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Review

Management of heart failure with reduced ejection fraction: challenges in patients with atrial fibrillation, renal disease and in the elderly

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Abstract

Heart failure with reduced ejection fraction (HFrEF) is an increasing global pandemic affecting more than 30 million individuals worldwide. Importantly, HFrEF is frequently accompanied by the presence of cardiac and non-cardiac comorbidities that may greatly influence the management and prognosis of the disease. In this review article, we will focus on three important comorbidities in HFrEF; atrial fibrillation (AF), advanced renal disease, and elderly, which all have a paramount impact on progression of the disease, management strategies, and response to therapy. AF is very common in HFrEF and shares many risk factors. AF aggravates heart failure and contributes to HF-related adverse clinical outcomes; hence it requires special consideration in HFrEF management. The kidney function is largely affected by the reduced cardiac output developed in the setting of HFrEF, and the neurohormonal feedback effects create a complex interplay that pose challenges in the management of HFrEF when renal function is significantly impaired. Cardiorenal syndrome is a challenging sequela with increased morbidity and mortality thereby reflecting the delicate and complex balance between the heart and the kidney in HFrEF and renal failure conditions. Furthermore, patients with advanced renal failure have poor prognosis in the presence of HFrEF with limited treatment options. Finally, aging and frailty are important factors that influence treatment strategies in HFrEF with greater emphasis on tolerability and safety of the various HFrEF therapies in elderly individuals.

Keywords: Heart failure with reduced ejection fraction; Atrial fibrillation; Advanced renal disease; Elderly; Management

1. Introduction

The prevalence of heart failure (HF) is estimated to be 1–2% in Europe and the US [1]. The disease burden has been described widely, and for decades it has been considered a global epidemic [2]. The most used categorization of different types of HF is based on the ejection fraction (EF). HF with preserved EF (HFpEF), defined as EF $\geq$50%, is a medical condition with uprising awareness and limited treatment options, and it is a considerably different disease from HF with reduced EF (HFrEF, EF <40%) [3]. The last group of HF is characterized by 40% < EF < 49% and currently referred to as HF with mildly reduced EF (HFmrEF) [4]. Each category of HF is unique in terms of risk factors, pathophysiology, and treatment options [4].

Several comorbidities and medical conditions commonly arise with or secondary to HFrEF, complicating its management and necessitating special clinical attention [5]. In this review, we chose to focus on three comorbidities: atrial fibrillation (AF), advanced renal disease, and elderly patients, which often coexist but many times are overlooked. Those comorbidities directly affect the optimal treatment for patients with HFrEF, as some treatments are preferred, and some are contraindicated. Many trials have excluded these populations, and the consequence is that minimal treatment options are offered in the standard guidelines to these challenging populations. Although other comorbidities exist, the complexity of the pathogenesis and approach in these three groups require special attention. AF has shared risk factors with HFrEF, and when arise together, distinct caution should be undertaken in its management due to specific contraindications, eventually the prognosis is also affected [6]. Patients with advanced renal disease also share predisposing conditions with HFrEF patients, which may precipitate and complicate the cardiac condition [7]. Elderly patients, usually neglected in most clinical trials [8], also need special attention due to fragility, comorbidities, and limited data regarding treatments at advanced age. This review will focus on these three sub-groups of HFrEF patients to emphasize the importance of special considerations regarding optimal management options for these cohorts in the presence of limited data and numerous challenges.

2. Heart failure with reduced ejection in patient with atrial fibrillation

The association between AF and HF was recognized over 70 years ago [9]. It is estimated that by 2030, the incidence of AF and HF in the US population will be around 12 million and 8 million, respectively [10,11]. Both conditions are prevalent individually, and they often co-exist due to overlapping risk factors such as hypertension, diabetes mellitus, ischemic heart disease, and valvular disease, but they also have mutual etiological, practical, and prognostic impact [12]. Previous data suggested that the prevalence of AF among patients with left ventricular dysfunction is 6–35%, correlating with the severity of cardiac dysfunction [13,14]. However, analysis of the data from the Framingham Heart Study showed that among 1166 participants with a new diagnosis of HF, 57% had AF [12]. HFpEF diagnosis had a trend for a stronger association with AF than HFrEF (hazard ratio (HR) 2.34 and 1.32 respectively, $p = 0.06$). Among 1737 patients with a new AF diagnosis, 37% had HF [12]. The prevalence of AF is rising in parallel with the severity of the HF, starting with 5% in patients with New-York heart association (NYHA) functional class I, up to 50% with NYHA IV [15].

