Journal of the Saudi Heart Association

Manuscript 1375

A Case-Based Implementation of Heart Failure Therapies, A Consensus Pathway by The Saudi Heart Failure Working Group

Abeer Bakhsh

Ibrahim Jelaidan

Ammar Gulzar Chaudhary

Sahar Al Amro

See next page for additional authors

A Case-Based Implementation of Heart Failure Therapies, A Consensus Pathway by The Saudi Heart Failure Working Group

Authors

Abeer Bakhsh, Ibrahim Jelaidan, Ammar Gulzar Chaudhary, Sahar Al Amro, Kamal Alghalayini, Osama Almogbel, Maryam Alqaseer, Hanan B. Albackr, Fayez Elshaer, and Fakhr Al Ayoubi

A Case-based Implementation of Heart Failure Therapies, a Consensus Pathway by the Saudi Heart Failure Working Group

Abeer Bakhsh [a,*], Ibrahim Jelaidan [b], Ammar G. Chaudhary [c], Sahar Al Amro [d], Kamal Alghalayini [e], Osama Almogbel [f], Maryam Alqaseer [g], Hanan B. Albackr [h], Fayez Elshaer [f], Fakhr Al Ayoubi [i]

[a] Heart Function Unit, Prince Sultan Cardiac Centre, Riyadh, Saudi Arabia
[b] Ministry of National Guard Health Affairs, King Saud Bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, Jeddah, Saudi Arabia
[c] Cardiovascular Diseases Department, King Faisal Specialist Hospital and Research Centre, Jeddah, Saudi Arabia
[d] Clinical Pharmacy Department, Prince Sultan Cardiac Centre, Riyadh, Saudi Arabia
[e] King Abdul-Aziz University, Jeddah, Saudi Arabia
[f] King Khaled University Hospital, King Fahad Cardiac Center, King Saud University, Riyadh, Saudi Arabia
[g] King Fahad Specialist Hospital, Dammam, Saudi Arabia
[h] Department of Cardiac Science, College of Medicine, King Saud University, Riyadh, Saudi Arabia
[i] Cardiology Clinical Pharmacist, College of Medicine, Adjunct Assistant Professor, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

Abstract

The implementation of guideline-directed medical therapy (GDMT) in heart failure (HF) has many challenges in real-world clinical practice. The consensus document is written considering the variability of the clinical presentation of HF patients. HF medical therapies need frequent dose adjustment during hospital admission or when patients develop electrolyte imbalance, acute kidney injury, and other acute illnesses. The paper describes clinical scenarios and graphs that will aid the managing physicians in decision-making for HF therapy optimization.

Keywords: Heart failure, GDMT, Hyperkalemia, Hypotension, CKD

1. Introduction

In clinical practice, a gap remains in implementing recommendations for optimizing GDMT for heart failure with reduced ejection fraction (HFrEF), defined as HF with an ejection fraction ≤40% [1,2]. This is due to multiple factors such as a variable patient profile, co-morbidities, difficulty of timely patient follow-up, and the increasing complexity of the treatment regimen [3].

The most recent HFrEF guidelines extend class I recommendations for four categories of HFrEF therapies [2,4,5]. These include the renin-angiotensin-aldosterone system inhibitors (RAASi), beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter 2 inhibitors (SGLT-2i) [4,5]. All of these medications should be initiated and titrated to the maximum tolerated dose to reduce the mortality and morbidity associated with HFrEF [3–5]. Experts suggest that profiling HFrEF patients based on their hemodynamics, renal function, and arrhythmia could aid in optimizing medical therapies [3]. Therefore, we propose algorithms for practical patient-centered initiation of GDMT for HFrEF patients. These algorithms apply to symptomatic HF patients in stage

Received 16 February 2024; revised 28 April 2024; accepted 5 May 2024.
Available online 26 May 2024

* Corresponding author at: Prince Sultan Cardiac Centre, Saudi Arabia.
E-mail address: abirmb@gmail.com (A. Bakhsh).

https://doi.org/10.37616/2212-5043.1375

C, presenting with new-onset (de novo) and chronic HFrEF in outpatient and inpatient settings.

This document aims to overcome common obstacles in optimizing guideline-directed medical therapy and bridge the gap between the evidence and clinical practice in ambulatory and hospitalized patients with HFrEF using typical patient case scenarios.

2. The hemodynamic effects of the guideline-directed medical therapy

The GDMT is shown to reduce cardiovascular mortality and HF hospitalization [4–7]. Key hemodynamic characteristics of the foundational therapies are summarized in Table 1. ARNi causes potent afterload reduction and blood pressure (BP) lowering [8]. It promotes diuresis, and although it may worsen the GFR initially, it preserves kidney function in the long run [9]. It causes less hyperkalemia compared with ACEi [8]. The ACEi and the ARB also reduce afterload and BP, but less when compared with ARNi [8]. The SGLT2i have a minimal effect on BP, promote diuresis, and protect the kidney long-term [10,11]. They may prevent hyperkalemia associated with other agents [12]. MRAs cause little effect on BP and produce no meaningful diuresis at the doses used in the treatment of HF but are associated with hyperkalemia [4,13]. BB causes bradycardia and hypotension (with carvedilol) and can worsen congestion [4,14].

The dose optimization is summarized in Table 2 for renin-angiotensin-aldosterone system inhibitors (RAASi). The common adverse events for RAASi are hypotension, renal impairment, and hyperkalemia. In addition, ARNi and ACEi are associated with angioedema and cough [15]. These agents require BP monitoring during optimization and renal function and potassium level monitoring two to four weeks from initiation and during dose titration.

The dose optimization is summarized in Table 3 for beta-blockers (BB). The common adverse events for BB are hypotension, bradycardia, and dizziness. These agents require BP and heart rate monitoring during optimization and signs of congestion every two weeks from initiation and during dose titration.

The dose optimization is summarized in Table 4 for Mineralocorticoid Receptor Antagonists (MRA).

Table 1. The hemodynamic effect of the guideline-directed medical therapy.

	BP lowering	diuresis	Kidney protection	Hyperkalemia	HR lowering
ARNi	+++	++	++	+	
ACEi/ARB	++		+	++	
SGLT2i	+	+++	+++		
MRA	+	+	+	+++	
BB	+++			+	+++

Table 2. Renin-angiotensin-aldosterone system inhibitors (RAASi).

GDMT Class	Initiation Dose	Target Dose	GDMT Class	Initiation Dose	Target Dose
Sacubitril-Valsartan	50 mg twice daily	200 mg twice daily	Lisinopril	2.5–5 mg daily	20–40 mg daily
Captopril	6.25 mg TID	50 mg TID	Perindopril	5 mg daily	5–10 mg daily
Enalapril	2.5 mg BID	10–20 mg BID	Ramipril	1.25–2.5 mg daily	10 mg daily
Fosinopril	5–10 mg daily	40 mg daily	Valsartan	20–40 mg BID	160 mg BID
Candesartan	4–8 mg daily	32 mg daily			

Table 3. Beta blockers.

GDMT Class	Initiation Dose	Target Dose	GDMT Class	Initiation Dose	Target Dose
Metoprolol succinate/XL	12.5–25 mg daily	200 mg daily	Nebivolol	1.25 mg daily	10 mg daily
Bisoprolol	1.25 mg daily	10 mg daily	Carvedilol	3.125 mg BID	50 mg BID

Table 4. Mineralocorticoid receptor antagonists (MRA).

