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Article

Clinical Features and Outcomes of Patients with Heart Failure and Advanced Chronic Kidney Disease: A Dangerous Association

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Abstract

Aims: To analyze in a contemporary registry of heart failure (HF) patients followed in specialized HF units in Spain the differences in clinical features, treatment and 1-year outcomes in HF with advanced chronic kidney disease (CKD). **Methods and results:** We analyzed data from the registry of the SEC-Excelente-IC quality accreditation program of the Spanish Society of Cardiology, with 1,567 patients with HF included between 2019 and 2022 by 45 specialized HF units. Treatment and 1-year mortality and HF hospitalizations rate were compared according to the existence of advanced CKD (glomerular filtration rate < 30 ml/minute/m²). Of the 1,567 patients, 11.1% had a GFR<30 and 88.9% ≥ 30 mL/min/m². Median LVEF was similar in both groups: 42 (30-58) vs 38% (29-54). The group with advanced CKD was older (77±9.6 vs 70.5±12.6 years; p<0.001), had greater HF severity (more admissions for HF in the last year, worse NYHA functional class and longer evolution time), and a higher prevalence of coronary heart disease, hypertension, diabetes mellitus, anemia, iron deficiency and hyponatremia. Patients with GFR <30 received in a significantly lower proportion all drugs for HF (p<0.001), except diuretics and potassium binders. One-year mortality (49.2 versus 13.7/100 persons-year; p<0.001) and 1-year HF hospitalizations rate (83.2 versus 30.7/100 persons-year; p<0.001) were higher in patients with HF and advanced CKD. **Conclusions:** In our contemporary cohort of real-life HF patients, patients with advanced CKD showed different clinical features, received indicated treatment in a lower proportion and had higher 1-year mortality and HF hospitalization rates.

Keywords: heart failure; advanced chronic kidney renal disease; treatment; outcomes

1. Introduction

Heart Failure (HF) is a severe health problem in western countries, due to its notable and increasing incidence and prevalence [1,2], its high short- and long-term mortality [3,4] and the important economic cost it generates for the system. As several studies have shown [3–7], despite the great advances made in recent years in its diagnosis and treatment [8], mortality and recurrence of decompensation and hospital admissions are still very high [3,4,7].

Chronic kidney disease (CKD) is increasingly prevalent in patients with HF, and HF is one of the leading causes of hospitalization and mortality in patients with impaired renal function [8]. It is reported that almost half of patients with HF have a degree of renal impairment and HF is prevalent

in 17–50% of patients with CKD, depending on the stage of the CKD and age of the patients [9,10]. In addition, the prevalence and mortality of HF increases with worsening renal failure [8]. Renal function is an independent predictor for inpatient mortality of patients with acute HF, length of hospital stay and re-admission rate [8]. Advanced severe CKD worsens HF prognosis. Drug treatment with favorable prognostic effect is suboptimally prescribed in HF patients with severe kidney function impairment, despite current strong evidence supporting the symptomatic and prognostic benefits of many of them (β -blockers, renin–angiotensin–aldosterone inhibitors, angiotensin receptor-neprilysin inhibitors and mineralocorticoid receptor antagonists) [11–14], mainly owing to concerns about hyperkalemia and worsening renal function [11,12]. There is growing evidence for the use of sodium–glucose co-transporter 2 inhibitors [15–17] in the management of HF in patients with CKD, but few studies have included patients with CKD stages 4–5 and patients receiving dialysis, limiting the assessment of the safety and efficacy of these therapies in advanced CKD. This problem will continue to grow, because with improving survival in both patients with HF and those with CKD, it is likely that the numbers of patients presenting with both these conditions will continue to rise.

In addition, there is not much knowledge in patients with more severe renal insufficiency, with $\text{GFR} < 30 \text{ ml/min/m}^2$, since clinical drug trials usually exclude these patients, and, moreover, real-life registries do not separately analyze the degree of renal dysfunction. Thus, the aims of our study were: 1) to analyze the prevalence of advanced CKD in a contemporary registry of patients with HF followed up in specialized HF units in Spain; 2) to compare clinical features and treatment of patients with HF and advanced CKD with those without advanced CKD; and 3) to evaluate 1-year outcomes (mortality and HF decompensations) in these 2 groups of HF patients.

