Incidence of, Associations With and Prognostic Impact of Worsening Renal Function in Heart Failure With Different Ejection Fraction Categories

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There are no studies of long-term worsening renal function (WRF) in heart failure (HF) with different ejection fraction (EF) groups. The aim was to compare incidence of, associations with and prognostic impact of WRF in HF with preserved (HFpEF), mid-range (HFmrEF), and reduced EF (HFrEF). The Swedish Heart Failure Registry (SwedeHF) was merged with the Stockholm Creatinine Measurement (SCREAM) registry 2006 to 2010. The associations between EF and WRF (≥25% decrease in eGFR) and the associations between WRF25-49% and WRF≥50% within year one and subsequent all-cause mortality were all assessed with multiadjusted Cox regression. Of 7,154 patients, 41.6% of HFpEF versus 34.5% and 35.4% of HFmrEF and HFrEF patients developed WRF≥25% during year one. The WRF risk was higher in HFpEF (reference) than in HFmrEF, hazard ratio (95% confidence interval) 0.890 (0.794 to 0.997) and HFrEF 0.870 (0.784 to 0.965). WRF within year one was strongly associated with subsequent long-term mortality in all EF groups, yielding adjusted HRs with WRF25-49% and WRF≥50%: HFpEF, 1.101 (0.913 to 1.328) and 2.096 (1.652 to 2.659), in HFmrEF 1.654 (1.353 to 2.022) and 2.375 (1.807 to 3.122) and in HFrEF 1.212 (1.060 to 1.386) and 1.694 (1.412 to 2.033). In conclusion, the long-term WRF risk was high in HF and highest in HFpEF. WRF was strongly associated with mortality in all EF groups, although in HFpEF only with the most severe WRF. **(Am J Cardiol 2019;124:1575−1583)**

Renal dysfunction is common in both heart failure (HF) with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF), and is a risk factor for worse outcome.[1,2] Worsening renal function (WRF) appears to be associated with worse prognosis.[3] Studies of WRF have mostly been in hospitalized patients with acute heart failure (AHF) and the definition of WRF has varied.[4] There are few studies of the long-term risk of WRF in HF.[5,6] Studies of WRF early after hospitalization have found WRF to be a negative predictor of survival.[7,8] The cause and effect relationship between renal dysfunction and HF is still poorly understood.[9−11] HFpEF and HFrEF have different pathogenesis and the role of WRF in HF may differ in the different EF categories.[12] We lack knowledge of WRF in the mid-range EF category (HFmrEF).[13,14] This study assesses and compares the long-term incidence of WRF in patients with HFpEF, HFmrEF, and HFrEF and examines which factors are associated with WRF and the prognostic impact of WRF in the different types of HF.

Methods

The Swedish heart failure register (SwedeHF) is a web-based national quality register, enrolling unselected HF patients since 2000.[15] The protocol, registration form, and annual reports are available at http://www.SwedeHF.se. Inclusion criterion is clinician-judged HF and approximately 80 variables are recorded at discharge from hospital or during out-patient visit to physician or health care team. Individual patient consent is not required but patients are informed of entry into national quality registers and allowed to opt out. The Stockholm Creatinine Measurement (SCREAM) cohort was established to assess the burden of kidney disease in Stockholm. The SCREAM cohort contains almost all creatinine measurements performed in the Stockholm population during 2006 to 2011, covering 98% of all patients with cardiovascular disease in Stockholm.[16] A real-life cohort of unique HF patients from Stockholm 2006 to 2010 with subsequent creatinine measurements was obtained by merging SwedeHF with SCREAM. Only the patients' first registrations in SwedeHF were included. Patients with no follow-up values (8.4%) after discharge or outpatient visit were excluded as were patients with no recorded measurements of EF at registration (Figure 1). Patients registered in 2011 were excluded to enable 1 year or more of creatinine measurements. EF was obtained from