GDMT Class	Initiation Dose	Targe Dose	GDMT Class	Initiation Dose	Target Dose
Aldactone	12.5–25 mg daily	25–50 mg daily	Eplerenone	25 mg daily	50 mg daily

Table 5. Sodium-glucose cotransporter 2 inhibitors (SGLT-2i).

GDMT Class	Initiation Dose	Maximum Dose	GDMT Class	Initiation Dose	Maximum Dose
Dapagliflozin	10 mg daily	10 mg daily	Empagliflozin	10 mg daily	10 mg daily

The common adverse events for MRAs are renal impairment and hyperkalemia. Gynecomastia is seen with non-selective MRA. These agents require monitoring renal function and potassium levels every two to four weeks from initiation and during dose titration.

Table 5 summarizes the currently approved SGLT-2i. These agents require monitoring of volume status, as the SGLT-2i may reduce the glomerular filtration rate at initiation but have a protective long-term effect on renal function [16,17]. They have a single dose, and no dose titration is required. The common adverse event for SGLT-2i is genital mycotic infection [10].

The dose optimization is summarized in Table 6 for Soluble Guanylate Cyclase (sGC) Stimulators. The common adverse events for (sGC) are hypotension, dyspepsia, nausea, and anemia. These agents require BP monitoring during optimization every two weeks from initiation and during dose titration. It should be used with caution in patients with concomitant nitrates or PDE-5 inhibitors.

Ivabradine is recommended to reduce the heart rate in HFrEF patients with sinus rhythm with a heart rate >75 bmp [5] (Table 7). It has been shown to reduce heart failure hospitalization in patients optimized with a maximum tolerated beta-blocker dose [5].

Potassium binders have growing evidence of effectiveness in controlling potassium levels while patients are on RAASi; thus, they can help optimize the doses of RAASi and MRAs [18–20] (Table 8).

Table 6. Soluble guanylate cyclase (sGC) stimulators.

GDMT Class	Initiation Dose	Maximum Dose
Vericiguat	2.5 mg daily	10 mg daily

Table 7. Ivabradine.

GDMT Class	Initiation Dose	Maximum Dose
Ivabradine	2.5 mg bid	7.5 mg bid

3. The de novo HFrEF patient in ambulatory clinic

3.1. The stages A and B HF

Treatment of HF should start prior to development of left ventricle (LV) dysfunction and HF symptoms [4]. The HF guideline recommend prevention of HF in patients at risk (stage A) through controlling risk factors such as diabetes, hypertension, obesity, chemotherapy and familial disease [4]. The initiation of ACEi and betablockers is recommended in patients with structural abnormality without HF symptoms (stage B) [4].

3.2. The stage C HF profiles

The patient's initial presentation may vary from acute HFrEF with clinical instability to ambulatory compensated presentation. The latter group may include patients without a history of HF symptoms. Such patients are classified as stage B HF, including those diagnosed on surveillance imaging after cancer chemotherapy or post-myocardial infarction [4,5,21]. Patients who have current or previous symptoms of HF are classified as stage C HF [4,5,21]. This distinction is important because patients with stage B HF have generally been excluded from clinical trials of ARNi and SGLT-2i, and the current practice is to treat them with a combination of ACEi and BB [4]. Because of the proven efficacy of SGLT-2i in reducing incident HF in patients with vascular disease and diabetes, we advise using SGLT-2i in patients with stage B HF who have diabetes [22,23]. The aim for patients in stage C HF is to treat them with the four “pillars” of HFrEF, namely ARNi, BB, MRA, and SGLT-2i [4,5]. We propose treatment algorithms and present their rationale to address key clinical scenarios in the outpatient setting for subjects who are newly diagnosed with HFrEF and have not received standard therapies. The following algorithms cover some of the common case scenarios that may present in an outpatient setting for new

Table 8. Potassium binder.

GDMT Class	Initiation Dose	Maximum Dose	GDMT Class	Initiation Dose	Maintenance Dose
Patiromer	8.4 g	25.2 g	sodium zirconium cyclosilicate (SZC)	10 g TID for 48h	10–15 g daily

HFrEF patients (Figs. 1–3). Other case scenarios, such as renal impairment and hyperkalemia, are discussed in the section covering the barriers to optimizing medical therapy. The medication titration selection depends on the patient's volume status, hemodynamics, and renal profile [3,6,15].

3.3. The importance of afterload reduction

Medical therapy initiation and titration will differ based on the patient's hemodynamic profile, renal function, and potassium level [4,5]. All four GDMTs should be initiated and titrated simultaneously if

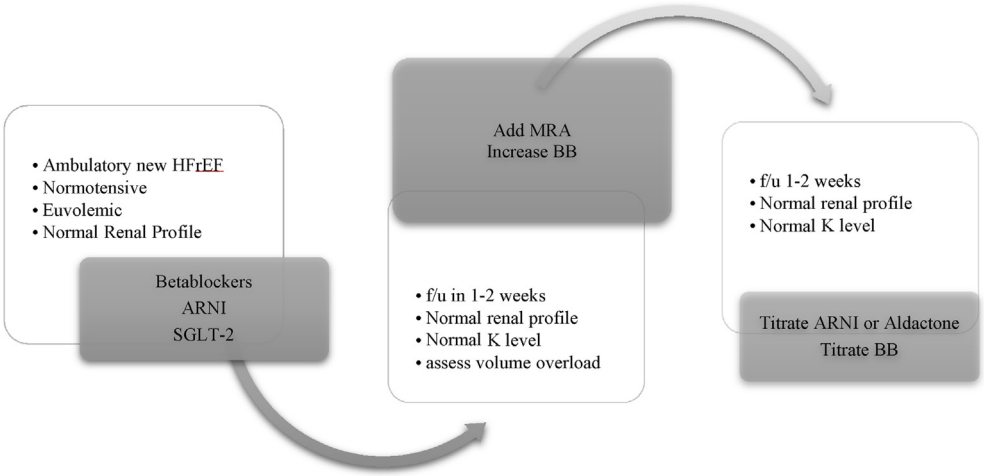

Fig. 1. De Novo HFrEF with euvolemia and Normal blood pressure.

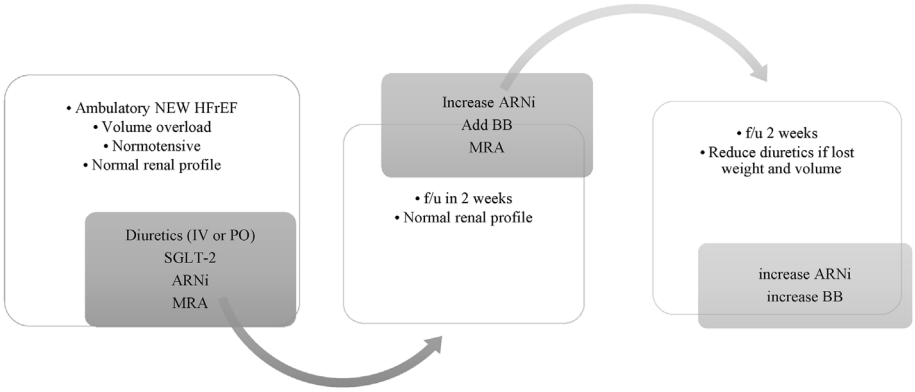

Fig. 2. De Novo HFrEF with volume overload and Normal blood pressure.

