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Do Elderly Patients with Heart Failure and Reduced Ejection Fraction Benefit from Pharmacological Strategies for Prevention of Arrhythmic Events?

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Keywords
Heart failure with reduced ejection fraction · Cardiac arrhythmia · Mortality · Sudden cardiac death · Elderly · Reduced left ventricular ejection fraction

Abstract
Background: Heart failure is associated with aging. It is one of the leading causes of morbidity and mortality in Western countries and constitutes the main cause of hospitalization among elderly patients. The pharmacological therapy of patients with heart failure with reduced ejection fraction (HFrEF) has greatly improved during the last years. However, elderly patients less frequently receive recommended medical treatment. ***Summary:*** The quadruple therapy (sacubitril/valsartan, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors) is nowadays the cornerstone of medical treatment since it associates lower risk of heart failure hospitalizations and mortality (also of arrhythmic origin). Cardiac arrhythmias, including sudden cardiac death, are common in patients with HFrEF, entailing worse prognosis. Previous studies addressing the role of blocking the renin-angiotensin-aldosterone system and beta-adrenergic receptors in HFrEF have suggested different beneficial effects on arrhythmia mechanisms. Therefore, the lower mortality associated with the use of the four pillars of HFrEF therapy depends, in part, on lower sudden (mostly arrhythmic) cardiac death. ***Key Messages:*** In this review, we highlight and assess the role of the four pharmacological groups that constitute the central axis of the medical treatment of patients with HFrEF in clinical prognosis and prevention of arrhythmic events, with special focus on the elderly patient, since evidence supports that most benefits provided are irrespective of age, but elderly patients receive less often guideline-recommended medical treatment.

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Introduction

Heart failure (HF) is one of the main causes of morbidity and mortality in developed countries. Its incidence increases with age, also constituting the leading cause of hospitalization in patients older than 65 years [1, 2]. During the last decades, the pharmacological therapy of patients with HF, especially those with HF and reduced ejection fraction (HFrEF), has greatly evolved. As a matter of a fact, the quadruple therapy, which includes sacubitril valsartan (SV), beta-blockers (β-blockers), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter 2 inhibitors (SGLT2is), is the cornerstone of the treatment recommended in current clinical guidelines, since their use is associated with lower risk of mortality and HF hospitalizations (HFH), together with left ventricular reverse remodeling [1, 3].

On the other hand, cardiac arrhythmias, including atrial and ventricular arrhythmias (VA), are common in patients with HFrEF, entailing adverse outcomes and mortality, and sudden cardiac death (SCD) is not uncommon in these patients [4, 5]. Beneficial effects on arrhythmia mechanisms have been suggested in previous studies addressing the role of blocking the renin-angiotensin-aldosterone system and beta-adrenergic receptors in HFrEF [6]. In fact, the lower mortality associated with the use of the four pillars of HFrEF therapy relies, in part, on lower sudden (mostly arrhythmic) cardiac death [1]. In this text, we highlight and review the role of the four pharmacological groups that constitute the central axis of the medical treatment of patients with HFrEF in both clinical prognosis and prevention of arrhythmic events, with special focus on the elderly patient (Fig. 1, central). Although recommendations do not specifically differ by age-groups, elderly HF patients receive less frequently guideline-recommended medical treatment [1]. Furthermore, conditions like comorbidities, frailty, and other geriatric conditions do also associate worse prognosis and should be carefully considered when approaching best medical options and prognosis in elderly patients with HF [7].

Sacubitril/Valsartan

SV is a safe drug that has shown to decrease cardiovascular mortality and hospitalization in patients with HFrEF in randomized clinical trials and in real-life studies [8–11]. Recent evidence suggests that SV may also play a role in reducing ventricular remodeling and arrhythmogenesis and thereby SCD [12, 13]. Some authors have even suggested considering SV an antiarrhythmic drug (AAD) [14]. Regarding VA, SV may reduce their occurrence by affecting three pathways (B-type natriuretic peptide, angiotensin II, and bradykinin) and reductions in the number of implantable cardioverter-defibrillator (ICD) shocks and VA have been described [15, 16].

Regarding atrial fibrillation (AF), SV attenuates atrial electrical and structural remodeling and inhibits atrial fibrosis. In patients with AF treated with ablation, it is superior to valsartan in attenuating atrial structural remodeling [17]. Also, it might reduce AF recurrence [18].

However, meta-analyses of randomized controlled trials have found conflicting results regarding the benefit of SV in the risk of arrhythmias. The most recent found no association between SV and the occurrence of atrial and VA, although SV reduced the risk of SCD [19]. This was an unexpected finding since most nonarrhythmic causes of SCD are related to ischemic heart disease [20].

On the other hand, some authors have found an increase in VA in patients with chronic HFrEF and sustained VA after recent SV initiation has been described [21, 22]. Using the US Food and Drug Administration adverse event reporting system (worldwide pharmacovigilance database), Gatti et al. [23] found that SCD occurred early after SV administration (average onset 124 days), with concomitant drugs known for pro-arrhythmic potential (e.g., amiodarone, escitalopram, mirtazapine) in 26% of records. These authors concluded that the unexpected reporting of SCD occurred well before the complete development of positive electrical remodeling induced by SV. Figure 2 summarizes the potential antiarrhythmic/pro-arrhythmic effects of SV that might be seen in specific HF patients. Further studies are needed to clarify this issue.

SV in Elderly Patients

Although SV is frequently used at a lower dose in advanced age patients than in young adults, pharmacokinetic studies suggest that dose adjustment based on age may not be necessary [24, 25]. However, further studies addressing dosage, rate of titration, and safety in the elderly are needed. Also, caution is prudent when commencing and uptitrating, particularly in the presence of hypotension, renal dysfunction, or hyperkalemia [26]. Compared with younger patients, patients with advanced age treated with SV present side effects more frequently [21]. However, SV is a safe drug in the elderly that is not associated with higher rates of acute kidney injury than other renin-angiotensin system inhibitors [24, 27].