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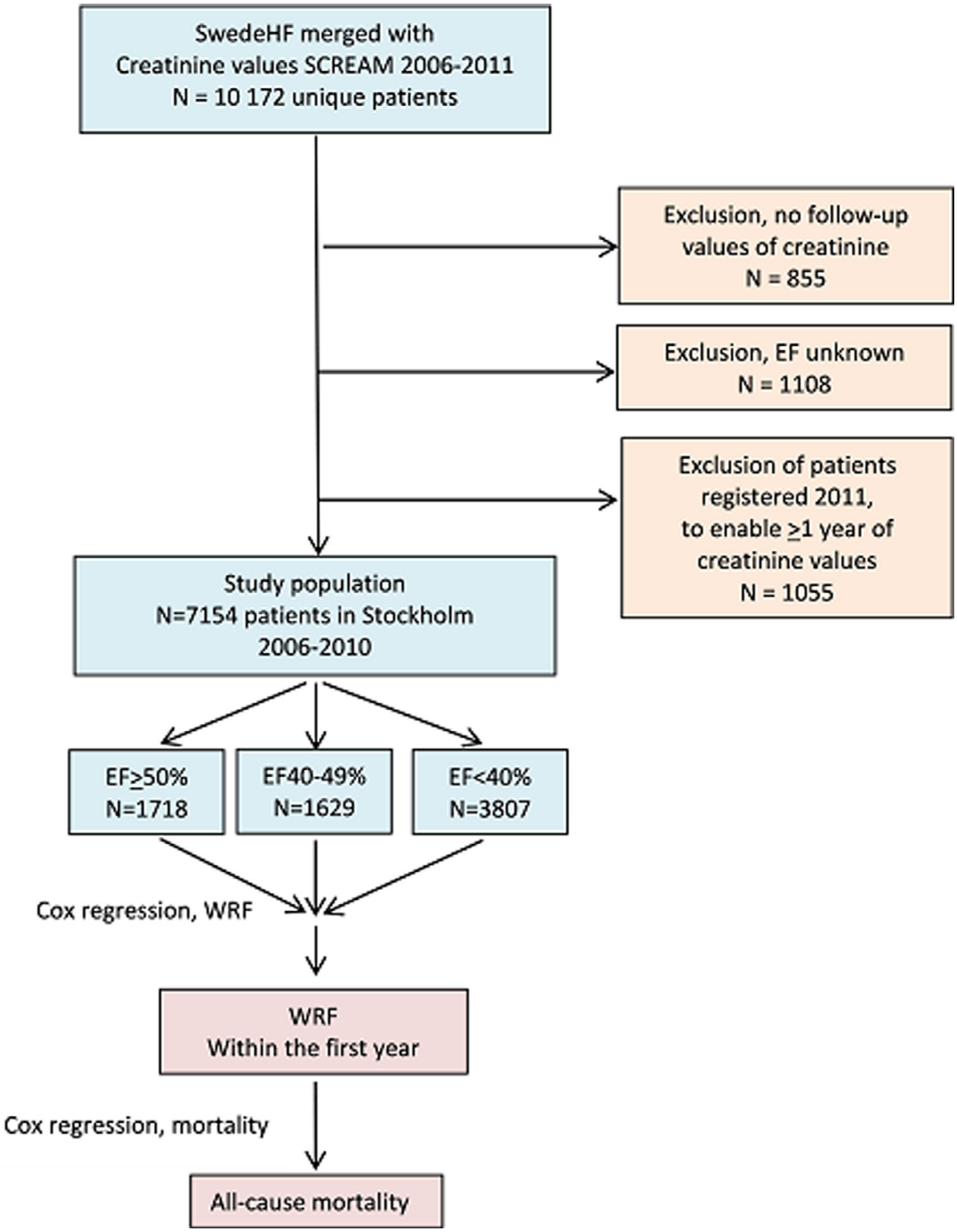

Figure 1. Study design; Selection of study population. EF = ejection fraction; WRF = worsening renal function.

the latest available measurement at registration and had been measured according to local practice (in Sweden generally echocardiography with the Simpson method). HFpEF was defined as HF with EF ≥50%, HFmrEF as HF with EF 40% to 49% and HFrEF as HF with EF <40% according to the 2016 ESC HF guidelines.[13] WRF was defined as ≥25% decrease in eGFR when studying associations between baseline characteristics and WRF within 1 year and within 5 years follow-up. WRF was divided in 25-49% and ≥50% decrease in eGFR when studying the association between WRF within year one and subsequent mortality up to 6 years follow-up. Baseline creatinine was obtained at the closest date preceding discharge from hospital or outpatient visit. Subsequent creatinine measurements (one or more) were performed as considered indicated in the clinical routine and could include both routine testing at outpatient visits as well as during hospitalization for acute disease. The time to the date when the definition for WRF was met, was analyzed. eGFR was estimated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[17] All-cause mortality data were obtained by running the registry against the Swedish population registry which includes the vital status of all Swedish citizens and permanent residents. The study conforms to the declaration of Helsinki and was approved by the regional ethical review board in Linköping.

