misclassification of eGFR. Nor was a follow-up creatinine available, and short-term deterioration of eGFR may have occurred. However, the creatinine was registered in

outpatients in a stable setting, and eGFR groups behaved as expected with respect to prediction of mortality risk and risk of ESRD, so misclassification seems not to be an issue. We defined ESRD as start of dialysis and not as progression of eGFR to 15 mL/min per 1.73 m² and may therefore have underestimated the true incidence of ESRD. However, the observed incidence seems realistic in relation to the mortality rate, if our data are compared with ESRD rates in patients with cardiovascular disease and diabetes mellitus, with a lower mortality rate but higher ESRD rate, where ESRD was defined as start of dialysis, a renal transplant, or death.[21] Unmeasured confounding by albuminuria, hemoglobin, cardiac and kidney injury markers might also have changed our results but were not available.[5,28] From 2002 to 2009, ≈5% to 10% of the patients with systolic HF received a cardiac resynchronization device or implantable defibrillator in Denmark and it may, therefore, be considered that a higher device implantation rate would have improve survival even more and thereby increase the risk of ESRD.[29] However, data comparable with ours from United Kingdom suggest that the survival benefit in systolic HF is driven by treatment with ACE-I/ARB and β-blockers.[9,11] The strengths of our data are the long follow-up period of a large number of patients with systolic HF treated in clinical practice in outpatient HF clinics and our possibility to obtain vital status and start of dialysis from nationwide registries without any patients lost to follow-up.

Conclusions

During a long period of follow-up we observed a low requirement for dialysis in outpatients with systolic HF and despite improved survival in systolic HF, mortality risk is still a much larger clinical problem than risk of ESRD. eGFR group, younger age, need for diuretics, and uncontrolled hypertension are important risk markers for the development of ESRD.

Disclosures

None.

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CLINICAL PERSPECTIVE

Renal dysfunction is the most frequent comorbidity in systolic heart failure (HF). For years it has been known that renal dysfunction is associated with an increased risk of death and risk of a HF admission. It is also known that therapy that improves survival in systolic HF has renal side effects and that monitoring of plasma creatinine and plasma potassium is necessary. Despite several publications of the role of the kidneys in HF it is still unknown if the proportion of patients with HF and renal dysfunction progress to end-stage renal disease (ESRD) requiring renal replacement therapy. In the present study, we investigated whether renal dysfunction progresses to ESRD in a large cohort of outpatients with systolic HF and identified predictors for ESRD. We observed that the incidence of ESRD is low and that the risk of death is substantially increased on progression. A low estimated glomerular filtration rate, young age, need of diuretics, and hypertension were associated with progression to ESRD. Our analyses suggest that despite improved survival in systolic HF, risk of death is still a much larger clinical problem than risk of ESRD, and that in patients with stable HF, fear of ESRD in patients with moderate renal dysfunction should not discourage uptitration of guideline-based therapy in HF clinics where renal function is closely monitored. Overall, the need of renal replacement therapy in outpatients with systolic HF is low.

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Incidence and Predictors of End-Stage Renal Disease in Outpatients With Systolic Heart Failure

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SUPPLEMENTAL MATERIAL

Supplemental Table 1: Cox Proportional Hazard Model for ESRD for eGFR II and III

ESRD: eGFR-group II	Hazard Ratio	95 % Confidence Interval	P-value
Age ≥70 and <80 (ref)	1.00		
Age <60	1.55	0.17-14.1	0.699
Age 60-69	1.60	0.39-6.40	0.529
Age ≥80	0.93	0.17-5.19	0.937
Uncontrolled hypertension	1.47	0.38-5.70	0.574
Diabetes	1.44	0.36-5.85	0.608
LVEF <30%	1.15	0.33-4.03	0.828
NYHA class III+IV	1.49	0.43-5.71	0.533
High doseiuretics*	1.42	0.80-2.46	0.236
ACE-I/ARB	0.39	0.11-1.40	0.148
ß-Blocker	0.64	0.16-2.54	0.524
Aldosterone Antagonist	1.08	0.28-4.21	0.909
Statin	1.67	0.44-6.32	0.451
Acetylsalicylic Acid	0.97	0.27-3.46	0.959
ESRD: eGFR-group III	**Hazard Ratio**	**95 % Confidence Interval**	**P-value**

Age ≥70 and <80 (ref)	1.00		
Age <60	3.78	1.23-12.69	0.031
Age 60-69	2.53	0.88-7.22	0.090
Age ≥80	0.13	0.02-1.04	0.054
Uncontrolled hypertension	3.56	1.35-9.42	0.011
Diabetes	1.56	0.57-4.25	0.385
LVEF <30%	0.57	0.22-1.45	0.238
NYHA class III+IV	1.77	0.66-4.72	0.255
High doseiuretics*	1.73	0.78-1.76	0.441
ACE-I/ARB	0.45	0.17-1.23	0.121
ß-Blocker	1.13	0.33-3.80	0.849
Aldosterone Antagonist	0.82	0.23-2.88	0.758
Statin	2.00	0.70-5.70	0.196
Acetylsalicylic Acid	0.39	0.15-1.05	0.062

ACE-I/ARB: Angiotensin Converting Enzyme Inhibitor or angiotensin receptor II blocker; CKD: Chronic Kidney Disease; ESRD: End-stage Renal Disease; LVEF: Left Ventricle Ejection Fraction; NYHA Class: New York Heart Association functional class. *Diuretics; use of more than 80mg Furosomid daily on average or equivalent

Supplemental Table 2: "Missing creatinine" vs. study population

Baseline	Study population		Missing creatinine		P-value
N	8204		2239		
Age	70.0		69.0		0.418
Gender fem.	28	%	29	%	0.434
LVEF <30%	56	%	67	%	<0.001
IHD	51.9	%	25.4	%	<0.001
Diabetes	14.8	%	14.6	%	0.779
NYHA I+II	77.4	%	87.5	%	<0.001
Uncontrolled hypertension	22.5	%	8.4	%	<0.001
ACE-I/ARB	89.8	%	88.1	%	0.009
ß-blocker	84.0	%	78.8	%	0.001
Aldosteron Antagonist	30.0	%	22.6	%	<0.001
Statin	51.7	%	49.4	%	0.023
Diuretics*	17.7	%	19.5	%	0.032
Acetylsalicylic Acid	53.6	%	50.9	%	0.007

Events	Study population (95%CI)		Missing creatinine 95%CI	
ESRD (N)	41		15	
ESRD rate	1.3	(0.9-1.7)	1.8	(0.9-2.8)

Death (N)	2652	709
Death rate	84.0 (81.0-87.1)	86.0 (80.0-92.1)

ACE-I/ARB: Angiotensin Converting Enzyme Inhibitor or angiotensin receptor II blocker; CKD: Chronic Kidney Disease; ESRD: End Stage Renal Disease; IHD: Ischemic Heart Disease; LVEF: Left Ventricle Ejection Fraction; "Missing Creatinine": Patients excluded from the study population due to missing value creatinine at baseline. NYHA Class: New York Heart Association functional class. Rate: events per 1000 patient years *Diuretics; use of less than 80mg Furosomid daily on average or equivalent.