Cardiorenal Medicine

Research Article

Cardiorenal Med 2024;14:202–214
DOI: 10.1159/000538030

Received: November 2, 2023
Accepted: December 27, 2023
Published online: April 3, 2024

Treatment of Chronic Heart Failure in Advanced Chronic Kidney Disease: The HAKA Multicenter Retrospective Real-World Study

Borja Quiroga[a, b] Alberto Ortiz[b, c] Sara Núñez[d] Maria Kislikova[e] Silvia González Sanchidrián[f] José Jesús Broseta[g] Zoila Stany Albines[h] Beatriz Escamilla Cabrera[i] Yaiza Rivero Viera[j] David Rodriguez Santarelli[k] Laura Salanova Villanueva[a] Francisca Lopez Rodriguez[l] Bárbara Cancho Castellano[m] María Ibáñez Cerezo[n] Carmen Patricia Gutierrez Rivas[o] Nuria Aresté[p] Belén Campos Gutiérrez[q] Ana Ródenas Gálvez[r] Maria Constanza Glucksmann Pizá[s] Sagrario Balda Manzanos[t] Amparo Soldevila Orient[u] Lucía Rodríguez Gayo[v] Esperanza Moral Berrio[w] Mayra Ortega Diaz[x] Sandra Beltrán Catalán[y] Adriana Puente García[z] Miguel Ángel Rojas[A] R. Haridian Sosa Barrios[B] Henar Santana Zapatero[C] Gema Rangel Hidalgo[D] Ana Maria Martinez Canet[E] Javier Díez[F, G]

on behalf of Cardiorenal Medicine Group (CaReSEN) of the Spanish Society of Nephrology

[a]Nephrology Department, IIS-La Princesa, Hospital Universitario de la Princesa, Madrid, Spain; [b]RICORS2040, Madrid, Spain; [c]Nephrology Department, IIS-Fundación Jiménez Díaz UAM, Madrid, Spain; [d]Nephrology Department, Hospital Sant Joan Despí – Moisès Broggi, Consorci Sanitari Integral, Barcelona, Spain; [e]Nephrology Department, Immunopathology Group, Marqués de Valdecilla University Hospital-IDIVAL, Santander, Spain; [f]Nephrology Department, Hospital San Pedro de Alcántara, Cáceres, Spain; [g]Nephrology and Renal Transplantation Department, Hospital Clinic de Barcelona, Barcelona, Spain; [h]Nephrology Department, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain; [i]Nephrology Department, Hospital Universitario de Canarias, Tenerife, Spain; [j]Nephrology Department, Complejo Hospitalario Universitario Insular Materno-Infantil, Las Palmas de Gran Canaria, Spain; [k]Nephrology Department, Hospital Universitario de Vinalopó, Elche, Alicante, Spain; [l]Nephrology Department, Hospital Costa del Sol, Marbella, Spain; [m]Nephrology Department, Hospital Universitario de Badajoz, Badajoz, Spain; [n]Nephrology Department, Complejo Hospitalario Universitario de Toledo, Toledo, Spain; [o]Nephrology Department, Hospital Universitario de Torrevieja, Alicante, Spain; [p]Nephrology Department, Hospital Universitario Virgen Macarena, Sevilla, Spain; [q]Nephrology Department Hospital Universitario Miguel Servet, Zaragoza, Spain; [r]Nephrology Department, Hospital General Universitario Morales Meseguer, Murcia, Spain; [s]Nephrology Department, Hospital de Palamós, Gerona, Spain; [t]Nephrology Department, Hospital Comarcal Alcañiz, Teruel, Spain; [u]Nephrology Department, Hospital Politècnic i Universitari La Fe, Valencia, Spain; [v]Nephrology Department, Hospital Universitario Doce de Octubre, Madrid, Spain; [w]Nephrology Department, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain; [x]Nephrology Department, Hospital Universitario Infanta Leonor, Madrid, Spain; [y]Nephrology Department, Hospital Universitario Doctor Peset, Valencia, Spain;

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Correspondence to:
Borja Quiroga, borjaqg@gmail.com

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[z]Nephrology Department, Hospital Universitario de Fuenlabrada, Madrid, Spain; [A]Nephrology Department, Hospital General La Mancha Centro, Ciudad Real, Spain; [B]Nephrology Department, Hospital Universitario Ramón y Cajal, IRYCIS, Madrid, Spain; [C]Nephrology Department, Hospital Clínico Universitario Valladolid, Valladolid, Spain; [D]Nephrology Department, Hospital Universitario Punta de Europa, Cadiz, Spain; [E]Nephrology Department, Hospital Arnau de Vilanova, Valencia, Spain; [F]Center of Applied Medical Research and School of Medicine, University of Navarra, Pamplona, Spain; [G]Centro de Investigación Biomédica en Red de la Enfermedades Cardiovasculares (CIBERCV), Carlos III Institute of Health, Madrid, Spain

Keywords
Advanced chronic kidney disease · Cardiorenal syndrome · Chronic heart failure · Heart failure therapy

Abstract

Introduction: Chronic heart failure (HF) has high rates of mortality and hospitalization in patients with advanced chronic kidney disease (aCKD). However, randomized clinical trials have systematically excluded aCKD population. We have investigated current HF therapy in patients receiving clinical care in specialized aCKD units. ***Methods:*** The Heart And Kidney Audit (HAKA) was a cross-sectional and retrospective real-world study including outpatients with aCKD and HF from 29 Spanish centers. The objective was to evaluate how the treatment of HF in patients with aCKD complied with the recommendations of the European Society of Cardiology Guidelines for the diagnosis and treatment of HF, especially regarding the foundational drugs: renin-angiotensin system inhibitors (RASi), angiotensin receptor blocker/neprilysin inhibitors (ARNI), beta-blockers (BBs), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter-2 inhibitors (SGLT2i). ***Results:*** Among 5,012 aCKD patients, 532 (13%) had a diagnosis of HF. Of them, 20% had reduced ejection fraction (HFrEF), 13% mildly reduced EF (HFmrEF), and 67% preserved EF (HFpEF). Only 9.3% of patients with HFrEF were receiving quadruple therapy with RASi/ARNI, BB, MRA, and SGLT2i, but the majority were not on the maximum recommended doses. None of the patients with HFrEF and CKD G5 received quadruple therapy. Among HFmrEF patients, approximately half and two-thirds were receiving RASi and/or BB, respectively, while less than 15% received ARNI, MRA, or SGLT2i. Less than 10% of patients with HFpEF were receiving SGLT2i. ***Conclusions:*** Under real-world conditions, HF in aCKD patients is sub-optimally treated. Increased awareness of current guidelines and pragmatic trials specifically enrolling these patients represent unmet medical needs.

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Plain Language Summary

Patients with advanced chronic kidney disease (aCKD) and heart failure (HF) are at high risk of poor outcomes including premature death and hospitalization. However, evidence on their management is scarce. Many pivotal clinical trials testing HF treatments have excluded patients with aCKD and there is a paucity of real-world data on the diagnosis and treatment of these patients. The cross-sectional and retrospective HAKA study has some novel findings. On the one hand, the large range in the prevalence of HF between centers suggests an underdiagnosed of HF in patients with aCKD cared for in some specialized aCKD units. On the other hand, foundational HF medications are markedly underprescribed in patients with HFrEF. The HAKA study results justify a call to action for clinicians to optimize the diagnosis and treatment of HF in patients with aCKD. In addition, they support that appropriate evidence-based pharmacological treatment of HF in patients with aCKD is an unmet medical need that urgently requires specific clinical trials.

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Introduction

Patients with chronic kidney disease (CKD) are at high risk for cardiovascular events. The prevalence of heart failure (HF) in patients with CKD reaches up to 40% [1, 2] and the incidence of HF rises even more when estimated glomerular filtration rate (eGFR) decreases [1]. It has been reported that up to two-thirds of patients with an eGFR lower than 30 mL/min/1.73 m^2 or advanced CKD (aCKD) have HF [3]. Patients with aCKD and HF are at high risk of premature death and hospitalization (HF-specific and all-cause) [1, 4].