Other than shared risk factors, both conditions precipitate each other. HF model in dogs showed extensive fibrosis in the atrium, promoting the formation of AF [16]. In a similar model, angiotensin-converting enzyme (ACE) inhibition prevented increased tissue angiotensin II, cellular apoptosis, and tissue fibrosis [17], suggesting neurohormonal changes similar to HF. There is a growing evidence that renin-angiotensin system (RAS) blockade in some patients might reduce the occurrence of AF [18]. Dogs with HF also demonstrated discrete changes in atrial action potential properties and currents, which are not seen in the induction of chronic atrial tachycardia [19]. Autopsies from hearts of dilated and hypertrophied cardiomyopathy showed a significantly greater extent of fibrosis in the left atrium, comparing patients after MI ($p < 0.01$) [20]. This data suggests that HF may precipitate AF in different mechanisms.

AF may worsen HF in several ways. Shorter diastolic filling time due to elevated heart rate and the loss of the atrial contraction may reduce cardiac output. In addition, AF is the most common cause of tachycardia-induced cardiomyopathy [21]. Restoration of sinus rhythm improves cardiac output, exercise capacity, and maximal oxygen consumption [22].

Retrospective data suggest that HF patients with concomitant AF have increased mortality risk compared with HF patients without AF (relative risk (RR) 1.34, $p = 0.002$) [13]. Among patients with acute myocardial infarct (AMI) complicated by HF, AF was associated with greater long-term mortality [23]. A meta-analysis showed that AF was associated with all-cause mortality in both randomized (odds ratio (OR) 1.4, $p < 0.0001$) and observational (OR 1.14, $p < 0.05$) studies of HF patients [24].

Although the high prevalence of joint conditions, treatment options for AF in patients with HF are limited. Maintaining a resting HR below 110 bpm is recommended, although not categorically proven [25]. The rate versus rhythm control debate is still ongoing, with no clear winner. The AF-CHF (atrial fibrillation and congestive heart failure) trial compared both strategies and showed no difference in mortality, stroke, or worsening HF [26]. Regarding rate-control of AF, calcium channel blockers are not recommended in HFrEF, and digoxin may be associated with increased mortality [27]. Beta-blockers, which represent the mainstay of HF and AF treatment, have yet to show improved outcomes when the conditions are combined [28]. Most rhythm-control drugs used to restore and maintain sinus rhythm are contraindicated in HF. The proarrhythmic effect of class I antiarrhythmic medications leaves some class III drugs, along with their prevalent adverse reactions, almost as the sole option [29]. SGLT-2 inhibitors are gaining momentum recently in the cardiovascular field. The DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58) trial studied the effect of dapagliflozin in patients with type 2 diabetes mellitus and either atherosclerotic risk factors or known atherosclerotic disease. It showed that dapagliflozin decreased the incidence of AF (and Atrial flutter) during follow-up, as compared to placebo (HR 0.81, $p = 0.009$) [30]. A systematic review of 31 articles including a total of 75,279 patients was recently published. This analysis showed that treatment with SGLT-2 inhibitors resulted in a 25% relative risk reduction in serious AF events and a similar reduction in total AF events [31].

The CASTLE-AF (Catheter Ablation versus Standard conventional Treatment in patients with Left ventricular dysfunction and Atrial Fibrillation) trial showed that treatment with catheter ablation for AF was superior to optimal medical therapy by improving EF, maintaining sinus rhythm, and reducing mortality and hospitalization [32]. The Ablation vs Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD/CRTD (AATAC) showed that catheter ablation of AF was more successful in maintaining sinus rhythm than amiodarone over 2-year follow-up (HR 2.5, $p < 0.001$). Hospitalization and mortality rates were significantly lower in the ablation group [33]. Subsequently, another study, the AMICA (Atrial fibrillation Management in Congestive heart failure with Ablation) trial, did not reveal any benefit of catheter ablation in patients with AF and advanced HF [34]. Nevertheless, as cumulative data suggest improved outcomes with ablation of AF in HF patients, most recent recommendations support catheter ablation as first-line treatment for AF in the right settings [25, 29]. In addition, surgical ablation is highly recommended for patients undergoing another cardiac surgery [35]. Patients with rapid AF refractory to rate control medical ther-

Table 1. Key clinical trials comparing catheter ablation to other interventions as treatment options for atrial fibrillation in patients with heart failure.

Author, year, (trial)	Sample size	Age, years	Comparator arm	Follow-up, months	Baseline LVEF, %	LVEF increase, %	LVEF increase Δ vs comparator, %	All-cause mortality, HR	HF admissions, HR
Khan 2008 [39]	81	60	AV node ablation w/CRT	6	27	8	+9	NA	NA
MacDonald 2011 [40]	41	62	Medical rate control	12	16	4.5	+1.7	NA	NA
Jones 2013 [41]	52	64	Medical rate control	12	22	11	+5.5	NA	NA
Hunter 2014 [42]	366	55	Medical rate control	20	31	8.1	+11.7	NA	NA
Di Biase 2016 [33]	203	62	Amiodarone	24	29	8	+2.9	0.44*	0.55*
Prabhu 2017 [43]	68	59	Medical rate control	6	32	17	+7.5	NA	NA
Marrouche 2018 [32]	363	64	Medical rate or rhythm control	38	31	8	+7.8	0.53*	0.56*
Kuck 2019 [34]	140	65	GDMT	12	27	8	-0.3	NA	NA

