Tailoring guideline-directed medical therapy in heart failure with reduced ejection fraction: A practical guide

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ABSTRACT

According to the 2021 European Society of Cardiology guidelines, the four pillars of medical therapy in heart failure with reduced ejection fraction (HFrEF) include sodium-glucose co-transporter-2 inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and angiotensin-converting enzyme inhibitors or angiotensin receptor-neprilysin inhibitors. However, in clinical practice, concomitant use of all four drug groups in target doses is often limited by their intolerance or fear of potential complications. Herein, we present strategies to initiate or modify HFrEF therapy in frequent but challenging clinical scenarios (symptomatic hypotension, atrial fibrillation, kidney disease or worsening renal function, hyperkalemia) in a way that does not lead to unnecessary reduction or cessation of life-saving treatment.

Key words: atrial fibrillation, hyperkalemia, hypotension, therapy optimization, worsening kidney function

INTRODUCTION

The 2021 European Society of Cardiology (ESC) guidelines have changed the algorithm of pharmacotherapy in heart failure with reduced ejection fraction (HFrEF) [1]. Apart from introducing sodium-glucose co-transporter-2 inhibitors (SGLT2i) as the fourth pillar of guideline-directed medical therapy (GDMT) in HFrEF, they have switched from a clearly outlined stepwise approach (with angiotensin-converting enzyme inhibitors [ACEi] and beta-blockers initiated in step 1, and mineralocorticoid receptor antagonists [MRA] in step 2) to a more general recommendation to implement the "fantastic four" (ACEi/angiotensin receptor-neprilysin inhibitors [ARNI], beta-blockers, MRA, and SGLT2i) in every patient with HFrEF [1, 2]. This has triggered a considerable debate about whether those four drug groups should be initiated simultaneously or stepwise, given their effects on hemodynamics, renal function, and potassium levels [3, 4]. In HFrEF, atrial fibrillation (AF), symptomatic hypotension, kidney disease, and hyperkalemia are common problems, which may mandate a modification in GDMT [5]. However, HFrEF patients mustn't be denied life-prolonging medications simply due to fear of their adverse effects in the setting of comorbidities or complications. Recently, consensus documents of the Heart Failure Association of the ESC have addressed common problems encountered in patients with HFrEF [5, 6]. Still, non-HF specialists often have concerns regarding full GDMT implementation and feel overwhelmed by the abundance of additional medications that may be indicated in HFrEF.

This practical guide aims to help non-HF specialists (general practitioners, internal medicine specialists, cardiologists, geriatricians, pulmonologists, nephrologists, and other physicians taking care of HFrEF patients) to develop an individualized approach to HFrEF pharmacotherapy based on patient clinical profiling.

INITIATION OF GDMT IN HFREF: GENERAL STRATEGY AND SPECIFIC SITUATIONS

If feasible, simultaneous initiation of drugs from all four groups (ACEi/ARNI, beta-blockers,

MRA, and SGLT2i) is advisable [3]. In fact, simultaneous initiation with rapid up-titration of GDMT has proven safe and is superior to sequential introduction with slow, stepwise titration, shortening the time required to reach the target doses of disease-modifying drugs [7]. Given that the reduction in cardiovascular endpoints with GDMT occurs as early as 2–6 weeks after its initiation, delaying its introduction with the traditional stepwise approach seems unjustified [7–10]. Notably, ARNI may be considered as first-line therapy in ACEi-naïve HFrEF patients, and such a strategy with cautious stepwise ARNI up-titration was proven safe and effective [1, 11–13]. Importantly, the STRONG-HF trial has demonstrated that rapid up-titration of GDMT in patients with acute HF reduces the risk of all-cause death or HF readmission in post-discharge follow-up [14].