Based on left ventricular ejection fraction (EF), the European Society of Cardiology (ESC) guidelines classify HF into three types [5, 6]: HF with reduced EF (HFrEF), HF with mildly reduced EF (HFmrEF), and HF with

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preserved EF (HFpEF). Well-established ESC guidelines provide treatment recommendations with a very strong level of evidence for HFrEF [5, 6] and weaker for HFmrEF and HFpEF [7].

However, many pivotal clinical trials have excluded HF patients with aCKD, as some HF medications may affect renal hemodynamics and/or be associated with electrolyte disturbances [8]. Therefore, there is a current significant lack of clinical trial-based evidence for the management of HF in patients with aCKD and information derived from real-world evidence is crucial to ensure their appropriate management [8].

In this context, the aim of this study was to investigate the current clinical practice regarding the HF treatment in patients with aCKD who are clinically managed in specialized aCKD units, with particular attention to the implementation of recommendations by the 2016 ESC Guidelines on treatment with foundational drugs (such as renin-angiotensin system inhibitors [RASi], angiotensin receptor blocker/neprilysin inhibitor [ARNI], beta-blockers [BBs], and mineralocorticoid receptor antagonists [MRAs]) in addition to sodium-glucose cotransporter-2 inhibitors [SGLT2i] [5–7].

Methods

Study Design

The Heart And Kidney Audit (HAKA) is a retrospective observational real-world study, promoted by the Spanish Society of Nephrology (S.E.N.), including outpatients with aCKD and HF cared for in specialized aCKD units between January 1, 2021, and March 31, 2021. We selected these dates to ensure adequate collection and availability of all required information, as well as to assess the adequacy of treatment in accordance with ESC recommendations for managing HFrEF [5, 6]. To have an updated overview of the implementation of the recommended treatment of patients with HFmrEF and HFpEF [7], we also analyzed the basic drugs prescribed to patients with aCKD presenting with these two types of HF.

Aims

The main objective was to assess the current treatment of all types of HF in aCKD outpatients, with particular emphasis on treatment with RASi/ARNI, BB, MRA, and SGLT2i. We also evaluated the management of comorbidities in this population.

Patients

In December 2022, the S.E.N. invited all centers in Spain with a specialized aCKD unit to participate in this study. Inclusion criteria were an age ≥18 years, having an eGFR <30 mL/min/1.73 m^2 calculated by the creatinine-based 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and a diagnosis of chronic HF, defined by clinical symptoms and signs, elevated natriuretic peptides and echocardiographic findings [5]. Exclusion criteria were patients on dialysis or who required dialysis within the prior 6 months, patients under conservative management (noncandidates for kidney replacement therapy), and those with a history of kidney or heart transplantation.

Variables

Using electronic medical records, we collected epidemiological, clinical, and analytical data on demographics, CKD stages 4 and 5, diagnosis of HF types, comorbidities, and pharmacological and non-pharmacological treatments.

CKD G4 or G5 were diagnosed when eGFR values were 15–29 and <15 mL/min/1.73 m^2, respectively. The diagnosis of HF was made by a combination of clinical criteria (signs and/or symptoms), elevated natriuretic peptides, and echocardiographic findings according to current ESC guidelines [5–7]. Patients with HF were divided into three groups: HFrEF (EF ≤40%), HFmrEF (EF 41–49%), and HFpEF (EF ≥50%) [5].

We collected history of hypertension, dyslipidemia, diabetes, coronary artery disease, hypertensive heart disease, peripheral vascular disease, atrial fibrillation, and stroke. Body mass index (BMI) was calculated to define obesity (body mass index ≥30 kg/m^2). Anemia was defined as hemoglobin <13 g/dL in men and Hb <12 g/dL in women [9]. Absolute iron deficiency was defined according to European Renal Best Practice (ERBP) guidelines as transferrin saturation index ≤20% and serum ferritin concentration ≤100 ng/mL [9]. Relative iron deficiency was defined as transferrin saturation index ≤20% and ferritin >500 ng/mL [9]. Hyperkalemia was considered when serum potassium was >5.5 mEq/L.

Beyond RASi/ARNI, BB, MRA, and SGLT2i, other HF therapies analyzed were furosemide, ivabradine, digoxin, chronic resynchronization therapy, and implantable cardioverter defibrillators. Additional comorbidities-related therapies were also assessed, including statins, proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), erythropoiesis-stimulating agents (ESAs), iron, and potassium binders. Maximum doses were considered according to technical data sheets and the 2016 and 2021 ESC Guidelines for RASi, ARNI, BB, and MRA [5, 6].

Statistics

Data are expressed using the mean (standard deviation) or median (interquartile range) depending on the distribution of the variable (tested with the Shapiro-Wilk test). Comparisons between categorical variables were done using the Fisher's exact test; between categorical and continuous variables using the t or Mann-Whitney tests, and between continuous variables and more than two categories with analysis of variance. Logistic regression was performed for assessing adjusted models. Statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). A p value <0.05 was considered statistically significant.

Results

Prevalence of Diagnosed HF

Twenty-nine centers with specialized aCKD units responded to the call made by the S.E.N. and provided the required information. Among the 5,012 included patients

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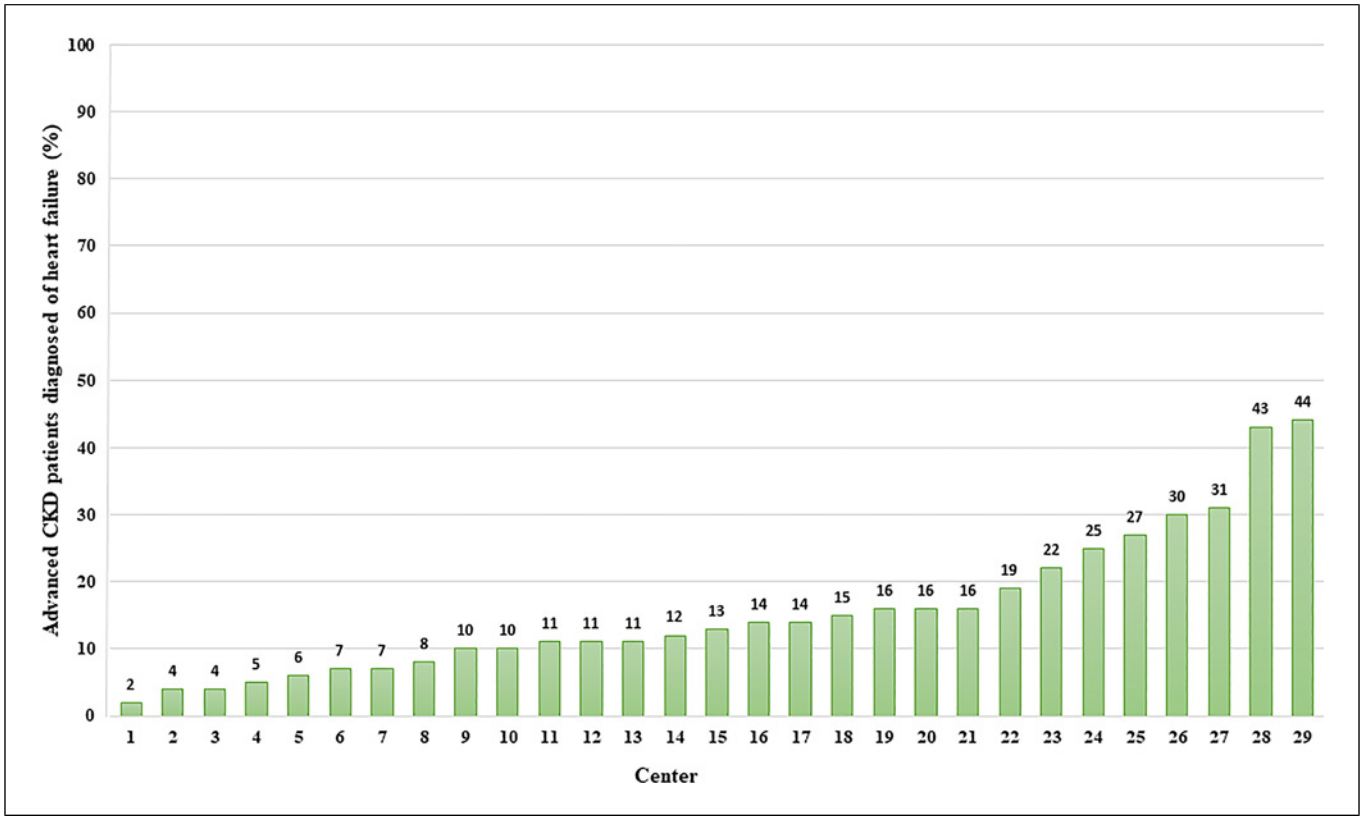

Fig. 1. Prevalence of a diagnosis of HF in patients from specialized aCKD units. Each column represents a participating center.

with aCKD, 532 had a medical record of HF (median 13% [range between centers 2–44%]) (Fig. 1). According to the KDIGO classification, 410 (77%) patients had CKD G4 and 122 (23%) CKD G5.

