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Management of Heart Failure with Reduced Ejection Fraction Globally and in Lebanon: Where Do SGLT-2is Stand?

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Abstract

Heart failure (HF) is a clinical syndrome due to structural and/or functional cardiac anomalies, accompanied by elevated natriuretic peptide levels and/or cardiogenic pulmonary or systemic congestion; severely compromising patients' health, performance and quality of life. The advancement of novel treatment and their endorsement by international medical and scientific societies have shifted the treatment of HF with reduced ejection fraction (HFrEF) towards quadruple therapy: an angiotensin receptor-neprilysin inhibitor or an angiotensin-converting enzyme inhibitor, a beta-blocker, a mineralocorticoid receptor antagonist and a sodium/glucose co-transporter-2 inhibitor (SGLT2i). This paper reviews the available literature on state-of-the-art diagnostic and therapeutic advances in HFrEF, discusses landmark trials that shifted the paradigm towards quadruple therapy in HFrEF, visits the potential challenges in Lebanon and globally, proposes an algorithm for treatment introduction and sequencing in HFrEF and highlights clinical considerations for HFrEF management and patient education and follow-up. This practical guidance could serve cardiologists and other medical specialists in identifying clinical signs of HFrEF, diagnosing patients, referring them or prescribing the components of quadruple therapy, and offering medical advice and follow-up. We highlight the role of SGLT2is in HF management and their effectiveness in reducing rates of hospitalization for HF as well as cardiovascular deaths, with satisfactory safety profile.

Keywords

Heart Failure, HFrEF Management, SGLT2i, Clinical Guidance, Quadruple Therapy

1. Introduction

Heart failure (HF) is a major global health problem with 1% - 2% worldwide prevalence and as many as one fifth of the population will develop HF in their lifetime [1]. Up to 4% of all hospitalizations are driven by HF, the leading cause of hospital admission after the age of 65 [2]. HF with reduced ejection fraction (HFrEF) accounts for 50% of patients and the prognosis is equally grim for patients with reduced (HFrEF) or with preserved EF (HFpEF) [3] [4] [5] [6] [7]. In addition, poorer quality of life reported among HF patients was found to strongly correlate with the rate of hospitalization for HF [8].

Triple therapy has been the mainstay of HFrEF treatment for two decades, but it leaves patients at a residual CV risk [9] [10]. Landmark trials have shifted the paradigm towards quadruple therapy with an angiotensin receptor-neprilysin inhibitor (ARNi) or an angiotensin-converting enzyme inhibitor (ACEi), a beta-blocker (BB), a mineralocorticoid receptor antagonist (MRA) and, recently, a sodium/glucose co-transporter-2 inhibitor (SGLT2i) [11] [12] [13] [14] [15].

Real-World Evidence data report on challenges in optimizing HF management [16]-[23]; 1) most HF patients are on suboptimal therapy (<50% are on target doses), 2) better outcomes are achieved with higher dosages, 3) initial doses are not regularly revisited and adjusted, leading to clinical inertia, 4) barriers to implementing guideline recommendations include age, blood pressure and comorbidities. The initiation of four different medications within one month entails frequent visits to the clinic, usage of resources, need for closer monitoring to avoid adverse drug reactions and pre-empt drug interactions. This may also lead to a similar clinical caution or clinical inertia.

While the addition of a SGLT2i to the medication set of patients with HFrEF has proven effective and protective, patients with low systolic blood pressure (<95 mmHg) and patients with an estimated glomerular filtration rate (eGFR) below 20 ml/min/1.73m^2 have been so far excluded from clinical trials [13] [24] [25] [26] [27]. Importantly, SGLT2i are now considered a pillar in the first-line quadruple therapy for HFrEF with left ventricular ejection fraction (LVEF) below 40% accompanied by symptoms, and its use is endorsed by major medical associations, such as the Canadian Cardiology Society (CCS)/Canadian Heart failure Society (CHFS), the European Society of Cardiology (ESC) and the American College of Cardiology (ACC)/American Heart Association (AHA) [28] [29] [30]. Dapagliflozin was granted Food and Drug Administration (FDA) approval in 2019 for the treatment of HFrEF to reduce cardiovascular (CV) death, hospitalizations for HF, especially in patients with CV disease (CVD) or CV risk factors, including type-2 diabetes mellitus [31] [32]. In 2021, FDA approval was ex-

tended to empagliflozin, for the same indication.

In light of the 2021 HF guidelines published by the ESC, the aim of this paper is to provide guidance for improved HFrEF care in Lebanon by removing barriers, promoting the achievement of optimal dosages and treatment sequencing, resolving ambivalence and hesitancy among treating physicians and positioning SGLT2i as an unequivocal pillar in the treatment of HFrEF.

2. Methods

A panel of cardiology experts in the management of HF in Lebanon convened to review the recent updates on evidence-based literature on the management of HFrEF (up until December 2021), during a structured meeting. In addition to established triple therapy for HFrEF, a special focus was made on SGLT-2is as a novel pillar in the quadruple therapy recommended by international societies concerned with HF management. All major trials on SGLT-2i use in HF were retrieved from PubMed and discussed in terms of study design, patient population, and outcomes; then these landmark trials were summarized to reflect the basis for paradigm shift in HFrEF to quadruple therapy. In addition, panel members discussed the challenges and ambivalence hindering quadruple therapy initiation in Lebanon; motivating up-scaling of physician and patient education. Sequencing, patient profiling and follow-up were also deliberated, in light of state-of-the-art literature, and an algorithm for HFrEF diagnosis and treatment was developed and approved by all participating cardiologists.

3. Heart Failure with Reduced Ejection Fraction (HFrEF)

1) Definition

According to the universal definition [33], HF is a clinical syndrome with current or prior symptoms and/or signs caused by structural and/or functional cardiac abnormalities and by either elevated natriuretic peptide level or objective evidence of cardiogenic pulmonary edema or systemic congestion. People with CV risk factors are susceptible to HF and are classified as stage A, subjects whose risk factors need to be addressed in a timely manner. Stage B or pre-HF characterizes people without any HF symptoms, but whose clinical status (structural heart disease, decreased cardiac function or elevated HF biomarkers) puts them at risk for HF onset. Patients with HF present either with a stage C disease (signs and symptoms of HF) or with a more severe stage D disease requiring advanced medical care. In addition, HF is classified into three main phenotypes according to the LVEF measurement: 1) HFrEF with LVEF ≤ 40%; 2) HF with mildly reduced/mid-range EF (HFmrEF) with LVEF ranging between 41% and 49%; 3) HF with preserved EF (HFpEF) with LVEF ≥ 50% [34].