SV improves cardiac function and structure of elderly patients with HFrEF and was more beneficial than enalapril across the spectrum of age in PARADIGM-HF [11, 28]. Even after accounting for "real-world" rates of drug discontinuation, discharge on SV is associated with a

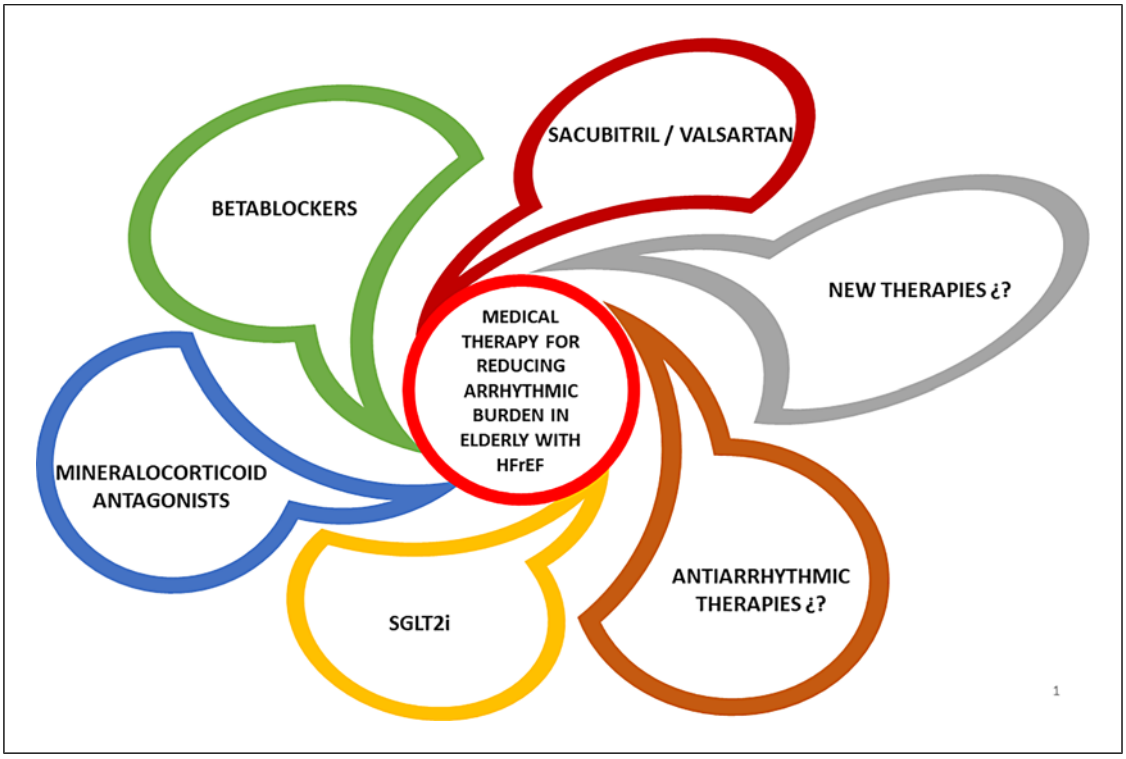

Fig. 1. (Central) Medical therapy for reducing arrhythmic burden in patients with HF and reduced ejection fraction. Central figure summaries current pharmacological therapies recommended in heart failure with reduced ejection fraction (HFrEF) patients in order to reduce mortality and HF hospitalizations. SV, β-blockers, mineralocorticoid antagonists, and sodium-glucose cotransporter 2 inhibitors (SGLT2is) constitute the standard HFrEF therapy nowadays. Amiodarone reduces the burden of VAs in HFrEF patients with no survival benefits. Other AADs have neutral or negative effects, while the role of other new pharmacological therapies has not been stablished yet. HFrEF, heart failure with reduced ejection fraction; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

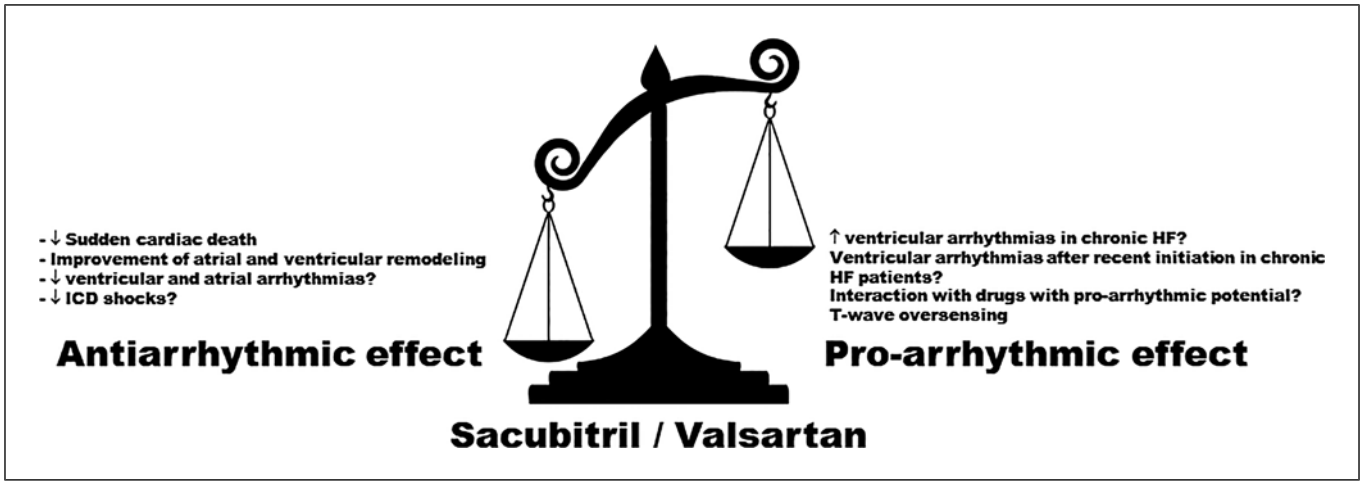

Fig. 2. Potential antiarrhythmic and pro-arrhythmic effects of sacubitril/valsartan (S/V). S/V has been related with a decreased incidence of SCD, VAs or appropriate defibrillator shocks, improvement in cardiac remodeling (both ventricular and atrial), and decreased incidence of atrial arrhythmias. However, some pro-arrhythmic effects have been described, especially in chronic HF patients. S/V has been related with a potential increase of VAs early after initiation of this drug. S/V may potentially interact with pro-arrhythmic drugs such as amiodarone. Finally, inappropriate defibrillator shocks have been described due to T-wave oversensing in chronic HF patients receiving S/V. ICD, implantable cardioverter defibrillator; ↑, increase; ↓, decrease.