2. Materials and Methods

The SEC-Excelente-IC Registry is an ongoing, prospective, multicentric, observational study of patients with HF presenting to HF units accredited by the SEC-Excelente-IC quality program of the Spanish Society of Cardiology. The design and logistics of this program have recently been published [18]. The registry was developed by a scientific committee with the aim to study clinical features, treatment and 1-year outcomes of HF patients managed in these accredited units. The study met all requirements of the Declaration of Helsinki for research involving human subjects and was approved by the locally appointed ethics committees of the participating centers. All patients signed the informed consent document. Each participating unit included all HF patients seen in their unit consecutively in two 1-month cutoffs (March and October) in the years 2019–2022. A total of 1,716 patients were included. Of the 91 HF units accredited by the SEC in its SEC-Excelente program between 2017 and 2023, the first 45 received such accreditation in 2017 and 2018 and carried out patient inclusion in 2019–2022, completing the 1-year follow-up in December 2023. Of the 1,761 patients included, no information was available at one year of follow-up in 149 cases (8,7%), so the final analysis was performed on 1,567 patients. Follow-up losses were evenly distributed in both GFR groups.

Inclusion Criteria and Follow-Up

Both inpatients and outpatients with a recent hospital admission (within the previous 3 months) with a primary diagnosis of HF could be included. There were no specific exclusion criteria, other than patients age less than 18 years. Echocardiographic assessment of left ventricular ejection fraction was performed at the enrolment visit unless the patients had a recent echocardiographic study (within the previous 4 weeks). HFrEF was considered when the left ventricular ejection fraction was less than 40%, HFmrEF when it was 41–49% and HFpEF when it was 50% or higher. Advanced CKD was defined by an estimated glomerular filtration rate (GFR) $< 30 \text{ ml/minute/m}^2$. Tables 1 and 2 summarize the clinical and treatment variables collected at the baseline visit in patients with $\text{GFR} < \text{or} \geq 30 \text{ mL/min/m}^2$. A follow-up visit one year after inclusion was mandatory for all patients to obtain information about changes in treatment and clinical outcomes (death, HF hospitalizations and

decompensations of HF without hospitalization). Total all-cause mortality was analyzed when the patient’s death was identified in the clinical history or after a telephone call if the patient did not attend the one-year follow-up visit. A hospital admission lasting more than 24 hours with a main diagnosis of HF according to the criteria of the European Society of Cardiology was considered as HF hospitalization⁷. Decompensation of HF without hospitalization was defined as a visit to the emergency room or the need for intravenous treatment with diuretics or inotropic drugs without hospital admission. Patients who died during the hospital admission that led to inclusion in the study were excluded from the follow-up analysis. Decompensation without the need for admission was defined as a visit to the emergency department or to the HF clinic because of clinical worsening of HF that required, in the opinion of the attending physician, an increase in diuretic doses or intravenous treatment with diuretics or inotropic drugs, without hospital admission. All patients were followed up and treated according to the criteria of their physicians, without any prespecified intervention as part of the registry protocol.

Table 1. Demographic characteristics, risk factors, comorbidities, and history of heart failure in patients with glomerular filtration rate < or % ≥ 30 mL/min/m2.