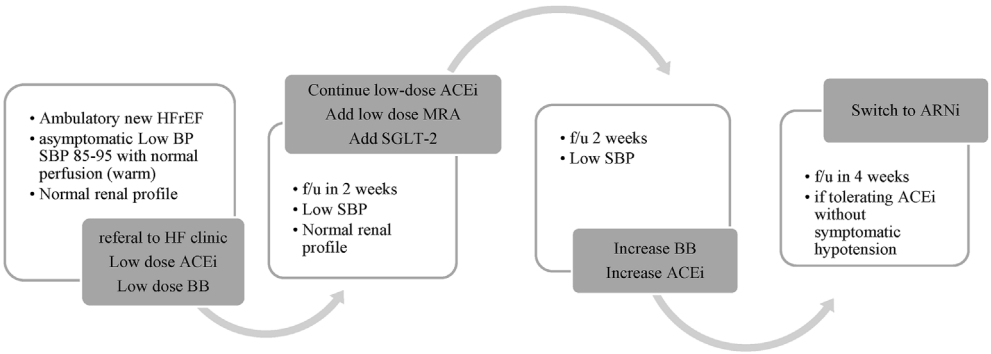

Fig. 3. De Novo HFrEF with euvolemia and low Blood Pressure.

the patient is hemodynamically stable with normal renal function [24]. Initiating GDMT in de novo HFrEF patients depends on their volume status at presentation. In patients who maintain a systolic BP > 90 mmHg, the treatment includes loop diuretics and RAASi inhibitors for afterload reduction. The basis for this recommendation is the rapid improvement in cardiac filling pressures with the use of afterload-reducing therapies in studies that used invasive hemodynamic measurements, along with the large amount of literature that showed the effectiveness of ACEi, ARB, and ARNi in stabilized acute and chronic HFrEF patients [8,24–26]. Afterload-reducing therapies were the first to be rigorously tested for HFrEF, and other agents have usually been evaluated on a background of afterload reduction with a RAASi. Because the use of ARNi was associated with rapid declines in NT-proBNP and improved clinical outcomes within weeks of its initiation compared with ACEi in the pre-discharge and ambulatory settings, ARNi is the preferred RAASi [8,27]. Caution and close follow-up are recommended when using ARNI in borderline SBP <100 mmHg [4–6]. The SGLT-2i can be initiated together with ARNi. The SGLT-2i are well-tolerated and associated with diuresis, weight reduction, and a rapid improvement in clinical outcomes post-discharge [28]. The treatment effect is additive to ARNi, and the therapy is well tolerated with a much smaller effect on blood pressure than ARNi.

3.4. The sequential use of MRA

The early initiation of MRA is also safe and effective in patients who have post-acute coronary syndrome (ACS) and have congestion with low EF, with the effect of treatment becoming apparent very early. A previous trial of MRA in chronic HFrEF had a small percentage of patients who received BBs, and the effect on outcomes was not blunted in a subsequent trial of MRA where the use of BB was higher, suggesting that the benefits of treatments that work through different mechanisms are additive and that the benefits of MRA would be realized even if initiated before BBs [13,29]. In EMPHASIS-HF, background therapy of RAASi was 94%, and BB was 87%, further reducing cardiovascular death and hospitalization at HR 0.63 (0.54–0.74) [30,31]. The MRAs have a higher likelihood of causing hyperkalemia, and because the use of ARNi and SGLT2i has been associated with a lowered risk of hyperkalemia, we recommend that the MRA be initiated after ARNi and SGLT2i in a rapid sequence.

3.5. Hemodynamics and BB

In patients who have low blood pressure (SBP <85) or symptomatic orthostatic hypotension despite ensuring the appropriate diuretic dose, we recommend starting an SGLT2i followed by an MRA. If the orthostatic symptoms resolve, then the conventional sequence of ACEi and BB could be considered. In the presence of volume overload, BBs can worsen congestion. Their initiation could be delayed until the patient is euvolemic [6] (Fig. 2). In the absence of hypervolemia, a BB could also be initiated with a low dose of a short-acting agent such as metoprolol tartrate, which can later be switched to the guideline-approved BBs for HFrEF [6].

3.6. The hypotensive patient

In hypotensive patients, closer follow-up is necessary with a more conservative initiation strategy, but the low blood pressure, particularly in the absence of orthostatic symptoms or advanced renal impairment, should not discourage treating the patient with the quadruple regimen. Symptoms that subside with drug withdrawal or dose reduction should not discourage a future re-challenge with the same agent. In patients with SBP in the 85–95 mm Hg range but without orthostatic symptoms, reassessing the dose of diuretic therapy is necessary to exclude the possibility of hypovolemia. Once it is ensured that diuretic dosing is appropriate, an ACEi can be considered instead of ARNi [8]. ARBs could be used if the ACEi is not tolerated because of cough [4,5]. Once the ACEi or ARB is well tolerated, an early switch to ARNi within 4–8 weeks is recommended while observing the 36-h window for transitioning from an ACEi to ARNi. In patients with low SBP with orthostatic symptoms or SBP <85 mm Hg despite ensuring the appropriate diuretic dose, we recommend starting an SGLT2i followed by an MRA. If the orthostatic symptoms resolve, then the conventional sequence of ACEi and BB could be considered (Fig. 3).

3.7. The natural change in GFR with RAASi and SGLT2i

Close follow-up of hemodynamics, renal profile, and the electrolyte is warranted as worsening of renal function can occur with starting RAASi [32]. Worsening renal function in HFrEF is defined as an increase in serum creatinine by 25% or a reduction in glomerular filtration rate GFR by > 25–30% [15,32]. This should not lead to treatment discontinuation, but rather, close monitoring of renal

profile with caution in up-titration of the dose. The initiation of SGLT-2i is also associated with a transient reduction in GFR [33]. If the reduction in GFR is more than 50%, evaluate for possible renal artery stenosis, excessive hyper- or hypovolemia, and nephrotoxic medication such as Non-Steroidal Anti-inflammatory Drugs (NSAID) [32].

4. The hospitalized HFrEF patient

Patients hospitalized for HF require treatment for volume overload while ensuring end-organ perfusion. The intravenous (IV) loop diuretic therapy dose should be 2.5 times the oral dose at home [5,34]. Intravenous administration of high-dose diuretics is safe and effective in reaching euvolemia within 72 h and improving HF symptoms [34,35]. The efficacy of IV loop diuretic therapy is assessed by urine output (UOP) of >100–150 ml/h and urinary sodium of >50–70meq/L [5]. The loop diuretics should be combined with metolazone or acetazolamide diuretics to improve net fluid decongestion and HF symptoms [5,35]. Adding Acetazolamide to loop diuretics is associated with better decongestion and reduced length of stay [35]. The ADVOR study excluded patients with SBP <90 mmHg, eGFR <20 [35]. The dose of Acetazolamide in the trial was 500 mg IV daily, for 3 days. Target urinary output >3L in 48 h with the resolution of signs and symptoms of congestion [35].