Table 1. Summary of the main randomized clinical trials with β-blockers in HFrEF

Trial	Year of publication	Type of β-blocker	Sample size (*N*)	Inclusion criteria	Effects on all-cause mortality	Effects on SCD
CIBIS [34]	CIBIS investigators 1994	Bisoprolol	641	LVEF <40% NYHA class III-IV	No significant differences between the two groups	No significant differences
CIBIS II [35]	CIBIS II investigators 1999	Bisoprolol	2,647	LVEF ≤35% NYHA class III-IV	34% relative risk reduction	44% relative risk reduction in SCD
MERIT HF [36]	MERIT-HF Study Group 1999	Metoprolol CR/XL	3,991	LVEF ≤40% NYHA class II–IV	34% relative risk reduction	41% relative risk reduction in SCD
CAPRICORN [37]	Dargie HJ, 2001	Carvedilol	1,959	Previous AMI and LVEF <40%	23% relative risk reduction	Nonsignificant trend to reduction in SCD
COPERNICUS [38]	Eichhorn EJ, 2001	Carvedilol	2,289	LVEF <25% NYHA class III-IV	35% relative risk reduction	Significant reduction of SCD (3.9% vs. 6.1%)
COMET [39]	Poole-Wilson PA, 2003	Metoprolol CR/XL and Carvedilol	2,309	LVEF <35% NYHA class II–IV	17% relative risk reduction in carvedilol group	3% absolute risk reduction in sudden death with carvedilol
SENIORS [40]	Flather MD, 2005	Nebivolol	2,128	LVEF ≤35% NYHA class II–IV, age >70 years	No significant differences between groups	No significant differences

AMI, acute myocardial infarction; CAPRICORN, Carvedilol Post-Infarct Survival Controlled evaluation; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; CIBIS/CIBIS-II, Cardiac Insufficiency Bisoprolol Study; COMET, Carvedilol Or Metoprolol European Trial; LVEF, left ventricular ejection fraction; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; NYHA, New York Heart Association.

survival advantage that does not appear to wane with increasing age [29]. However, the benefit of SV in the most common type of HF at advanced age, HF with preserved ejection fraction (HFpEF) is unclear. In PARAGON-HF, SV failed to improve cardiovascular outcomes or reduce new-onset AF in patients with HFpEF [30]. Moreover, real-life HFpEF patients have a higher risk profile when compared with those included in PARAGON-HF trial, with poorer functional class, higher levels of natriuretic peptides, and worse renal function [31]. Notably, in a sub-analysis of PARAGON-HF trial, SV seemed to show a greater reduction in the primary endpoint in frail patients [32].

We can conclude that SV should be used in older adults in a similar way as it is used in younger patients. Also, elderly patients with acute HF also benefit from SV initiation during hospitalization as shown in real-life studies [33], although lower doses and longer uptitration might be needed in octogenarians with hypotension, renal dysfunction, and hyperkalemia.

β-Blockers

β-Blockers reduce mortality and morbidity and improve symptoms in patients with HFrEF [1]. Table 1 summarizes the main results of the trials addressing their beneficial effect in terms of all-cause mortality and SCD.

The antiarrhythmic effect of β-blockers therapy is probably multifactorial. They have been associated with left ventricular reverse remodeling and a reduction of ischemia. Furthermore, β-blockers have direct effects on electrical conduction, with increased conduction times and refractory periods, decreasing the risk of malignant arrhythmias, as well as increasing the chance of early termination of an arrhythmic episode [41]. In a study including patients with

Table 2. Summary of the main randomized clinical trials with MRAs in HF with reduced and preserved ejection fraction

Study	Year	Event	HR	95% confidence interval	*p* value
Reduced ejection fraction					
Spironolactone					
RALES trial [50]	Pitt B, 1999	Cardiac death	0.70	0.60–0.82	<0.001
		Death due to progression of HF	0.64	0.51–0.80	<0.001
		SCD	0.71	0.54–0.95	0.02
Eplerenone					
EPHESUS trial [51]	Pitt B, 2003	Death from any cause	0.85	0.75–0.96	0.008
		Death from cardiovascular causes or hospitalization for cardiovascular events	0.87	0.79–0.95	0.002
		SCD	0.79	0.64–0.97	0.03
EMPHASIS-HF trial [52]	Zannad F, 2011	Death from cardiovascular causes or hospitalization for HF	0.63	0.54–0.74	<0.001
		Death from any cause	0.76	0.62–0.93	0.008
		Cardiac death	0.76	0.61–0.64	0.01
		SCD	0.76	0.54–1.07	0.12
Preserved ejection fraction					
Spironolactone					
TOPCAT trial [53]	Lewis EF, 2016	Death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of HF	0.89	0.77–1.04	0.14
		Death from cardiovascular causes	0.90	0.73–1.12	0.35
		Hospitalization for HF	0.83	0.69–0.99	0.04
		Aborted cardiac arrest	0.60	0.14–2.50	0.48

RALES, Randomized Aldactone Evaluation Study; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; EMPHASIS-HF, Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist.

ICD and left ventricle dysfunction due to ischemic or dilated cardiomyopathy, a significant reduction in the rate of appropriate ICD therapies was observed with increasing doses of β-blockers [42]. Moreover, in a nationwide cohort of primary prevention ICD patients, increasing doses of carvedilol or metoprolol were associated with decreased risk of ventricular tachyarrhythmia supporting the notion of a dose-dependent effect of β-blockers therapy [43].

AF is the most frequent arrhythmia in patients with HF [44]. However, a meta-analysis performed some years ago did not report any benefit in mortality or HFH in patients with HFrEF and AF [45]. On the other hand, recent research has described a beneficial prognostic effect of β-blockers in patients with HFrEF regardless of the presence of AF [46]. Thus, the use of β-blockers is recommended in all the patients with HFrEF, irrespective of AF [1].

β-Blockers in Elderly Patients

Age is considered an independent predictor of lower tolerability and side effects of β-blockers. Remarkably, when health education is provided, these agents remain tolerated in >75% of patients aged ≥80 years [2]. Nevertheless, sub-optimal doses of β-blockers are often used in elderly patients with chronic HF [47]. Apart from SENIORS trial, few studies have addressed the effect and tolerability of β-blockers in old patients with HFrEF. Current guidelines recommend their use irrespective of age, supported by the absence of interaction with age in the main pivotal studies (although elderly patients were underrepresented) [1]. In this regard, a meta-analysis analyzed data from 11 trials including nearly 4,000 patients aged 40–85 (median age 64 years old) in sinus rhythm and left ventricular ejection fraction (LVEF) <45%; compared with placebo, β-blockers reduced mortality across all ages, including those older (HR 0.77 [0.64–0.92] for the fourth quarter of age distribution, with a median age of 75 years old) [48].

There is limited evidence about the beneficial effect of β-blockers in elderly patients with frailty and comorbidities. One of the few studies in this field included a retrospective cohort over 10,000 elderly patients (median age 79 years old) with HF and chronic kidney disease. β-Blocker use was associated with lower all-cause mortality in the whole sample, including those with estimated glomerular filtration rate <30 mL/min/1.73 m^2 [49].

Mineralocorticoid Receptor Antagonists

MRA has been shown to reduce mortality, the risk of HFH, and symptom burden in all patients with HFrEF [1]. Table 2 depicts main findings of principal trials in this scenario.

In the RALES trial (*Randomized Aldactone Evaluation Study*) 1663 patients (mean age 65 ± 12 years, 21% ≥ 75 years; 27% women) with LVEF ≤35% were randomized to receive 25 mg–50 mg spironolactone daily or placebo. Due to early benefits of spironolactone, the study was prematurely stopped after a follow-up of 24 months. Spironolactone use was associated with a significant 30% reduction in the risk of death. SCD was also significantly reduced [50].