	All n=1,567	GFR < 30 ml/min/m2 n=174 (11.1%)	GFR ≥ 30 mL/min/m2 n=1,393 (88.9%)	P value
Age (years)	71.2±12.5	76.9±9.7	70.6±12.7	<0.001
Female sex	37.1%	39.7%	36.4%	0.741
Hypertension	72.9%	85.5%	71.1%	<0.001
Diabetes mellitus	43.8%	59.9%	41.1%	<0.001
Coronary artery disease	31.6%	40.8%	28.9%	0.001
Coronary revascularization	31.3%	37.4%	30.7%	0.013
Stroke	9.8%	11.1%	9.6%	0.535
Malnutrition	4.5%	8.2%	4.1%	0.016
Anemia	34.4%	63.6%	30.6%	<0,001
Cancer	6.5%	8.1%	6.1%	0.292
Atrial fibrillation	52.5%	49.5%	53.5%	0,015
Permanent atrial fibrillation	28.4%	23.2%	27.6%	<0.001
Chronic pulmonary obstructive disease	17.0%	16.3%	17.4%	0.644
Ferropenia	33.8%	42.9%	32.6%	0.007
LVEF (%)	40.8±15.8	42.8±16.0	40.5±15.6	0.063
HFrEF	55.5%	56.7%	52.8%	0.246
De novo HF	49.5%	35.7%	52.4%	<0.001
HF admissions within the previous year	33.5%	48.3%	31.3%	<0.001
Previous CRT	7.9%	8.2%	7.8%	0.730
Previous AID	14.5%	12.6%	14.8%	0.735
HF etiology				<0.001
- Ischemic	31.6%	39.1%	30.5%	
- Hypertensive	8.2%	13.8%	6.9%	
- Idiopathic	13.7%	5.7%	15.2%	
- Valvular	17.4%	16.1%	17.6%	
- Tachycardiomyopathy	12.3%	7.5%	13.5%	
NHYA III-IV class	60.8%	77.3%	58.5%	<0.001
Left bundle branch block	23.7%	26.6%	23.7%	0.409
Body mass index (Kg/m2)	28.2±6.1	28.5±6.5	28.2±6.1	0.643
Glomerular filtration rate (ml/min/m2)	59.0±23.4	26.7±3.5	65.8±24.2	<0.001

Hemoglobyn (g/dl)	13.0±2.2	11.7±2.1	13.2±2.2	<0,001
NTproBNP (ng/ml)	4239±6886	9775±11661	3464±5486	<0.001

GFR: glomerular filtration rate. HF: heart failure. LVEF: left ventricular ejection fraction. HFrEF: heart failure with reduced ejection fraction. CRT: cardiac resynchronization therapy. AID: automatic implantable cardioverter.

Table 2. Treatment at the inclusion visit in the registry in patients with glomerular filtration rate < or % ≥ 30 mL/min/m2.

	All n=1,567	GFR < 30 ml/min/m2 n=174 (11.1%)	GFR ≥ 30 mL/min/m2 n=1,393 (.9%)	P value
ACEI/ARB	36.6%	29.3%	37.2%	<0.001
Sacubitril-valsartan	38.0%	17.2%	40.6%	<0.001
Mineral receptor antagonists	56.6%	22.9%	61.1%	<0.001
Betablockers	80.0%	69.5%	81.3%	<0.001
SGLT2 inhibitors	40.1%	26.6%	42.7%	<0.001
Diuretics	84.9%	90.2%	83.6%	0.024
Digoxin	8.2%	5.2%	10.3%	0.139
Ivabradine	9.1%	7.5%	9.4%	0.404
Antiplatelets	32.9%	37.8%	32.1%	0.136
Oral anticoagulants	57.8%	50.6%	59.4%	0.007
Direct anticoagulants	39.8%	29.3%	41.7%	<0.001
Potassium chelators	1.9%	4.1%	1.6%	0.024
Cardiac rehabilitation program	9.6%	5.2%	11.1%	0.020

GFR: glomerular filtration rate. ACEI: angiotensin converting enzyme inhibitors. ARB: angiotensin receptor blockers.

Statistical Analysis

Qualitative variables are expressed as percentages and quantitative variables are presented as mean ± standard deviation. To compare the differences between the 2 groups of GFR < or ≥ 30 mL/min/m2, we used the chi-square test or Fisher’s exact test, when appropriate, in the case of qualitative variables, and the Kruskal-Wallis test for quantitative variables. We analyzed the incidence per year, in the overall series and in the 2 subgroups, of the following events: a) mortality; b) admission for HF; c) combined event of mortality or admission for HF (whichever occurred first); d) HF decompensation without hospitalization; and e) HF decompensation (including hospital admissions for HF and care for HF decompensation without hospitalization attended both in the emergency room and in the day hospital). For the analysis of admissions and decompensation, all recurrent events were considered. Incidence was expressed as incidence rates per 100 person-years. The incidences of the different events were compared between the 3 types of HF, in the form of relative risks (Table 3). Finally, a predictor analysis was performed for mortality, HF admission, and HF decompensation. Multivariate Cox regression analysis was performed to determine the factors associated with mortality. To determine the factors associated with HF admissions and HF decompensations, a negative binomial regression model was used as an alternative to Poisson regression, because the negative binomial distribution allows us to correct for the phenomenon of overdispersion of the data, and, furthermore, the likelihood ratio test (p-value<0.001) allowed to reject the Poisson model in favor of the negative binomial model. The models were performed with a backward procedure, using a value of p<0.05 to remain in the final model. The variables that were significant in the univariate analysis (p value<0.10) were included in the multivariate model (Table 4). The STATA 12.0 statistical package was used for data analysis.