The use of ARNi is safe following an acute decompensation, provided that the patients are not on inotropic support for 24 h, do not require IV vasodilator agents, and are on stable doses of IV diuretic therapy [24]. In the Get With The Guidelines HF registry (GWTG-HF), patients who were newly started on ACEi after hospitalization had lower readmission rates and mortality rates than those who did not receive ACEi on the discharge [36]. Moreover, the early use of empagliflozin in patients with de novo or chronic HF who present with acute decompensated HF is associated with reduced mortality and HF events [28,37]. Using clinical criteria similar to those for ARNi in the acute HF setting, the use of SGLT2i is safe, with less hypotension and acute renal failure compared with placebo [37]. Eplerenone was initiated within 14 days of the index of myocardial infarction with HF on the background of ACEi and BB [38]. There is a significant reduction in mortality and hospitalization with early initiation of mineralocorticoids [29,38]. All three aforementioned classes of therapies yielded improved outcomes within days-weeks of initiation, were well-tolerated, and benefits were observed regardless of background treatment. SGLT2i and MRA had the least effect on blood pressure, and SGLT2i was the best tolerated when interactions with renal function and potassium were considered and were, therefore, the most feasible agents to initiate. BB use predischarge has been shown to reduce mortality and HF readmission [4,14,39]. Extra caution is advised when initiating BB in patients who received inotropes, as clinical euvolemia and a period of 96 h were required after discontinuing inotrope therapy and before the initiation of BB in a key randomized trial of BB [4,40].

We suggest that the treatments that apply to patients in the outpatient setting also apply to the inpatient setting, and to categorize patients based on the key aspects of volume status and blood pressure when deciding the therapy sequence. Because the hospitalized patient with HF is high-risk and typically congested, our proposed strategies for the normotensive/hypervolemic and hypotensive patients discussed above are more relevant to the inpatient setting. Same-day low–dose combination of 2 therapies may be used, although spacing each therapy by 1–3 days may be better tolerated in subjects with borderline physiologic reserve. Up-titration in hospitals has traditionally been cautious, and small doses of multiple agents are better tolerated and likely confer greater benefits when compared with higher doses of 1–2 agents (Fig. 4). Recent data suggests that a strategy of aggressive up-titration pre and post-discharge aided by a close follow-up is well-tolerated and achieves improved outcomes [41].

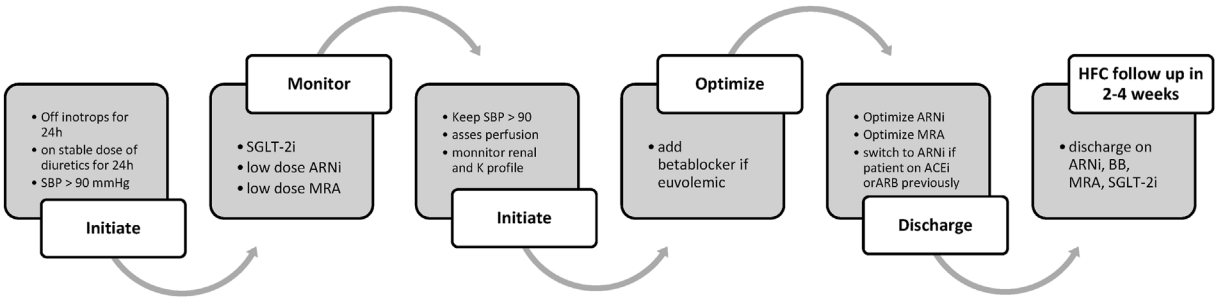

Fig. 4. Case IV: HF management during hospitalization.

5. Optimizing medical therapy in the chronic HFrEF patients

The patient with long-standing HFrEF will have a progressive clinical course over the years. The HFrEF therapies will be frequently adjusted based on hospitalization for decompensated HF, acute non-cardiac illness, or worsening co-morbidities. These patients need closer follow-up, education, and a clear management plan to prevent the discontinuation of GDMT.

The patients with HFrEF need close follow-up and further optimization of the GDMT. The (STRONG-HF) trial has shown that early optimization of medical therapy post-hospitalization or worsening HF symptoms is safe [41]. Intensifying medical therapy within 90 days of worsening HF significantly reduces the HF symptoms and the level of natriuretic peptides (NPs) [41]. The doses should be optimized to the target doses as indicated by HF guidelines even when the patient has clinically improved. The ARNi should be considered in all patients if hemodynamically stable. Especially, predischarge ARNi initiation is associated with a greater reduction of biomarkers, hospitalization, and mortality [7,32]. ARNi is effective at all doses, thus, maintaining ARNi therapy is important [42]. The SGLT-2i is effective in hospitalized HF patients either de novo HF or patients who were already optimized with RAASi, BB, or MRA [37]. The ARNi and SGLT-2i affect natriuresis and gluco-uresis, thus, the dose of the diuretic should be reduced to avoid hypovolemia [7]. In HFrEF, the heart rate is strongly associated with the outcome [6]. Reducing heart rate to less than 70 bpm is related to a decrease in mortality and morbidity [6]. Ivabradine works on the I*f* channel and has been proven to reduce HFrEF hospitalization [6,43]. However, the optimization may be challenging in patients with CKD or with new increases in serum creatinine, hyperkalemia, and hypotension. This may require withholding or down-titrating the dose of GDMT. After maximizing the medical therapy, the LV function evaluation is recommended [4].

6. Managing common barriers to GDMT implementation

6.1. Managing hypotension

New symptomatic hypotension can be due to acute febrile illness, dehydration, medication changes, or worsening HFrEF and low cardiac output. These conditions require reducing or withholding GDMT, mainly RAASi inhibitors or vasodilator therapy, for a limited time [15]. Once the acute episode is resolved, the medicines should be restarted as tolerated, preferably before discharge if the patient was hospitalized.

6.2. Managing tachycardia

In HFrEF, the heart rate is strongly associated with the outcome [6]. Reducing heart rate to less than 70 bpm is related to decreased mortality and morbidity [6] (Fig. 5). Ivabradine works on the I*f* channel and has been proven to reduce HFREF hospitalization [6].

6.3. Renal impairment

HFrEF patients have a high prevalence of chronic kidney disease (CKD), 49% [17]. In the GWTG-HF registry, in patients with CKD stage 3 with a GFR of 44-30 ml/min/m2, the use of GDMT was 15%, while in CKD stage 4 with a GFR of <30 ml/min/m2, the use of GDMT was 5% only [11,44]. The inclusion

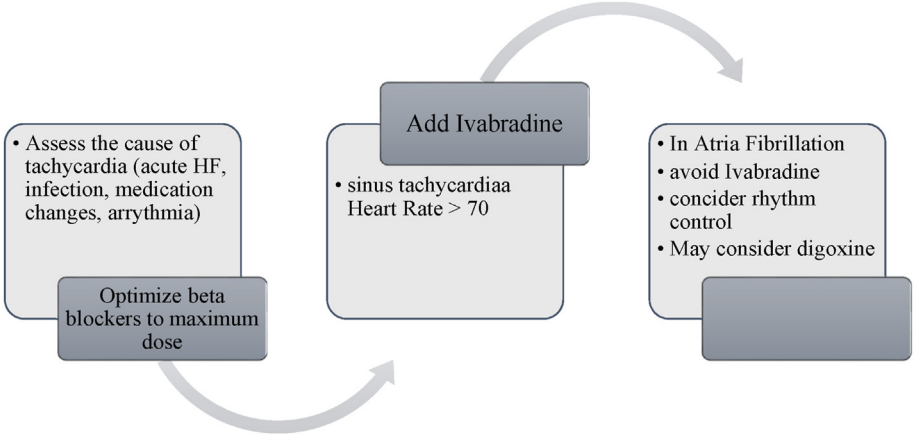

Fig. 5. Case V: Management of tachycardia in HF.