Abbreviations: AV indicates atrioventricular; GDMT, guideline directed medical treatment; HR, hazard ratio; LVEF, left ventricular ejection fraction; NA, not applicable. *p values < 0.05.

apy may be offered atrioventricular (AV) node ablation and pacemaker insertion with improved clinical outcomes [36], although the positive effect on mortality is still unproven [37]. The Ablate and Pace for Atrial Fibrillation—cardiac resynchronization therapy (APAF-CRT) trial recently showed that AV junction ablation and biventricular pacemaker insertion reduced all-cause mortality compared to rate control therapy (HR 0.26, $p = 0.004$) among patients with permanent AF. The benefit was similar when the EF was lower than 35% [38]. Table 1 (Ref. [32–34,39–43]) summarizes the main findings of key clinical trials investigating the efficacy of catheter ablation versus other medical or interventional options for treatment of AF in patients with HF. Collectively, HF and AF often co-exist due to shared risk factors and mutual effects. Treating AF is challenging in HF patients, although successful management may improve outcomes (Fig. 1).

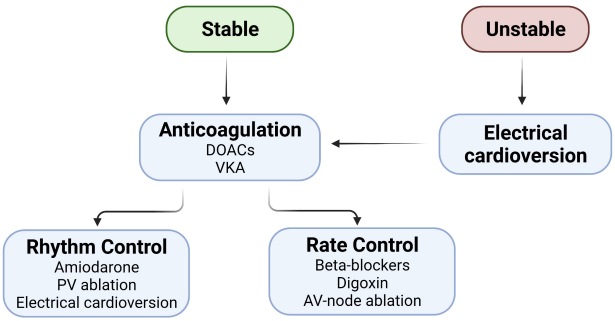

Fig. 1. Recommended management of atrial fibrillation in patients with heart failure and reduced ejection fraction. AV, atrioventricular; DOAC, direct oral anticoagulant; PV, pulmonary veins; VKA, vitamin-K antagonists.

3. Heart failure with reduced ejection fraction in patients with advanced renal disease

Patients with concurrent HFrEF and chronic kidney disease (CKD) experience significant morbidity and mortality. The negative effects of CKD on short- and long-term cardiovascular outcomes is more significant as renal disease advances [44,45]. This prognostic effect is amplified by the high prevalence of advanced CKD in patients with HFrEF, where up to 10% have CKD grades 4–5 and more than 50% have CKD greater than grade 3 [46–48]. In 2016, the prevalence of CKD and HF in the US was estimated to be 37 million and 6.2 million patients, respectively [49].

Many challenges in treatment of HFrEF-CKD patients stem primarily from cross mechanisms predisposing HF patients to acute, chronic, or end-stage renal disease, worsening renal function, and hyperkalemia. In addition, the negative impact of CKD on the cardiovascular system eventually leads to increased cardiovascular morbidity and mortality [50].

The heart-kidney crosstalk is best illustrated in the cardiorenal syndrome (CRS), which represents the bidirectional nature of heart-kidney interaction where acute or chronic dysfunction in one organ may provoke acute or chronic dysfunction in the other. Whether CRS is one pathophysiological continuum representing impaired cardiorenal function or different subtypes stemming from specific contributing factors is unknown. However, it is well recognized that several systemic diseases, in addition to neurohormonal, immunologic, inflammatory, and fibrotic effects, may disrupt and bring about various clinical alterations in cardiac and renal function [51–53].

This complex crosstalk between the heart and kidneys poses significant clinical challenges, particularly in patients with underlying HFrEF. These challenges are emphasized when discussing evidence-based therapeutic opportunities for this cohort of patients with HFrEF and advanced CKD