Symptomatic hypotension

Still, some patients will not tolerate simultaneous introduction and/or up-titration of all four GDMT drug groups. One of the main barriers, especially in advanced HFrEF or in older, fragile patients is symptomatic hypotension. The prevalence of hypotension in HF is reported in 10-15% of clinical trials; however, it is significantly higher in routine clinical practice [15]. In the WET-HF registry, in patients discharged after HFrEF decompensation, 35% had systolic blood pressure (BP) lower than 100 mm Hg, and the GDMT prescription rate in those patients was 63% [16]. ARNI should not be introduced if systolic blood pressure (BP) is lower than 100 mm Hg [5]. Symptomatic hypotension may also hinder initiation/up-titration of ACEi and beta-blockers, while SGLT2i and MRA have only a modest effect on BP [5]. Among MRA, eplerenone might be preferred in the setting of hypotension, given its lower antihypertensive potency compared to spironolactone [17, 18]. Within beta-blockers, bisoprolol or metoprolol CR/XL may be preferred in hypotensive patients over vasodilating beta-blockers, especially if the heart rate (HR) exceeds 70 bpm. In patients with sinus rhythm and HR over 70 bpm., ivabradine may be added if beta-blockers cannot be up-titrated due to symptomatic hypotension [5]. In contrast to sinus rhythm, there is no evidence for a prognostic benefit of beta-blockers in HFrEF with atrial fibrillation (AF), and HR of <70 bpm has been associated with unfavorable outcomes [19, 20]. Thus, in hypotensive HFrEF patients with AF, beta-blockers may be reduced or even discarded, with digoxin used for rate control if needed (maintaining a ventricular rate of >70 bpm) [5]. This approach may allow initiation and up-titration of ACEi/ARNI.

Chronic kidney disease

Another common problem in HFrEF is chronic kidney disease (CKD), which affects up to half of all HFrEF patients [21]. In CKD patients, a common concern is an anticipated, further decrease in estimated glomerular filtration rate (eGFR) and a rise in serum potassium after initiation of renin-angiotensin-aldosterone system inhibitors (RAASi). In the ESC HF Long-Term registry, serum potassium ≥5.0 mmol/l was present in 16%, and ≥5.5 mmol/l — in 3.5% of chronic HF patients [22]. In long-term follow-up, approximately one-quarter of HF patients develop hyperkalemia [23]. However, given that CKD is associated with a doubled risk of all-cause death in HFrEF (and thus constitutes a stronger prognostic factor than left ventricular ejection fraction), HFrEF patients with concomitant CKD are most likely to benefit from GDMT [24]. Furthermore, most of the HFrEF "fantastic four" (namely ACEi/ARNI and SGLT2i) exert not only cardioprotective but also nephroprotective actions [25-28]. Thus, while contraindications should, naturally, be followed (MRA contraindicated with eGFR of <30 ml/min/1.73 m^2, dapagliflozin — with eGFR of <25 ml/min/1.73 m^2, and empagliflozin — with eGFR of <20 ml/min/1.73 m^2), HFrEF patients with CKD should not be denied life-saving pharmacotherapy for HFrEF, and GDMT should be implemented and cautiously up-titrated in those patients [6]. Importantly, a drop in eGFR after introduction of RAASi and SGLT2i is not only acceptable (and with no need for RAASi dose reduction unless a rise in creatinine exceeds 50% from baseline) but actually indicative of a more potent nephroprotective effect, as it results from lowering the hydrostatic pressure in glomerulus due to predominant vasodilation of *vas efferens* with ACEi and SGLT2i [6]. Reduction of intraglomerular hypertension initially manifests itself as lower glomerular filtration but, over time, protects the kidneys from glomerular loss and, thus, reduces the slope of eGFR decline. In HF, this positive effect on eGFR slope is most evident with SGLT2i, strong with ARNI, and for ACEi and angiotensin receptor blockers — observed only in those with diabetes [6, 25–30].

Table 1 presents the recommended approaches to GDMT initiation in HFrEF patients, depending on clinical profiles.

ADJUSTING DIURETIC THERAPY IN HFREF

Although they are not disease-modifying drugs, diuretics are a mainstay of HF therapy. Diuretics are recommended in HFrEF patients with symptoms and/or signs of congestion to alleviate symptoms and reduce HF hospitalization admissions [1]. Diuretic therapy aims to achieve and maintain euvolemia with the lowest diuretic dose. Complete diuretic withdrawal is also a viable option in stable euvolemic HFrEF patients [31]. Achieving and maintaining euvolemia is important, not solely for improving symptom control and quality of life, but also for prognosis, and even residual congestion after HF decompensation was shown to be associated with adverse outcomes [31, 32].