The clinical characteristics of patients grouped by CKD stage are shown in Table 1. Patients with CKD G5 were younger, more frequently men and presented higher prevalence of peripheral arterial disease, hypertensive heart disease, valvular heart disease, atrial fibrillation, and a lower E/e' ratio (14 ± 6 vs. 12 ± 4, p = 0.006). In addition, anemia and the presence of an arteriovenous fistula were significantly more frequent in patients with CKD G5 than in patients with CKD G4. Patients with CKD G5 required significantly more Cardiology and Nephrology outpatient visits per year than patients with CKD G4.

HF was diagnosed based on cardinal HF symptoms and signs (86%), elevated natriuretic peptide values (50%), and the presence of structural abnormalities on echocardiography (75%). There were some differences in these diagnostic criteria according to HF type (Fig. 2a), but not according to CKD category (Fig. 2b).

The distribution of HF types was as follows: 20% HFrEF, 13% HFmrEF, and 67% HFpEF. The clinical characteristics of the patients grouped according to HF types are shown in Table 2. Significant differences across the types of HF were found in sex, the prevalence of hypertension, coronary artery disease, hypertensive heart disease, anemia, EF, and E/e' ratio. Annual outpatient visits in Cardiology were significantly more frequent for HFrEF patients than for the other two types of HF (Table 2). However, yearly outpatient visits in nephrology were similar across all subtypes of HF.

Treatment of HF

Treatment of HF according to the CKD Category

Table 3 shows the distribution of HF therapies in the entire group of patients with HF and in patients separated by type of HF, in both cases according to CKD category. In the entire HF population, furosemide was administered to the majority of patients. However, BB was the only foundational drug prescribed to more than half of the population. The low prescription of foundational

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Table 1. Clinical characteristics of patients according to chronic kidney disease category

	CKD G4 (*n* = 410)	CKD G5 (*n* = 122)	*p* value
Age, years	75±10	72±12	0.019
Sex (male), *n* (%)	245 (60)	89 (73)	0.008
Hypertension, *n* (%)	392 (96)	120 (98)	0.161
Dyslipidemia, *n* (%)	349 (85)	105 (86)	0.168
Diabetes, *n* (%)	261 (64)	79 (65)	0.825
Obesity, *n* (%)	179 (44)	58 (50)	0.101
HF types, *n* (%)			0.174
HFrEF	90 (22)	18 (15)	
HFmrEF	52 (13)	14 (12)	
HFpEF	268 (65)	90 (74)	
Coronary artery disease, *n* (%)	171 (42)	43 (35)	0.195
Peripheral vascular disease, *n* (%)	81 (20)	34 (28)	0.053
Stroke, *n* (%)	62 (15)	20 (16)	0.741
Hypertensive heart disease, *n* (%)	221 (54)	83 (68)	0.007
Valvular heart disease, *n* (%)	209 (51)	47 (38)	0.013
COPD, *n* (%)	92 (22)	20 (16)	0.147
Atrial fibrillation, *n* (%)	173 (42)	38 (31)	0.027
Anemia, *n* (%)	250 (61)	94 (77)	0.001
Baseline serum creatinine, mg/dL	2.6±0.5	4.4±1.1	<0.001
Baseline eGFR, mL/min/1.73 m^2	21±4	12±2	<0.001
AVF, *n* (%)	20 (5)	38 (31)	<0.001
Hemoglobin, g/dL	12 (11–13)	11 (10–12)	<0.001
Ferritin, ng/mL	155 (75–294)	199 (79–378)	0.096
TSAT (%)	21 (16–28)	20 (16–27)	0.458
Hyperkaliemia, *n* (%)	74 (18)	38 (31)	0.002
LVEF (%)	53±14	56±13	0.067
E/e' ratio	14±6	12±4	0.006
Annual cardiology outpatient visits, *n*	1 (0–2)	1 (0–2)	0.001
Annual nephrology outpatient visits, *n*	4 (3–5)	5 (4–7)	<0.001

CKD, chronic kidney disease; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; AVF, arteriovenous fistulae; TSAT, transferrin saturation index; LVEF, left ventricular ejection fraction; E/e' ratio, ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity. Values are expressed as *n* (percentage), mean ± standard deviation, or median (interquartile range).

drugs should be highlighted, especially in patients with CKD G5. Very few patients were treated with other HF drugs and devices, regardless of CKD category.

Treatment of Comorbidities according to CKD Category

Table 4 shows that treatment with erythropoietin and potassium binders was significantly more frequent in patients with CKD G5 than in patients with CKD G4. There were no other significant differences in therapies between the two groups.

Treatment of HF according to Type of HF and CKD Category

Among patients with HFrEF, those with CKD G5 received ARNI significantly less frequently than patients with HFrEF and CKD G4. The percentages of patients with HFrEF receiving the remaining pharmacological and non-pharmacological therapies were similar in both CKD categories. Of interest, the number of patients with HFrEF receiving triple (RASi/ARNI, BB, and MRA) or quadruple (RASi/ARNI, BB, MRA, and SGLT2i) for HF was low (35%, Fig. 3a). Indeed, no patients with CKD G5 were receiving all foundational HF drugs (Fig. 3c) compared to 11% of patients with CKD G4 (Fig. 3b). Factors associated to receive triple or quadruple therapy in HFrEF were diabetes ($p = 0.048$), lower GFR ($p = 0.003$) and higher annual cardiology outpatient visits ($p = 0.015$). Adjusted logistic regression demonstrated that GFR was the only associated factor to triple or quadruple therapy prescription (HR 1.13, 95% CI: [1.03–1.24], $p = 0.010$).

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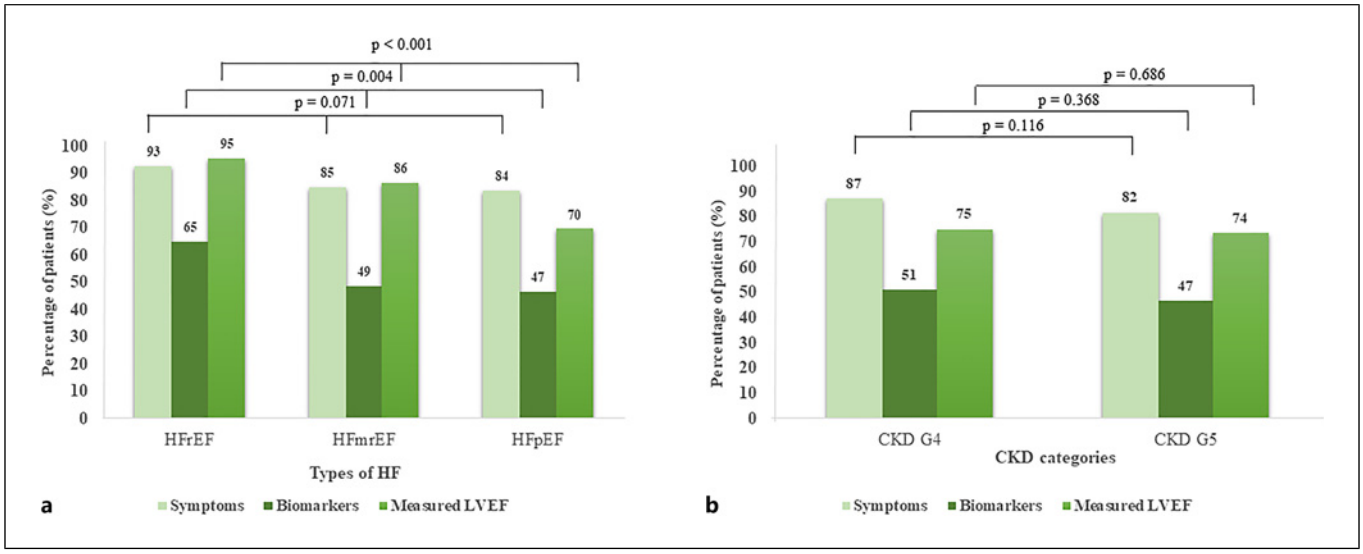

Fig. 2. Diagnostic criteria for heart failure in patients from specialized aCKD units. Bars represent the percentage of patients who met each of the three diagnostic criteria for heart failure (HF) in the three types of HF (panel **a**) and in the two categories of chronic kidney disease (CKD) (panel **b**). HFrEF, HF with reduced ejection fraction (EF); HFmrEF, HF with mildly reduced EF; HFpEF, HF with preserved EF.