criteria in HF trials for CKD patients used the cutoff GFR of >30 ml/min/m^2. In the SOLVD trial, a small percentage of patients, 9%, had stage 4 CKD [11,25]. The use of ACEi is safe in stage 4 CKD [11]. The use of ARNi in the PARADIGM and PIONEER trials was limited to the GFR >30 ml/min/m^2 [8,24]. There were no significant adverse renal events leading to ARNi discontinuation in either trial [11]. However, the subgroup analysis of patients with CKD in RAASi trials had shown consistent mortality and hospitalization reduction with ACEi 4–13%, ARB 6–24%, and ARNi 27% for GFR 45–59 ml/min/m^2, and 10% for GFR 44-30 ml/min/m^2 with ARNi [9,11,25,26,45–47]. Moreover, the MRA trials in HF had a cutoff GFR >30 ml/min/m^2. The use of MRA is associated with an increase in episodes of hyperkalemia in CKD patients, leading to discontinuation of MRA [11,13,29].

The EMPEROR-reduced and DAPA-HF had excluded patients with a GFR of <20 ml/min/m^2 and <30 ml/min/m^2, respectively [10,37]. Thus, stage 4 CKD was studied in SGLT2i trials and shown to be safe. In addition, the SGLT-2i are protective of the kidneys [11]. They have shown a 44% reduction in a progressive decline in GFR, end-stage renal disease, and cardiovascular mortality in the DAPA-CKD trial [7,48]. Finally, the VICTORIA trial enrolled patients with worsening HF, and Vericiguat can be used at eGFR >15 ml/min/m2 [3,11,49,50]. Fig. 6 represent optimization of GDMT in patients with CKD.

6.4. Hyperkalemia

Hyperkalemia is defined as serum K^+ levels ≥5.0 mEq/L, and it is common in patients with HFrEF, Diabetes, and CKD [51,52]. Hyperkalemia is divided into mild (≥5.0 - < 5.5 mEq/L), moderate (≥5.5- < 6.0 mEq/L), and severe hyperkalemia ≥6 mEq/L that requires emergency department visits [5]. In HF, the renal hypoperfusion reduces sodium load in the distal tubules, leading to less K^+ excretion. In addition, HF patients have the triad of renal impairment; diuretics, RAASi, and BB use can reduce the K^+ shift into the cells [48]. The incidence of hyperkalemia in HF patients ranges from 25% to 40 %, and it is difficult to maintain target serum potassium levels [5,51]. Cardiovascular mortality and HF hospitalization occur more in patients who develop hyperkalemia compared to patients with normal potassium levels [51]. The rate of discontinuation of RAASi due to hyperkalemia was reported to be up to 26% [53]. Among RAASi, ARNi has shown less hyperkalemia than enalapril [3,8]. The prevalence of hyperkalemia >5.5 mEq/L in EPHESUS and EMPHESIS-HF were 16% and 12%, respectively (Field [29,30]. The polymeric potassium binder agent

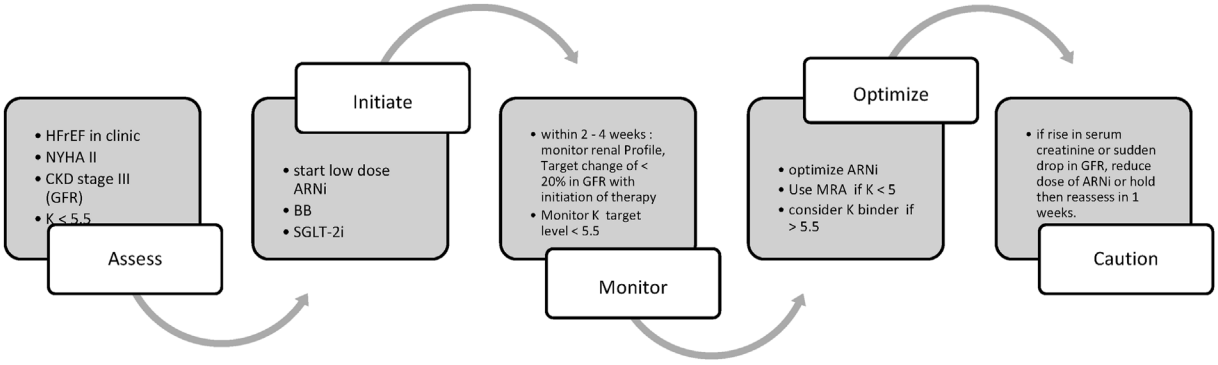

Fig. 6. Case VI: HF management in patients with CKD.

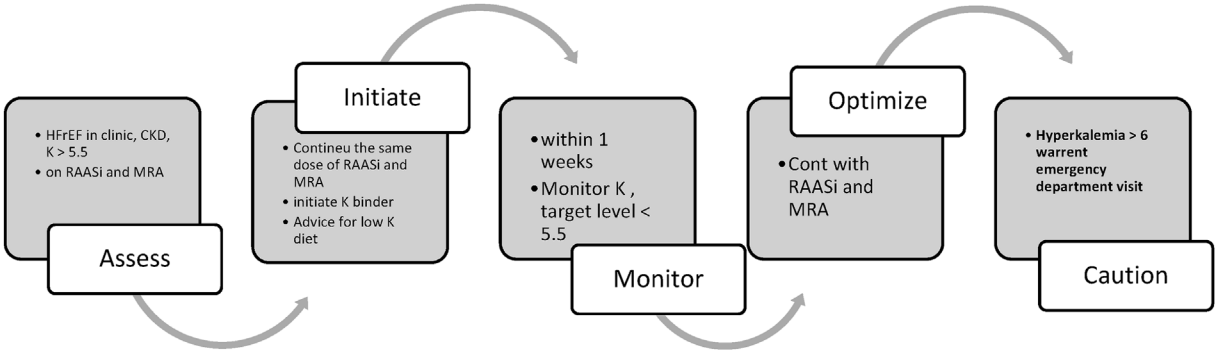

Fig. 7. Case VII: HF management with Hyperkalemia.

studied in the HF population prevents hyperkalemia and ensures the continuation of RAASi and MRA when used for hyperkalemia management [19,54]. The polymeric potassium binder in the OPAL trial was initiated in patients with CKD, Hyperkalemia 5.1–6.5 mEq/L on RAASi therapy [20]. The DIAMOND study looked at patients with hyperkalemia on RAASi or normal potassium levels with a history of RAASi discontinuation due to hyperkalemia [18]. Moreover, the HARMONIZE trial showed the efficacy of sodium zirconium cyclosilicate in reducing serum potassium levels [55]. However, significant edema (6%) with the 10g and (14%) with the 15g dose [55]. Fig. 7 describes the management of hyperkalemia in setting of HF.