Table 3. Pharmacological treatment at the inclusion visit in the subgroup of patients with heart failure with reduced left ventricular ejection fraction according to glomerular filtration rate < or % ≥ 30 mL/min/m2.

	GFR < 30 ml/min/m2 n=91 (10.4%)	GFR ≥ 30 mL/min/m2 n=779 (89.6%)	P value
ACEI/ARB	19.5%	29.2%	0.063
Sacubitril-valsartan	30.5%	59.2%	<0.001
Mineral receptor antagonists	31.7%	77.8%	<0.001
Betablockers	76.8%	89.5%	0.001
SGLT2 inhibitors	34.1%	52.9%	0.001
Diuretics	91.4%	81.7%	0.031
Digoxin	7.3%	8.8%	0.837
Ivabradine	14.6%	14.1%	0.888
Antiplatelets	43.9%	37.6%	0.267
Oral anticoagulants	47.6%	52.5%	0.005
Direct anticoagulants	21.9%	37.4%	0.005
Potassium chelators	3.6%	1.9%	0.405

GFR: glomerular filtration rate. ACEI: angiotensin converting enzyme inhibitors. ARB: angiotensin receptor blockers.

Table 4. Overall incidence rate of the events of interest and according to glomerular filtration rate < or % ≥ 30 mL/min/m2. Rate expressed in events/100 patient-years.

	Events number	Incidence rate	95% CI	Relative risk	95% CI	P value
Mortality						
GFR < 30	51	37.26	28.32 49.03	Reference		
FG ≥ 30	172	14.44	12.44 16.77	0.38	0.28 0.53	<0.001
HF hospitalization						
GFR < 30	84	61.37	49.56 76,00	Reference		
GFR ≥ 30	328	27.55	24.72 30.69	0.44	0.35 0.57	<0.001
Death/HF hospitalization						
GFR < 30	77	64.26	51.40 80.35	Reference		
GFR ≥ 30	328	29.89	26.82 33.30	0.46	0.36 0,59	<0.001
HF decompensation without hospitalization						
GFR < 30	33	24.11	17.14 33.91	Reference		
GFR ≥ 30	131	11.00	9,27 13.06	0.45	0.31 0,66	<0.001
All HF decompensation						
GFR < 30	117	85.48	71.31 102.46	Reference		
GFR ≥ 30	459	38.55	35.18 42.24	0.45	0.36 0.55	<0.001

CI: confidence interval. GFR: glomerular filtration rate (ml/min/m2).

3. Results

Baseline Features and Treatment

Of the 1,567 patients, 11.1% had a glomerular filtration rate < 30 mL/min. Patients with advanced CKD were older and had a higher prevalence of hypertension, diabetes mellitus, coronary heart disease, malnutrition, anemia and iron deficiency. There was no difference in the proportion of women. Left ventricular ejection fraction was similar, as the proportion of HFrEF and HFpEF (Table 1). Etiology was more frequently of ischemic and hypertensive origin in the group with GFR < 30 mL/min/m2.

Patients with GFR < 30 mL/min/m2 received a lower proportion of all drugs with a feasible prognostic effect (Table 2), including beta-blockers, sacubitril-valsartan, MRA and SGLT2 inhibitors. They also received a smaller proportion of direct oral anticoagulants. They were taking diuretics and potassium chelators in a higher proportion than those in the group with less impaired renal function. These results were similar when the analysis was limited to patients with HFrEF. Patients with HFrEF and GFR < 30 mL/min/m2 received sacubitril-valsartan, MRA, betablockers and SGLT2 inhibitors in a significantly lower proportion than those with HFrEF and GFR ≥ 30 mL/min/m2 (Table 3). In the overall series, there were no differences in the use of AIDs and CRT (Table 1), and they underwent a lower proportion of cardiac rehabilitation programs (Table 2). Figure 1 graphically shows the differences in the prescribed drugs between the 2 groups of patients.