2) Diagnosis

The ESC 2021 guidelines stipulate that all patients with suspected HF should have an electrocardiogram, a transthoracic echocardiogram, chest X-ray, blood tests including cell count, urea and electrolytes, thyroid function, glycated hemoglobin (HbA1c), lipid, iron analyses. In particular, patients seeking medical

care for HF should undergo clinical assessment for dyspnea, congestion and biomarker analysis (brain natriuretic peptide [BNP] or N-terminal pro-BNP [NT-proBNP]). In fact, both BNP and the more stable NT-proBNP are widely considered as excellent biomarkers for HF diagnosis [35] [36] [37] [38]. HF is diagnosed in ambulatory patients with NT-proBNP > 125 pg/ml (or BNP > 35 pg/ml) and hospitalized patients with NT-proBNP > 300 pg/ml (or BNP > 100 pg/ml) [39]. When testing for these HF biomarkers is not possible, due to elevated cost for instance, an echocardiography might be performed. However, these diagnostic tests present some limitations. Echocardiography might overlook a case of HF when LVEF is within normal limits and filling pressure evaluation is indeterminate [40], and echocardiograms should be analyzed in light of other individual parameters [41]. There are others factors that modulate BNP and NT-proBNP levels, which could be misleading and either over- or underestimate the patient's condition. For instance, ARNi therapy induces decrease of NT-proBNP and increase of BNP levels [42] and levels of both biomarkers might be elevated due to cardiac or non-cardiac conditions such as ischemic heart disease, acute pulmonary embolus, chronic obstructive pulmonary disease, chronic kidney disease (CKD), thyroid disease and stroke [43]. **Figure 1** resumes the parameters universally adopted in the diagnosis of HF [39].

HF is a clinical syndrome with current or prior:

Symptoms and/or signs typical of heart failure and at least one or more of the following structural and/or functional cardiac abnormality

-EF < 50%,

-abnormal cardiac chamber enlargement,

-E/E′ > 15,

-moderate/severe ventricular hypertrophy or

-moderate/ severe valvular obstructive or regurgitant lesion

And corroborated by at least one of the following:

1. Elevated natriuretic peptide levels

BNP ≥ 35 pg/ml and NT-proBNP ≥ 125 pg/ml for ambulatory patients

BNP ≥ 100 pg/ml and NT-proBNP ≥ 300 pg/ml for hospitalized/decompensated patients

2. Objective evidence of cardiogenic pulmonary or systemic congestion by:

Imaging (e.g. by chest X-ray or elevated filling pressures by echocardiography) or

Haemodynamic measurement (e.g. right heart or pulmonary artery catheter) at rest or provocation

Figure 1. Universal definition of HF.

3) Management

Patients with HFrEF should be prescribed quadruple therapy, while those HFmrEF could be given triple therapy. At the time of the most recently published HF guidelines [27] [28] [29] [33], there was no therapeutic agent with class I evidence recommended for patients with HFpEF. The management of HFrEF currently relies on quadruple therapy with ARNi, MRA, BB and SGLT2i; as will be discussed below in addition to other specific guided therapy depending on the patients' condition.

To avoid ambiguity and unnecessary risk, patients with therapy-induced improvement of their EF should be made aware of the dangers of quitting their medication; since as many as 40% of patients with dilated cardiomyopathy, who had discontinued their treatment upon improved LVEF, had relapsed to a more severe disease [44].

4) Management Challenges

Given the unstable social, economic and political situation in Lebanon, the country is facing challenges to cope with medical demands and ensure safe and sustained patient care. **Table 1** below+ gives an overview of the challenges encountered among HF patients and healthcare professionals, as reported by members of Lebanese Society of Cardiology (LSC).

Patients tend to adjust their lifestyle to address HF symptoms; hindering consultation and diagnosis. This underscores the need to promote awareness campaigns on HF, via lectures, media, leaflets distributed at clinics, etc. One example would be the annual HF campaign launched in 2011 by the LSC HF working group, which aims to raise awareness of symptoms of HF and provide education material for patients and their families. Patients need to understand that HF is not a normal stage of ageing, be aware of early symptoms of HF, the importance of keeping up with proper health hygiene and with medications. Through digital and social media on top of conventional educational material (pamphlets, brochures, etc.), a much broader population of patients and their caregivers are reached. This initiative is in collaboration with the ESC Heart Failure Association and it plans to invest more effort into reaching out to patients at high risk for HF. The 2021 HF campaign, endorsed by the World Heart Federation and the LSC HF working group, witnessed the adaptation of HF educational material to Arabic, featured over the social media page of the LSC and the Sohtak Hayetak initiative.

We propose the creation of a "National HF Management Program" managed by the LSC HF working group. This program aims to implement national HF healthcare centers, train specialized nurses, educate residents and physicians, and train them on the diagnosis, management and referral of HF patients. The presence of HF centers and the training of patients to self-manage their disease now stand as a class 1A recommendation [45] [46]. Moreover, the majority of HF deaths happen in seemingly stable patients [47], which warrants more rigorous monitoring, starting at the primary care level. Regular scientific meetings, workshops, clinical case discussions and collaboration with the Lebanese

Table 1. HF management challenges.

	Challenges
Signs and Symptoms	• Breathlessness, ankle swelling and fatigue are atypical • Lack of specificity and accuracy
Patient limitations	Lack of awareness about: • Risk factors • Signs and symptoms • The need to consult
Identifying patients at risk	Conditions that should prompt cardiac function evaluation include: • MI • Arterial HTN • CAD • Diabetes • Chemotherapy • CKD • LVH • A-fib In addition to alcohol abuse, family history of cardiomyopathy or sudden death
Testing limitations	• Availability and cost of: HF biomarker tests, echocardiography, CT scan, coronary angiography • Availability of tests in remote areas • Confounding factors biasing test results: obesity, diabetes, age, etc.
HF unit in hospitals	• Lack of multidisciplinary HF management with home-based or clinic-based programs • Lack of HF patient self-management education
Medications	Knowledge of: • Disease-modifying drugs (starting and target doses) • Optimal sequencing according to patient profile • Drugs or drug combinations contraindicated in HF, such as class I antiarrhythmic drugs, calcium channel blockers (verapamil, diltiazem, nifedipine, etc.), thiazolidinediones in patients with NYHA class III or IV HF, NSAIDs and others [48]
Follow-up	• Need to detect asymptomatic disease or risk factor progression • Need to monitor adequacy of treatment and doses • Implement new advances in care
Telemonitoring and e-records	• Absence of telemonitoring system • Inability to obtain patient data to guide therapy or seek medical care

A-Fib: Atrial Fibrillation; CAD: Coronary Artery Disease; CKD: Chronic Kidney Disease; CT: Computerized Tomography; HF: Heart Failure; HTN: Hypertension; LVH: Left Ventricular Hypertrophy; MI: Myocardial Infarction.