Loop diuretics are the first-line treatment used for decongestion. In acute, congested HFrEF patients, they are given intravenously, and their efficacy should be monitored with systematic measurements of urine output and sodium excretion (urine spot analysis). Inadequate diuresis and/or sodium excretion dictates doubling the dose of a loop diuretic, repeated until the maximum dose has been

Table 1. Initiation of guideline-directed medical therapy in heart failure with reduced ejection fraction depending on the patient's clinical profile

Clinical profile of a HFrEF patient	ACEi / ARNI	BB	MRA	SGLT2i	Other agents
Sinus rhythm					
Sinus rhythm, normotension, normocardia, eGFR >60 ml/min/1.73 m^2, normokalemia	ACEi[1] → ARNI *or* ARNI[2]	BB[3]	MRA[4]	SGLT2i[5]	Loop diuretic[6] (if congested)
Sinus rhythm, SBP <100 mm Hg, HR >70 bpm, eGFR >60 ml/min/1.73 m^2, normokalemia	ACEi ARNI	BB (bisoprolol or metoprolol CR/XL may be preferred)	MRA (eplerenone may be preferred)	SGLT2i	Ivabradine Loop diuretic (if congested)
Sinus rhythm, SBP <100 mm Hg, HR <70 bpm, eGFR >60 ml/min/1.73 m^2, normokalemia	ACEi ARNI	BB	MRA (eplerenone may be preferred)	SGLT2i	Loop diuretic (if congested)
Atrial fibrillation					
Non-paroxysmal AF, normotension, eGFR >60 ml/min/1.73 m^2, normokalemia	ACEi → ARNI *or* ARNI	BB (for rate control)	MRA	SGLT2i	OAC[7] Digoxin (if needed for rate control) Loop diuretic (if congested)
Non-paroxysmal AF, SBP <100 mm Hg, eGFR >60 ml/min/1.73 m^2, normokalemia	ACEi ARNI	BB (can be discarded)	MRA (eplerenone may be preferred)	SGLT2i	OAC Digoxin (if needed for rate control) Loop diuretic (if congested)
Kidney disease and hyperkalemia					
Sinus rhythm, normotension, normocardia, eGFR 30–60 ml/min/1.73 m^2	ACEi → ARNI *or* ARNI	BB	MRA (initiate triple therapy with ACEi/ARNI + BB + SGLT2i → in 1–2 weeks if eGFR >30 ml/min/1.73 m^2 and K+ <5.0 mmol/l → add MRA)	SGLT2i	Loop diuretic (if congested)
Sinus rhythm, normotension, normocardia, eGFR 15–30 ml/min/1.73 m^2	ACEi ARNI[8]	BB	MRA	SGLT2i (empagliflozin when eGFR >20 ml/min/1.73m^2; dapagliflozin when eGFR >25 ml/min/1.73 m^2)	Loop diuretic (if congested)
Sinus rhythm, normotension, normocardia, eGFR <15 ml/min/1.73 m^2	ACEi ARNI	BB	MRA	SGLT2i	Hydralazine or isosorbide dinitrate (may be considered)
Sinus rhythm, normotension, normocardia, hyperkalemia	ACEi / ARNI (do not initiate if K+ >5.4 mmol/l)	BB	MRA (do not initiate if K+ >5.0 mmol/l)	SGLT2i	K$^+$ binders[9] Loop diuretic

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter-2 inhibitor; HR, heart rate; bpm, beats per minute; SBP, systolic blood pressure; AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; OAC, oral anticoagulant; K+, potassium

[1] ACEi listed in the ESC guidelines and registered for use in HF: captopril, enalapril, lisinopril, ramipril, trandolapril; ACEi not listed in the ESC guidelines but registered for HF in Poland: benazepril, quinapril, cilazapril, perindopril; ACEi not registered for HF in Poland: imidapril, zofenopril (zofenopril is registered for use in acute myocardial infarction with or without HF). [2]Sacubitril/valsartan. [3]BB listed in the ESC guidelines and registered for use in HFrEF: bisoprolol, carvedilol, metoprolol succinate (CR/XL), nebivolol. [4]MRA listed in the ESC guidelines and registered for use in HFrEF: eplerenone, spironolactone. [5]SGLT2i listed in the ESC guidelines and registered for use in HFrEF: dapagliflozin, empagliflozin. [6]Loop diuretics registered for use in HFrEF in Poland: furosemide, torasemide. [7]Non-vitamin K antagonist oral anticoagulants (NOAC) should be preferred to vitamin K antagonists (VKA), except for patients with moderate-to-severe mitral stenosis or mechanical prosthesis; NOAC registered for AF in Poland: dabigatran, rivaroxaban, apixaban. [8] According to the ESC guidelines [1] and ESC consensus documents [2, 3], ARNI should not be used when eGFR is <30 ml/min/1.73 m^2; according to Summary of Product Characteristics sacubitril/valsartan may be cautiously used in a lower dose in patients with eGFR <30 ml/min/1.73 m^2 and is contraindicated in end-stage kidney disease. [9]Unavailable in Poland