Eplerenone, a more selective aldosterone blocker, was first studied in the EPHESUS trial (*Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study*). In this study, patients with acute myocardial infarction complicated with left ventricular dysfunction (LVEF ≤40%) or diabetes were randomized to receive eplerenone (25–50 mg daily) or placebo during the first 14 days after an ACS. The mean age of the population enrolled was 64 ± 11 years. Eplerenone was significantly associated with fewer death from any cause and time to death from cardiovascular causes or HFH, acute myocardial infarction, stroke, or VA. Those patients taking eplerenone also had significantly fewer SCD [51].

After those positive results, eplerenone was studied in the EMPHASIS-HF trial (*Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms*), which enrolled mild symptomatic (New York Heart Association NYHA functional class II) HF patients (mean age 68.7 years old, 22% women, 24% ≥ 75 years) with LVEF ≤35% to receive eplerenone (25–50 mg daily) or placebo. Patients treated with eplerenone had with fewer rates of the primary endpoint a combination of death from cardiovascular cause or HFH (HR 0.63; 95% CI, 0.62–0.93; p 0.008). Although eplerenone significantly reduced the risk of cardiac death, there was no benefit in reducing the incidence of SCD in this trial (HR 0.76; 95% CI, 0.54–1.07; p 0.12) [52].

A meta-analysis including more than 11,000 patients with HF and LVEF ≤45% published afterward demonstrated patients treated with MRA had a 23% relative risk reduction in SCD rates (OR 0.77; 95% CI, 0.66–0.89; p = 0.001) when compared with patients receiving placebo, as well as lower cardiovascular mortality (OR 0.75; 95% CI, 0.68–0.84; $p < 0.001$) and total mortality rates (OR 0.74; 95% CI, 0.63–0.86; $p < 0.001$) [54]. These results highlight the benefit of MRA therapy in prevention of SCD in patients with HFrEF.

Regarding the therapeutic role of MRA treatment in patients with VA, it has been explored in a retrospective registry recently published. In HF survivors after ventricular tachyarrhythmia (LVEF ≤45%, mean age 66 years, 20% women), treatment with MRA was not associated with improved all-cause mortality at 3 years follow-up [55]. However, only 20% of patients with HF who survived ventricular tachyarrhythmia were discharged with MRA. Thus, further studies are needed to explore the effect of MRA treatment in this population.

In the HFpEF setting, spironolactone was studied in the TOPCAT trial (*Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonis*t). More than 3,000 patients (mean age 68.7 years, 51% women, and 27% ≥ 75 years) with HF and LVEF ≥45% were randomized to receive either spironolactone (15–45 mg daily) or placebo. After a follow-up of 3 years, there was no statistical difference in the primary endpoint (a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of HF) (Table 2) [53]. However, significant differences in the primary composite were found between those patients randomized from eastern Europe (Russia and Georgia) compared to those enrolled from the Americas (USA, Canada, Brazil, and Argentina). Post hoc analysis showed significantly lower rates of the primary outcome in those patients treated with spironolactone from the Americas subgroup (HR 0.82; 95% CI, 0.69–0.98; p 0.026) [56]. Symptomatic benefits (improvement in Kansas City Cardiomyopathy Questionnaire scores) and potential benefits in cardiac structure and function, such as a decrease in left ventricular filling pressure and reverse cardiac remodeling, were also described in post hoc analysis of the TOPCAT trial [57].

Then again, MRA has been shown to reduce atrial fibrosis and prevent AF development. In the EMPHASIS trial, new-onset AF was described in 2.7% patients in the eplerenone group versus 4.5% patients in the placebo group (HR 0.58; 95% CI, 0.35–0.96; p 0.034) [52]. A meta-analysis showed a 31% lower risk of AF in patients treated with spironolactone, but this effect was shown with no eplerenone [58]. The potential underlying mechanism may be the inhibition of aldosterone activity, reducing myocardial fibrosis, reducing activated channels, or just from overall better control of comorbidities such as hypertension or chronic kidney disease.

MRA in Elderly Patients

Particularly, MRA is largely under prescribed in this subgroup [59]. A recent meta-analysis has been published highlighting the effects of MRA therapy in the elderly HF population. This study included 1,756 patients ≥75 years old (352 from RALES trial, 657 from EMPHASIS-trial, and 747 from the TOPCAT-Americans trial). MRA was associated with lower rates of death from cardiovascular

Table 3. Summary of the main randomized clinical trials with SGLT2 inhibitors in HFrEF

	DAPA-HF [61] (McMurray JJV, 2019)			EMPEROR-reduced [64] (Packer M, 2020)		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Primary endpoint (cardiovascular death and worsening HF)	074	0.65–0.85	<0.001	0.75	0.65–0.86	<0.001
65–75 years	0.76	0.61–0.95	0.015	0.72	0.57–0.93	0.015
≥75 years	0.68	0.53–0.88	0.003	0.86	0.67–1.10	NS
Most frail	0.71	0.54–0.93	NA			
Cardiovascular death	0.82	0.69–0.98	NA	0.92	0.75–1.12	NS
65–75 years	0.78	0.58–1.04	0.089	0.94	0.67–1.31	NS
≥75 years	0.83	0.58–1.19	NS	0.90	0.63–1.28	NS
Most frail	0.97	0.67–1.40	NA			
HF hospitalization/urgent HF visit	0.70	0.59–0.83	NA			
65–75 years	0.76	0.58–1.01	NS			
≥75 years	0.64	0.47–0.88	0.006			
Most frail	0.68	0.49–0.94	NA			
Total number of hospitalizations for HF				0.70	0.58–0.85	<0.001
All-cause death	0.83	0.71–0.97	NA	0.92	0.77–1.10	NS
≤75 years	0.80	0.62–1.05	NS	0.87	0.64–1.16	NS
>75 years	0.79	0.58–1.08	NS	0.94	0.70–1.25	NS
Most frail	0.91	0.66–1.26	NA			
Serious ventricular arrhythmia, resuscitated cardiac arrest, or sudden death	0.79	0.63–0.99	0.037			

Results of the main clinical outcomes are summarized according to age. DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; EMPEROR-reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction; HF, heart failure; NA, nonapplicable; NS, nonsignificant.

causes or HFH (HR 0.74; 95% CI, 0.63–0.86; $p < 0.001$). The beneficial effect of MRA was higher in elderly patients with reduced LVEF. Older patients taking MRA experienced more frequently worsening renal function, defined as a drop of >30% in glomerular filtration rate during follow-up. There was no difference in the prevalence of hyperkalemia [60]. In light on these results, the benefit of MRA treatment is consistent also in elderly patients, but closer monitoring of renal function may be considered.