Society of general, family and internal medicine practitioners are highly needed. Despite guideline recommendations, a large proportion of patients are not offered optimal therapy [17].

In addition, third party payers (private insurance and national social security fund) and other stakeholders should be involved in price lowering and coverage, but also in active participation in educational campaigns.

Lebanon has not yet stepped into the tele-medicine world. Remote consultation and monitoring promote patient care and allow physicians to adjust therapy according to electronic patient data. Such records also inform on patient compliance and adherence to treatment.

Actions must be taken through the management program, the HF working group and the Lebanese Society of Cardiology to address the challenges reported below and will prioritize unmet needs and set up achievable targets.

4. Role of SGLT2is in Cardiovascular Disease and Heart Failure

1) Mechanism of action of SGLT2i

SGLT2 is found in the proximal convoluted tubule of the nephron; it is a co-transporter that operates by moving glucose and sodium ions from the tubular fluid back into the bloodstream. SGLT2is exert glycosuric and natriuric effects, which lead to glycemia control and reduction of fat accumulation, arterial stiffness and blood pressure reduction, modulation of cardiac bioenergetics, as well as mitigation of oxidative stress and inflammation. Collectively, improvement of these parameters contributes to the renal and CV benefits reported with SGLT2i use. Contrary to loop diuretics, SGLT2i decrease intravascular volume without compromising kidney function [49].

2) SGLT2i and Cardiovascular Disease Prevention in Patients with Type-2 Diabetes

Diabetes is increasing dramatically in the world, and its prevalence in the Middle-East ranks among the highest worldwide [50]. Type-2 diabetes is a potent, independent risk factor for HF [6]. In fact, 68% of patients with type-2 diabetes had evidence of left ventricular dysfunction 5 years after type-2 diabetes diagnosis [51] [52]. While insulin resistance and/or deficiency is the leading physiological abnormality behind type-2 diabetes, the SGLT2 in the nephrons also plays a role by reabsorbing glucose back into the bloodstream. Moreover, multiple studies (EMPA-REG, CANVAS, DECLARE TIMI 58, CREDENCE, VERTIS CV) have reported that SGLT2is reduce the risk of hospitalization for HF in patients with type-2 diabetes, independently of HF history [53] [54] [55] [56] [57]. Meta-analysis of studies on SGLT2is have shown that in primary prevention, SGLT2is prevent HF and renal disease but do not reduce major adverse cardiovascular events (MACE); while in secondary prevention, all three conditions were reduced.

Based on available evidence, the ESC published the 2021 guidelines on CV prevention that recommended SGLT2is (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) in patients with type-2 diabetes at high CV risk to reduce hospitalization for HF, major CV events, end-stage renal dysfunction and CV death (Class 1, Level A). The specific SGLT2is dapagliflozin, empagliflozin, sotagliflozin are recommended in patients with type-2 diabetes and HFrEF to reduce hospitalizations for HF and CV death (Class 1, Level A) [58].

Since 2018, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) endorse SGLT2is as first-line treatment after metformin in patients with type-2 diabetes and HF or renal dysfunction [59]. The ADA guidelines were updated in 2021 and SGLT2is are now a preferred class of treatment in patients with type-2 diabetes at high-risk or estab-

lished atherosclerotic CVD, HF, or chronic kidney disease, independently of baseline HbA1c, individualized HbA1c target, or metformin use [60]. The 2021 ESC guidelines also provide specific recommendations for glucose treatment, in patients with type-2 diabetes and CVD or who are at high/very high CV risk; these patients should be readily prescribed a SGLT2i or a GLP-1RA with metformin [58].

Recent meta-analyses [61] [62] concluded that SGLT2is offer 1) Moderate benefits on CV events that appear confined to patients with established atherosclerotic CVD; 2) Robust reduction in hospitalization for HF regardless of the presence of established atherosclerotic CVD or HF; 3) Marked slowdown of renal disease progression in patients with and without atherosclerotic CVD.

There is a need to leverage awareness among Lebanese physicians on the use of SGLT2is among their type-2 diabetes patients at risk for CVD, chronic kidney disease, and/or HF.

3) SGLT2i and HFrEF (with or without type-2 diabetes)

As mentioned above, the ESC updated their guidelines on HF to recommend SGLT2is (namely dapagliflozin or empagliflozin) for HFrEF treatment, regardless of type-2 diabetes status [29]. This is based on two landmark trials conducted in HFrEF patients regardless of diabetes status.

The ***DAPA-HF***, an international, multicenter, parallel-group, randomized, double-blind, placebo-controlled was the first trial to evaluate dapagliflozin's effect on the primary composite outcome of CV death, hospitalization for HF or emergency room visit for HF in patients with HFrEF [24] [63], on guideline-directed medical therapy (GDMT). The primary endpoint was met significantly, with a 26% risk reduction ($P < 0.05$) and effectiveness observed as early as day 28 post-randomization. The primary endpoint demonstrated consistent benefit of dapagliflozin use among the subpopulation of HFrEF patients with or without type-2 diabetes [64]. The secondary endpoint of all-cause mortality was also markedly decreased upon dapagliflozin treatment [24], as well as the risk of first and subsequent HF events [65]. Importantly, dapagliflozin was outstandingly associated with a significant reduction of CV death by 18%, in addition to a 30% significant reduction in the rate of hospitalization for HF. In addition, patients on dapagliflozin reported a significant improvement in their quality of life [66].

All primary outcomes were met across age groups [67], regardless of baseline LVEF [68], and HF treatment associations [69] [70].

The ***EMPEROR-Reduced*** trial, the second study to evaluate SGLT2is in HFrEF, was a phase III randomized double-blind placebo-controlled trial that investigated the safety and efficacy of empagliflozin *versus* placebo on top of GDMT in patients with HFrEF. The composite primary endpoint was achieved (with 25% reduction in CV death or hospitalization for HF among empagliflozin-treated patients, $P < 0.0001$) and the rate of hospitalization for HF was significantly reduced by 30% with empagliflozin compared to placebo ($P < 0.001$). However, taken separately, the risk of CV death was not significantly attenuated

in patients on empagliflozin. Empagliflozin treatment also resulted in improved eGFR, attributing a nephroprotective role for SLGT2is [30] [71] [72] [73] [74]. Empagliflozin also greatly improved the quality of life of HFrEF patients [75].