Descriptive continuous variables were mostly skewed and presented as median with interquartile range (IQR) and categorical variables are presented as proportions (%). The crude associations between exposure and outcome were illustrated in Kaplan-Meier analyses. Differences were assessed by Pearson Chi-Square for proportions and Mann Whitney U test for continuous variables. The associations between EF category and subsequent WRF (within 1 year and within 5 years) were assessed with multivariable Cox regression analyses using in addition a total of 31 clinically relevant variables that may influence the risk of WRF (marked with *, Table 1a and 1b), including baseline eGFR (≥60, 30 to 59, <30 ml/min/1.73 m^2), WRF during hospitalization (defined as a 25% decrease in eGFR and 26.5 μmol/l increase in creatinine) and medication at discharge. The association between WRF within year one and subsequent mortality were assessed with multivariable Cox regression using the same 31 clinically relevant variables that may influence both the risk of WRF and of death. The adjustments were made stepwise for baseline eGFR and then for the remaining variables, when analyzing the association between WRF25-49% and WRF≥50% within year one and subsequent mortality in the different EF groups. The adjusted associations between exposure and outcome were illustrated with Forest plots. Variables with missing data were handled by multiple imputation (n = 20 dataset) using the same variables and outcome. Interaction tests were performed by creating an interaction term, multiplying the two variables.

Results

Of all 7,154 patients in the three EF groups, 5,186 (72.5%) were included at discharge from hospital, whereas 1,968 (27.5%) patients were included at an out-patient visit. Within the first year after discharge, 41.7% developed WRF≥25% and 14.4% WRF≥50%, whereas of the out-patients, 23.5% developed WRF≥25% and 6.4% WRF≥50%. Of all patients, median (IQR) time to WRF≥25% during follow-up was 174 (52 to 439) days in HFpEF, 207 (55 to 498) days in HFmrEF and 218 (57 to 503) days in HFrEF and to WRF≥50% 350 (129 to 604), 394 (147 to 772), and 396 (160 to 733) days respectively. During the first year, more patients with HFpEF than HFmrEF and HFrEF developed WRF≥25% (Table 1a and 1b). The cumulative incidence of WRF increased during 5 years follow-up. At 2 years over 50% of the patients had WRF≥25%, with a slightly higher proportion in HFpEF and a slightly lower in HFmrEF (Figure 2). At 2 years 25% of the patients had WRF≥50%, even here a slightly higher proportion in HFpEF (Figure 2). Patients that were hospitalized had an earlier increase in and a higher proportion of WRF≥25% than the outpatients, but after the first year there were a similar rate of new cases with WRF over time in both groups (Supplementary material, Figure 1s).

In the three EF groups analyzed separately, the patients with WRF≥25% within the first year were older, had more often hypertension, atrial fibrillation, ischemic heart disease, were more often hospitalized at inclusion, had more often higher New York Heart Association (NYHA) class, had more comorbidities, less often eGFR ≥60 ml/min/1.73 m^2 and were more often treated with mineralocorticoid receptor antagonists (MRA) and diuretics (Table 1a and 1b). In HFmrEF and HFrEF, patients with WRF≥25% had also more frequently HF with duration >6 months. In the multivariable analyses of the entire cohort, the risk for WRF≥25% during the first year was higher in HFpEF (reference) than in HFmrEF and HFrEF (hazard ratio [HR] 95% confidence interval [CI]) 1.0 vs 0.890 [0.794 to 0.997] and 0.870 [0.784 to 0.965]) and the trends were similar during 5 years follow-up (Figure 3). Other variables that were independently associated with WRF ≥ 25% were higher age, enrolment at hospital discharge versus as out-patient, comorbidities such as diabetes, chronic obstructive pulmonary disease (COPD), and anemia, HF duration over 6 months, valvular heart disease, worse NYHA class, treatment with iv. inotropes, use of cardiac resynchronization therapy (CRT), low systolic blood pressure, use of digoxin and treatment with MRA, and diuretics (Supplementary material, Table 1s). When stratifying for EF groups there were few significant interactions. In HFrEF but not in HFmrEF and HFpEF, the duration of HF was associated with WRF (Supplementary material, Table 2s).

After registration, 16.3%, 15.7%, and 15.6% respectively of the HFpEF, HFmrEF and HFrEF patients died within the first year. Patients alive and with WRF≥25% within year one had higher long-term mortality from year one than the patients with no WRF regardless of EF group (Supplementary material, Figure 2s). There were clear associations between WRF25-49% and WRF≥50% within year one and subsequent mortality during follow-up, with the strongest association for those with WRF≥50%, both unadjusted, after adjustment for baseline eGFR and in the fully adjusted analyses (Figure 4) (Supplementary material, Table 3s). The association between WRF25-49% and mortality was weaker in patients with HFpEF (HR, 95% CI) 1.101 (0.913 to 1.328) than in those with HFmrEF 1.654 (1.353 to 2.022) or HFrEF, 1.212 (1.06 to 1.386). The association between WRF≥50% and mortality was similar regardless of EF group, in HFpEF (HR, 95% CI) 2.096 (1.652 to 2.659), in HFmrEF 2.375 (1.807 to 3.122), and in HFrEF 1.694 (1.412 to 2.033).