Medication that should be initiated from the start in all patients, preferably simultaneously, at low doses but with subsequent timely up-titration to target doses or maximum doses tolerated by the patient (up-titration refers to ACEi/ARNI, BB, and MRA)

Medication that should not be used

Medication that should be initiated cautiously, possibly step by step rather than simultaneously, in very small doses with subsequent cautious up-titration to maximum doses tolerated by the patient (up-titration refers to ACEi/ARNI, BB, and MRA). Loop diuretics should be intiated only in congested patients and continued at a minimum dose required for euvolemia (or disontinued if not needed)

Medication that can be discontinued

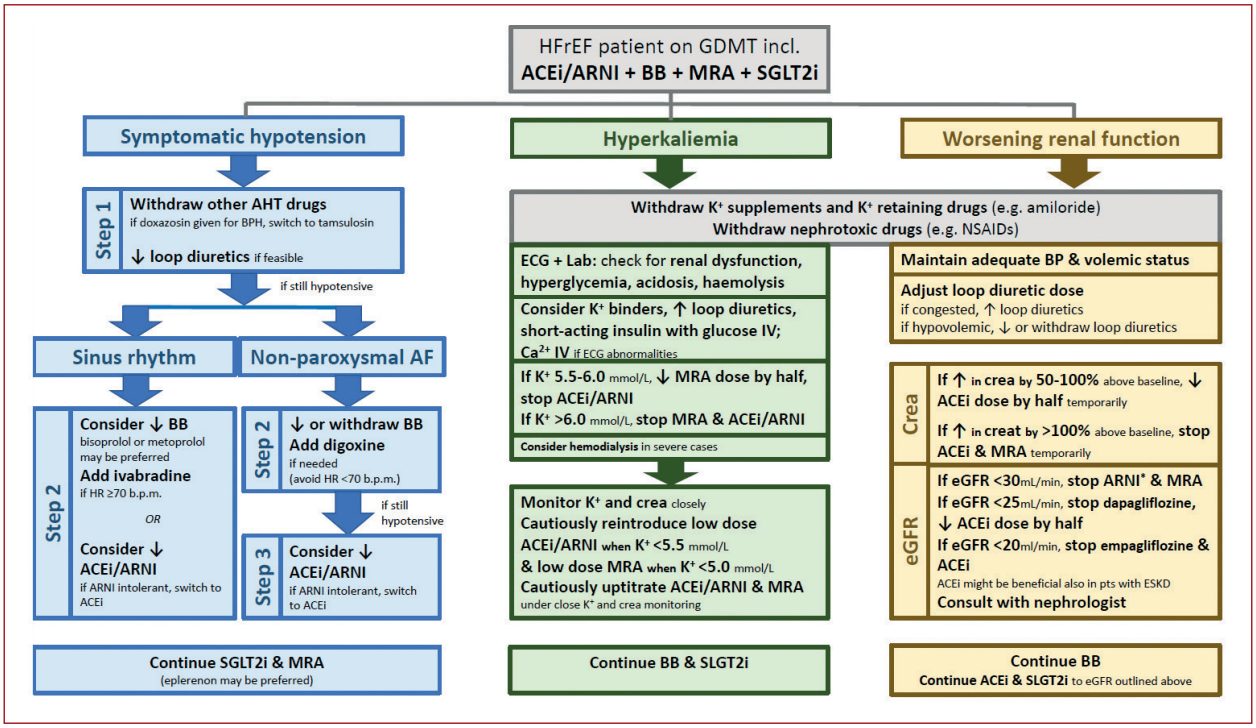

Figure 1. Modification of guideline-directed medical therapy in heart failure with reduced ejection fraction in specific clinical situations

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AHT, antihypertensive; ARNI, angiotensin receptor-neprilysin inhibitor; bpm, beats per minute; BB, beta-blocker; BP, blood pressure; BPH, benign prostatic hyperplasia; Ca^{2+}, calcium; crea, creatinine; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; GDMT, guideline-directed medical therapy; HR, heart rate; HRrEF, heart failure with reduced ejection fraction; incl., including; K^+, potassium; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter-2 inhibitor