6.5. Hyponatremia

Hyponatremia (HN) in HF is a marker of advanced disease and is associated with poor prognosis [4,56]. HN in patients with acute HF hospitalization is associated with a longer length of stay and higher readmission rates [56]. In HF patients, HN can occur due to serum sodium dilution or depletion [57]. The dilutional HN is due to baroreceptor activation and increased release of arginine vasopressin [57]. In addition, renal hypoperfusion increases proximal tubular reabsorption [57]. Serum sodium depletion in HF patients occurs due to exaggerated sodium loss in urine due to diuresis, dietary salt restriction, and intracellular shift with potassium and magnesium deficiency [57]. Monitoring of the urine osmolality is recommended during diuretic therapy in acute HF [5,35,57]. The urine osmolality can differentiate between HN due to sodium dilution or depletion [57]. In sodium depletion HN, the urinary osmolality is < 100 mOsmol/L and urinary sodium is < 50 mEqL [57]. In dilutional HN, the urinary osmolality is > 100 mOsmol/L [57].

The dietary restriction of serum sodium may benefit HF patients with stage C [4,5]. Excessive dietary sodium restriction may lead to poor intake and micronutrient depletion [4]. A registered dietitian-guided sodium diet of 2–3 g/d is recommended in chronic HF patients [4]. For hospitalized patients with symptomatic HN of serum sodium <125 meq, treatment with hypertonic saline with a slow rate of sodium correction of 5 meq/d and consultation with a nephrologist is advised.

6.6. Iron deficiency

Iron deficiency (ID) is associated with mortality, recurrent hospitalization, and lower quality of life in HF patients [58]. The HF patients should be screened for ID with iron, ferritin, and transferrin saturation (TSAT) serum levels [58]. The definition of ID is ferritin <100 ng/ml or ferritin 100–299 ng/ml with a TSAT <20% [5]. Iron replacement is recommended for these patients to improve their quality of life and reduce hospitalization [4,5].

7. The worsening HF patient

There are challenges in accurately defining worsening HF. This reflects the disease trajectory to progressively declining patients with a higher rate of adverse events [59]. The episode of worsening HF needs objective evidence of the signs and symptoms of the deteriorating clinical condition, including volume overload and increased biomarkers [4,60]. In addition, there is a need for acute treatments such as an increase in oral diuretic dose, administration of intravenous diuretics, and hospitalization for intravenous vasodilators and inotropes [4]. The addition of Vericiguat, an sGC stimulant, is recommended for patients with worsening HF with the maximum tolerated medical therapy [4,5]. The variegate can be

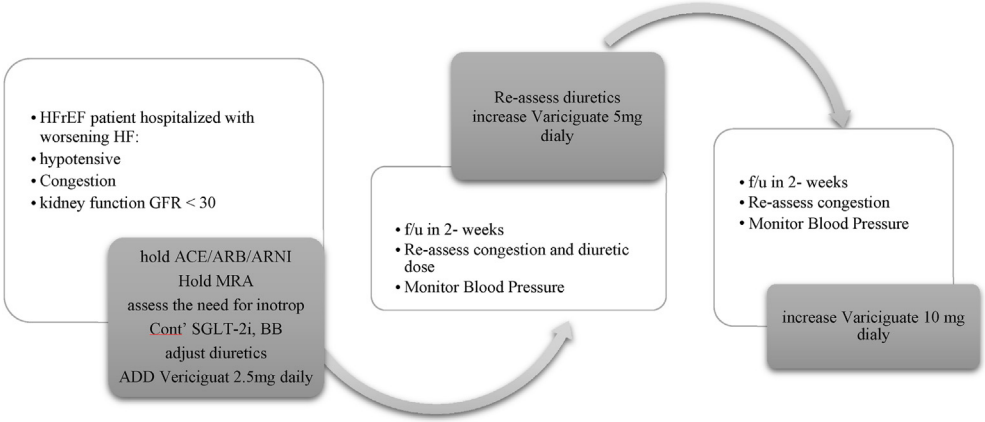

Fig. 8. Case VIII: Management of the worsening HF.

considered an additional therapy in patients hospitalized with HF or outpatients with New York Heart Association (NYHA) Class II-IV [2,49,50] (Fig. 8).

8. Cardiac resynchronization therapy in HF

Cardiac resynchronization therapy (CRT) has been shown to reduce mortality and morbidity in HF [2]. The CRT is indicated in symptomatic HFrEF with LVEF <35%, with left bundle branch block and QRS duration of >150 ms after optimizing medical therapy [2].

9. The advanced HF patient

The HF patients will progress to advanced stage D when they need to be evaluated for a heart transplant or durable left ventricle assist device. The following are the criteria that should prompt the referral for advanced HF therapies: NYHA III with recurrent emergency department visit >1 in 6 months, or recurrent hospital admission for HF, an escalating dose of diuretics, intolerant to medical therapy, inotrope dependent and refractory ventricular arrhythmia [2,4,5].

10. The improved LVEF

The HF with improved LVEF (HFimpEF) is defined as HF with previous LVEF <40%, with improved LVEF >40% on follow-up [4]. The GDMT must continue post-improvement of LVEF. Studies have shown that discontinuation of medical therapy is associated with deterioration of LV function and rebound HF symptoms [61,62]. In TRED-HF, the rate of relapse was 36% after the discontinuation of medical therapy. In patients with reversible causes of cardiomyopathy, such as myocarditis or peripartum cardiomyopathy, the withdrawal of medical therapy is uncertain [61].

11. Summary

The GDMT optimizing sequence is based on the evidence, the pathophysiology of HF, and the patient profiles. Table 9 summarizes the case-based approach to implementing GDMT.

Table 9. Summary of the GDMT implementation sequence.

Scenario	Proposed Sequence
Adequate/High BP with congestion	ARNi, SGLT2i, MRA, BB
Low blood pressure with congestion	SGLT2i, MRA, RAASi (ARNi or ACEi), BB
Tachycardia	If congestion excluded, BB
Tendency for Hyperkalemia	SGLT2i and ARNi, K binders
Renal Impairment	SGLT2i, ARNi, BB

12. Conclusion

Profiling HFrEF patients based on their hemodynamics, renal function, and arrhythmia could aid in optimizing medical therapies [3]. The proposed algorithms for practical patient-centered initiation of GDMT for HFrEF patients facilitate management with guideline-directed medical therapy. These algorithms apply to symptomatic HF patients in stage C, presenting with new-onset (de novo) and chronic HFrEF in outpatient and inpatient settings.

Author contribution

Conception and design of Study: AB, IAJ. Literature review: AB, IAJ, AGC, SAA. Acquisition of data: AB, IAJ, AGC, SAA. Drafting of manuscript: AB, IAJ, AGC, SAA, KA. Revising and editing the manuscript critically for important intellectual contents: OA, MA, HBA, FE, FAA. Research coordination and management: AB.

Conflict of interest

None.

References

[1] Dunlay SM, Killian JM, Roger VL, Schulte PJ, Blecker SB, Savitz ST, et al. Guideline-directed medical therapy in newly diagnosed heart failure with reduced ejection fraction in the Community. J Card Fail 2022;28(10):1500–8. https://doi.org/10.1016/j.cardfail.2022.07.047.