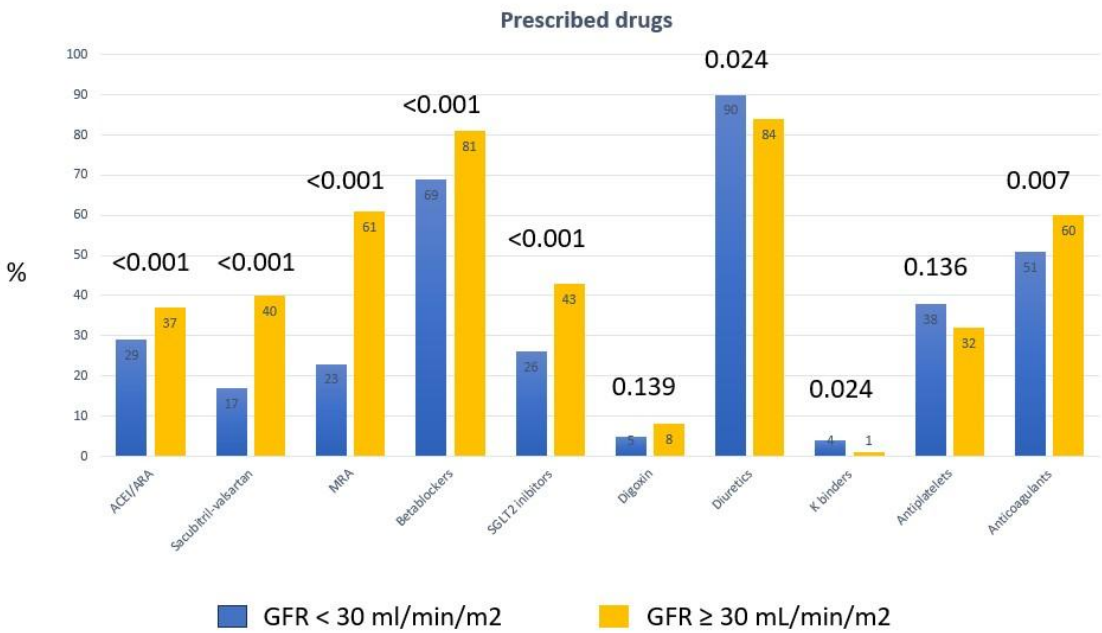


Figure 1. Prescribed drugs in the 2 subgroups of glomerular filtration rate. ACEI: angiotensin converting enzyme inhibitors. ARB: angiotensin receptor blockers. MRA: mineral receptor antagonists. K: potassium.

Incidence of Events at One Year of Follow-Up

Table 4 shows the incidence rates of the different events per 100 patient-years. Of the 1,239 patients included in the registry during an episode of hospitalization for HF, 32 died during admission (in-hospital mortality 2.6%). During the follow-up year, there were 241 deaths, 434 admissions for HF and 170 decompensations of HF without hospitalization. The incidence rate of mortality in the overall series was 16.9 (95% CI: 14.9-19.1), that of HF admissions was 30.4 (27.7-33.4), that of HF decompensations without admission was 11.9 (10.2-13.8), and that of total decompensations, including admissions, was 42.4 (39.1-45.9) per 100 patient-years.

Mortality, HF hospitalization rate, incidence of HF decompensation and total decompensation rate at 1 year were statistically higher in the group with GFR < 30 mL/min/m2 (p<0.001 for all events, Table 4). Patients with GFR ≥ 30 ml/min/m2 had a 62% lower mortality, a 56% lower HF admission rate, and a 55% lower HF decompensation rate (Table 4). Figure 1 graphically shows the differences in the event incidence between the 2 groups of patients.