*According to the ESC guidelines [1] and ESC consensus documents [2, 3], ARNI should not be used when eGFR is <30 ml/min/1.73 m^2; according to SmPC, sacubitril/valsartan may be cautiously used in a lower dose in patients with eGFR <30 ml/min/1.73 m^2, and is contraindicated in end-stage kidney disease

reached [1, 31, 33]. In refractory cases, a combination of loop diuretics with diuretic agents that block sodium reabsorption at different sites in the nephron, such as thiazides (distal convoluted tubule) or acetazolamide (proximal convoluted tubule), i.e. sequential nephron blockade, may help overcome diuretic resistance [1, 31]. Importantly, of disease-modifying drugs, not only MRA but also SGLT2i and ARNI possess diuretic properties and may enhance the diuretic effect of loop diuretics [31, 34, 35].

Modification of GDMT in HFrEF: Specific situations

Patients with chronic HFrEF experience not only HF exacerbations but also other problems (e.g. hypotension, worsening renal function, hyperkalemia, hypokalemia, hyponatremia), which may represent GDMT complications but can also result from disease progression (or, usually, the interplay between both) [5, 31, 36–38]. Irrespective of their etiology, these problems may require modification of HFrEF pharmacotherapy. Nonetheless, every effort should be made to maintain disease-modifying drugs, if possible, in adequate dosing. For example, hyperkalemia in HF was associated with discontinuation and lower doses of MRA during follow-up, and discontinuation of MRA due to hyperkalemia was associated with higher all-cause mortality in HFrEF [23].

Detailed algorithms for problem solving have been proposed in Figure 1. In each case, an attempt should be made to identify and treat the specific cause of deterioration. This includes a scrupulous assessment and, if needed, correction of the patient's volemic status. A decision to down-titrate disease-modifying drugs should always be preceded by a careful revision of current pharmacotherapy, and reduction or withdrawal of other agents (e.g. other antihypertensives or loop diuretics in patients with symptomatic hypotension, nephrotoxic drugs, and potassium supplements in those with worsening renal function and/or hyperkalemia, thiazide-type diuretics in those with hyponatremia) [36–38]. If disease-modifying drugs are reduced or temporarily withdrawn, an attempt to re-introduce or up-titrate them should be made as soon as the complication has resolved [5].

PRACTICAL CHECKLISTS TO OPTIMIZE GDMT IMPLEMENTATION IN CHALLENGING CLINICAL SCENARIOS

In HFrEF, cardiac and extracardiac comorbidities as well as complications arising in the course of the disease may impose therapy modification, which, in real-world practice, often results in underutilization of GDMT. Even more worrisome, a fear of potential complications (such as fear of

hypotension with concomitant use of ACEi/ARNI, MRA, and beta-blockers, or fear of worsening renal function and/or hyperkalemia with concomitant ACEi/ARNI and MRA use), even before they occur, often limits full implementation of GDMT. This is unjustified, given the long-term positive effect of HFrEF medications on left-ventricular remodeling and function (leading to increased cardiac output and less hypotension), nephroprotective actions of ACEi/ARNI and SGLT2i (leading to preservation of kidney function), and reduced risk for hyperkalemia with MRA when used in combination with ARNI or SGLT2i [25–31, 39–41].

Thus, despite evidence for prognosis improvement with GDMT, its implementation remains poor, and most HFrEF patients do not receive drugs from all recommended groups or do not reach their target doses [42–44]. Herein, we provide practical checklists to help non-HF specialists adjust pharmacotherapy in some common clinical situations in a way that would prevent any unnecessary down-titration or cessation of life-saving HFrEF medications (*Checklists 1–3*). Notably, different clinical scenarios require different strategies, and handling of the same problem (e.g. hypotension) may differ depending on patient comorbidities (e.g. atrial fibrillation; see *Checklists 1 and 2*). Furthermore, patients' clinical and laboratory status changes over time, which should lead to appropriate adjustment of hitherto therapy. For example, a patient's kidney function may deteriorate (requiring therapy modification) but also improve under treatment (enabling introduction of previously contraindicated agents or drug up-titration; see *Checklist 3*). One of the key factors determining therapy modification in different