Figure 4 shows that the maximum recommended dose of RASi/ARNI, BB, and MRA [5, 6] was not reached in over half of the patients with HFrEF regardless of CKD stage. SGLT2i are not represented because there is no maximum recommended dose for these compounds in patients with HFrEF [5].

No significant differences in the treatment of HFmrEF were observed between CKD stages (Table 4). It should be noted that very few patients with HFmrEF were treated with SGLT2i, especially patients with GKD G5.

As seen in Table 4, patients with HFpEF and CKD G5 significantly received less frequently treatment with RASi than patients with HFpEF and CKD G4. The opposite was true for implantable cardioverter defibrillators. No other significant therapeutic differences were observed between CKD categories in the treatment of HFpEF. It is worth mentioning that very few patients with HFpEF were treated with SGLT2i, especially patients with GKD G5.

Treatment of Comorbidities according to the Type of HF and CKD Category

No great differences were observed in treating of comorbidities by type of HF (Table 4). Potassium binders were given significantly more in patients with HFrEF and CKD G5 than in patients with HFrEF and CKD G4. In addition, ESAs were significantly more prescribed in patients with HFpEF and CKD G5 than in patients with HFpEF and CKD G4.

Discussion

Several findings of this study are noteworthy. First, we observed a high degree of heterogeneity in the prevalence of HF across various aCKD units, which may indicate an underdiagnosis in some units. Second, our research revealed suboptimal HF treatment, as evidenced by the limited use of the three foundational drugs recommended for HF therapy in the 2016 ESC HF guidelines. Third, a low prevalence of full dosing of therapeutic agents was observed. Overall, most patients were treated with HF pharmacological regimens recommended in the 20th century rather than with 21st-century regimens (Fig. 5) [5, 6, 7, 10]. Fourth, other aspects of the comorbidity treatment were also suboptimal.

Our data revealed that 13% of aCKD patients attended in specialized aCKD units during the study period of the study had a diagnosis of HF. This prevalence is not far from the prevalence of aCKD in patients with HF found in a recent Spanish study [11]. In that study, performed in 13 HF clinics over 4 months, among 1,107 outpatients with HF diagnosed according to the ESC guidelines [5–7], 16.2% had aCKD [11]. Both cross-sectional studies are in line with data on the high prevalence of HF in patients with aCKD from long-term longitudinal studies with large population samples [1–3].

The prevalence of HF was highly variable across participating centers, ranging between 2% and 44%. This

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Table 2. Clinical characteristics of patients according to HF types

	HFrEF (*n* = 108)	HFmrEF (*n* = 66)	HFpEF (*n* = 358)	*p* value
Age, years	73±10	72±12	75±10	0.102
Sex (male), *n* (%)	79 (73)	45 (68)	210 (59)	0.015
Hypertension, *n* (%)	98 (91)	65 (98)	349 (97)	0.003
Dyslipidemia, *n* (%)	85 (79)	54 (82)	315 (88)	0.117
Diabetes, *n* (%)	69 (64)	39 (59)	232 (65)	0.674
Obesity, *n* (%)	37 (38)	21 (34)	156 (47)	0.068
Coronary artery disease, *n* (%)	64 (59)	30 (46)	120 (34)	<0.001
Peripheral arterial disease, *n* (%)	25 (23)	18 (27)	72 (20)	0.405
Stroke, *n* (%)	22 (20)	14 (21)	46 (13)	0.065
Hypertensive heart disease, *n* (%)	40 (37)	34 (51)	230 (64)	<0.001
Valvular heart disease, *n* (%)	54 (51)	31 (47)	171 (48)	0.946
COPD, *n* (%)	21 (19)	18 (27)	73 (20)	0.411
Atrial fibrillation, *n* (%)	52 (48)	23 (35)	136 (38)	0.119
Anemia, *n* (%)	54 (50)	44 (67)	246 (68)	0.009
CKD categories, *n* (%)				0.174
G4	90 (83)	52 (79)	268 (75)	
G5	18 (17)	14 (21)	90 (25)	
Baseline serum creatinine, mg/dL	2.9±0.8	3.0±0.9	3.1±1.1	0.214
Baseline eGFR, mL/min/1.73 m^2	20±5	20±5	19±5	0.062
Hemoglobin, g/dL	12 (11–14)	12 (11–13)	12 (11–13)	0.012
Ferritin, ng/mL	183 (83–340)	157 (77–299)	154 (74–302)	0.841
TSAT (%)	22 (17–31)	20 (16–26)	21 (15–27)	0.151
Hyperkaliemia, *n* (%)	24 (22)	15 (23)	73 (20)	0.863
LVEF (%)	31±7	45±2	62±7	<0.001
E/e′ ratio	16±6	14±6	13±6	0.028
Annual cardiology outpatient visits, *n*	3 (1–4)	1 (0–3)	0 (1–2)	<0.001
Annual nephrology outpatient visits, *n*	4 (3–5)	4 (3–5)	4 (3–6)	0.444

HFrEF, heart failure patients with reduced ejection fraction; HFmrEF, heart failure patients with mildly reduced ejection fraction; HFpEF, heart failure patients with preserved ejection fraction; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; TSAT, transferrin saturation index; LVEF, left ventricular ejection fraction; E/e′ ratio, ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity. Values are expressed as number (percentage), mean ± standard deviation or median (interquartile range).

variability may reflect important differences in the perception of the relevance of HF and/or in the reliability of criteria for its diagnosis in the real-world of aCKD units. Diagnosis of HF requires the presence of nonspecific typical symptoms that are common in aCKD and, consequently, cannot be used alone to make a diagnosis. Therefore, additional recommended diagnostic criteria include elevated plasma concentrations of natriuretic peptides and demonstration of structural heart disease by echocardiography [5–7]. The renal clearance of natriuretic peptides decreases when eGFR falls below 30 mL/min/1.73 m^2, supporting the diagnostic imprecision of the standard cut-off for natriuretic peptides in HF in patients with aCKD [12]. Conversely, structural heart diseases such as left ventricular hypertrophy are prevalent in CKD patients, and this prevalence increases as renal function declines, regardless of other confounding factors. Consequently, it is present in over 80% of aCKD patients [13]. These limitations may explain why the three recommended diagnostic criteria for HF were not applied in all aCKD patients included in this study, especially in those with HFmrEF and HFpEF.