Figure 2. Incidence of events at 1 year of follow-up, expressed as rates per 100 patient-years, in the 2 subgroups of glomerular filtration rate. HF: heart failure. GFR: glomerular filtration rate.

Predictors of Events (Multivariate Study)

Table 5 shows the independent predictors of death, HF admission, and HF decompensation at 1-year follow-up. Advanced CKD was a significant predictor of all events. The HR for mortality was 1.62 (95% CI: 1.23-2.13). The incidence risk ratio for HF hospitalizations was 1.44 (95% CI: 1.09-1.92), and for HF decompensations 1.58 (95% CI:1.23-2.01) (p<0.001 for all events; Table 5). Type of HF (HFrEF, HFmrEF, and HFpEF) was not a predictor of death, HF admissions, or HF decompensations in the multivariate study. The strongest independent predictors for the three types of events were variables related to greater severity and duration of HF, ischemic etiology, advanced CKD and some functionally limiting comorbidities (Table 5). Age was an independent predictor only of mortality, but with a low level of statistical significance (Table 5).

Table 5. Predictors of death, heart failure admissions and heart failure decompensations at one-year follow-up HF at multivariant analysis.

DEATH				
	HR	95% CI		P value
Hospitalized during inclusion	2.20	1.47	3.29	<0.001
Age	1.03	1.01	1.04	0.001
Ischemic etiology	1.47	1.13	1.91	0.004
NYHA class III-IV	1.46	1.04	2.05	0.029
Previous follow-up in a heart failure unit	1.66	1.25	2.21	0.001
HF admissions in the previous year	1.62	1.23	2.13	0.001

Advanced CKD	1.63	1.22	2.16	0.001
COPD	1.43	1.03	1.97	0.032
Sleep-apnea syndrome	1.50	0.30	0.81	0.005
Hemiplegia	2.80	1.69	4.65	<0.001
Cancer	1.78	1.18	2.68	0.006
Trauma/falls in the previous year	1.87	1.20	2.92	0.006
Malnutrition	1.76	1.16	2.67	0.008
HF ADMISSIONS				
IRR				
Hospitalized during inclusion	1.85	1.30	2.65	0.001
NYHA class III-IV	1.49	1.08	2.05	0.015
Previous follow-up in a heart failure unit	1.68	1.25	2.27	0.001
HF admissions in the previous year	2.33	1.74	3.13	<0.001
Previous coronary artery disease	1.60	1.20	2.14	0.001
Previous atrial fibrillation	1.82	1.37	2.41	<0.001
Advanced CKD	1.44	1.09	1.92	0.011
COPD	1.50	1.08	2.08	0.016
Trauma/falls in the previous year	1.82	1.02	3.23	0.041
Anemia	1.36	1.02	1.81	0.035
HF DECOMPENSATIONS				
IRR				
Hospitalized during inclusion	1.79	1.31	2.44	<0.001
NYHA class III-IV	1.41	1.07	1.86	0.016
Previous follow-up in a heart failure unit	1.85	1.44	2.39	<0.001
HF admissions in the previous year	2.14	1.66	2.76	<0.001
Previous coronary artery disease	1.58	1.23	2.02	<0.001
Previous atrial fibrillation	1.62	1.27	2.07	<0.001
Advanced CKD	1.58	1.23	2.01	<0.001
COPD	1.64	1.24	2.17	0.001
Trauma/falls in the previous year	1.70	1.02	2.84	0.043
Anemia	1.43	1.12	1.84	0.005

HR: Hazard ratio (Cox regression analysis). IRR: incidence risk ratio (negative binomial regression). CI 95%: 95% confidence intervals. HF: heart failure. CKD: chronic kidney disease. COPD: chronic obstructive pulmonary disease.