Checklist 1. Heart failure with reduced ejection fraction (HFrEF) and sinus rhythm

HFrEF + sinus rhythm	
☐ ACEi/ARNI ☐ Beta-blockers ☐ MRA ☐ SGLT2i	To improve prognosis
Problem-solving: symptomatic hypotension	
STEP 1	☐ Withdraw other antihypertensives ☐ Consider reduction or withdrawal of loop diuretics (in hypo- or euvolemic patients)*
If still hypotensive	
STEP 2	☐ Continue SGLT2i and MRA • Consider switching from spironolactone to eplerenone ☐ Consider dose reduction of ACEi/ARNI or beta-blocker but refrain from withdrawal if possible • Consider switching beta-blocker to bisoprolol or metoprolol CR/XL • Consider switching from ARNI to ACEi

*Assessment of volemia/congestion should include: clinical assessment (weight change, presence of pulmonary congestion, peripheral edema, hepatomegaly, pleural effusion, ascites, and signs of increased jugular venous pressure) and laboratory testing (natriuretic peptides concentrations and their changes, echocardiography with estimation of left ventricular filling pressures, assessment of the inferior vena cava, and assessment of congestion on chest X-ray and/or lung ultrasound) [31, 44, 45].

Checklist 2. Heart failure with reduced ejection fraction (HFrEF) and non-paroxysmal atrial fibrillation (AF)

HFrEF + non-paroxysmal AF	
☐ OAC ☐ ACEi/ARNI ☐ MRA ☐ SGLT2i	To improve prognosis
☐ Beta-blocker ☐ Digoxin	For HR control
Problem-solving: symptomatic hypotension	
STEP 1	☐ Withdraw other antihypertensives ☐ Consider reduction or withdrawal of loop diuretics (in hypo- or euvolemic patients)*
If still hypotensive	
STEP 2	☐ Continue SGLT2i and MRA • Consider switching from spironolactone to eplerenone ☐ Consider dose reduction or withdrawal of a beta-blocker • Use digoxin (with or without a beta-blocker) for HR control • Keep HR >70 b.p.m • If still on beta-blocker, switch to bisoprolol or metoprolol CR/XL ☐ Continue ACEi/ARNI
If still hypotensive	
STEP 3	☐ Consider dose reduction of ACEi/ARNI but refrain from withdrawal if possible • Consider switching from ARNI to ACEi

*Assessment of volemia/congestion should include: clinical assessment (weight change, presence of pulmonary congestion, peripheral edema, hepatomegaly, pleural effusion, ascites, and signs of increased jugular venous pressure) and laboratory testing (natriuretic peptides concentrations and their changes, echocardiography with estimation of left ventricular filling pressures and assessment of the inferior vena cava, and assessment of congestion on chest X-ray and/or lung ultrasound) [31, 44, 45].

Checklist 3. Heart failure with reduced ejection fraction (HFrEF) and renal dysfunction

HFrEF + chronic kidney disease (CKD)			
☐ ACEi/ARNI ☐ SGLT2i		of HFrEF and CKD (cardio- and nephro-protection)	To improve prognosis
☐ MRA ☐ Beta-blocker		of HFrEF (cardio-protection)	
Problem-solving: GDMT in HFrEF with CKD			
eGFR, ml/min/1.73 m²	**Drugs to be initiated/continued**	**Drugs to be discontinued**	
>30	☐ ACEi/ARNI ☐ MRA ☐ Beta-blocker ☐ SGLT2i		
25–30	☐ ACEi (low dose) ☐ Beta-blocker ☐ SGLT2i	☐ ARNI* ☐ MRA	
20–25	☐ ACEi (low dose) ☐ Beta-blocker ☐ Empagliflozin	☐ ARNI* ☐ MRA ☐ Dapagliflozin	
<20	☐ Beta-blocker	☐ ARNI* ☐ MRA ☐ SGLT2i	
	☐ ACEi (low dose) may be beneficial in end-stage CKD (especially if on dialysis) – consult with a nephrologist		
Problem-solving: worsening renal function (WRF) in HFrEF			
STEP 1 **General measures**	☐ Identify WRF cause (pre-renal, renal, post-renal) and treat it ☐ Withdraw nephrotoxic drugs (e.g. NSAIDs) ☐ Withdraw K+ supplements and K+ retaining drugs (e.g. amiloride) ☐ Monitor serum creatinine, urea/BUN, electrolytes and urine output ☐ Assess BP, congestion, and volume status • If congested, intensify diuretic treatment** • If hypovolemic, withdraw loop diuretics**		
STEP 2 **GDMT modification**	**Increase in serum creatinine from baseline**	**Serum creatinine, mg/dl**	**eGFR, ml/min/1.73 m²**	**GDMT modification**
	<50%	<3.0	>25 (<10% decrease from baseline)	NO
	50%–100%	3.0–3.5	20–25	Temporarily reduce ACEi/ARB dose by half
	>100%	>3.5	<20	Stop RAASi