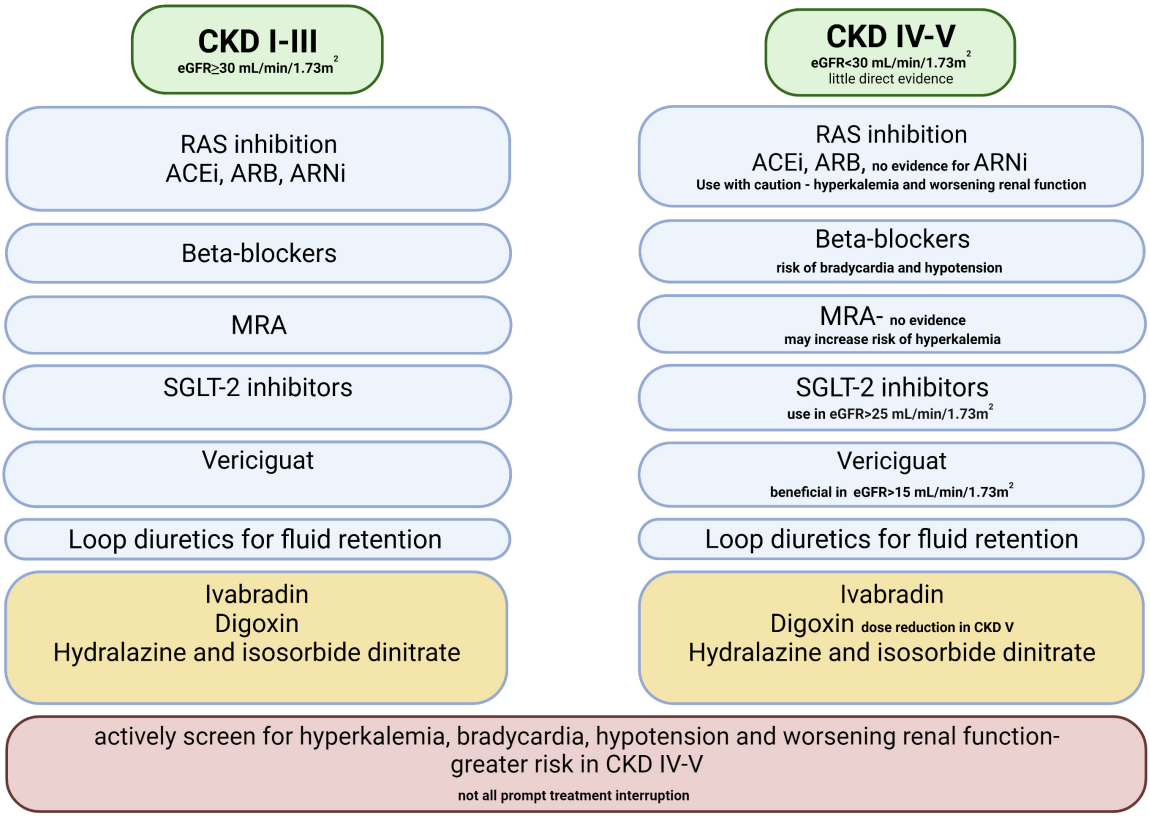

Fig. 2. Management of heart failure with reduced ejection fraction in patients with advanced renal disease. CKD, chronic kidney disease; RAS, renin angiotensin aldosterone; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; SGLT-2, sodium-glucose co-transporter 2.

because these patients were markedly underrepresented in most randomized controlled trials, thus leading to sparse guideline-directed medical therapy (GDMT) options left for this high risk population when compared to the general HFrEF population (Fig. 2) [47].

New data regarding the beneficial effects of sodium-glucose cotransporter-2 (SGLT-2) in HFrEF is accumulating, and it has been shown to slow the progression of chronic kidney disease [30,54–56]. The Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial recently investigated the effect of initiation of sotagliflozin upon discharge from an admission related to CHF. Comparing placebo, sotagliflozin reduced the composite outcome of cardiovascular death, hospitalizations and urgent visits for HF (HR 0.67, $p < 0.001$), without compromising the renal function [57]. The recently published 2021 ESC guidelines for the diagnosis and treatment of acute and chronic HF recommend quadruple therapy for HFrEF patients, including a beta-blocker, angiotensin receptor-neprilysin inhibitor (ARNi), MRA, and an SGLt-2 inhibitor as first line medical therapy [58,59]. However, generalizability for CKD is lacking, as patients with severe renal dysfunction (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2) have systematically been excluded from randomized clinical trials. MRA and ARNi may not be safe in patients with advanced CKD due to increased risk of hyperkalemia, and SGLT-2 inhibitor safety has not been examined in patients with eGFR below 20 mL/min/1.73 m^2.

Despite the lack of evidence-based therapies in these patients, some data advocate for RAS inhibition in severe renal dysfunction [60] with reduced risk for renal failure and CV events [61]. A prospective study of the Swedish HF registry supported this, as RAS inhibition in severe CKD was associated with a lower one-year all-cause mortality [62]. PARADIGM-HF (Prospective Comparison of ARNI with ACE inhibition to Determine Impact on Global Mortality and Morbidity in Heart Failure) study, which excluded patients with advanced CKD, found that compared to Enalapril, patients with grade 3 CKD receiving sacubitril/valsartan had a slower rate of decline in eGFR and better CV outcomes despite a modest increase in proteinuria [63]. Over two decades have passed since MRA's have been shown to decrease morbidity and mortality among patients with severe HF [64]. However, although similar positive CV outcomes were observed, analysis of the effect of this drug class on patients with CKD has raised concerns of adverse events, notably hyperkalemia [65]. In light of valid safety concerns, current guidelines suggest ex-

ercising caution when considering MRA treatment in patients with CKD or hyperkalemia [54,55]. Data regarding the effects of Finerenone on patients with type 2 diabetes and advanced CKD have shown lower risks of CKD progression and cardiovascular events than placebo. This effect was enhanced in patients with a history of CV disease [66,67]. Finerenone is a novel, nonsteroidal, selective MRA with anti-inflammatory and antifibrotic effects. In the recently published FIGARO-DKD trial, patients with type 2 diabetes mellitus and CKD were treated with finerenone or placebo. Finerenone resulted in a significant reduction in the composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for HF (HR 0.87, $p = 0.003$) [68]. In the FIDELIO-DKD trial involving participants with similar characteristics, finerenone significantly decreased the risk of CKD progression (primary outcome) and the risk of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for HF (HR 0.86, $p = 0.03$) (secondary outcomes) [66]. It is worth noting that both studies examining the safety and efficacy of finerenone have excluded patients with clinical diagnosis of chronic HFrEF with persistent symptoms (New York Heart Association class II–IV), hence its clinical use in HFrEF and advanced CKD has yet to be determined.