4. Discussion

CKD is increasingly prevalent in patients with HF. Almost half of patients with HF have a degree of renal impairment and HF is prevalent in 17–50% of patients with CKD, depending on the stage of the CKD and age of the patients [9,10]. In addition, the prevalence and mortality of HF increases with worsening renal failure [8]. Renal function is an independent predictor for inpatient mortality of patients with acute HF and severe CKD worsens HF prognosis [8]. But there are few studies that have

specifically analyzed the impact of advanced CKD, with $\text{GFR} < 30 \text{ mL/min/m}^2$, on the prognosis of HF, as well as on its pharmacological treatment, because HF registries do not distinguish the degree of renal function impairment [3,19–22], and clinical trials exclude these patients [14–17,24]. Our study specifically analyzes the results in HF and advanced CKD, comparing clinical features, treatment and outcomes between patients with $\text{GFR} < \text{or} \geq 30 \text{ mL/min/m}^2$. Prevalence of advanced CKD was high, 11.1% in our study, without differences according to the type of HF (HFrEF, HFmrEF or HFpEF). As shown in Table 3, 10.4% of patients with HFrEF had a $\text{GFR} < 30 \text{ mL/min/m}^2$, a figure like that in the overall series.

Other main results on our study indicate that patients with HF and advanced CKD receive a significantly lower proportion of the drugs with a favorable prognostic effect in HF (tables 2 and 3) and that the incidence of serious events at one year of follow-up (death, admissions and HF decompensations) is 2 to 3 times higher in this group, as shown in Table 4. Patients with advanced CKD were older and had a higher prevalence of hypertension, diabetes mellitus, coronary heart disease, malnutrition, anemia and iron deficiency, and etiology was more frequently of ischemic and hypertensive origin in the group with $\text{GFR} < 30 \text{ mL/min/m}^2$. This higher risk profile and prevalence of severe comorbidities may influence this worse prognosis, but in the multivariate study, a $\text{GFR} < 30 \text{ mL/min/m}^2$ was shown to be an independent predictor of higher total mortality and incidence of HF admissions and decompensations at one year. As Table 5 shows, advanced CKD was a strong predictor of such events, with a hazard ratio of 1.63 for mortality, 1.44 for HF admissions and 1.58 for HF decompensation at 1 year. These figures are higher than those shown by several recent European registries, which only analyze globally the impact of the existence of renal dysfunction, defined by a $\text{GFR} < 90$ or $< 60 \text{ mL/min/m}^2$, without separating the degree of severity of renal failure [3,4,19–22].

Once the degree of renal function impairment has already reached a high level of severity, the prognosis of patients worsens, and it is difficult to reduce the incidence of events. Therefore, it would be important to initiate drug treatment with favorable prognostic effect in patients with HF, especially with HFrEF, but also in HFpEF and HFmrEF, in less advanced stages of CKD, I to III, when these treatments can be introduced and optimized with certain safety [13–17]. In any case, even in patients with $\text{GFR} < 30 \text{ mL/min/m}^2$, pharmacological treatment should be introduced, prioritizing drugs with lower risk of renal function deterioration, such as beta-blockers and inhaled SGLT2, and even sacubitril-valsartan, closely monitoring renal function and serum potassium, to improve the prognosis of these patients. It is possible that the introduction of new MRA, such as finerenone, with a greater protective effect on renal function impairment [24,25], may help this problem.

5. Conclusions

Our study has the limitations of an uncontrolled observational study, but like those of most comparable registries. Another limitation, impossible to avoid, is the lack of use of drugs that we know today have a favorable prognostic effect, recommended by clinical practice guidelines, but whose evidence was not available at the time of inclusion of patients in the registry, such as SGLT2 inhibitors. However, it covers a very recent period and has the strength of the mandatory participation of all the centers invited to participate, which reduces the inclusion bias. With these limitations in mind, it can be concluded from our results that patients with HF and advanced CKD receive a significantly lower proportion of drugs with a favorable prognostic effect in HF and that the incidence of serious events at one year of follow-up (death, admissions and HF decompensations) was 2 to 3 times than in patients with less severe degree of renal dysfunction. A greater effort in the prevention of renal damage and a better optimization of treatment, including new drugs with nephroprotective effects, may help to improve this unfavorable prognosis.

Author Contributions: All authors whose names appear on the submission: 1) made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work. 2) drafted the work or re-revised it critically for important intellectual content. 3)

approved the version to be published; and 4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated.

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Institutional Review Board Statement: The study met all requirements of the Declaration of Helsinki for research involving human subjects and was approved by the locally appointed ethics committees of all participating centers.

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