Outcomes of the EMPEROR-Reduced trial confirmed data reported in the DAPA-HF trial, all in favor of SGLT2is for the treatment of HFrEF, across patient characteristics and medical history. Based on both trials' eligibility criteria, patients with eGFR < 30 ml/min/1.73m^2 or with systolic BP < 95 mmHg are not eligible for dapagliflozin treatment, and those with eGFR < 20 ml/min/1.73m^2 or with systolic BP < 100 mmHg or >180 mmHg are not eligible for empagliflozin treatment.

A recent meta-analysis of DAPA-HF and EMPEROR-Reduced concluded that dapagliflozin and empagliflozin were beneficial in HF management, as they consistently decreased the rate of hospitalization for HF, improved renal outcomes and reduced CV death in patients with HFrEF [30].

Based on these two robust trials, the 2021 ESC guidelines recommend dapagliflozin or empagliflozin as first-line treatment for patients with HFrEF to reduce the risk of HF hospitalization and death (Class 1 Level A) [29] [58].

5. Sequencing of Quadruple Therapy in HFrEF: Where Do SGLT2is Stand?

1) Sequencing of HFrEF therapy in 2021

With quadruple therapy turning into the mainstay of HFrEF management, the sequence of introducing these medications has become a point of discussion. One common recommendation by the ACC, ESC and CCS HF guidelines is to initiate the quadruple therapy within the first 4 weeks or one month. An initiation phase is suggested and a consecutive up-titration phase that may take around 7 - 12 weeks. Two sequencing protocols have been proposed recently. The first protocol, by Packer and McMurray, suggested a three-step sequencing approach of the quadruple therapy. In a first step, a SGLT2i and a BB should be started simultaneously due to the efficacy of BB on reducing sudden death and SGLT2is in reducing hospitalization for HF and in mitigating the potential risk of short-term HF exacerbation upon BB treatment. This is followed 1 - 2 weeks later by the initiation of ARNi therapy (step 2), and 1 - 2 weeks later by a MRA (step 3) [76]. The favorable effects of ARNi and SGLT2i consist in improving renal function and potassium hemostasis and MRA is introduced last since prior treatment with ARNi and SGLT2is increase its tolerability [26].

The second protocol proposed by Greene *et al.* consists in a simultaneous or rapid sequence initiation where all four classes will be initiated simultaneously on day one [14]. ARNi/ACEi, BB and MRA will be initiated at low dosages while SGLT2i has the same initiation and maintenance dose. Then up-titration phase will start between day 7 and day 42.

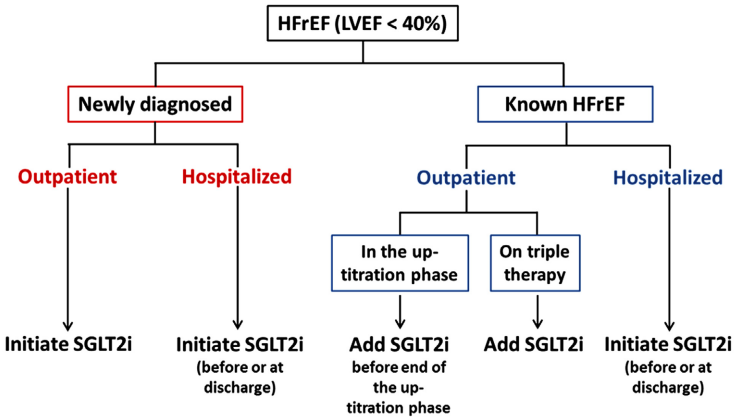
However, in either sequencing proposals, eGFR, blood pressure, heart rate and rhythm as well as potassium level should be taken into consideration and decision of sequencing is based on patient profile and on clinical judgement.

2) HFrEF and Patient Profiling

Patients should be evaluated for health parameters such as heart rate, blood pressure, renal function, and electrolyte levels before treatment initiation, since patient phenotyping may help guide drug layering on a case-by-case basis [77]. Individual cardiac, hemodynamic and biochemical parameters that determine a patient eligibility for quadruple HFrEF therapy include heart rate (>60 bpm), blood pressure (optimally > 90/60 mmHg), volume status (avoid hypovolemia or orthostatic symptoms), potassium level (optimally < 5.0 mmol/l) and kidney function (eGFR > 20 ml/min/1.73m^2) [71]. Interestingly, while BBs, ARnis and MRAs must be discontinued or reduced in patients with one or more of the above conditions, SGLT2is can be sustained in all patients with HFrEF [78]. Figure 2 provides guidance on HFrEF patient eligibility for SGLT2i treatment.

3) SGLT2is in newly diagnosed HFrEF

In newly diagnosed HFrEF patients, all four first-line therapies should be initiated within four weeks, followed by up-titration *pro re nata* [68]. According to ESC 2021 guidelines, dapagliflozin or empagliflozin are recommended as first-line therapy for all patients with HFrEF, to reduce the risk of hospitalization or death (Class I, Level A) [45]. Recent trials have shown SGLT2i efficacy around one month after initiation of treatment and a sustained benefit thereafter, hence



Patient profile	SBP (mmHg)		Cardiac Rhythm		eGFR (ml/min/1.73m^2)		Hemodynamics		HR	K$^+$
	> 90	< 90	A-Fib	Sinus/ paced	< 20*	> 20	Congestion/ Euvolemia	Hypovolemia **	Any	Any
SGLT2i use	✓	X	✓	✓	X	✓	✓	X	✓	✓

A-Fib: atrial fibrillation; eGFR: estimated glomerular filtration rate; HR: heart rate; K$^+$: potassium ion; SBP: systolic blood pressure; SGLT2i: sodium/glucose co-transporter-2 inhibitor

Figure 2. The conditions and profiles of HFrEF patients who can be initiated on SGLT2is. Upper panel: SGLT2i should be initiated in patients with HFrEF whether as outpatients or during hospitalization. Lower panel: Patients with SBP < 90 mmHg, eGFR < 20 ml/min/1.73m^2, or with hypovolemia should not be prescribed SGLT2i. A-Fib: atrial fibrillation; eGFR: estimated glomerular filtration rate; HFrEF: heart failure with reduced ejection fraction; HR: heart rate; K$^+$: potassium ion; SBP: systolic blood pressure; SGLT2i: sodium/glucose co-transporter-2 inhibitor. *Dapagliflozin was evaluated and FDA approved for eGFR > 30 ml/min/1.73m^2. **Intravascular depletion or hypovolemia is not an absolute contraindication and SGLT2i can be reinitiated after correction of the condition.

the importance of introducing it in a timely manner [64] [74] [79]. Depending on the patient profile, a drug sequencing strategy can be initiated as shown in Figure 2.