Promising data regarding the use of potassium binders in patients with renal disease receiving RAS inhibitors [69,70] may enable better GDMT for these patients. However, additional studies are needed to confirm clinical outcomes and long-term effects [71].

Since the 1990s, the three beta-blocker agents bisoprolol, metoprolol, and carvedilol have been shown to reduce all-cause and cardiovascular mortality, HF hospitalization, and improve functional capacity [72]. Analysis of the MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure) [73], CIBIS-II (Cardiac Insufficiency Bisoprolol Study II) [74] and COPERNICUS (Carvedilol Prospective Randomized, Cumulative Survival study) [75] studies suggest beneficial effects of beta-blockade on clinical outcomes among patients with HF and renal disease. However, generalizability is limited due to the fact that few participants with severe renal impairment were included in these studies. Data for a 10-year cohort in Taiwan regarding hemodialysis patients receiving beta-blockers for HF demonstrated improved long-term survival among these patients [76]. Whether one beta-blocker is superior to others in hemodialysis patients is unknown; however recent data suggest that both metoprolol and bisoprolol may be associated with lower major adverse cardiovascular event (MACE) and mortality rates [77,78]. Although these data demonstrate a class effect of beta blockers, this potential benefit may be accompanied by risk of bradyarrhythmia and hypotension which should be monitored. The key clinical trials involving patients with significant CKD and relevant outcomes are outlined in Table 2 (Ref. [56,62,63,65,79–84,87]).

The lack of evidence-based GDMT for comorbid HFrEF-CKD may expose these patients to more common side effects than HFrEF patients without significant CKD. While traditional RAS inhibitors and MRA show positive outcomes, they should be used cautiously as the risk of hyperkalemia could be relatively high. ARNi may provide a better safety profile, but further evaluation is needed. The efficacy of potassium binders is yet to be determined, but these may provide clinical benefits in patients who may benefit from ARNi or MRA but restricted due to hyperkalemia. Although widely used and generally tolerated by comorbid HFrEF-CKD, beta-blockers require careful monitoring for hypotension and bradycardia due to higher risk of developing these sequalae in advanced CKD patients.

4. Heart failure with reduced ejection fraction in the elderly

The prevalence of HF increases significantly with age and approximately 18 million patients with HF are aged $\geq$65 [86]. Acute decompensated HF is the leading cause of hospitalization among older persons in the United States [87]. The development of life-prolonging therapies for patients with HF and the aging of the general population is expected to increase the burden of HF [88]. The prevalence of HF in the United States was estimated to rise by 46% from 2012 to 2030, and an estimate of 2 million octogenarians living with HF in 2030 in the US alone [87].

Evidence-based data regarding HF diagnosis, treatment, and prognosis in this population is lacking [86]. Most HF diagnosis and treatment protocols are extrapolated from studies performed on the younger population. The older population is unique in higher prevalence of comorbidities, physical disabilities, unique medical conditions, and perhaps different responses to treatment.

The cumulative prevalence of chronic diseases increases with age [89]. Most HF patients older than 75 years have multiple cardiovascular and non-cardiovascular comorbidities, such as hypertension, AF, ischemic heart disease, arthritis, diabetes mellitus, CKD, anemia, cancer, severe chronic respiratory disease, and cognitive or psychiatric disorders [90], emphasizing the unique characteristics of this population.

Diagnosis of HF in these patients is challenging because of multiple comorbidities, sedentary lifestyle or physical disabilities that overshadow exertional dyspnea, and cognitive impairment that interferes with proper anamnesis. Diagnosis of HFpEF or cardiac amyloidosis requires a higher index of suspicion since it is more common in this population [91]. In light of these limitations, HF diagnosis in the older population may require greater attention to less specific or atypical symptoms, such as sudden changes in mental status and anorexia. The commonly used natriuretic peptide test for HF diagnosis is less helpful in this population because age and many other comorbidities are

Table 2. Key clinical studies of class I heart failure therapies in patients with heart failure with reduced ejection fraction and advanced renal disease.