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARNI, angiotensin receptor-neprilysin inhibitor; bpm, beats per minute; BUN, blood urea nitrogen; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HR, heart rate; HFrEF, heart failure with reduced ejection fraction; K+, potassium; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose co-transporter-2 inhibitor; OAC, oral anticoagulant; WRF, worsening renal function; NSAID, non-steroidal anti-inflammatory drugs; RAASi, renin-angiotensin-aldosterone system inhibitors

*According to the ESC guidelines [1] and ESC consensus documents [2, 3], ARNI should not be used when eGFR is <30 ml/min/1.73 m²; according to SmPC, sacubitril/valsartan may be cautiously used in a lower dose in patients with eGFR <30 ml/min/1.73 m² and is contraindicated in end-stage kidney disease. **Assessment of volemia/congestion should include: clinical assessment (weight change, presence of pulmonary congestion, peripheral edema, hepatomegaly, pleural effusion, ascites, and signs of increased jugular venous pressure) and laboratory testing (natriuretic peptides concentrations and their changes, echocardiography with estimation of left ventricular filling pressures and assessment of the inferior vena cava, and assessment of congestion on chest X-ray and/or lung ultrasound) [26, 39, 40]

clinical scenarios is assessment of the patient's volemic status and signs of congestion [31, 45, 46].

Clinical case 1: Ambulatory HFrEF patient with chronic kidney disease

A 68-year-old man was referred to an ambulatory HF center due to newly diagnosed HFrEF (on transthoracic echocardiogram: EF 33%, regional contractile abnormalities suggestive of ischemic HF etiology). He reported moderate limitation in physical activity (New York Heart Association [NYHA], class II) in the previous few months and denied any chest pain. He was a smoker, with untreated hypercholesterolemia and a history of posttraumatic left nephrectomy 20 years earlier. On physical examination, there were no signs of congestion and BP was 135/80 mm Hg. Electrocardiogram showed sinus rhythm of 80 bpm, and a QS complex in leads V2–V3. Laboratory tests showed a creatinine level of 1.48 mg/dl with eGFR of 47 ml/min/1.73 m², potassium of 4.4 mmol/l, NT-proBNP of 2100 pg/ml, and low-density lipoprotein (LDL) cholesterol of 136 mg/dl.

Given reduced eGFR, triple HFrEF therapy was initiated, including metoprolol CR 25 mg once daily (o.d.), empagliflozin 10 mg o.d., and sacubitril/valsartan 24/26 mg twice daily (b.i.d). Furthermore, due to suspected ischemic etiology, antiplatelet and statin treatment was initiated, and elective coronary angiography was scheduled.

Two weeks later, the patient came for ambulatory control. He reported improved exercise tolerance. His BP was 128/75 mm Hg and HR — 75 bpm. In laboratory tests, creatinine increased to 1.67 mg/dl (with eGFR of

41 ml/min/1.73 m^2), and potassium to 4.7 mmol/l. Given that the increase in creatinine was below 50%, and eGFR remained above 30 ml/min with potassium below 5.0 mmol/l, eplerenone 25 mg o.d. was initiated. Metoprolol CR dose was increased to 50 mg o.d.

On the subsequent control, 2 weeks later, creatinine was 1.71 mg/dl (with eGFR of 40 ml/min/1.73 m^2) and potassium was 4.9 mmol/l. Metoprolol CR and sacubitril/valsartan were further up-titrated (to 100 mg o.d. and 49/51 mg b.i.d., respectively).