Sodium-Glucose Cotransporter 2 Inhibitors

Different studies have shown the benefit of iSGLT2 across all the spectrum of HF. In DAPA-HF (*Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure*), dapagliflozin 10 mg once a day added to guideline-recommended therapy reduced the risk of mortality and HFH and improved symptoms in patients with HFrEF [61]. The primary outcome, a composite of worsening HF or cardiovascular death, was significantly less often in patients receiving dapagliflozin. Other secondary endpoints were also significantly reduced (Table 3). Symptoms assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) were also improved. These benefits were consistent in patients with and without AF [62]. Dapagliflozin also reduced the risk of any serious VA, cardiac arrest, or SCD when added to conventional therapy in patients with HFrEF (Table 3), irrespective of age [63].

The EMPEROR-reduced (*Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction*) trial assigned 3,730 HFrEF patients with NYHA class II–IV and ejection fraction of 40% or less to receive either empagliflozin or placebo [64]. The primary outcome was a composite of cardiovascular death or hospitalization for worsening HF and was significantly reduced in the empagliflozin group. Empagliflozin also reduced the total number of HFH, the mean slope change in eGFR (HR 1.73; 95% CI, 1.10–2.37; $p < 0.001$), the number of hospitalizations for any cause, and the composite renal outcome (HR 0.5; 95% CI, 0.32–0.77) but not death from any cause (Table 3).

The benefits of SGLT2i in patients with HF and mildly reduced or preserved ejection fraction have also been addressed. In EMPEROR-preserved, 5,988 patients with HF, NYHA class II–IV, and EF ≥40% were assigned to

Table 4. Specific AADs, contraindications and specific dose reductions in the elderly

Drug	Class and mechanism	Contraindications	Dose reduction in the elderly (%)
Amiodarone	Multichannel	Long QT	≈50%
Flecainide	Class I, Na channels	IHD/cardiomyopathy QRS >130 ms CrCl <50 mL/min Liver disease	≈30%
Propafenone	Class I, Na channels	IHD/cardiomyopathy QRS >130 ms	≈50%
Dronedarone	Multichannel	NYHA III-IV, HFrEF Unstable HF Long QT	No reduction
Sotalol	Class III, K channels	Long QT	≈30%
Metoprolol	Class II, β-blocker	Liver disease	≈40%
Diltiazem	Class IV, Ca channels	HFrEF Unstable HF Liver disease	≈20%
Verapamil	Class IV, Ca channels	HFrEF Unstable HF Liver disease	≈25%

Ca, calcium; CrCL, creatinine clearance; HFrEF, heart failure with reduced ejection fraction; IHD, ischemic heart disease; K, potassium; Na, sodium; NYHA, New York Heart Association.

receive empagliflozin or placebo. The primary outcome, a composite of cardiovascular death or HFH, occurred in 13.8% of patients in the empagliflozin group and in 17.1% in the placebo group (HR 0.79; 95% CI, 0.69–0.90; $p < 0.001$) [65]. In the DELIVER Trial, 6,263 patients with HF and a LVEF> 40% were assigned to receive dapagliflozin or placebo. The primary outcome, a composite of worsening HF or cardiovascular death, occurred in 16.4% of patients in the dapagliflozin group and in 19.5% in the placebo group (HR 0.82; 95% CI, 0.73–0.92; $p < 0.001$) [66]. In this study, benefits were consistent irrespective of AF at baseline [67].

SGLT2i in the Elderly

Elderly patients were widely represented in SGLT2i clinical trials and post hoc analysis focused on age has confirmed the benefit of these drugs in this specific population. Notably, 36.2% of patients included in DAPA-HF trial were 65–74 years old and 24.2% were ≥75 years old. The HR for the effect of dapagliflozin compared with placebo on the primary outcome was consistent across the spectrum of age (p value for interaction = 0.76). This outcome in the placebo group was higher in patients 75 years or older and lower in those <55 years of age meaning that the oldest group was the one with the greatest benefit. This finding was mostly due to a higher benefit of dapagliflozin in this population for reducing HF events. The benefit of dapagliflozin in improving symptoms and preventing deterioration was also consistent across age-groups (p for each interaction = 0.96) [68]. Interestingly, another sub-analysis of DAPA-HF investigated the efficacy of dapagliflozin according to frailty status. Remarkably, the benefit of reducing the primary endpoint was independent of frailty status and serious adverse events were not more frequent, regardless of frailty. Larger improvements in KCCQ scores were achieved in the most frail patients who received dapagliflozin. Other endpoints like HFH, cardiovascular death, all-cause death, and recurrent HFH or cardiovascular death had larger absolute reductions in the most frail patients [69].

Half of the patients recruited in the EMPEROR-reduced trial were older than 65 years (35% of patients were 65–74 and 27% were ≥75 years). A substudy according to age showed that empagliflozin reduced the primary endpoint in all the age-groups (p value for trend = 0.24) [70]. The effects of empagliflozin were also consistent across age-groups for secondary endpoints of first and recurrent HFH (p for interaction = 0.30), the rate of decline in eGFR (p for interaction = 0.78), and the renal composite endpoint (p = 0.94). Empagliflozin also significantly improved quality of life according to KCCQ-CSS,

even in those patients in the higher tertile, finding that was consistent across the spectrum of age (p value for trend = 1) [64].

Benefits of SGLT2i in mildly or preserved ejection fraction are consistent in elderly patients. A subanalysis of the EMPEROR-preserved showed similar benefits in elderly patients including patients 80 years or older [71]. In the DELIVER trial, 41% of patients were 75 years or older and the benefit of dapagliflozin on reducing the primary outcome was again consistent in all age categories (p interaction = 0.95) [72].

New Pharmacological Therapies in HF

Current guidelines include new therapies that have recently reported significant benefits in HF patients.

Vericiguat

Vericiguat showed a 10% reduction in the combined event (cardiovascular death or admission for HF) in patients with HFrEF after an episode of decompensation. The rate of AF, ventricular tachycardia, and syncope was similar to the placebo group. The incidence of cardiovascular death, which included SCD, was similar in both groups (16.4 vs. 17.5%) [73]. Both the patients with baseline AF and those who developed AF during follow-up had higher cardiovascular mortality, without differences in benefit from treatment with vericiguat [74]. However, in those aged 75 or more vericiguat did not provide any statistically significant benefit although safety was similar to younger patients [75].

Omecamtiv Mecarbil

Omecamtiv mecarbil reduced the combined event (cardiovascular death or HF admission) by 8% in symptomatic patients with LVEF <35%. There were no differences in the incidence of cardiovascular death or death from any cause, without differences in the rate of arrhythmias QT prolongation, although a lower benefit was observed in patients with underlying AF [76].

Potassium Binders

Hyperkalemia has been associated with increased mortality and arrhythmias, often also leading to HF treatment discontinuation, thus entailing worse prognosis [77]. In this setting, potassium binders such as sodium zirconium cyclosilicate and patiromer allow to normalize and control potassium levels and, in consequence, to maintain renin-angiotensin-aldosterone system inhibitors without arrhythmic-related events [78].