Discussion

This is the first comprehensive study of long-term WRF in HF in relation to EF in unselected HF patients. The principal findings were that the long-term risk of WRF was high in HF and especially in HFpEF. WRF was predicted by variables associated with more severe HF and WRF within one year was strongly associated with increased subsequent mortality in all EF groups, but in HFpEF this was only the case in those with the most severe WRF.

Over one-third of the patients developed WRF during the first year which is higher than earlier noted[8,18] and probably related to different definitions of WRF and to the unselected nature of the register. Compared with out-patients, patients discharged from hospital had a doubled risk of WRF which is in line with previous descriptions of the first phase after discharge from hospital as vulnerable with increased

Table 1a
Background variables in patients without and with ≥25% decrease in eGFR within one year, in different EF groups, n = 7154

Variable	% missing of all	EF ≥ 50% n = 1718 (24.0%)		p Value	EF 40-49% n = 1629 (22.8%)		p Value	EF < 40% n = 3807 (53.2%)		p Value
		No WRF n = 1003 (58.4%)	WRF≥25% n= 715 (41.6%)		No WRF n = 1067 (65.5%)	WRF≥25% n = 562 (34.5%)		No WRF n = 2460 (64.6%)	WRF≥25% n = 1347 (35.4%)	
Years*	0	79 (67-85)	80 (73-86)	<0.001	75 (65-83)	79 (71-84)	<0.001	71 (61-80)	76 (66-83)	<0.001
Women*	0	52.1%	58.2%	0.013	37.7%	40.9%	0.201	28.1%	30.3.%	0.152
Single*	6.6	52.1%	57.2%	0.001	43.7%	48.6%	0.071	40.7%	45.4%	0.007
Independent living	24.0	94.1 %	92.9%	0.142	95.3%	95.4%	0.928	95.7%	95.3%	0.633
Cardiac care*	0.5	91.0%	92.5%	0.287	85.2%	87.0%	0.320	87.6%	89.6%	0.067
Specialist follow-up	10.4	50.2%	41.4%	0.001	61.9%	54.3%	0.005	70.9%	63.5%	<0.001
Heart Failure unit follow-up	8.7	14.5%	15.0%	0.807	20.0%	17.7%	0.301	29.4%	24.1%	0.001
Hypertension*	3.4	53.8%	60.4%	0.007	49.0%	52.8%	0.152	43.0%	46.1%	0.071
Diabetes*	1.1	21.3%	30.2%	<0.001	22.6%	34.8%	<0.001	20.8%	30.0%	<0.001
Smoker	25.5	11.7%	11.0%	0.680	15.3%	13.6%	0.445	17.9%	16.0%	0.189
Heart disease										
Ischemic heart disease*	4.9	36.0 %	39.2%	0.181	47.6%	50.4%	0.292	46.5%	53.2%	<0.001
Atrial fibrillation*	0.9	53.2%	57.0%	0.130	51.2%	59.5%	0.002	44.0%	49.1%	0.002
Valvular heart disease*	2.1	23.7%	25.9%	0.290	16.5%	24.2%	<0.001	15.7%	21.1%	<0.001
Comorbidity										
Previous stroke	79.6	13.6 %	9.0%	0.380	6.5%	15.4%	0.143	8.9%	12.5%	0.288
Chronic obstructive pulmonary disease*	3.5	17.7%	26.7%	<0.001	16.8%	23.8%	0.001	14.3 %	17.9%	0.008
Intervention										
Revascularization*	2.6	16.4%	16.3%	0.973	27.3%	22.7%	0.045	26.0%	25.5%	0.753
Valve intervention	2.1	8.5%	8.1%	0.794	6.4%	6.6%	0.883	4.4%	5.5%	0.134
Inotropes IV*	4.2	1.1%	0.7%	0.403	0.9%	1.7%	0.171	2.0%	3.7%	0.003
Cardiac resynchronization therapy*	1.8	1.1%	1.0%	0.810	1.2%	1.6%	0.504	4.9%	8.9%	<0.001
Discharge from hospital at inclusion*	0	77.5%	88.8%	<0.001	61.7%	80.1%	<0.001	64.6%	80.0%	<0.001
Heart failure >6 months*	0.7	55.6%	56.4 %	0.016	54.4%	60.6%	0.016	51.5%	64.1%	<0.001
New York Heart Association class I*	19.0	29.2%	14.7%	<0.001	25.3%	13.1%	<0.001	11.5%	6.7%	<0.001
New York Heart Association class II		49.9%	51.2%		53.9%	55.7%		48.5%	39.5%	
New York Heart Association class III		19.2%	30.1%		19.5%	25.8%		37.2%	48.3%	
New York Heart Association class IV		1.6%	3.9%		1.4%	2.5%		2.8%	5.7%	
Left ventricular ejection fraction ≥50%		100%	100%		-	-		-	-	
Left ventricular ejection fraction 40-49%		-	-		100%	100%		-	-	
Left ventricular ejection fraction 30-39%		-	-		-	-		46.5%	44.3%	<0.188
Left ventricular ejection fraction <30%		-	-		-	-		53.5%	55.7%	