The 2016 and 2021 ESC guidelines highlight the challenges in extrapolating prospective HF randomized clinical trial data to clinical practice when aCKD remains an exclusion criterion in most studies [5, 6]. However, even patients with CKD and HF who have eGFR well above 30 mL/min/1.73 m^2 are less likely to be prescribed HF-modifying therapies [14]. Therefore, independent groups have proposed that given the clear benefit, the use of RASi/ARNI, BB, MRA, and SGLT2i should be strongly supported by nephrologists in patients with non-dialysis aCKD and HFrEF, with

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Table 3. Treatment of HF according to type of HF and to chronic kidney disease category

HF therapies	All HF (n = 532)			HFrEF (n = 108)			HFmrEF (n = 66)			HFpEF (n = 358)		
	CKD G4	CKD G5	p value	CKD G4	CKD G5	p value	CKD G4	CKD G5	p value	CKD G4	CKD G5	p value
RASi	210 (51)	54 (44)	0.170	40 (44)	10 (56)	0.388	26 (50)	8 (57)	0.635	144 (54)	36 (40)	0.022
ARNI	55 (13)	4 (3)	0.002	38 (42)	3 (17)	0.041	9 (17)	1 (7)	0.346	8 (3)	0 (0)	0.099
BBs	275 (67)	69 (57)	0.030	77 (86)	16 (89)	0.709	39 (75)	9 (64)	0.424	159 (60)	44 (49)	0.077
MRA	76 (18)	13 (11)	0.041	32 (36)	3 (17)	0.118	8 (15)	1 (7)	0.425	36 (13)	9 (10)	0.395
SGLT2i	50 (12)	5 (4)	0.010	22 (24)	1 (6)	0.074	8 (15)	1 (7)	0.425	20 (7)	3 (3)	0.167
Furosemide	339 (83)	101 (83)	0.979	80 (89)	16 (89)	1.000	40 (77)	11 (79)	0.896	219 (82)	74 (82)	0.914
Ivabradine	21 (5)	4 (3)	0.405	8 (9)	3 (17)	0.319	6 (11)	1 (7)	0.635	7 (3)	0 (0)	0.123
Digoxin	14 (3)	1 (1)	0.130	5 (6)	0 (0)	0.306	0 (0)	0 (0)	–	9 (3)	1 (1)	0.266
CRT	26 (6)	4 (3.3)	0.202	13 (15)	1 (6)	0.299	4 (7)	1 (7)	0.945	9 (3)	2 (2)	0.599
ICD	24 (6)	7 (6)	0.963	23 (26)	4 (22)	0.710	1 (2)	1 (7)	0.312	0 (0)	2 (2)	0.014

HF, heart failure; EF, ejection fraction; CKD, chronic kidney disease; RASi, renin-angiotensin system inhibitors (i.e., angiotensin converting enzyme inhibitors or angiotensin receptor blockers); ARNI, angiotensin receptor blocker/neprilysin inhibitor; MRA, mineralocorticoid receptor antagonists; SGLT2i, sodium-glucose cotransporter-2 inhibitors; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator. Data are presented as n and (%).

Table 4. Treatment of comorbidities in patients with HF according to chronic kidney disease category

HF therapies	All HF (n = 532)			HFrEF (n = 108)			HFmrEF (n = 66)			HFpEF (n = 358)		
	CKD G4	CKD G5	p value	CKD G4	CKD G5	p value	CKD G4	CKD G5	p value	CKD G4	CKD G5	p value
Statins +/− ezetimibe	328 (80)	98 (80)	0.974	70 (79)	15 (83)	0.654	38 (73)	11 (79)	0.676	220 (82)	72 (80)	0.658
PCSK9i	5 (1)	0 (0)	0.220	0 (0)	0 (0)	–	1 (2)	0 (0)	0.601	4 (1)	0 (0)	0.244
ESA	160 (39)	69 (58)	<0.001	28 (31)	5 (28)	0.779	24 (46)	7 (50)	0.798	108 (40)	57 (65)	<0.001
Iron	176 (43)	54 (45)	0.702	39 (43)	5 (28)	0.220	25 (48)	9 (64)	0.281	112 (42)	40 (45)	0.564
Potassium binders	51 (12)	24 (20)	0.040	10 (11)	7 (39)	0.003	9 (17)	3 (23)	0.632	32 (12)	14 (16)	0.375

HF, heart failure; EF, ejection fraction; CKD, chronic kidney disease; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors; ESA, erythropoietin stimulating agents. Data are presented as n and (%).

usual cautions and close monitoring of serum creatinine and potassium [8, 15]. In this sense, it is striking that, apart from BB, other foundational drugs for the treatment of HF are being used well below these expectations in patients with aCKD and HFrEF, especially in patients with CKD G5. Moreover, the proportion of patients with HFrEF who receive the full dose of each of these drugs is very low. And last but not least, the percentage of patients with aCKD and HFrEF receiving all four foundational drugs simultaneously is unacceptably low, especially in patients with CKD G5.

The use of RASi/ARNI, BB, and MRA in patients with HFrEF was already recommended with a high level of evidence in the 2016 ESC guidelines for the treatment of HFrEF [5]. Data from the present study indicate that little progress has been made in the treatment of patients with aCKD and HFrEF with these drugs 5 years later.

Although the use of SGLT2i for the treatment of HFrEF was recommended with a high level of evidence in the 2021 ESC guidelines for the first time [6], the low prescription of these drugs in patients with HFrEF is especially astounding. In fact, the beneficial effects of dapagliflozin on cardiovascular death and HF hospitalization in patients with HFrEF and eGFR 25–30 mL/min/1.73 m^2 were comparable to those seen in patients with early stage CKD [16]. Additionally, empagliflozin has shown to reduce HF hospitalization in patients with HFrEF and with eGFR as low as 20 mL/min/1.73 m^2 [17].

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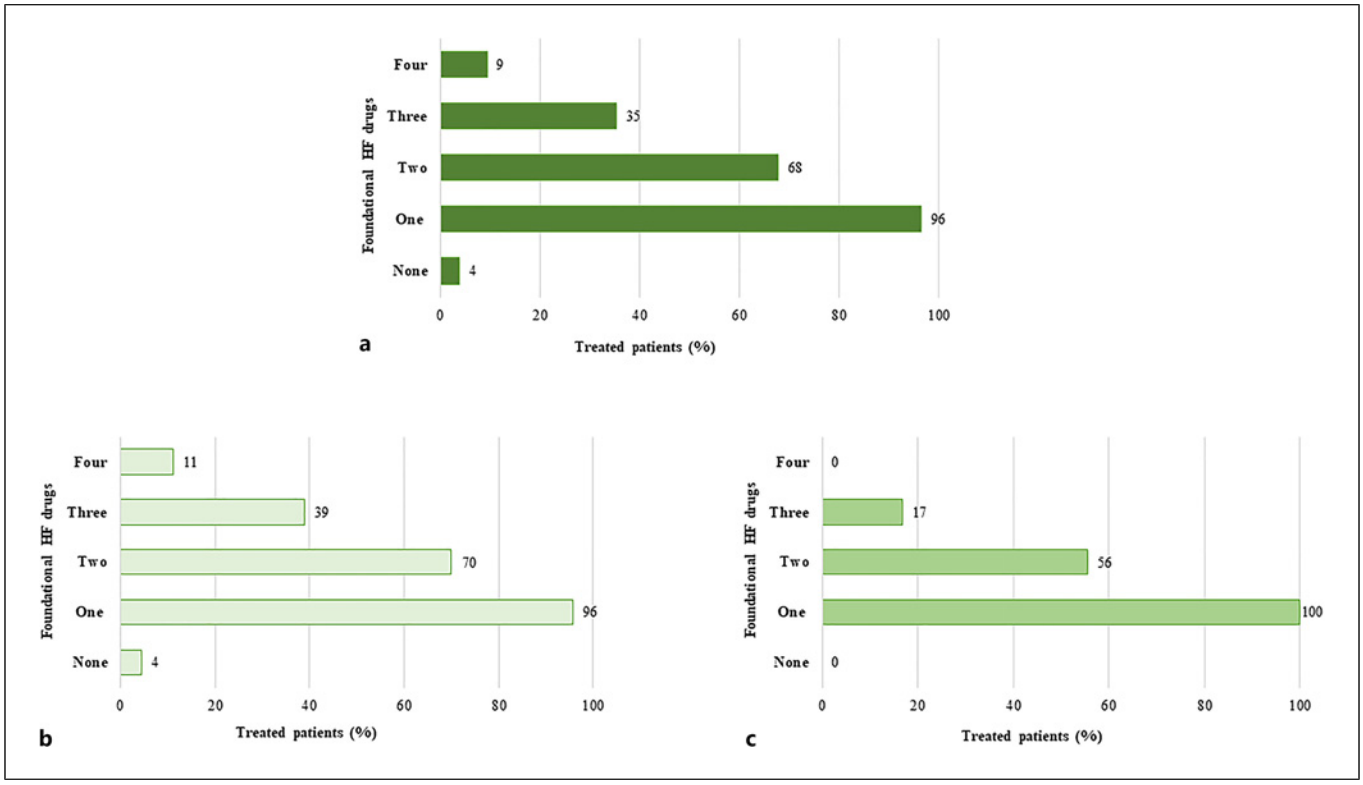

Fig. 3. Treatment for HF in patients from specialized aCKD units. Bars represent the percentage of patients with HF with reduced ejection fraction (HFrEF) receiving none, 1, 2, 3, or 4 of the foundational HF drugs (i.e., renin-angiotensin system inhibitors [RASi]/angiotensin receptor blocker-neprilysin inhibitor [ARNI], beta-blockers [BBs], mineralocorticopid receptor antagonists [MRA], sodium-glucose cotransporter-2 inhibitors [SGLT2i]). Panel **a** corresponds to all advanced chronic kidney disease (aCKD) patients with HFrEF, panel **b** to patients with CKD G4, and panel **c** to patients with CKD G5.