Antiarrhythmic Drugs

Antiarrhythmic Drugs for VA

In ICD carriers with systolic dysfunction, amiodarone (in combination with β-blockers) is the most effective AAD reducing VAs (with no survival impact). Ablation techniques would be a more efficient strategy since they show similar efficacy with fewer adverse effects [79].

AAD for Atrial Fibrillation

AADs continue to be highly relevant in the rhythm control strategy of patients with AF (used in ≈50% of AF for rhythm-control therapy). However, clinical benefit of AADs is controversial since the publication of the AFFIRM study, in which there was no survival benefit of rhythm-control strategy with AAD (mean age ≈70 years); the reduction in AF recurrences was overshadowed by the appearance of adverse effects [80]. Later, dronedarone showed a reduction in the incidence of cardiovascular events, but an increased mortality when used in patients with HF [81]. Recently, in EAST-AFNET 4 Trial, rhythm control strategy (80% with AAD) was associated with a lower rate of cardiovascular events [82]. Overall, we can say that the strategy of rhythm control with AADs (combined with pulmonary veins ablation) can reduce cardiovascular events if started early, being less effective in cases of long-term AF. In patients with AF and HF, AADs did not show clinical benefit (neutral effect of amiodarone and β-blockers and deleterious with other AADs); only rhythm control with pulmonary veins ablation reduces mortality in these patients [83].

Special Aspects in Elderly Patients

Age-related physiologic changes (different myocardial sensitivity, changes in pharmacokinetics and pharmacodynamics, polypharmacy) may increase adverse reactions to AADs. Except for dronedarone, AADs typically require a 50% reduction in starting dose in the elderly (Table 4 depicts AADs contraindications and specific dose reductions) [84]. In any case, a closer follow-up of these patients is necessary.

Conclusion

In conclusion, HF associates high morbidity and mortality burden, in part due to cardiac arrhythmias. Evidence supports the use of the four pillars that constitute the cornerstone of medical therapy in patients with HFrEF since they all reduce HFH and mortality (also from arrhythmic cause). Some important benefits are irrespective of age, although initiation and titration of drug therapy should be done cautiously in the elderly.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dr. Pablo Díez-Villanueva: conception and design. All authors (Dr. Pablo Díez-Villanueva, Dr. Cesar Jimenez-Mendez, Dr. Ángel Pérez, Dr. Alberto Esteban-Fernández, Dr. Tomás Datino, Dr. Manuel Martínez-Sellés, and Dr. Ana Ayesta) were involved in literature review, and critical revision of the manuscript, and completed, read, and approved the final manuscript.

References

1 McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599–726.
2 Díez-Villanueva P, Jiménez-Méndez C, Alfonso F. Heart failure in the elderly. J Geriatr Cardiol. 2021;18(3):219–32.
3 Chudý M, Goncalvesová E. Prediction of left ventricular reverse remodelling: a mini review on clinical aspects. Cardiology. 2022;147(5–6):521–8.
4 Correa A, Rochlani Y, Aronow WS. Current pharmacotherapeutic strategies for cardiac arrhythmias in heart failure. Expert Opin Pharmacother. 2020;21(3):339–52.
5 Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2018;72(14):e91–220.
6 Sutanto H, Dobrev D, Heijman J. Angiotensin receptor-neprilysin inhibitor (ARNI) and cardiac arrhythmias. Int J Mol Sci. 2021;22(16):8994.
7 Jiménez-Méndez C, Díez-Villanueva P, Bonanad C, Ortiz-Cortés C, Barge-Caballero E, Goirigolzarri J, et al. Frailty and prognosis of older patients with chronic heart failure. Rev Esp Cardiol. 2022;75(12):1011–9.
8 Senni M, McMurray JJ, Wachter R, McIntyre HF, Reyes A, Majercak I, et al. Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens. Eur J Heart Fail. 2016;18(9):1193–202.
9 McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993–1004.
10 Vicent L, Esteban-Fernández A, Gómez-Bueno M, De-Juan J, Díez-Villanueva P, Iniesta ÁM, et al. Sacubitril/valsartan in daily clinical practice: data from a prospective registry. J Cardiovasc Pharmacol. 2019;73(2):118–24.
11 Vicent L, Esteban-Fernández A, Gómez-Bueno M, De-Juan J, Díez-Villanueva P, Iniesta ÁM, et al. Sacubitril/valsartan in daily clinical practice: data from a prospective registry. J Cardiovasc Pharmacol. 2019;73(2):118–24.
12 Díez-Villanueva P, Vicent L, de la Cuerda F, Esteban-Fernández A, Gómez-Bueno M, de Juan-Bagudá J, et al. Left ventricular ejection fraction recovery in patients with heart failure and reduced ejection fraction treated with sacubitril/valsartan. Cardiology. 2020;145(5):275–82.
13 Chang PC, Wo HT, Lee HL, Lin SF, Chu Y, Wen MS, et al. Sacubitril/valsartan therapy ameliorates ventricular tachyarrhythmia inducibility in a rabbit myocardial infarction model. J Card Fail. 2020;26(6):527–37.
14 Huang E, Bernard ML, Elise Hiltbold A, Khatib S, Polin GM, Rogers PA, et al. Sacubitril/valsartan: an antiarrhythmic drug? J Cardiovasc Electrophysiol. 2022 Sep 7;33(11):2375–81.
15 Wei Z, Zhang M, Zhang Q, Gong L, Wang X, Wang Z, et al. A narrative review on sacubitril/valsartan and ventricular arrhythmias. Medicine. 2022;101(27):e29456.
16 de Diego C, González-Torres L, Núñez JM, Centurión Inda R, Martin-Langerwerf DA, Sangio AD, et al. Effects of angiotensin-neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices. Heart Rhythm. 2018;15(3):395–402.
17 Yang L, Zhang M, Hao Z, Wang N, Zhang M. Sacubitril/valsartan attenuates atrial structural remodelling in atrial fibrillation patients. ESC Heart Fail. 2022;9(4):2428–34.
18 Wang Q, Zhuo C, Xia Q, Jiang J, Wu B, Zhou D, et al. Sacubitril/valsartan can reduce atrial fibrillation recurrence after catheter ablation in patients with persistent atrial fibrillation. Cardiovasc Drugs Ther. 2022 Feb 9.
19 Liu XH, Wang GL, Xu Q, Zhang L, Liu HJ. Effect of sacubitril/valsartan on the occurrence of cardiac arrhythmias and the risk of sudden cardiac death in heart failure: a meta-analysis of randomized controlled trials. Front Cardiovasc Med. 2022;9:943377.
20 Bob-Manuel T, Jenkins JS, Morin DP. Non-arrhythmic causes of sudden death: a comprehensive review. Prog Cardiovasc Dis. 2019;62(3):265–71.
21 Abumayyaleh M, El-Battrawy I, Kummer M, Pilsinger C, Sattler K, Kuschyk J, et al. Comparison of the prognosis and outcome of heart failure with reduced ejection fraction patients treated with sacubitril/valsartan according to age. Future Cardiol. 2021;17(6):1131–42.
22 Vicent L, Juárez M, Bruña V, Devesa C, Sousa-Casasnovas I, Fernández-Avilés F, et al. Clinical profile and ventricular arrhythmias after sacubitril/valsartan initiation. Cardiology. 2019;142(1):26–7.
23 Gatti M, Antonazzo IC, Diemberger I, De Ponti F, Raschi E. Adverse events with sacubitril/valsartan in the real world: emerging signals to target preventive strategies from the FDA adverse event reporting system. Eur J Prev Cardiol. 2021;28(9):983–9.
24 Esteban-Fernández A, Díez-Villanueva P, Vicent L, Bover R, Gómez-Bueno M, De Juan J, et al. Sacubitril/Valsartan is useful and safe in elderly people with heart failure and reduced ejection fraction. Data from a real-word cohort. Rev Esp Geriatr Gerontol. 2020;55(2):65–9.
25 Gan L, Langenickel T, Petruck J, Kode K, Rajman I, Chandra P, et al. Effects of age and sex on the pharmacokinetics of LCZ696, an angiotensin receptor neprilysin inhibitor. J Clin Pharmacol. 2016;56(1):78–86.
26 Sharkey AT, Ghafar MZ, O'Keeffe ST, Mulkerrin EC. Angiotensin receptor neprilysin inhibitors in older patients with heart failure. BMJ Evid Based Med. 2019;24(1):5–7.
27 Bhatt AS, Vaduganathan M, Zhuo M, Fu EL, Solomon SD, Desai RJ. Risk of acute kidney injury among older adults with heart failure and with reduced ejection fraction treated with angiotensin-neprilysin inhibitor vs renin-angiotensin system inhibitor in routine clinical care. J Card Fail. 2023;29(2)138–146.