Figure 3 provides a detailed algorithm for drug layering during the initiation and up-titration of HFrEF quadruple therapeutic pillar.

4) SGLT2is in known HFrEF

From the US experience, around 70% of patients with prior HFrEF diagnosis might be candidates for SGLT2i add-on therapy [80]. This population-wide study once again confirms the substantial benefit of adding SGLT2i to the established HFrEF therapeutic arsenal to alleviate HF burden; despite the challenge of introducing yet an additional therapeutic class in patients already on polypharmacy. Another study also reports on the unequivocal and reproducible benefits of SGLT2i in patients with known HFrEF [81]. Patients on current triple therapy for HFrEF must be considered for SGLT2i treatment, barring any contraindication. Figure 4 below provides punchline tips for HFrEF treatment optimization.

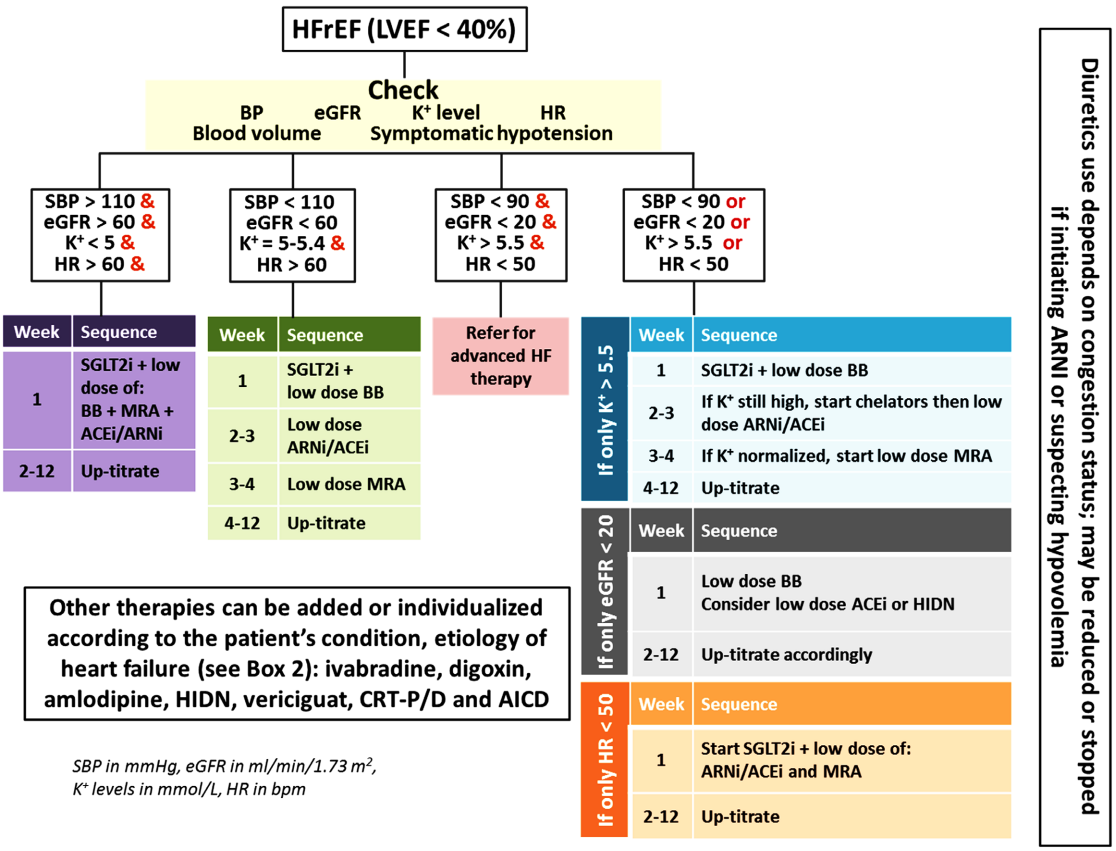


Figure 3. Proposed algorithm for initiation, sequencing and optimization of HFrEF medical therapy. Beta blockers, ARNis/ACEis and MRAs must be initiated at low dose, and up-titrated. SLGT2is are given in a single dose, without a need for up-titration. ACEi: angiotensin-converting enzyme inhibitors; AICD: automatic implantable cardioverter-defibrillator; ARNi: angiotensin receptor-neprilysin inhibitor; BB: beta blockers; BP: blood pressure; CRT-P/D: cardiac resynchronization therapy with pacemaker/defibrillator; eGFR: estimated glomerular filtration rate; HFrEF: heart failure with reduced ejection fraction; HIDN: hydralazine isosorbide dinitrate; HR: heart rate; K: potassium; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; SBP: systolic blood pressure; SGLT2i: sodium/glucose co-transporter-2 inhibitor.

1. In case of normal sinus rhythm and heart rate > 70 bpm on maximal BB therapy or intolerant to higher dosages of BB, start Ivabradine and titrate accordingly
2. In case of atrial fibrillation and heart rate > 80 bpm on maximal BB or intolerant to higher dosages, start digoxin keeping heart rate between 70 and 80 bpm
3. If heart rate < 50 bpm in sinus rhythm or <70 bpm in atrial fibrillation, first reduce Ivabradine or Digoxin doses and if persistent, reduce BB
4. In end-stage renal disease and after titration of BB and ACEi (if possible), if blood pressure is still elevated, consider hydralazine/nitrate or amlodipine; whichever is available although HIDN is preferable
5. If on optimal medical therapy, hypertension persists, consider hydralazine/nitrate or amlodipine; whichever is available although HIDN is preferable
6. If patient develops hyperkalemia, treat the etiology and if persistent, reduce or hold MRA dose first. If still persisting, reduce ACEi/ARNi as a second step; if this fails to normalize kalemia, initiate chelators
7. In low blood pressure, first consider the dose reduction or the discontinuation of all non-class I HFrEF medications that affect blood pressure
8. In low BP in sinus rhythm ivabradine can be considered before BB then BB maybe added
9. If low blood pressure and atrial fibrillation, digoxin can be considered before BB
10. Starting SGLT2i first may reduce the chance of hyperkalemia in those with borderline elevated potassium levels and may offer a chance to initiate or up-titrate ARNi/ACEi or MRAs
11. Starting ARNi may give a better chance to initiate or up-titrate MRAs without the risk of hyperkalemia
12. No indication to reduce diuretic dose when initiating SGLT2i, except if patient is hypovolemic or intravascularly depleted

Figure 4. Tips for optimizing HFrEF therapy.