Our data revel that GFR is independently associated to the prescription of triple or quadruple therapy, showing that renal function is considered as the main limiting factor for an optimal treatment of HFrEF.

In the case of with HFmrEF and HFpEF the 2016 and 2021 ESC Guidelines made weak or no recommendations for the use of disease-modifying therapies that have class I evidence for use in patients with HFrEF [5, 6]. In the 2023 Focused Update of the 2021 ESC Guidelines, RASi, ARNI, BB, and MRA have a recommendation evidence IIb for the treatment of HFmrEF [7]. Findings from the present study show that the prevalence of prescription of foundational drugs does not exceed 50% in aCKD patients with HFmrEF or HFpEF, with the sole exception of BB.

Since 2021, two trials testing the SGLT2i empagliflozin [18] and dapagliflozin [19] in patients with HF and EF >40% support the recent recommendation (with class I evidence) to prescribe SGLT2i to reduce the risk of HF hospitalization or cardiovascular death in patients with HFmrEF and HFpEF7. Of interest, the empagliflozin study included patients with eGFR ≥20 mL/min/1.73 m^2 and the dapagliflozin study patients with eGFR ≥25 mL/min/1.73 m^2. Based on these results, SGLT2i is currently recommended in patients with HFmrEF or HFpEF, including those with an eGFR ≥20–25 mL/min/1.73 m^2, to reduce the risk of HF hospitalization or cardiovascular death. Data from a recent meta-analysis including 13 large trials suggest that this recommendation applies to diabetic patients, but not to nondiabetic patients [20]. The findings from the present study show the paucity of aCKD patients with HFmrEF or HFpEF receiving SGLT2i, especially among patients with CKD G5, and most of them had type 2 diabetes mellitus.

Regarding other treatments, dyslipidemia was treated with statins in 80% of patients but only in 55% at full doses. This is quite surprising, as aCKD is considered a very high-risk comorbidity for CV events and requires treatment targeting a cLDL <55 mg/dL as stated in 2019 ESC/EAS Guidelines [21], which is difficult to achieve with suboptimal dosing of statins [22]. PCSK9i, an effective alternative for patients with uncontrolled

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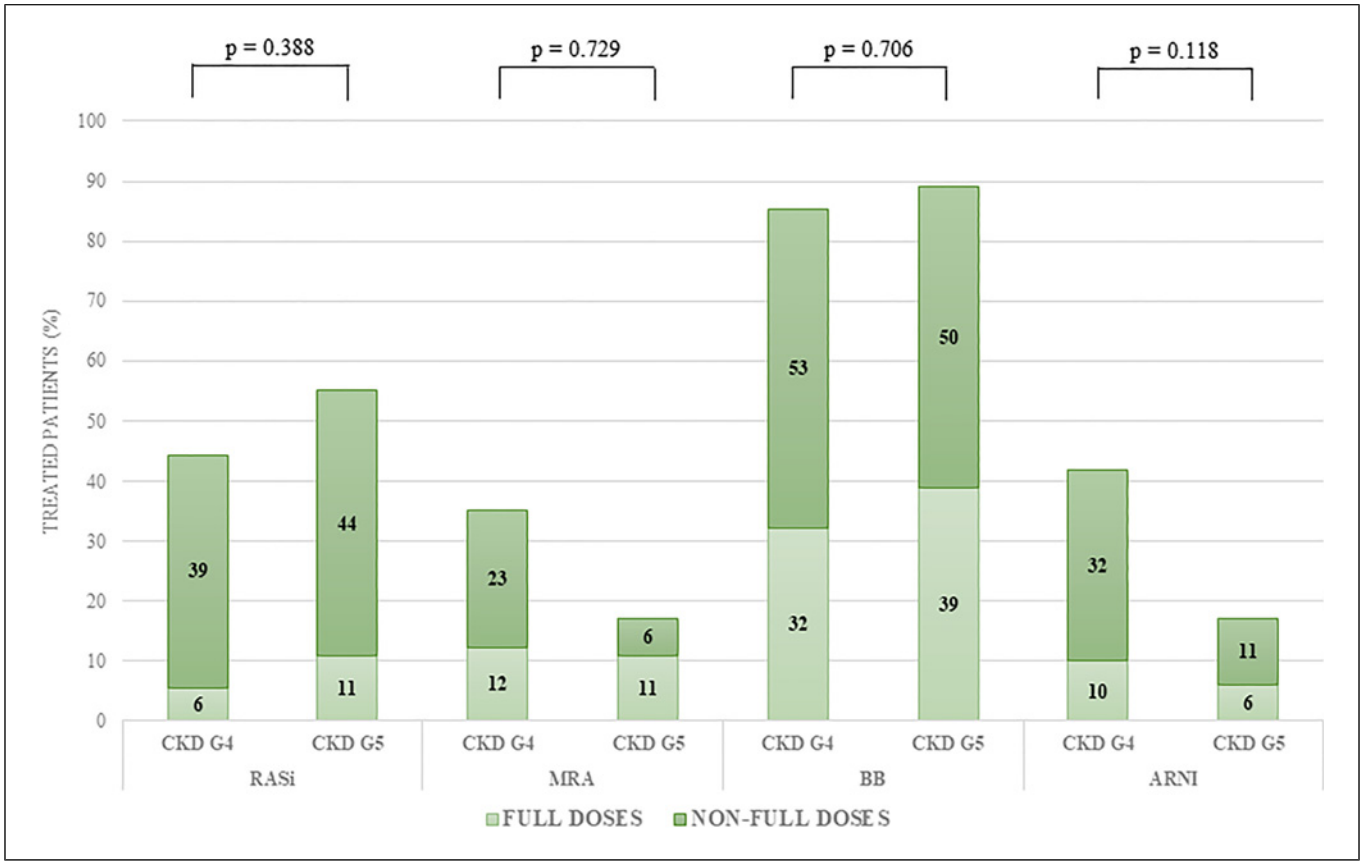

Fig. 4. Treatment for HF in patients from specialized aCKD units. Bars represent the percentage of patients with HF with reduced ejection fraction (HFrEF) receiving the full or non-full dose of the corresponding drug class in each chronic kidney disease (CKD) stage. Sodium-glucose cotransporter-2 inhibitors are not included because there is no maximum recommended dose for these compounds in patients with HFrEF. RASi, renin-angiotensin system inhibitors; ARNI, angiotensin receptor blocker/neprilyisn inhibitor; BBs, beta-blockers; MRA, mineralocorticoid receptor antagonists.

LDLc, was prescribed residually in aCKD patients from the present study [22].

Finally, the IROMAN Trial demonstrated that iron administration in HFrEF reduced the risk of hospital admissions for HF and cardiovascular death [23]. In patients with aCKD, treatment of absolute and relative iron deficiency in the context of anemia is associated with lower CV events [24]. However, our study found that 29% of patients with absolute iron deficiency were not receiving iron, while nearly 50% of patients with iron deficiency were receiving ESA (but no iron). Indeed, ESA was prescribed in at least 16% of the non-anemic patients. ESA overshooting of hemoglobin values is associated with an increased risk of CV events, while iron deficiency is associated with higher rates of ESA hypo-responsiveness [25].