Drug class	Author, year, (trial)	Renal criteria	Intervention	Primary outcome	Results
RAS inhibition	Swedberg *et al*., 1990 [79] (CONSENSUS)	sCr <3.4 mg/dL; 12% estimated with CKD G4	Enalapril vs placebo	ACM	30% vs 55%; $p = 0.004$
	Masoudi *et al*., 2004 [80]	sCr >2.5 mg/dL	ACE inhibitor vs no ACE inhibitor prescription at discharge	ACM	RR = 0.65 (0.51–0.80)
	Edner *et al*., 2015 [62]	CKD G4–5 or sCr >2.5 mg/dL	RAS inhibitor vs no RAS inhibitor prescription at discharge	ACM	HR = 0.76 (0.67–0.86)
	Berger *et al*., 2007 [81]	CKD G4–5	RAS-I vs no RAS inhibitor prescription in hospital	30-day ACM	CKD G4: 9.4% vs 18.5%; $p = 0.008$ CKD G5: 11.9% vs 22.8%; $p = 0.03$
ARNI	Damman *et al*., 2018 [63] (PARADIGM-HF)	CKD G3–4	Valsartan/sacubitril vs enalapril	CV death and HF hospitalization	HR = 0.79 (0.69–0.90) Slower decline in eGFR
	Solomon *et al*., 2016 [82] (IMPRESS OVERTURE PARADIGM-HF)	CKD G3–4	ARNI vs single RAS inhibitor therapy	Adverse events	Increased symptomatic hypotension, but decreased hyperkalemia and renal dysfunction
Beta-blockers	Badve *et al*., 2011 [83]	CKD G3–5	Beta-blocker vs placebo	ACM	RR = 0.72 (0.64–0.80) CV mortality: RR = 0.66 (0.49–0.89)
	McAlister *et al*., 2004 [84]	CKD G3–5	Beta-blocker vs no beta-blocker prescription at discharge	1-yr ACM	OR = 0.40 (0.23–0.70)
MRA	Lu *et al*., 2016 [85]	Adults with CKD	MRA vs non-MRA treatment	ACM, MACE, hyperkalemia	ACM: RR = 0.78 (0.62–0.97) MACE: RR = 0.65 (0.50–0.83) Hyperkalemia: RR = 2.32 (1.83–2.94)
	Vardeny *et al*., 2012 [65] (RALES)	sCr <2.5 mg/dL Stratification at eGFR 60 mL/min per 1.73 m^2	MRA vs non-MRA treatment	Baseline or WRF on spironolactone efficacy	Not significant in patients with HF Similar RRR in all cause death below and above eGFR = 60, greater ARR with Egfr <60
SGLT-2 inhibitor	Packer *et al*., 2020 [56] (EMPEROR-Reduced)	eGFR >20 mL/min/1.73 m^2 Stratification at eGFR 60 mL/min per 1.73 m^2	Empagliflozin vs placebo	CV death or hospitalization for HF rate of decline in eGFR (mL/min/1.73 m^2/year)	eGFR >60 HR 0.67 (0.55–0.83) eGFR <60 HR 0.83 (0.69–1.00) empagliflozin –0.55 ± 0.23 placebo –2.28 ± 0.23 AD 1.73 (1.10 to 2.37) $p < 0.001$

Abbreviations: HF indicates heart failure; HFrEF, heart failure with reduced ejection fraction; CKD, chronic kidney disease; RAS, renin-angiotensin system; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; sCR, serum creatinine; ACE, angiotensin converting enzyme; ACM, all-cause mortality; RR, relative risk; HR, hazard ratio; ARNI, angiotensin receptor-neprilysin inhibitor; PARADIGM-HF, Prospective Comparison of ARNI with ACE inhibition to Determine Impact on Global Mortality and Morbidity in Heart Failure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; OR, odds ratio; MACE, major adverse cardiovascular event; MRA, mineralocorticoid receptor antagonist; RALES, Randomized Aldactone Evaluation Study; WRF, worsening renal function; RRR, relative risk reduction; ARR, absolute risk reduction; SGLT-2, sodium glucose cotransporter 2; EMPEROR, Empagliflozin outcome trial in Patients With chronic heart Failure With Reduced Ejection Fraction; AD, absolute difference.

Table 3. Heart failure treatment considerations in the elderly.

Drug class	Effects on HF	Treatment considerations	Recommendations	References
Beta-blockers	• Decrease mortality • Preserve myocardial function • Prevent reverse remodeling • Improve beta adrenergic response • Reverse adverse effects of neurohormonal activation • Beneficial effects on mortality and hospital admissions	• No statistically significant age differences in mortality reduction • Older patients are at increased risk for sinus bradycardia and AV-nodal conduction disorders	• Initiate at the lowest available dose and up titrate gradually • Obtain ECG after initiation and dose escalation • Permanent pacemaker should be considered in symptomatic bradycardia	Rich *et al*., 2012 [108] Hernandez *et al*., 2009 [109] Krum *et al*., 2006 [110] Dulin *et al*., 2005 [111]
RAS inhibitors and ARNi	• Decrease mortality, myocardial infarction, and hospitalization for HF in patients with LV dysfunction	• Hypotension, hyperkalemia, renal dysfunction. • Usually manageable with lower doses • ACEI may cause cough and stress incontinence, particularly in older women	• Initiate at the lowest available dose and titrate gradually • Monitor renal function and serum potassium levels • Target doses as in younger patients • Reduce doses when adverse reactions occur Avoid in elderly patients with stage IV or stage V CKD who are not on dialysis • Subgroup analysis suggests that ARB can be a better first line therapy in the elderly	Flather *et al*., 2000 [112] ACE inhibitor Myocardial Infarction Collaborative Group, 1998 [113] Rich *et al*., 2012 [108] Massie *et al*., 2011 [114] Packer *et al*., 1999 [115]