Table 1b
Physical signs, laboratory results and medical treatment in patients without and with ≥25% decrease in eGFR within 1 year

Variable	% missing	EF ≥ 50% n=1718 (24.0%)		p Value	EF 40-49% n= 1629 (22.8%)		p Value	EF < 40% n = 3807 (53.2%)		p Value
		No WRF n = 1003 (58.4%)	WRF≥25% n = 715 (41.6%)		No WRF n = 1067 (65.5%)	WRF≥25% n = 562 (34.5%)		No WRF n = 2460 (64.6%)	WRF≥25% n = 1347 (35.4%)	
Status										
Heart rate*	4.9	71 (64-80)	71 (64-80)	0.906	70 (62-81)	73 (65-83)	0.003	72 (65-83)	72 (65-82)	0.731
Blood pressure systolic, mm Hg*	1.7	130 (118-145)	130 (120-150)	0.058	130 (120-140)	130 (115-140)	0.965	120 (110-135)	120 (110-135)	0.157
Blood pressure diastolic, mm Hg	1.8	70 (65-80)	70 (60-80)	0.030	75 (66-80)	72 (65-80)	0.521	75 (65-80)	70 (64-80)	<0.001
Body mass index, kg/m^2	40.6	26.2 (22.6- 30.0)	26.1 (22.5-30.9)	0.420	26.0 (23.4-29.8)	25.9 (22.9-30.5)	0.747	25.3 (22.5-29.2)	25.1 (22.4-28.4)	0.082
Nonsinus rhythm*	2.2	50.7%	52.5%	0.470	49.5%	61.3%	<0.001	45.0%	52.7%	<0.001
Left bundle branch block	27.2	8.3%	8.4%	0.962	16.1%	11.6%	0.040	24.5%	29.5%	0.006
QRS width, ms	46.1	94 (84-108)	96 (86-114)	0.231	98 (88-120)	98 (88-118)	0.611	106 (94-130)	110 (94-138)	0.005
Laboratory data										
Hemoglobin, g/l*	0	130 (117-142)	122 (111-134)	<0.001	134 (120-145)	126 (114-139)	<0.001	137 (124-149)	129 (117-141)	<0.001
Creatinine μmol/l	0	93 (76-121)	95 (79-127)	0.018	91 (75-115)	98 (80-130)	<0.001	96 (79-119)	101 (82-129)	<0.001
eGFR ≥ 60 ml/min/1.73 m^2*	0	47.6%	42.2%	0.011	58.2%	45.4%	<0.001	57.8%	48.1%	<0.001
eGFR 30-59 ml/min/1.73 m^2		43.9%	45.3%		33.6%	44.5%		34.3%	43.1%	
eGFR < 30 ml/min/1.73 m^2		8.6%	12.5%		8.3%	10.1%		7.9%	8.8%	
WRF in hospital*	0	13.6%	14.1%	0.737	10.4%	9.8%	0.696	9.6%	13.8%	<0.001
Potassium, mmol/l	58.8	4.0 (3.8-4.3)	4.0 (3.8-4.3)	0.670	4.1 (3.8-4.4)	4.0 (3.8-4.3)	0.410	4.1 (3.9-4.4)	4.1 (3.8-4.4)	0.010
NT-proBNP, ng/l	79.1	1430 (620-3260)	2130 (1150-4730)	<0.001	1380 (611-3515)	2995 (1330-6440)	<0.001	2653 (1081-5730)	4525 (2080-10200)	<0.001
Medication at discharge										
ACE-inhibitors	1.4	50.8%	52.5%	0.539	64.5%	58.1%	0.012	73.8%	70.5%	0.030
Angiotensin receptor blocker	2.2	19.7%	23.3%	0.082	18.4%	23.3%	0.019	18.9%	20.1%	0.381
ACE-inhibitors/ Angiotensin receptor blocker*	1.5	69.4%	72.7%	0.145	81.6%	80.0%	0.449	91.3%	88.3%	0.003
Beta blockers*	1.3	82.3%	80.6%	0.371	88.2%	87.6%	0.752	92.0%	91.9%	0.894
Mineralocorticoid receptor antagonists*	1.3	20.9%	32.1%	<0.001	21.7%	39.0%	<0.001	32.1%	43.5%	<0.001
Digoxin*	1.2	18.7%	19.5%	0.697	16.6%	18.3%	0.401	19.5%	18.5%	0.458
Statins*	1.1	37.4%	35.7%	0.787	43.3%	46.0%	0.304	42.3%	44.2%	0.266
Nitrates*	1.5	19.3%	21.3%	0.298	17.4%	19.5%	0.307	16.0%	19.5%	0.006
Anticoagulants*	1.3	39.8%	36.5%	0.167	36.9%	42.3%	0.033	40.0%	39.9%	0.958
Antiplatelets*	1.1	44.8%	49.5%	0.053	50.5%	51.2%	0.790	49.5%	51.7%	0.184
Diuretics*	1.1	77.6%	91.0%	<0.001	68.0%	86.6%	<0.001	76.7 %	88.3%	<0.001
Death within 1 year		9.8%	25.3%	<0.001	10.6%	25.3%	<0.001	10.4%	25.0%	<0.001