This study has some limitations to be acknowledged. First, it carries the inherent biases of a retrospective design. There were few missing data, likely related to the accreditation programs of HF and aCKD units in Spain that started 10 years ago, leading to improved registration of clinical data. Second, albuminuria values are scarce and reported in heterogeneous units, preventing an accurate description and analysis of this important variable. However, our study focused on optimizing HF treatment in aCKD, where albuminuria is not a decisive factor for the prescription of drugs in HF. In any case, we encourage using standardized procedures and units to assess and report albuminuria values in all CKD patients, as the level of albuminuria influences the risk of death. Our study was conducted during the first trimester of 2021 as the study period to avoid the COVID-19 pandemic and also because all evaluated drugs were available and reimbursed. Third, as a transversal study, we do not have information of prognosis. Finally, it may be questionable whether the

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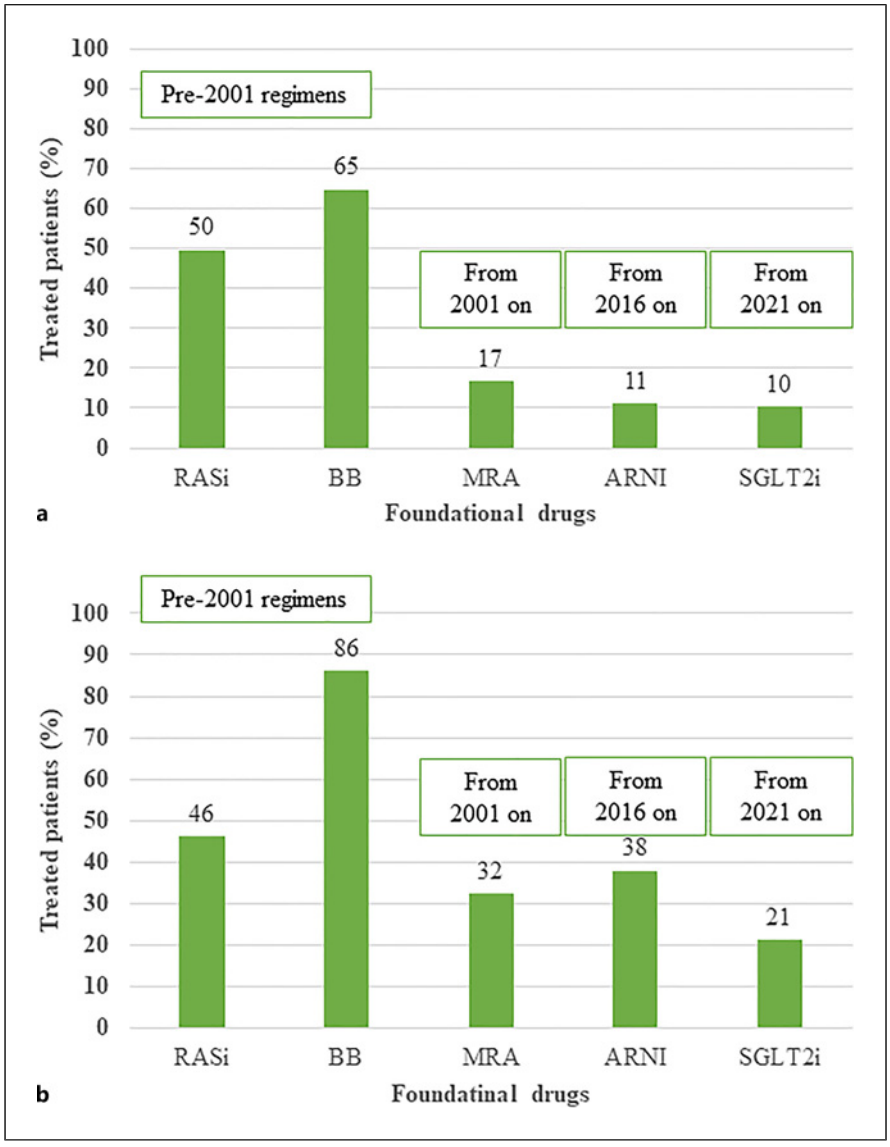

Fig. 5. Treatment for HF in patients from specialized aCKD units. **a** % of patients with HF treated with each drug. **b** % of patients with HFrEF treated with each drug. Bars represent the percentage of all patients with HF treated with different drug classes. Bars are color-coded for the first year that the drug class was recommended by ESC guidelines for the treatment of HF, which is also represented by color-coded numbers on top of the bars. From 2008 onwards, guidelines provide recommendations for HFrEF instead of for HF in general. Information on ESC guidelines obtained from references [5, 6, 7, 10].

2021 ESC Guidelines [6] and the 2023 Focused Update of the 2021 ESC Guidelines [7] used as reference were already implemented during the study period. Therefore, the results should serve as a reference for the evolving implementation of ESC guidelines on the treatment of HF in future analyses.

In conclusion, the suboptimal treatment of HF in patients with aCKD in real-life may underlie the suboptimal HF-specific outcomes in this population. As renal function is a limiting factor for an accurate prescription, cardiorenal units appear to be the solution for an optimal management of HF. Population-based, pragmatic real-world clinical trials are necessary to confirm the disease-modifying beneficial impact of HF therapy optimization in aCKD.

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of Hospital Universitario de la Princesa, Madrid, Spain, approval number 5040, 12/12/22. The study has been granted an exemption from requiring written informed consent by the Ethics Committee of Hospital Universitario de la Princesa, Madrid, Spain.

Conflict of Interest Statement

Borja Quiroga has received honoraria for conferences, consulting fees and advisory boards from Vifor-Pharma, Astellas, Amgen, Bial, Ferrer, Novartis, AstraZeneca, Sandoz, Laboratorios Bial, Esteve, Sanofi-Genzyme, Otsuka. Alberto Ortiz has received

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grants from Sanofi and consultancy or speaker fees or travel support from Adviccene, Alexion, Astellas, AstraZeneca, Amicus, Amgen, Boehringer Ingelheim, Fresenius Medical Care, GSK, Bayer, Sanofi-Genzyme, Menarini, Mundipharma, Kyowa Kirin, Lilly, Freeline, Idorsia, Chiesi, Otsuka, NovoNordisk, Sysmex and Vifor Fresenius Medical Care Renal Pharma and Spafarma and is Director of the Catedra UAM-AstraZeneca of chronic kidney disease and electrolytes. He has stock in Telara Farma. José Jesús Broseta has received honoraria for conferences, consulting fees, and advisory boards from Novo-Nordisk, Kyowa Kirin, AstraZeneca, Daichii-Sankyo, Esteve, Lilly, CSL Vifor, and Chiesi. Beatriz Escamilla Cabrera has received honoraria for conferences or travel support from Vifor-Pharma, Astellas, AstraZeneca, and NovoNordisk. David Rodriguez Santarelli has received honoraria for Conferences from Lilly, Boehringer Ingelheim, AstraZeneca, for the manuscript writing from Vifor-Pharma, and travel support from Vifor-Pharma, Boehringer Ingelheim, Zambon, Servier, Esteve and Novo-Nordisk. Francisca Lopez Rodriguez has received honoraria for conferences, meetings and travel support from Vifor-Pharma, Abbott, AstraZeneca, Esteve, Otsuka, Astellas. Bárbara Cancho Castellano has received honoraria for conference from Vifor-Pharma. Adriana Puente García has received honoraria for conferences, consulting fees, and travel support from Aztra Zeneca, Boehringer Ingelheim, Faes Farma, Lilly, Menarini, Novo-Nordisk, Sanofi-Genzime, Otsuka, Viatris. Nuria Aresté has received honoraria for conferences, consulting fees, advisory boards, or travel support from Vifor, AstraZeneca, Boehringer Ingelheim, Baxter, Astellas, GSK. Miguel Ángel Rojas has received honoraria for conferences consulting fees, and travel support from: CLS-Vifor-Pharma, Servier, Astellas, Sanofi, AstraZeneca, and Boehringer Ingelheim. R. Haridian Sosa Barrios has received honoraria for conferences, consulting fees, and advisory boards from AstraZeneca. Sara Núñez, Amparo Soldevila Orient, Maria Kislikova, Henar Santana Zapatero, Esperanza Moral Berrio, María Ibáñez Cerezo, Maria Constanza Glucksmann Pizá, Yaiza Rivero Viera, Zoila Stany Albines, Ana Ródenas Gálvez, Belén Campos Gutiérrez, Sagrario Balda Manzanos, Silvia González Sanchidrián, Carmen Patricia Gutierrez Rivas, Laura Salanova Villanueva, Gema Rangel Hidalgo, Sandra Beltrán Catalán, Mayra Ortega Diaz, Lucía Rodríguez Gayo, Ana Maria Martinez Canet, and Javier Díez do not present any conflict of interest that need to be declared.