28 Jhund PS, Fu M, Bayram E, Chen CH, Negrusz-Kawecka M, Rosenthal A, et al. Efficacy and safety of LCZ696 (sacubitril-valsartan) according to age: insights from PARADIGM-HF. Eur Heart J. 2015;36(38):2576–84.
29 Gilstrap L, Zipkin RJ, Barnes JA, King A, O'Malley AJ, Gaziano TA, et al. Sacubitril/valsartan vs ACEi/ARB at hospital discharge and 5-year survival in older patients with heart failure with reduced ejection fraction: a decision analysis approach. Am Heart J. 2022;250:23–8.
30 Piccini JP, Arps K. Sacubitril/valsartan therapy for AF and HFpEF: is the glass half empty or half full? JACC Heart Fail. 2022;10(5):347–9.
31 Vicent L, Esteban-Fernández A, Gómez-Bueno M, De-Juan J, Díez-Villanueva P, Iniesta ÁM, et al. Clinical profile of a nonselected population treated with sacubitril/valsartan is different from PARADIGM-HF trial. J Cardiovasc Pharmacol. 2018;72(2):112–6.
32 Butt JH, Dewan P, Jhund PS, Anand IS, Atar D, Ge J, et al. Sacubitril/valsartan and frailty in patients with heart failure and preserved ejection fraction. J Am Coll Cardiol. 2022;80(12):1130–43.
33 López-Azor JC, Vicent L, Valero-Masa MJ, Esteban-Fernández A, Gómez-Bueno M, Pérez Á, et al. Safety of sacubitril/valsartan initiated during hospitalization: data from a non-selected cohort. ESC Heart Fail. 2019;6(6):1161–6.
34 A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS Investigators and Committees. Circulation. 1994;90(4):1765–73.
35 The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353(9146):9–13.
36 Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). Lancet. 1999;353(9169):2001–7.
37 Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet. 2001;357(9266):1385–90.
38 Eichhorn EJ, Bristow MR. The carvedilol prospective randomized cumulative survival (COPERNICUS) trial. Curr Control Trials Cardiovasc Med. 2001;2(1):20–3.
39 Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol or Metoprolol European Trial (COMET): randomised controlled trial. Lancet. 2003;362(9377):7–13.
40 Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005;26(3):215–25.
41 Anh D, Marine JE. Beta blockers as antiarrhythmic agents. Heart Fail Rev. 2004;9(2):139–47.
42 Deftereos S, Giannopoulos G, Kossyvakis C, Kaoukis A, Raisakis K, Panagopoulou V, et al. Relation of ventricular tachycardia/fibrillation to beta-blocker dose maximization guided by pacing mode analysis in nonpacemaker-dependent patients with implantable cardioverter-defibrillator. Am J Cardiol. 2011;107(12):1812–7.
43 Ruwald AC, Gislason GH, Vinther M, Johansen JB, Nielsen JC, Philbert BT, et al. Importance of beta-blocker dose in prevention of ventricular tachyarrhythmias, heart failure hospitalizations, and death in primary prevention implantable cardioverter-defibrillator recipients: a Danish nationwide cohort study. Europace. 2018;20(FI2):f217–24.
44 Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol. 2003;91(6A):2D–8D.
45 Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, et al. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet. 2014;384(9961):2235–43.
46 Cadrin-Tourigny J, Shohoudi A, Roy D, Talajic M, Tadros R, Mondesert B, et al. Decreased mortality with beta-blockers in patients with heart failure and coexisting atrial fibrillation: an AF-CHF substudy. JACC Heart Fail. 2017;5(2):99–106.
47 Lee DS, Tu JV, Juurlink DN, Alter DA, Ko DT, Austin PC, et al. Risk-treatment mismatch in the pharmacotherapy of heart failure. JAMA. 2005;294(10):1240–7.
48 Kotecha D, Manzano L, Krum H, Rosano G, Holmes J, Altman DG, et al. Effect of age and sex on efficacy and tolerability of beta blockers in patients with heart failure with reduced ejection fraction: individual patient data meta-analysis. BMJ. 2016;353:i1855.
49 Molnar AO, Petrcich W, Weir MA, Garg AX, Walsh M, Sood MM. The association of beta-blocker use with mortality in elderly patients with congestive heart failure and advanced chronic kidney disease. Nephrol Dial Transplant. 2020;35(5):782–9.
50 Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709–17.
51 Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348(14):1309–21.
52 Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011;364:1121.
53 Lewis EF, Kim HY, Claggett B, Spertus J, Heitner JF, Assmann SF, et al. Impact of spironolactone on longitudinal changes in health-related quality of life in the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial. Circ Heart Fail. 2016;9(3):e001937.
54 Bapoje SR, Bahia A, Hokanson JE, Peterson PN, Heidenreich PA, Lindenfeld J, et al. Effects of mineralocorticoid receptor antagonists on the risk of sudden cardiac death in patients with left ventricular systolic dysfunction: a meta-analysis of randomized controlled trials. Circ Heart Fail. 2013;6(2):166–73.
55 Schupp T, von Zworowsky M, Reiser L, Abumayyaleh M, Weidner K, Mashayekhi K, et al. Effect of mineralocorticoid receptor antagonists on the prognosis of patients with ventricular tachyarrhythmias. Pharmacology. 2022;107(1–2):35–45.
56 Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, et al. Regional variation in patients and outcomes in the treatment of preserved cardiac function heart failure with an aldosterone antagonist (TOPCAT) trial. Circulation. 2015;131(1):34–42.
57 Kapelios CJ, Murrow JR, Nührenberg TG, Montoro Lopez MN. Effect of mineralocorticoid receptor antagonists on cardiac function in patients with heart failure and preserved ejection fraction: a systematic review and meta-analysis of randomized controlled trials. Heart Fail Rev. 2019;24(3):367–77.
58 Liu T, Korantzopoulos P, Shao Q, Zhang Z, Letsas KP, Li G. Mineralocorticoid receptor antagonists and atrial fibrillation: a metaanalysis. Europace. 2016;18(5):672–8.
59 Akita K, Kohno T, Kohsaka S, Shiraishi Y, Nagatomo Y, Izumi Y, et al. Current use of guideline-based medical therapy in elderly patients admitted with acute heart failure with reduced ejection fraction and its impact on event-free survival. Int J Cardiol. 2017;235:162–8.
60 Ferreira JP, Rossello X, Eschalier R, McMurray JJV, Pocock S, Girerd N, et al. MRAs in elderly HF patients: individual patient-data meta-analysis of RALES, EMPHASIS-HF, and TOPCAT. JACC Heart Fail. 2019;7(12):1012–21.
61 McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martínez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995–2008.