Variables are median (interquartile range) or percent.
* Variables adjusted for in Cox regression analyses, imputation of missing.

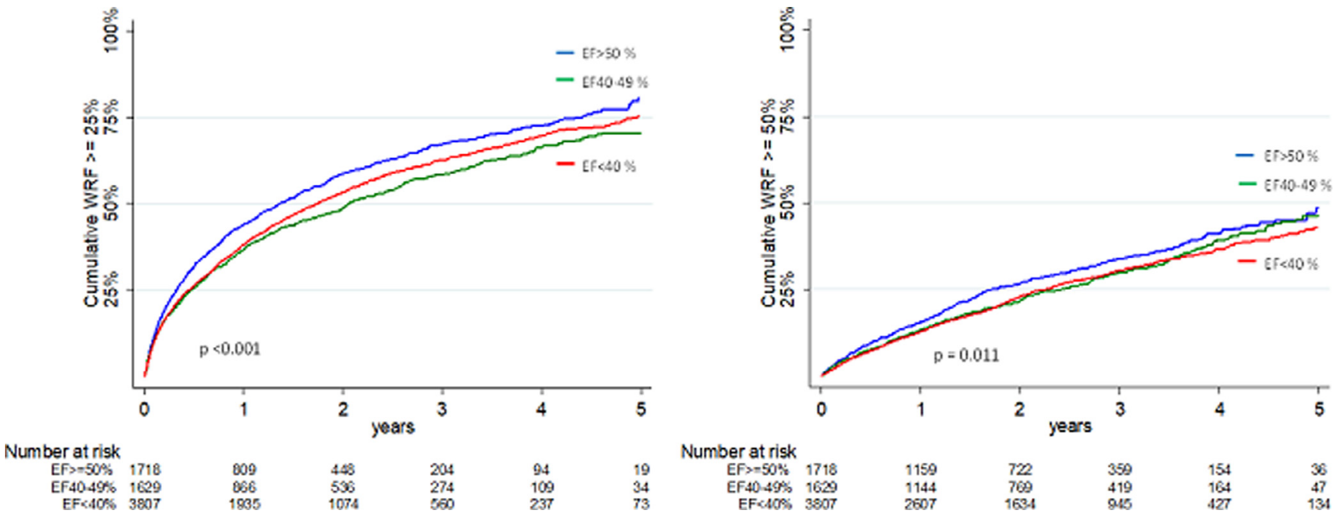

Figure 2. Cumulative incidence of WRF stratified on different EF groups; WRF≥25% and WRF≥50% during follow-up. EF = ejection fraction; WRF = worsening renal function.