SGLT2is can be initiated before achieving the target or maximally tolerated dose of the three other HFrEF therapeutic pillars [31].

A large phase IV study is currently running. It plans to enroll 2400 patients with HFrEF admitted for decompensated HF and randomized to in-hospital initiation of dapagliflozin. This investigator-initiated, randomized, double-blind, placebo-controlled trial will collect clinical outcomes of CV death or worsening HF over two months (DAPA ACT HF-TIMI 68, NCT04363697). Until study results are out, current recommendations endorse SGLT2i treatment initiation upon HFrEF diagnosis and in patients with known chronic HFrEF, both in in-patient and out-patient settings prior to discharge [12] [32] [82].

6. SGLT2is in Acute Heart Failure Settings

With all the progress in chronic HFrEF management there is still scarcity of therapy in the acute HF settings. Since volume overload and congestion are the mainstay of acute HF presentation, diuretic therapy is still the leading intervention in the acute setting followed by vasodilators and to a lesser extent inotropic therapy. Although loop diuretics remain at the forefront of treatment, they still do not always result in adequate decongestion and patients often deteriorate [10] [78] [83].

Given their undeniable success in mitigating HFrEF-associated morbidity and mortality and their diuretic activity, SGLT2is come by as promising agents in addressing episodes of acute HF, during hospital stay and beyond. A recent trial reported disappointing benefits of empagliflozin on dyspnea, diuretic response, NT-proBNP levels and length of hospital stay in patients with acute HF; while it

significantly reduced the composite endpoint of worsening HF, re-hospitalization for HF and death and increased urine output [84]. Possible limitations of this trial consist of a small sample size (80 acute HF patients randomized to empagliflozin or placebo) and the relatively limited follow-up period (30 months). A second trial, the EMPULSE trial that was presented in the American Heart Association 2021 meeting randomized 530 patients with acute HF regardless of LVEF and diabetes status into either empagliflozin 10 mg or placebo and followed up for 90 days [85]. Empagliflozin arm *versus* placebo was associated with significant clinical benefit that includes composite endpoint of death, number of HF events (including hospitalization for HF, urgent HF visits and unplanned outpatient visits), time to first HF event and change from baseline in the Kansas City Cardiomyopathy Questionnaire-total symptom score. Empagliflozin *versus* placebo was also associated with fewer deaths, improvement in quality of life, and greater reduction in body weight. There were no safety concerns with empagliflozin [86]. More studies are needed to see the acute effect of SGLT2is in the initial phase of acute HF management.

The ESC 2021 HF guidelines currently recommend initiating oral medication before discharge if patient is admitted to the hospital, and following up on the patient within one or two weeks afterwards to assess signs of congestion, drug tolerance and need for dose up-titration (Class 1, Level C) [29].

As part of the TRANSLATE-HF research series, the eligibility of HFrEF patients to initiate dapagliflozin treatment based on the US FDA was evaluated. Among the 154,714 hospitalized HFrEF patients, over 80% were found to be candidates for dapagliflozin. The analysis found that compromised kidney function topped the reasons for non-eligibility for dapagliflozin use [87]. In a nutshell, this very large study suggests that 4 out of 5 HFrEF patients (with or without type-2 diabetes) are candidates for initiation of dapagliflozin.

Noteworthy, patients admitted to the hospital with acute HF decompensation will not need to stop SGLT2i medication [88], except if presenting with eGFR < 20 ml/min/1.73m^2, cardiogenic shock or diabetic ketoacidosis. If the patient was not on SGLT2is, this treatment can be initiated after stabilization and pre-discharge [89]; or in the first post-discharge visit barring any contraindications or hypersensitivity.

7. Clinical Considerations While Prescribing SGLT2is

In addition to their efficacy and safety, SGLT2is have clear indications, rare contraindications, hypersensitivity or precautions for use, simple dosing regimen, straightforward patient counseling and few red flags.

1) Indications and dosage

Most trials included HF patients who had an EF < 40% and, according to the New York Heart Association (NYHA) Functional Classification, class II or III HF. Irrespective of their diabetes status, all patients equally benefited from SGLT2i treatment in terms of mortality, morbidity and quality of life. Dapaglif-

lozin and empagliflozin are given as a 10 mg daily tablet, with no up-titration or dose escalation needed, and they can be prescribed for patients with compromised kidney function (eGFR > 30 ml/min/1.73m^2 for dapagliflozin and eGFR > 20 ml/min/1.73m^2 for empagliflozin). SGLT2is impart a low risk of hypoglycemia, unless combined with sulfonylureas and/or insulin. Based on trial success and with robust literature support, SGLT2is should be prescribed to most patients with HFrEF [80] [81].

2) Contraindications

SGL2is are not indicated in type-1 diabetes and must not be given to patients with a history of or susceptibility to diabetic ketoacidosis, a systolic blood pressure below 90 mmHg or with advanced (class 4) chronic HF, due to limited clinical experience. Pregnant patients should not be taking SGLT2i treatment, which is contraindicated past the first trimester and patients breastfeeding their babies should not be on SGLT2is given the lack of clinical evidence [90].

An initial drop in eGFR after initiation of SGLT2i treatment does not indicate worsening of kidney function, but represents hemodynamic changes that are renoprotective upon long-term use of SLGT2is [91].

3) Clinical scenarios to hold and resume SGLT2i

SGLT2i treatment must be withheld in case of acute illness (infection, stroke, gastroenteritis), while preparing for bariatric surgery and on low-carbohydrate diet and while at risk for dehydration (extensive exercise, preparing for a colonoscopy, diarrhea). SGLT2i treatment must be stopped immediately in case of an alcohol binge [92]. In the rare but likely event of diabetic ketoacidosis (suspected or diagnosed), SGLT2i treatment should be discontinued and the exact cause of ketoacidosis must be determined. SGLT2i treatment should also be interrupted in patients undergoing major surgical procedures (3 days before the intervention) or suffering from an acute serious medical illnesses. In case SGLT2i treatment had to be discontinued, it can be reinitiated once the above-mentioned complications are resolved, the relationship between SGLT2i treatment and diabetic ketoacidosis is ruled out, and the patient becomes hemodynamically stable [31].

4) Combination therapies in HFrEF

Clinical experience has shown that SGLT2is do not entail undesirable interactions with other agents, combinations and devices used for HF management [70]. In particular, patients on diuretics [93], on sacubitril/valsartan [94], and on MRA [95] are candidates for SGLT2i use. The limited possibility of drug-drug interactions further endorsed the inclusion of SGLT2is in the quadruple HF therapy.