[2] Waleed Al Habeeb AT, Elasfar Abdelfatah, Ali ALmasood, Bakhshi Abeer, Elshaer Fayez, Al Fakhr, et al. 2023 national heart center/Saudi heart association focused update of the 2019 Saudi heart association guidelines for the management of heart failure. 2212-5043/© 2023 Saudi heart association. 2023. https://doi.org/10.37616/2212-5043.1334.

[3] Rosano GMC, Moura B, Metra M, Bohm M, Bauersachs J, Ben Gal T, et al. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2021;23(6):872–81. https://doi.org/10.1002/ejhf.2206.

[4] Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: executive summary: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. J Am Coll Cardiol 2022;79(17):1757–80. https://doi.org/10.1016/j.jacc.2021.12.011.

[5] McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm 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. https://doi.org/10.1093/eurheartj/ehab368.

[6] Writing C, Maddox TM, Januzzi Jr JL, Allen LA, Breathett K, Butler J, et al. 2021 update to the 2017 acc expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American college of cardiology solution set oversight committee. J Am Coll Cardiol 2021;77(6):772–810. https://doi.org/10.1016/j.jacc.2020.11.022.

[7] McDonald M, Virani S, Chan M, Ducharme A, Ezekowitz JA, Giannetti N, et al. CCS/CHFS heart failure guidelines

update: defining a new pharmacologic standard of care for heart failure with reduced ejection fraction. Can J Cardiol 2021;37(4):531–46. https://doi.org/10.1016/j.cjca.2021.01.017.
[8] 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. https://doi.org/10.1056/NEJMoa1409077.
[9] Damman K, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz MP, et al. Renal effects and associated outcomes during angiotensin-neprilysin inhibition in heart failure. JACC Heart Fail 2018;6(6):489–98. https://doi.org/10.1016/j.jchf.2018.02.004.
[10] McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381(21):1995–2008. https://doi.org/10.1056/NEJMoa1911303.
[11] Beldhuis IE, Lam CSP, Testani JM, Voors AA, Van Spall HGC, Ter Maaten JM, et al. Evidence-based medical therapy in patients with heart failure with reduced ejection fraction and chronic kidney disease. Circulation 2022;145(9): 693–712. https://doi.org/10.1161/CIRCULATIONAHA.121.052792.
[12] Neuen BL, Oshima M, Agarwal R, Arnott C, Cherney DZ, Edwards R, et al. Sodium-glucose cotransporter 2 inhibitors and risk of hyperkalemia in people with type 2 diabetes: a meta-analysis of individual participant data from randomized, controlled trials. Circulation 2022;145(19):1460–70. https://doi.org/10.1161/CIRCULATIONAHA.121.057736.
[13] 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. https://doi.org/10.1056/NEJM199909023411001.
[14] Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Carvedilol use at discharge in patients hospitalized for heart failure is associated with improved survival: an analysis from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). Am Heart J 2007; 153(1):82 e1–e11. https://doi.org/10.1016/j.ahj.2006.10.008.
[15] Yancy CW, Januzzi Jr JL, Allen LA, Butler J, Davis LL, Fonarow GC, et al. 2017 acc expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American college of cardiology task force on expert consensus decision pathways. J Am Coll Cardiol 2018; 71(2):201–30. https://doi.org/10.1016/j.jacc.2017.11.025.
[16] 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. https://doi.org/10.1056/NEJMoa2206286.
[17] Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020; 383(15):1436–46. https://doi.org/10.1056/NEJMoa2024816.
[18] Butler J, Anker SD, Siddiqi TJ, Coats AJS, Dorigotti F, Filippatos G, et al. Patiromer for the management of hyperkalaemia in patients receiving renin-angiotensin-aldosterone system inhibitors for heart failure: design and rationale of the DIAMOND trial. Eur J Heart Fail 2022;24(1): 230–8. https://doi.org/10.1002/ejhf.2386.
[19] Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. Eur Heart J 2011;32(7):820–8. https://doi.org/10.1093/eurheartj/ehq502.
[20] Weir MR, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med 2015; 372(3):211–21. https://doi.org/10.1056/NEJMoa1410853.
[21] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, 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. https://doi.org/10.1002/ejhf.592.
[22] Ferreira JP, Kraus BJ, Zwiener I, Lauer S, Zinman B, Fitchett DH, et al. Cardio/kidney composite end points: a post hoc analysis of the EMPA-REG outcome trial. J Am Heart Assoc 2021;10(7): e020053. https://doi.org/10.1161/JAHA.120.020053.
[23] Verma S, Leiter LA, Zinman B, Sharma A, Mattheus M, Fitchett D, et al. Time to cardiovascular benefits of empagliflozin: a post hoc observation from the EMPA-REG OUTCOME trial. ESC Heart Fail 2021;8(4):2603–7. https://doi.org/10.1002/ehf2.13374.
[24] Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al. Angiotensin-Neprilysin inhibition in acute decompensated heart failure. N Engl J Med 2019;380(6):539–48. https://doi.org/10.1056/NEJMoa1812851.
[25] Investigators S, Yusuf S, Pitt B, Davis CE, Hood Jr WB, Cohn JN. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327(10): 685–91. https://doi.org/10.1056/NEJM199209033271003.
[26] Group CTS. Effects of enalapril on mortality in severe congestive heart failure. Results of the cooperative north scandinavian enalapril survival study (CONSENSUS). N Engl J Med 1987;316(23):1429–35. https://doi.org/10.1056/NEJM198706043162301.
[27] Myhre PL, Prescott MF, Claggett B, Felker GM, Butler J, Pina IL, et al. Comparative effect of angiotensin receptor neprilysin inhibition on B-type natriuretic peptide levels measured by three different assays: the PROVE-HF study. Clin Chem 2022; 68(11):1391–8. https://doi.org/10.1093/clinchem/hvac148.
[28] Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med 2021;384(2): 117–28. https://doi.org/10.1056/NEJMoa2030183.
[29] Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364(1): 11–21. https://doi.org/10.1056/NEJMoa1009492.
[30] Eschalier R, McMurray JJ, Swedberg K, van Veldhuisen DJ, Krum H, Pocock SJ, et al. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization and SurvIval Study in Heart Failure). J Am Coll Cardiol 2013; 62(17):1585–93. https://doi.org/10.1016/j.jacc.2013.04.086.
[31] Shen L, Jhund PS, Docherty KF, Vaduganathan M, Petrie MC, Desai AS, et al. Accelerated and personalized therapy for heart failure with reduced ejection fraction. Eur Heart J 2022;43(27): 2573–87. https://doi.org/10.1093/eurheartj/ehac210.
[32] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Rev Esp Cardiol 2016;69(12):1167. https://doi.org/10.1016/j.rec.2016.11.005.
[33] Packer M, Butler J, Zannad F, Pocock SJ, Filippatos G, Ferreira JP, et al. Empagliflozin and major renal outcomes in heart failure. N Engl J Med 2021;385(16):1531–3. https://doi.org/10.1056/NEJMc2112411.
[34] Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364(9): 797–805. https://doi.org/10.1056/NEJMoa1005419.
[35] Mullens W, Dauw J, Martens P, Verbrugge FH, Nijst P, Meekers E, et al. Acetazolamide in acute decompensated heart failure with volume overload. N Engl J Med 2022; 387(13):1185–95. https://doi.org/10.1056/NEJMoa2203094.
[36] Gilstrap LG, Fonarow GC, Desai AS, Liang L, Matsouaka R, DeVore AD, et al. Initiation, continuation, or withdrawal of

angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and outcomes in patients hospitalized with heart failure with reduced ejection fraction. J Am Heart Assoc 2017;6(2). https://doi.org/10.1161/JAHA.116.004675.