Table 3. Continued.

Drug class	Effects on HF	Treatment considerations	Recommendations	References
MRA	• Decrease mortality and hospitalization for HF in patients with LV dysfunction	• Hyperkalemia and renal dysfunction	• Serum creatinine and potassium level monitoring, patient education regarding symptoms of hyperkalemic • Contraindicated in patients with stage IV or stage V CKD who are not on dialysis • Initiate at low doses in older patients with stage III CKD, increase as tolerated	Juurlink *et al*., 2004 [116] Tamirisa *et al*., 2004 [117] Braunstein *et al*., 2007 [118] Pitt *et al*., 1999 [65]
Digoxin	• May improve quality of life and reduce HF hospitalization, but does not impact survival	• Digoxin toxicity at lower doses, especially in older women	• Aim at a therapeutic digoxin serum level of 0.5–0.9 nmol/L. • Adjust for renal function and lean body mass, and monitor closely for electrolyte abnormalities • High index of suspicion for toxicity symptoms	Rich *et al*., 2001 [119] Hanratty *et al*., 2000 [120] Hauptman *et al*., 2013 [121] Ahmed *et al*., 2006 [122]
Vasodilators and nitrates	• Improve resting and exercise hemodynamics, exercise capacity, and clinical status	• Headache, dizziness, flushing, and palpitations	• Initiate at low doses and increase as tolerated • No evidence for higher rates of adverse reactions in the older population	Leier *et al*., 1983 [123]

Abbreviations: HF indicates heart failure; ARNi, angiotensin receptor-neprilysin inhibitor; AV, atrioventricular; ECG, electrocardiogram; RAS, renin angiotensin system; LV, left ventricle; ACEI, angiotensin converting enzyme inhibitor; CKD, chronic kidney disease; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonists.

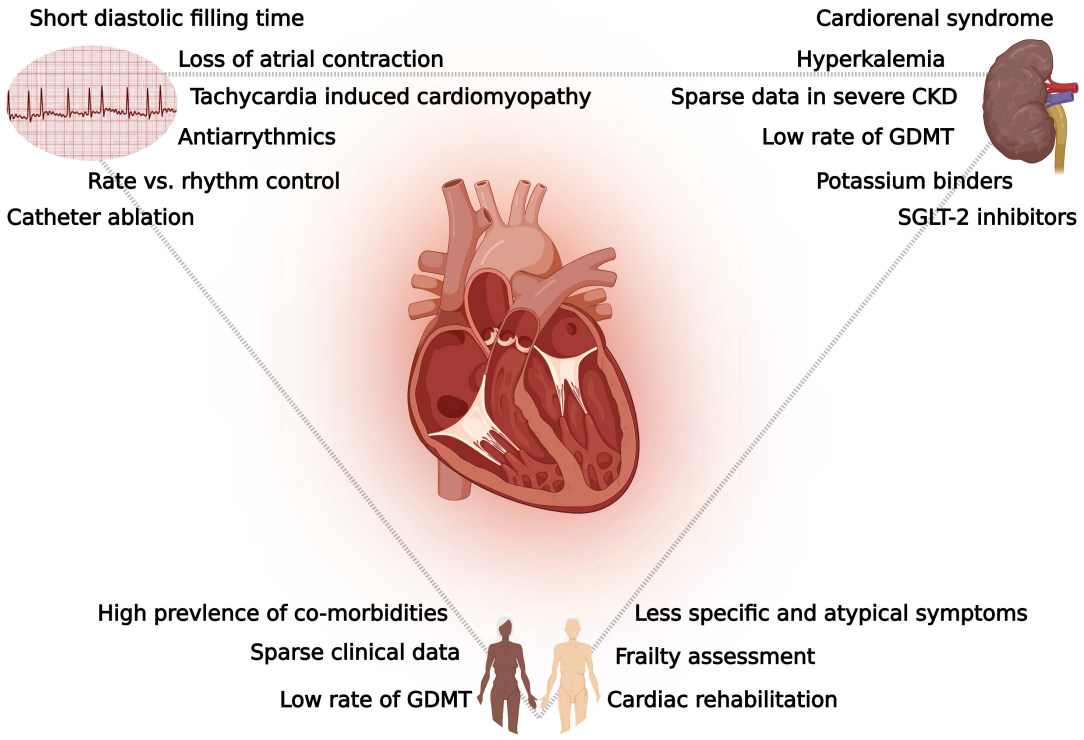

Fig. 3. Key considerations in the management of heart failure with reduced ejection fraction in patients with atrial fibrillation, advanced renal disease and in the aged populations. GDMT, guideline directed medical therapy; CKD, chronic kidney disease; SGLT-2, sodium-glucose co-transporter 2.

associated with elevated serum natriuretic peptide concentrations [92]. Measurement can be beneficial when using higher thresholds for diagnosing or ruling out HF, but overall, the clinician must be aware of atypical symptoms as mentioned above.