Funding Sources

Alberto Ortiz research is supported by FIS/Fondos FEDER (PI22/00469, PI22/00050, PI21/00251, ERA-PerMed-JTC2022 (SPAREKID AC22/00027), FRIAT, Comunidad de Madrid en Biomedicina P2022/BMD-7223, CIFRA_COR-CM. Instituto de Salud Carlos III (ISCIII) RICORS program to RICORS2040 (RD21/0005/0001) funded by European Union – NextGenerationEU, Mecanismo para la Recuperación y la Resiliencia (MRR) and SPACKDc PMP21/00109, FEDER funds. This publication is based upon work from COST Action PERMEDIK CA21165, supported by COST (European Cooperation in Science and Technology) 2023-2027. PREVENTCKD Consortium Project ID: 101101220 Programme: EU4H DG/Agency: HADEA.

Author Contributions

Conceptualization and methodology: Borja Quiroga and Javier Díez. Formal analysis and writing – original draft: Borja Quiroga, Alberto Ortiz, and Javier Díez. Investigation, visualization, and writing (review and editing): Borja Quiroga, Alberto Ortiz, José Jesús Broseta, Beatriz Escamilla Cabrera, David Rodriguez Santarelli, Francisca Lopez Rodriguez, Bárbara Cancho Castellano. Adriana Puente García, Nuria Aresté, Miguel Ángel Rojas. R. Haridian Sosa Barrios, Sara Núñez, Amparo Soldevila Orient, Maria Kislikova, Henar Santana Zapatero, Esperanza Moral Berrio, María Ibáñez Cerezo, Maria Constanza Glucksmann Pizá, Yaiza Rivero Viera, Zoila Stany Albines, Ana Ródenas Gálvez, Belén Campos Gutiérrez, Sagrario Balda Manzanos, Silvia González Sanchidrián, Carmen Patricia Gutierrez Rivas, Laura Salanova Villanueva, Gema Rangel Hidalgo, Sandra Beltrán Catalán, Mayra Ortega Diaz, Lucía Rodríguez Gayo, Ana Maria Martinez Canet, and Javier Díez.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1 Kottgen A, Russell SD, Loehr LR, Crainiceanu CM, Rosamond WD, Chang PP, et al. Reduced kidney function as a risk factor for incident heart failure: the atherosclerosis risk in communities (ARIC) study. J Am Soc Nephrol. 2007;18(4):1307–15. doi: 10.1681/ASN.2006101159.

2 USRDS Annual Data Report. Chapter 4: cardiovascular disease in patients with CKD. Am J Kidney Dis. 2019;79(Suppl 1):S79–98. doi: 10.1053/j.ajkd.2018.12.004.

3 Smith DH, Thorp ML, Gurwitz JH, McManus DD, Goldberg RJ, Allen LA, et al. Chronic kidney disease and outcomes in heart failure with preserved versus reduced ejection fraction: the Cardiovascular Research Network PRESERVE Study. Circ Cardiovasc Qual Outcomes. 2013;6(3):333–42. doi: 10.1161/CIRCOUTCOMES.113.000221.

4 Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296–305 Erratum in: N Engl J Med. 2008;18(4):4. doi: 10.1056/NEJMoa041031.

5 Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129–200 Erratum in: Eur Heart J. 2016 Dec 30. doi: 10.1093/eurheartj/ehw128.

6 McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599–726 Erratum in: Eur Heart J. 2021 Oct 14. doi: 10.1093/eurheartj/ehab368.

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7 McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. ESC Scientific Document Group. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2023;44(37):3627–39 Epub ahead of print. doi: 10.1093/eurheartj/ehad195.
8 Banerjee D, Wang AY. Personalizing heart failure management in chronic kidney disease patients. Nephrol Dial Transpl. 2022;37(11): 2055–62. doi: 10.1093/ndt/gfab026.
9 Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl. 2012;2:279–335.
10 Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Authors/Task Force Members, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18(8): 891–975. doi: 10.1002/ejhf.592.
11 Cobo Marcos M, de la Espriella R, Gayán Ordás J, Llàcer P, Pomares A, Fort A, et al. Prevalence and clinical profile of kidney disease in patients with chronic heart failure. Insights from the Spanish cardiorenal registry. Rev Esp Cardiol. 2024;77(1):50–9 Epub ahead of print. doi: 10.1016/j.rec.2023.05.003.
12 van Kimmenade RR, Januzzi JL Jr, Bakker JA, Houben AJ, Rennenberg R, Kroon AA, et al. Renal clearance of B-type natriuretic peptide and amino terminal pro-B-type natriuretic peptide a mechanistic study in hypertensive subjects. J Am Coll Cardiol. 2009;53(10): 884–90. doi: 10.1016/j.jacc.2008.11.032.
13 Nardi E, Mulè G, Giammanco A, Mattina A, Geraci G, Nardi C, et al. Left ventricular hypertrophy in chronic kidney disease: a diagnostic criteria comparison. Nutr Metab Cardiovasc Dis. 2021;31(1):137–44. doi: 10.1016/j.numecd.2020.08.028.
14 Janse RJ, Fu EL, Dahlström U, Benson L, Lindholm B, van Diepen M, et al. Use of guideline-recommended medical therapy in patients with heart failure and chronic kidney disease: from physician's prescriptions to patient's dispensations, medication adherence and persistence. Eur J Heart Fail. 2022; 24(11):2185–95. doi: 10.1002/ejhf.2620.
15 Beltrami M, Milli M, Dei LL, Palazzuoli A. The treatment of heart failure in patients with chronic kidney disease: doubts and new developments from the last ESC guidelines. J Clin Med. 2022;11(8):2243. doi: 10.3390/jcm11082243.
16 Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al, DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15): 1436–46. doi: 10.1056/NEJMoa2024816.
17 Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413–24. doi: 10.1056/NEJMoa2022190.
18 Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385(16): 1451–61. doi: 10.1056/NEJMoa2107038.
19 Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. 2022;387(12):1089–98. doi: 10.1056/NEJMoa2206286.
20 Nuffield Department of Population Health Renal Studies GroupSGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists'Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet. 2022; 400(10365):1788–801. doi: 10.1016/S0140-6736(22)02074-8.
21 Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimón L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020; 41(1):111–88. doi: 10.1093/eurheartj/ehz455.
22 Quiroga B, Muñoz Ramos P, Álvarez Chiva V. Efficacy and safety of the PCSK9 inhibitors in the treatment of dyslipidemia in chronic kidney disease. Nefrologia. 2020; 40(5):499–505. doi: 10.1016/j.nefro.2020.04.020.
23 Kalra PR, Cleland JGF, Petrie MC, Thomson EA, Kalra PA, Squire IB, et al, IRONMAN Study Group. Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. Lancet. 2022;400(10369):2199–209. doi: 10.1016/S0140-6736(22)02083-9.
24 Ambrosy AP, von Haehling S, Kalra PR, Court E, Bhandari S, McDonagh T, et al. Safety and efficacy of intravenous ferric derisomaltose compared to iron sucrose for iron deficiency anemia in patients with chronic kidney disease with and without heart failure. Am J Cardiol. 2021;152:138–45. doi: 10.1016/j.amjcard.2021.04.042.
25 Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, et al, TREAT Investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361(21):2019–32. doi: 10.1056/NEJMoa0907845.

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