5) Peri-, pre- and post-discharge therapy in HFrEF

Hospital readmission is frequent among HF patients and the frequency of admissions will determine the prognosis and CV outcome [96] [97]. Almost half of patients hospitalized for HF are re-admitted for any cause at least once within 12 months of discharge [98] and one quarter within 30 days of discharge [99].

Mortality is twice as likely during the first 30 days, compared to 6 months post-discharge [100]. However, patients discharged after re-hospitalization for HF are twice as likely to initiate GDMT [101] [102] [103], which translates into a decrease in complication rate. This was confirmed in a registry carried out by the HFA of the ESC [104]. One common strategy is to initiate treatment at low dose and titrate slowly upward as tolerated. Therefore, GDMT during hospitalization provides an opportunity to optimize chronic HF therapy. High starting doses and/or overly aggressive titration can result in hypotension and worsening kidney function, setbacks that limit both decongestion and initiation of different components of GDMT.

All hospitals in Lebanon would benefit from a unified protocol for pre- and post-discharge of HF patients. **Supplementary Figure S1** offers a diagram to guide the implementation of optimal HF care in Lebanon. A multidisciplinary team should consort efforts to elaborate the protocols (and checklists) and oversee their implementation. This team should include the cardiologist in charge of HF unit, the fellows (in academic hospitals), the HF unit nurse, a nutritionist and potentially a patient representative of HF patients, if feasible.

The discharge protocol for HF patients can be based on the 2019 ACC Expert Consensus Decision Pathway, a complete, well done and simple protocol that includes patient's data, type of HF, ejection fraction, comorbidities, GDMT discharge medications and follow up data [105]. The multidisciplinary team should also verify that a discharge checklist (based on the admission checklist) has been duly completed. Besides individual patient benefit, such checklists inform on the the degree of adherence to a standard of care. Key Performance Indicators (KPIs) for HF care reflect adherence to standard of care recommendations. KPIs should be reported on a yearly basis and they include items shown in **Supplementary Figure S1(c)**. Another tool by the ACC, the TreatHF downloadable for free (https://www.acc.org/Tools-and-Practice-Support/Mobile-Resources/Features/TreatHF), is a simple, easy-use application for physicians, to follow up on their HF patients.

8. Patient Education in HFrEF

1) Role of Patient Counselling in HFrEF

Misunderstandings, misconceptions, and lack of knowledge all contribute to insufficient self-care and therefore patient education is vital to improve self-care skills. In order to reach the broadest possible population, information can be provided in a multitude of formats, taking into account educational grade and health literacy. Patients can also be actively involved in learning, through the ask-tell-ask, the teach-back or the motivational interviewing approaches. Barriers to communication but also barriers to change must be recognized; including language, social skills, cognitive ability, mental health, hearing or visual impairment, as well as perceived benefits and readiness to learn and change. The https://www.heartfailurematters.org/ online tool offers help and guidance to pa-

tients with HF and their caregivers, in 10 different languages, including Arabic. Patients newly diagnosed with HFrEF or patients whose therapeutic management is being modified are encouraged to participate in educational activities, preferably along with a family member or caregiver. In addition to daily management of their condition, patients must be counselled on the importance of genital/perineal hygiene, foot examination, and symptoms of orthostatic hypotension and diabetic ketoacidosis [106] [107].

2) Patient education on SGLT2is

Patients with HFrEF or other chronic conditions or on metabolism-modulating medications must learn to gauge their physical status and response to treatment. In particular, patients on SGLT2i should take their medications as prescribed, contact their treating physician in case of any doubt concerning their treatment. Patients must keep up with recommended fluid intake by their healthcare providers. In case of loss of appetite, diarrhea or vomiting, patients should seek medical care to check whether they have to adjust their medications, reduce or temporarily hold them (whether SGLT2i or other glucose-lowering agents) [81] [108].

Patients newly initiated on SGLT2i must be made aware of some side effects, such as the potential risk of genital mycotic infections [109]; however, individual patient profiles might bring about different potential risks [77]. The healthcare provider team is responsible for explaining the different conditions to patients and their caregivers.

Patients must be advised to avoid alcohol excess and ketogenic diet, watch for orthostatic symptoms and ensure proper perineal and foot hygiene [109]. They should report abnormal urination, gastrointestinal disturbances and other new adverse events to their physician.

3) Physician education

The four key specialties (cardiologists, nephrologists, endocrinologists and primary care physicians) dealing with HFrEF patients and with patients on SGLT2i as part of a polypharmacy regimen must stay updated on the rapidly changing clinical management of HFrEF and emerging adverse effects of agents taken separately or in combination.

While designing the therapeutic management for their patients, physicians should adjust/discard non-evidence-based treatments for HF before initiating SGLT2is. While patients with low blood pressure (<90 mmHg) or hypovolemia must not be prescribed SGLT2is (or any other drug with diuretic effects), those with hypertension or hypervolemia can be started on SGLT2is without adjusting other blood pressure-lowering medications [110]. Patients with HFrEF and type-2 diabetes should be examined and managed collaboratively with a diabetologist [109].

9. Potential Role of SGLT2is in HFpEF and HFmrEF

No major therapy for this group of patients has been so far established. In the

2021 ESC HF guidelines, pharmacological treatments for HFmrEF include diuretics (Class I, Level C), ACEi, ARB, BB, MRA and sacubitril/valsartan (all Class IIb, Level C) [29]. No new recommendations for HFpEF treatment were included in the updated guidelines, but key trials (briefly reviewed thereafter) have recently reported on the beneficial effects of empagliflozin in this category of HF patients.

The ***EMPEROR preserved*** trial (results published after the 2021 ESC HF guidelines) evaluated empagliflozin in patients with chronic HF and preserved LVEF > 40% (HFpEF), who have previously never used SGLT2is and for whom a SGLT2i can be prescribed. The composite primary endpoint included time to CV death or time to hospitalization for HF, over 38 months. Compared to placebo, the empagliflozin arm was associated with a 21% lower rate of hospitalization for HF and CV death ($P < 0.001$); even in patients with type-2 diabetes and regardless of LVEF [71]. In particular, close to one third of hospital admissions dodged the need for cardiac or intensive care unit, and there was a 33% reduction in the need for vasopressor or positive ionotropic drugs during hospitalization [71]. Over half of the patients had chronic kidney disease at trial entry. The yearly decline of eGFR was significantly slower (by 1.36 ml/min/1.73m^2) in patients on empagliflozin, compared to placebo [111]. Empagliflozin improved kidney function across the full range of eGFR and improved CV outcomes in patients regardless of their kidney function.