HF is a leading cause of disability and mortality in the aged population [93], as baseline physical function in these patients is impaired. The characteristic acute decompensation of HF requires hospitalizations and bed rest, which worsen the baseline disability, and many patients never recover to baseline functions after discharge [94]. Readmission and HF-related hospitalization rates keep rising with age [95]. Geriatric conditions, such as dementia and mobility disorders, are strongly associated with mortality among older patients admitted with worsening HF, both during and after hospitalization [86].

Despite the growing number of aged individuals, HF treatment protocols focusing on the elderly are still sparse. Overall, studies highlight a tendency to under-prescribe recommended treatments [96,97], and lower demand for diagnostic exams, such as echocardiograms in this population [98]. Potential reasons for these findings can be attributed to fear of side effects and comorbidities, focusing on the short-term rather than long-term outcomes, and poor adherence and understanding of physician instructions. The lack of definitive data for a very old population may leave physicians with the belief that the accepted treatments do not include their geriatric patients. It is important to emphasize that all the randomized trials conducted in HFrEF have shown benefit from RAS inhibition and beta-blocker use, regardless of age. Small trials have also demonstrated that these medications improve outcomes, specifically in older HF patients [93,99]. Diuretics for maintaining euvolemic status and improving quality of life, as well as the use of nitrates in elderly patients with HF should be used with particular attention to side effects, orthostatic hypotension, and falls [98].

Interventions relevant for older patients are beginning to raise awareness. Frailty is a geriatric syndrome of increased vulnerability to stressors due to cumulative declines across different physiological systems [100]. The prevalence of frailty increases in elderly subjects diagnosed with HF, and the co-occurrence of HF and frailty increases the risk of mortality in patients with HF [101]. It has been shown that moderate or borderline frailty in various medical conditions is responsive to a targeted intervention [102–104], making frailty assessments relevant for clinical decisions in patients with HF, and developing specific interventions designed to prevent subsequent disability in frail HF patients is strongly warranted.

Several studies have investigated the efficacy and safety of various The FRAIL-HF study [105] assessed frailty in older patients with acute decompensated HF and showed prognostic value that was independent of chronic

comorbidity and acute coexisting diseases. Interventions, such as adapted cardiac rehabilitation, physical exercise, nutrition guidance and HF self-care and treatment optimization could be beneficial to delay the transition from frailty to disability and reduce mortality after discharge in frail patients [106]. In the REHAB-HF (Rehabilitation Therapy in Older Acute Heart Failure patients) trail [107], an early, transitional, tailored, progressive rehabilitation intervention during and after an HF hospitalization in a diverse population of older patients (mean age 72) resulted in better outcomes, including physical function, than usual care.

In conclusion, the prevalence of HF continues to increase with age, and HF is one of the leading causes of hospitalization, disability, and mortality in the elderly. This population has unique features that must be evaluated and considered while diagnosing and establishing a treatment plan. Weighing the benefits and risks of treatment in the context of comorbidities requires special attention with avoidance of under-treatment (Table 3, Ref. [65,108–123]). The use of predicting factors to assess prognosis and particular rehabilitation interventions have been shown to improve quality of life as well as long-term outcomes.

5. Conclusions

Treatment of HFrEF has evolved dramatically during the past three decades. The benefits of therapy for the general population are gaining evidence with current guidelines suggesting beta-blockers, RAS inhibitors, MRA, SGLT-2 inhibitors as well as other medical and device treatments in specific populations. These therapeutic options have been proven, during these years, to lower hospitalization rates for HF, improve quality of life and reduce mortality. However, some high-risk populations have yet to benefit from the abundance of data. Successful medical treatment or electrophysiological procedures for AF may improve outcomes for these patients. Implementing GDMT in the elderly and patients with advanced CKD while reducing treatment adverse effects related to these comorbidities can improve quality of life and may also have a prognostic impact (Fig. 3). As life expectancy continues to increase, in addition to the prevalence of HF-associated comorbidities, greater emphasis should be made on the establishment of GDMT for the treatment of high-risk populations with HFrEF.

Author contributions

YK, AK, and RA—conceptualized the review; YK, AK, and RA—wrote the first draft; YK, AK, GP, DN, PA, AB, and RA—provided critical editing and review. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

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