[37] Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nat Med 2022;28(3):568–74. https://doi.org/10.1038/s41591-021-01659-1.

[38] 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. https://doi.org/10.1056/NEJMoa030207.

[39] Hernandez AF, Hammill BG, O'Connor CM, Schulman KA, Curtis LH, Fonarow GC. Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (organized program to initiate lifesaving treatment in hospitalized patients with heart failure) registry. J Am Coll Cardiol 2009;53(2):184–92. https://doi.org/10.1016/j.jacc.2008.09.031.

[40] Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation 2002;106(17):2194–9. https://doi.org/10.1161/01.cir.0000035653.72855.bf.

[41] Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. Lancet 2022;400(10367):1938–52. https://doi.org/10.1016/S0140-6736(22)02076-1.

[42] DeVore AD, Braunwald E, Morrow DA, Duffy CI, Ambrosy AP, Chakraborty H, et al. Initiation of angiotensin-neprilysin inhibition after acute decompensated heart failure: secondary analysis of the open-label extension of the PIONEER-HF trial. JAMA Cardiol 2020;5(2):202–7. https://doi.org/10.1001/jamacardio.2019.4665.

[43] Chaudhary AG, Alreefi FM, Aziz MA. Emerging pharmacologic therapies for heart failure with reduced ejection fraction. CJC Open 2021;3(5):646–57. https://doi.org/10.1016/j.cjco.2021.01.006.

[44] Patel RB, Fonarow GC, Greene SJ, Zhang S, Alhanti B, DeVore AD, et al. Kidney function and outcomes in patients hospitalized with heart failure. J Am Coll Cardiol 2021;78(4):330–43. https://doi.org/10.1016/j.jacc.2021.05.002.

[45] Bowling CB, Sanders PW, Allman RM, Rogers WJ, Patel K, Aban IB, et al. Effects of enalapril in systolic heart failure patients with and without chronic kidney disease: insights from the SOLVD Treatment trial. Int J Cardiol 2013;167(1):151–6. https://doi.org/10.1016/j.ijcard.2011.12.056.

[46] Kiernan MS, Gregory D, Sarnak MJ, Rossignol P, Massaro J, Kociol R, et al. Early and late effects of high- versus low-dose angiotensin receptor blockade on renal function and outcomes in patients with chronic heart failure. JACC Heart Fail 2015;3(3):214–23. https://doi.org/10.1016/j.jchf.2014.11.004.

[47] Lesogor A, Cohn JN, Latini R, Tognoni G, Krum H, Massie B, et al. Interaction between baseline and early worsening of renal function and efficacy of renin-angiotensin-aldosterone system blockade in patients with heart failure: insights from the Val-HeFT study. Eur J Heart Fail 2013;15(11):1236–44. https://doi.org/10.1093/eurjhf/hft089.

[48] Sweitzer NK, Airhart S. New therapeutic target in heart failure: achieving and maintaining normokalemia. Circulation 2018;137(13):1331–3. https://doi.org/10.1161/CIRCULATIONAHA.118.033854.

[49] Armstrong PW, Roessig L, Patel MJ, Anstrom KJ, Butler J, Voors AA, et al. A multicenter, randomized, double-blind, placebo-controlled trial of the efficacy and safety of the oral Soluble guanylate Cyclase stimulator: the VICTORIA trial. JACC Heart Fail 2018;6(2):96–104. https://doi.org/10.1016/j.jchf.2017.08.013.

[50] 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. https://doi.org/10.1056/NEJMoa1915928.

[51] Jain N, Kotla S, Little BB, Weideman RA, Brilakis ES, Reilly RF, et al. Predictors of hyperkalemia and death in patients with cardiac and renal disease. Am J Cardiol 2012;109(10):1510–3. https://doi.org/10.1016/j.amjcard.2012.01.367.

[52] AlSahow A, AbdulShafy M, Al-Ghamdi S, AlJoburi H, AlMogbel O, Al-Rowaie F, et al. Prevalence and management of hyperkalemia in chronic kidney disease and heart failure patients in the Gulf Cooperation Council (GCC). J Clin Hypertens 2023;25(3):251–8. https://doi.org/10.1111/jch.14633.

[53] Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. Am J Manag Care 2015;21(11 Suppl):S212–20.

[54] Pitt B, Bakris GL, Weir MR, Freeman MW, Lainscak M, Mayo MR, et al. Long-term effects of patiromer for hyperkalaemia treatment in patients with mild heart failure and diabetic nephropathy on angiotensin-converting enzymes/angiotensin receptor blockers: results from AMETHYST-DN. ESC Heart Fail 2018;5(4):592–602. https://doi.org/10.1002/ehf2.12292.

[55] Kosiborod M, Rasmussen HS, Lavin P, Qunibi WY, Spinowitz B, Packham D, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. JAMA 2014;312(21):2223–33. https://doi.org/10.1001/jama.2014.15688.

[56] Dunlap ME, Hauptman PJ, Amin AN, Chase SL, Chiodo 3rd JA, Chiong JR, et al. Current management of hyponatremia in acute heart failure: a report from the hyponatremia registry for patients with euvolemic and hypervolemic hyponatremia (HN registry). J Am Heart Assoc 2017;6(8). https://doi.org/10.1161/JAHA.116.005261.

[57] Verbrugge FH, Steels P, Grieten L, Nijst P, Tang WH, Mullens W. Hyponatremia in acute decompensated heart failure: depletion versus dilution. J Am Coll Cardiol 2015;65(5):480–92. https://doi.org/10.1016/j.jacc.2014.12.010.

[58] Beavers CJ, Ambrosy AP, Butler J, Davidson BT, Gale SE, Pina IL, et al. Iron deficiency in heart failure: a scientific statement from the heart failure society of America. J Card Fail 2023;29(7):1059–77. https://doi.org/10.1016/j.cardfail.2023.03.025.

[59] Tavazzi L, Senni M, Metra M, Gorini M, Cacciatore G, Chinaglia A, et al. Multicenter prospective observational study on acute and chronic heart failure: one-year follow-up results of IN-HF (Italian Network on Heart Failure) outcome registry. Circ Heart Fail 2013;6(3):473–81. https://doi.org/10.1161/CIRCHEARTFAILURE.112.000161.

[60] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013;128(16):1810–52. https://doi.org/10.1161/CIR.0b013e31829e8807.

[61] Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. Lancet 2019;393(10166):61–73. https://doi.org/10.1016/S0140-6736(18)32484-X.

[62] Bakhsh A, Thanassoulis G, Engert JC, Elstein E, Huynh T, Giannetti N. P253 Withdrawal of beta- blockers and ACE inhibitors after left ventricular systolic function recovery in patient with dilated cardiomyopathy randomized control trial. Eur Heart J 2020;41(Supplement_1). https://doi.org/10.1093/ehjci/ehz872.081.