The ***PRESERVED-HF*** trial, a large and comprehensive trial reporting on the benefits of a SGLT2i on patient-reported outcomes, as well as on objectively evaluated performance of HFpEF patients revealed improved quality of life after 12 weeks of treatment with dapagliflozin. Patients reported significant improvement of symptoms, physical limitations, and 6-minute walking distance [112].

The ***DELIVER*** trial evaluated dapagliflozin in HFpEF or HFmrEF patients in a phase III international, multicenter, parallel group, event-driven trial that randomized 6263 patients to 10 mg dapagliflozin once daily *versus* placebo, on top of standard of care [113] [114]. The primary outcome was a composite of worsening heart failure or CV death and it occurred in more patients on placebo (19.5%) than on dapagliflozin (16.4%, $P < 0.001$). Additionally, the overall symptom burden was lower in the dapagliflozin group and the safety profile was similar across treatment arms [114].

Subgroup analyses from the ***DELIVER*** and the ***EMPEROR preserved*** trials will help guide clinical decision in this group of HF patients. In the near future, further development on HFpEF and HFmrEF will be established with ongoing trials and real-world evidence that may be a mainstay of another new national guidance.

10. Conclusion

Awareness should be promoted among physicians in Lebanon as to the importance of prescribing SGLT2is to HFrEF patients, in line with international guide-

lines. The establishment of a national protocol for HFrEF management and the launching of educational campaigns and materials can be managed by the HF working group within the LSC. The evidence is unequivocal and quadruple therapy including SGLT2is will protect Lebanese HFrEF patients from CV death, heart failure hospitalization, worsening renal failure and improve their quality of life.

11. Take-Home Messages

- When suspecting HF, it is recommended to perform: electrocardiogram, transthoracic echocardiogram, chest X-ray, blood tests including cell count, urea and electrolytes, thyroid function, HbA1c, lipid, iron studies, and BNP/NT-proBNP.
- SGLT2i (mainly dapagliflozin and empagliflozin) are now a cornerstone in the first-line quadruple therapy for HFrEF with LVEF < 40%; together with ARNi/ACEi, BB and MRA.
- In newly diagnosed HFrEF, BB, ARNis and MRAs must be initiated within the first 4 weeks at low doses and up-titrated accordingly over 4 - 12 weeks. SLGT2is are given in a single dose with no need for up-titration. GDMT during hospitalization allows optimizing chronic HF therapy.
- Overall, 4 out of 5 patients with HFrEF, with and without type-2 diabetes, would be candidates for dapagliflozin based on FDA labeling, as per the TRANSLATE-HF data.
- SGLT2is (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are now recommended in patients with type-2 diabetes at risk of CV events to reduce hospitalizations for HF, major CV events, end-stage renal dysfunction, and CV death (Class 1A).
- SGLT2is (dapagliflozin, empagliflozin, and sotagliflozin) are now recommended in patients with type-2 diabetes and HFrEF to reduce hospitalizations for HF and death (Class 1A).
- Dapagliflozin and empagliflozin provided a significant reduction in the primary endpoint, in hospitalization for HF and CV death for dapagliflozin, irrespective of type-2 diabetes status, across baseline LVEF, age groups, and other HF treatments.
- Dapagliflozin is the only SGLT2i to significantly reduce the rate of CV death from HF.
- Dapagliflozin and empagliflozin significantly improve quality of life and performance.
- Despite rare but potential risks, the net clinical benefit of starting SGLT2is among patients with HFrEF is undeniable.
- The need to promote awareness campaigns on HF, via lectures, media, leaflets distributed at clinics has been identified. The creation of a "National HF Management Program" to train specialized nurses, educate residents and physicians, and drive awareness campaigns and training on the diagnosis, management and referral of HF patients has been proposed.

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Supplementary

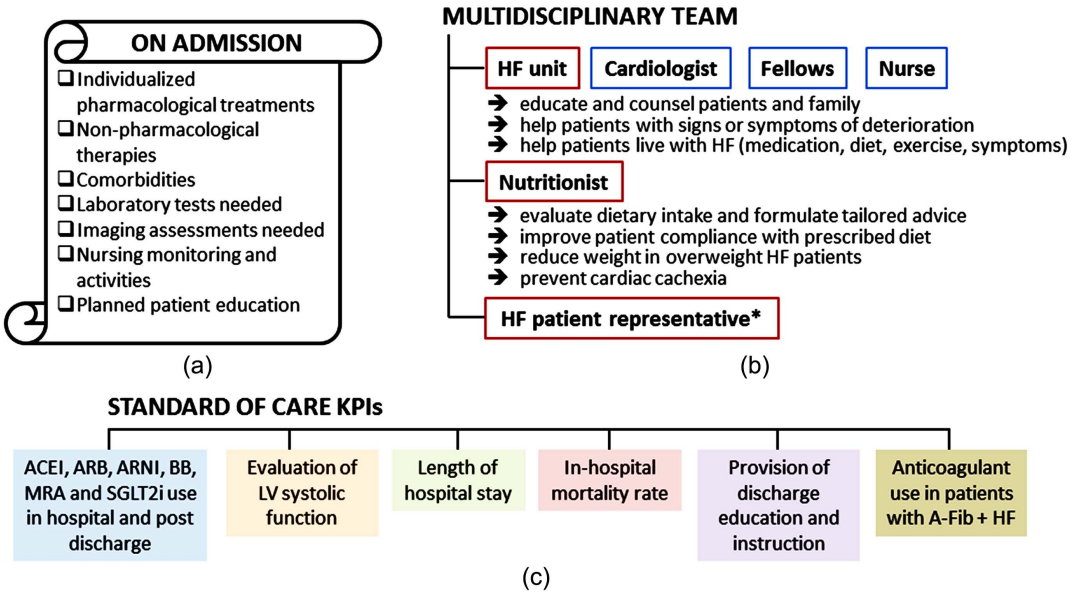

Figure S1. Management of hospitalized HF patients. (a) Proposed outline of a checklist that can be completed at admission and revised prior to discharge. (b) The multidisciplinary team works together to verify that patient care takes place as per applicable local protocols and international guidelines. A nutritionist advice might be indispensable for weight reduction among HF patients and for adjusting the diet to the prescribed pharmacological medications. (c) KPIs quantify the degree of adherence to standard of care. ACEi: angiotensin-converting enzyme inhibitor; A-Fib: atrial fibrillation; ARNi: angiotensin receptor-neprilysin inhibitor; BB: beta-blocker; HF: heart failure; KPI: key performance indicator; LV: left ventricular; MRA: mineralocorticoid receptor antagonist; SGLT2i: sodium/glucose co-transporter-2 inhibitor. *Optional.