62 Butt JH, Docherty KF, Jhund PS, de Boer RA, Böhm M, Desai AS, et al. Dapagliflozin and atrial fibrillation in heart failure with reduced ejection fraction: insights from DAPA-HF. Eur J Heart Fail. 2022;24(3):513–25.
63 Curtain JP, Docherty KF, Jhund PS, Petrie MC, Inzucchi SE, Køber L, et al. Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest, or sudden death in DAPA-HF. Eur Heart J. 2021;42(36):3727–38.
64 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.
65 Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385(16):1451–61.
66 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.
67 Butt JH, Kondo T, Jhund PS, Comin-Colet J, de Boer RA, Desai AS, et al. Atrial fibrillation and dapagliflozin efficacy in patients with preserved or mildly reduced ejection fraction. J Am Coll Cardiol. 2022;80(18):1705–17.
68 Martinez FA, Serenelli M, Nicolau JC, Petrie MC, Chiang CE, Tereshchenko S, et al. Efficacy and safety of dapagliflozin in heart failure with reduced ejection fraction according to age: insights from DAPA-HF. Circulation. 2020;141(2):100–11.
69 Butt JH, Dewan P, Merkely B, Belohlávek J, Drożdż J, Kitakaze M, et al. Efficacy and safety of dapagliflozin according to frailty in heart failure with reduced ejection fraction: a post hoc analysis of the DAPA-HF trial. Ann Intern Med. 2022;175(6):820–30.
70 Filippatos G, Anker SD, Butler J, Farmakis D, Ferreira JP, Gollop ND, et al. Effects of empagliflozin on cardiovascular and renal outcomes in heart failure with reduced ejection fraction according to age: a secondary analysis of EMPEROR-Reduced. Eur J Heart Fail. 2022;24(12):2297–304.
71 Böhm M, Butler J, Filippatos G, Ferreira JP, Pocock SJ, Abdin A, et al. Empagliflozin improves outcomes in patients with heart failure and preserved ejection fraction irrespective of age. J Am Coll Cardiol. 2022;80(1):1–18.
72 Peikert A, Martinez FA, Vaduganathan M, Claggett BL, Kulac IJ, Desai AS, et al. Efficacy and safety of dapagliflozin in heart failure with mildly reduced or preserved ejection fraction according to age: the DELIVER trial. Circ Heart Fail. 2022;15(10):e010080.
73 Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, et al. Vericiguat in patients with heart failure and reduced ejection fraction. N Engl J Med. 2020;382(20):1883–93.
74 Ponikowski P, Alemayehu W, Oto A, Bahit MC, Noori E, Patel M, et al. Vericiguat in patients with atrial fibrillation and heart failure with reduced ejection fraction: insights from the VICTORIA trial. Eur J Heart Fail. 2021;23(8):1300–12.
75 Hias J, Hellemans L, Walgraeve K, Tournoy J, Vandenbriele C, Van Aelst L, et al. Should vericiguat be initiated in geriatric inpatients with heart failure with reduced ejection fraction and a worsening heart failure event prior to discharge? Eur J Hosp Pharm. 2022; ejhpharm-2022-003305.
76 Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, et al. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. N Engl J Med. 2021;384(2):105–16.
77 Núñez J, Bayés-Genís A, Zannad F, Rossignol P, Núñez E, Bodí V, et al. Long-term potassium monitoring and dynamics in heart failure and risk of mortality. Circulation. 2018;137(13):1320–30.
78 Butler J, Anker SD, Lund LH, Coats AJS, Filippatos G, Siddiqi TJ, et al. Patiromer for the management of hyperkalemia in heart failure with reduced ejection fraction: the DIAMOND trial. Eur Heart J. 2022;43(41):4362–73.
79 Chiang CE, Goethals M, O'Neill JO, Naditch-Brule L, Brette S, Gamra H, et al. Inappropriate use of antiarrhythmic drugs in paroxysmal and persistent atrial fibrillation in a large contemporary international survey: insights from RealiseAF. Europace. 2013;15(12):1733–40.
80 Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002;347(23):1825–33.
81 Køber L, Torp-Pedersen C, McMurray JJ, Gøtzsche O, Lévy S, Crijns H, et al. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med. 2008;358(25):2678–87.
82 Kirchhof P, Camm AJ, Goette A, Brandes A, Eckardt L, Elvan A, et al. Early rhythm-control therapy in patients with atrial fibrillation. N Engl J Med. 2020;383(14):1305–16.
83 Simader FA, Howard JP, Ahmad Y, Saleh K, Naraen A, Samways JW, et al. Catheter ablation improves cardiovascular outcomes in patients with atrial fibrillation and heart failure: a meta-analysis of randomized controlled trials. Europace. 2023;25(2):341–50.
84 Deneer VH, van Hemel NM. Is antiarrhythmic treatment in the elderly different? a review of the specific changes. Drugs Aging. 2011;28(8):617–33.