Further 3 weeks later, the patient was in the New York Heart Association class I/II, with BP of 115/70 mm Hg and HR of 70 bpm, and had a creatinine level of 1.65 mg/dl and potassium level of 4.8 mmol/l, which allowed up-titration of eplerenone to the maximum dose of 50 mg o.d.; metoprolol CR dose was also increased. On the subsequent visit, 3 weeks later, sacubitril/valsartan was up-titrated to the maximum dose of 97/103 mg b.i.d.

Comment: This case demonstrates initiation of a triple HFrEF therapy in a patient with a baseline eGFR of 30–60 ml/min /1.73 m^2, followed by a timely introduction of an MRA, and subsequent up-titration of all HFrEF medication to target doses within 10 weeks from his initial presentation.

Clinical case 2: Hospitalized HFrEF patient with atrial fibrillation, hypotension, and worsening renal function

A 77-year-old woman with a long-standing history of dilative cardiomyopathy (EF 27%, left ventricular diastolic diameter of 62 mm) and paroxysmal AF (after 2 procedures of pulmonary vein isolation in the past, with a left atrial volume index of 61 ml/m^2) was admitted to hospital for HF decompensation. She reported increasing dyspnea and edema one month before hospitalization. Her previous HFrEF treatment consisted of carvedilol 25 mg b.i.d., ramipril 5 mg b.i.d., spironolactone 25 mg o.d., and dapagliflozin 10 mg o.d. She was also on chronic oral anticoagulation with apixaban. Her last known creatinine level before hospitalization was 1.1 mg/dl (eGFR, 48 ml/min/1.73 m^2). On admission, she was in AF with a ventricular rate of approximately 120 bpm and had BP of 100/55 mm Hg (without signs of hypoperfusion), with signs of both pulmonary and peripheral congestion (ankle edema, jugular vein distention). Her creatinine was 1.7 mg/dl, eGFR 29 ml/min/1.73 m^2, and potassium 5.8 mmol/l.

Attempted electrical cardioversion was unsuccessful. Carvedilol and spironolactone were stopped, ramipril dose was reduced, and digoxin was introduced together with intravenous furosemide treatment. This led to significant decongestion (improvement in symptoms and signs, weight reduction of 6 kg over 3 days), a reduction in creatinine (to 1.2 mg/dl) and potassium level (to 4.8 mmol/l), and a reduction in ventricular rate (to 100 bpm). The treatment was switched to oral furosemide. Bisoprolol was introduced (initially 2.5 mg o.d., later up-titrated to 5 mg o.d. to maintain a ventricular rate of approximately 80 bpm). Eplerenone (25 mg o.d.) was introduced, and ramipril was carefully up-titrated to 5 mg b.i.d. The patient's BP remained low (95/60 mm Hg, although without symptomatic hypotension) which precluded switching from ramipril to ARNI. The patient was discharged on day 7, in good general condition, with symptoms in NYHA class II, no signs of residual congestion, and with permanent AF. On discharge, she received bisoprolol 5 mg o.d. and digoxin 0.1 mg o.d. for rate control within AF, ramipril 5 mg b.i.d, eplerenone 50 mg o.d., dapagliflozine 10 mg o.d. and furosemide 40 mg o.d.

Comment: This case demonstrates HFrEF decompensation (possibly due to rapid ventricular rate within AF) with hypotension and worsening renal function. An increase in creatinine of >50% demanded a reduction in ACE inhibitor dose and temporary cessation of MRA. However, after decongestion with loop diuretics, kidney function was restored enabling up-titration of an ACE inhibitor and re-introduction of MRA (eplerenone was chosen due to its smaller hypotensive effect). Due to hypotension in this decompensated HFrEF patient, the beta-blocker (carvedilol) was temporarily stopped and subsequently exchanged for another (bisoprolol), with a smaller relative impact on BP and a greater impact on HR. Given that the patient remained hypotensive and in AF, up-titration of a beta-blocker was not deemed a priority, instead, digoxin was introduced for rate control. SGLT2i was maintained throughout hospitalization.

CONCLUSIONS

Patients with HFrEF remain under the care of many non-HF specialists, thus, this article aimed to provide practical guidance including checklists on initiation of HFrEF therapy and its modification in challenging clinical situations. Optimal HFrEF treatment should be based on the four pillars of GDMT (ACEi/ARNI, beta-blockers, MRA, and SGLT2i) and also utilize other therapies, depending on the patient's clinical profile, to provide the maximum benefit for each patient. Appropriate drug choice and titration enable effective HFrEF treatment even in complex clinical scenarios.

Article information

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