morbidity and mortality.[19] HFpEF patients had more often WRF during follow-up than HFrEF and HFmrEF. We have previously shown that HFpEF is associated with higher prevalence of chronic kidney disease (CKD), and we could now demonstrate that the association between HFpEF and WRF was independent of baseline renal function.[20] The higher prevalence of kidney dysfunction in HFpEF is thought to be driven by hemodynamic, neurohormonal and inflammatory pathways[21] but less is known about the changes in kidney function over time. Right ventricular dysfunction is more common in HFpEF than earlier noted and increases the risk for progressive kidney dysfunction.[22,23] As CKD has been found to be independently associated with higher pulmonary pressures and lower right and left ventricular and atrial strain in HFpEF, there may be a two way association between worsening cardiac function and WRF.[24] The chronotropic insufficiency that has been observed in HFpEF is thought to be caused by autonomic dysfunction and has also been found to be associated with kidney dysfunction, likely both by fixed cardiac out-put and by the effect of the autonomic dysfunction on the kidney.[25] We also found that age, diabetes, hospitalization, NYHA class and anemia were associated with WRF which is in line with the study of Damman et al who concluded that baseline eGFR, age, diabetes type II and the presence of anemia were independent predictors of both in- and out-hospital WRF.[8] In our analyses, COPD was also associated with WRF. Pulmonary disease is more frequent in HFpEF and related to right ventricular dysfunction[23] and patients with COPD may have more vascular disease and higher risk for reduced renal function.[6] Variables related to the severity of HF as HF duration, CRT and use of inotropes were also predictors of WRF. In all EF groups MRA and diuretics were associated with WRF. This is in line with the reduction of GFR with MRA treatment[26] and the earlier noted association

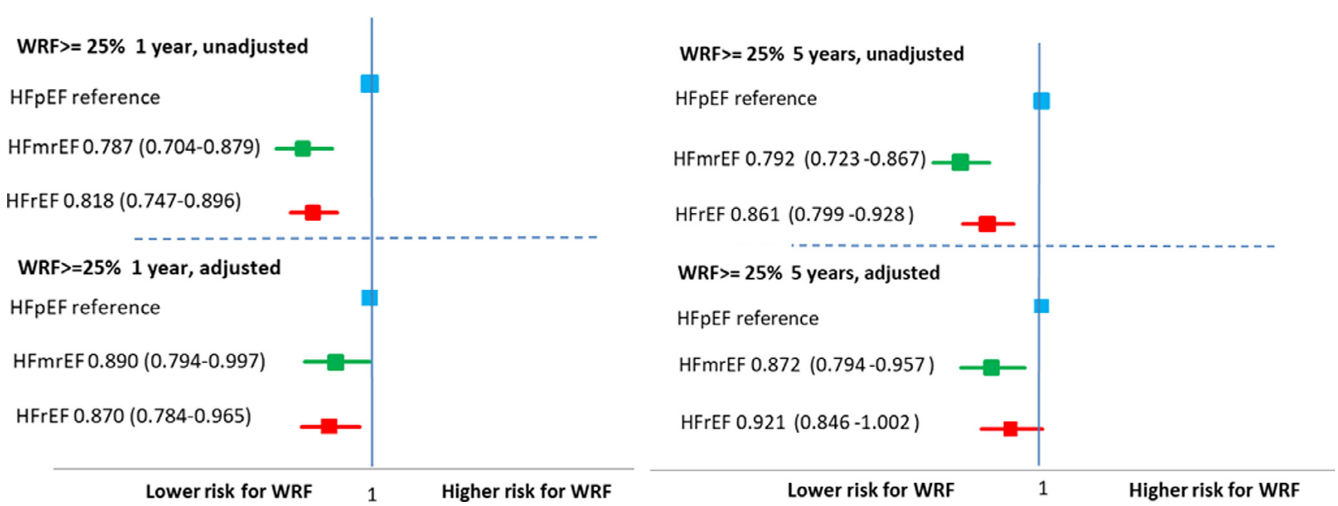

Figure 3. Risk for WRF in the different EF groups; WRF≥25% within 1 year and 5 years, HR 95% CI. EF = ejection fraction; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; WRF = worsening renal function.

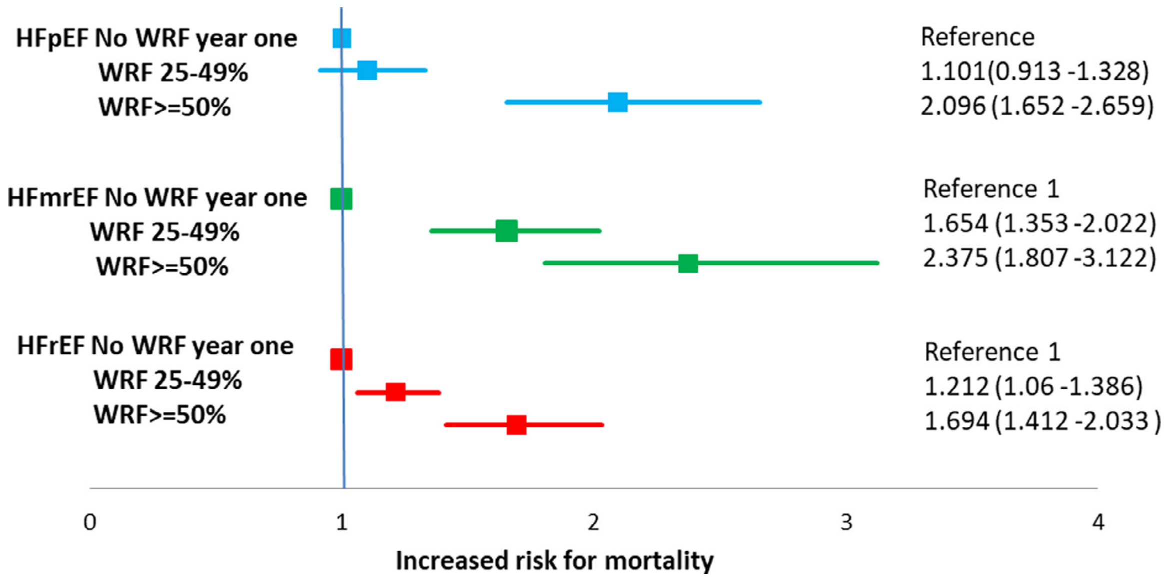

Figure 4. Mortality risk with WRF in different EF groups: Risk with WRF25-49% and WRF≥50% within year one, HR 95% CI. EF = ejection fraction; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; WRF = worsening renal function.

between loop diuretics and WRF in chronic HF patients.[5] One must although be cautious regarding the potential causality as MRA is commonly used in CKD patients with hypertension and diuretics are part of the basic medication in CKD.

A 25% reduction in renal function during the first year after inclusion was associated with subsequent increased mortality during long-term follow-up. This confirms the results in the smaller study of Ueda et al.[18] In our study the mortality risk in all EF groups increased with increasing WRF, with the highest mortality risk in patients with WRF≥50%. Adjustment for baseline eGFR resulted in only minor changes which indicate that WRF is a strong risk factor independent of underlying kidney function. There was a high cumulative mortality in patients with HFmrEF and WRF had a similar association with mortality in HFmrEF as in HFrEF. This confirms earlier findings that HFmrEF appear similar to HFrEF in many regards, whereas intermediate to HFpEF and HFrEF in other.[27,28] We observed a weaker association between WRF and mortality in HFpEF compared with HFmrEF and HFrEF indicating that the mechanism by which WRF is associated with mortality in the different EF categories may differ. The prognosis in patients with HFpEF and WRF may be more related to comorbidities and right ventricular dysfunction where comorbidity related factors drive development of kidney dysfunction and HF in parallel.[21] Therefore in HFpEF, kidney dysfunction may not directly reflect a worse HF status. In HFrEF and perhaps even in HFmrEF, kidney dysfunction may be more related to progressive HF, therefore kidney dysfunction may be less common, but once present, associated with greater risk.

This study is based on a nationwide quality registry continuously collecting data from HF patients in the everyday routine, resulting in highly generalizable results. But this will also lead to inherent limitation. Thus, HF was defined as clinically judged HF by the clinician following current guidelines, and EF was determined according to local routines and not by a central core lab. Moreover, this is a register study merged with a laboratory data base that covered patients with cardiovascular disease during a certain timeperiod. We had to exclude patients with no follow-up values (8.4%) of creatinine. The registered creatinine data in SCREAM reflect the follow-up and course of HF patients in real life as creatinine is controlled in most clinical situations. There may have been different reasons for the subsequent laboratory tests (routine outpatient testing as well as during hospitalizations because of acute disease) which may have had an impact on the incidence of WRF during follow-up. As there is no generally accepted definition of WRF,[29] we chose to define WRF as ≥25% and ≥50% to have 2 degrees of WRF. There may have been individuals with WRF who later improved their renal function. Still, WRF was strongly associated with mortality. Since this is an observational study, all indications of causality must be interpreted with great caution. The decision of which variables to include in the multivariate analyses is demanding as some variables influence each other more by selection than biological reasons and there may be bidirectional effects between the variables. We did not study rehospitalization and changes in the medical treatment during follow-up.

In conclusion, the long-term risk of WRF was high in HF and especially in HFpEF. Variables related to more severe HF were predictive of WRF. WRF was strongly associated with mortality in all EF groups, although in HFpEF this was only with the most severe WRF.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.07.065.

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