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Focused Clinical Practice Update

Canadian Cardiovascular Society-Canadian Heart Failure Society Focused Clinical Practice Update of Patients With Differing Heart Failure Phenotypes

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ABSTRACT

A number of societies produce heart failure (HF) management guidelines, comprising official recommendations on the basis of recent research discoveries, but their applicability to specific situations encountered in daily practice might be difficult. In this clinical practice update we aim to provide responses to fundamental questions that face health care providers, like appropriate timing for the introduction and

RÉSUMÉ

Un certain nombre de sociétés élaborent des lignes directrices sur la prise en charge de l'insuffisance cardiaque (IC), qui comprennent des recommandations officielles fondées sur les dernières découvertes scientifiques, mais qui peuvent être difficiles à appliquer dans certaines situations particulières rencontrées dans la pratique quotidienne. Cette mise à jour concernant la pratique clinique vise à fournir

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This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of interdisciplinary experts on this topic. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources.

Patients living with heart failure (HF) can have different characteristics, traits, and clinical presentation, defined as HF phenotypes. For instance, HF can be classified according to the acuity of clinical presentation, duration of disease, etiology, left ventricular (LV) ejection fraction (LVEF), and associated comorbid conditions. It is increasingly evident that the clinical management of HF and the trajectory of disease progression also depend on these factors. There are comprehensive guidelines and position statements by the Canadian Cardiovascular Society (CCS) and Canadian Heart Failure Society[1-4] that were updated over the past decade. Unfortunately, widespread adoption of these guidelines has been inadequate, leaving the majority of patients receiving suboptimal therapy.[5] Good adherence to the guidelines can be achieved when HF management is managed by a multidisciplinary specialized team,

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optimization of different classes of medication according to specific patient phenotypes, when second-line therapies and valvular interventions should be considered, and management of difficult clinical scenarios such as cardiorenal syndrome and frailty. A consensus-based methodology was used. Approaches to 5 different phenotypes are presented: (1) The wet HF phenotype is the easiest to manage, decongestion being performed alongside introduction of guideline-directed medical therapy (GDMT); (2) The *de novo* HF phenotype requires the introduction of the 4 pillars of GDMT, personalizing the order on the basis of the individuals' biological and physiological characteristics; (3) The worsening HF phenotype is a marker of poor prognosis, and therefore should motivate optimization of GDMT, start second-line therapies, and/or reevaluate goals of care/advanced HF therapies; (4) The cardiorenal phenotypes require correct volume assessment, because renal function usually improves with decongestion; and (5) The frail HF phenotype require special attention, careful drug titration, and consideration of cardiac rehabilitation programs. In conclusion, specific common HF phenotypes call for a personalized approach to improve adoption of the HF guidelines into clinical practice.

des réponses aux questions fondamentales que se posent les dispensateurs de soins de santé, comme le moment approprié pour instaurer et optimiser des médicaments de classes différentes en fonction des phénotypes particuliers des patients, lorsque des traitements de deuxième intention et des interventions valvulaires doivent être envisagés, et la gestion de scénarios cliniques difficiles tels que le syndrome cardiorénal et la fragilisation. Une méthodologie basée sur le consensus a été utilisée. Des approches ciblant cinq phénotypes différents sont présentées : 1) le phénotype d'IC avec congestion est le plus facile à maîtriser, la décongestion étant réalisée parallèlement à l'instauration d'un traitement médical fondé sur les lignes directrices (TMLD); 2) le phénotype d'IC *de novo* nécessite la mise en œuvre des quatre piliers du TMLD, en personnalisant la séquence de mise en œuvre en fonction des caractéristiques biologiques et physiologiques du patient; 3) le phénotype d'IC avec épisodes d'aggravation est un marqueur de pronostic défavorable, et doit donc motiver l'optimisation du TMLD, l'instauration de traitements de deuxième intention ou la réévaluation des objectifs de soins/traitements avancés de l'IC; 4) les phénotypes cardiorénaux exigent l'évaluation correcte de la volémie, car la fonction rénale s'améliore habituellement avec la décongestion; et 5) le phénotype d'IC dans un contexte de fragilité qui exige une attention particulière, un ajustement rigoureux de la posologie des médicaments, et la prise en considération de programmes cardiaques de réadaptation. En conclusion, les phénotypes d'IC courants requièrent une prise en charge personnalisée afin d'améliorer l'adoption des lignes directrices relatives à cette affection dans la pratique clinique.

focusing on patients' physiological and biological limitations in addition to target dosage of the recommended pharmacological agents.[6] A personalized approach might lead to improved outcomes.[7] In this clinical practice update (CPU), we focus our attention on the important clinical phenotypes of HF and how the health care team can recognize them and provide phenotypic-based care applying the current guidelines to a specific individual. These phenotypes are not necessarily mutually exclusive and might coexist in the same patient with any given presentation. Also, these are dynamic presentations and potentially modifiable with treatment targeted at the principal hemodynamic derangements.

Specifically, we focus on the following HF phenotypes: (1) the wet hypertensive HF patient; (2) the patient with *de novo* HF; (3) the patient with worsening HF (WHF); (4) the HF patient with cardiorenal syndrome (CRS); and (5) the frail HF and/or hypotensive patient. Each of these patients with HF have unique considerations for diagnosis and treatment on the basis of their clinical presentation and their disease prognosis.

HF Phenotypes: Diagnosis and Management Considerations

1. The wet HF phenotype

Patients with acute HF (AHF) often present with a variety of different clinical features, regardless of LVEF and can be managed in acute and ambulatory care settings. Early efforts to outline the phenotypes have provided only a rough guide with many overlapping features. In many of the classification systems used, elevated blood pressure (BP) and the presence of volume overload or maldistribution are consistent across definitions.[8]

The wet hypertensive patients are relatively easier to care for, because of an elevated systolic BP (SBP), which provides for a greater range of options for initial treatment. A higher BP upon presentation is linked to better outcomes,[9] although SBP is dynamic and changes rapidly because of many variables, including ischemia, atrial arrhythmias, renal function, volume loading, and tachypnea.

Most patients with AHF have volume overload or redistribution, as evidenced by the constellation of pulmonary edema, ascites, and/or lower extremity edema, which might have been present for hours (in rapid pulmonary edema) to days or weeks (in patients who slowly decompensate at home). The fluid shifts between compartments (eg, intra- and extravascular spaces) and increase in total body water lend themselves well for approaches to therapy.

Overall, the mainstay of initial treatment remains loop diuretics and/or a combination of loop and thiazide diuretics.[4] Intravenous (I.V.) furosemide is the most common initial diuretic, and time to diuresis has been put forward as a potential quality indicator because of the ubiquity of this therapy in the treatment pathways.[10] In the **A**cetazolamide in Acute **D**ecompensated Heart Failure With **V**olume **Ov**er**l**oad (ADVOR) trial, the additional use of acetazolamide (500 mg bolus and 500 mg/d infusion with 3 g of magnesium for 2 days or until decongestion) to I.V. loop diuretics (prescribed at twofold the oral dose) led to superior decongestion of patients admitted for acute decompensated HF[11]; the incidence of adverse effects was comparable, including renal failure, hypokalemia, and hypotension. It is important to note that patients who received sodium glucose cotransporter-2 inhibitor (SGLT2i) were excluded because their site of action is the same as acetazolamide.[11] Therefore, SGLT2i

should be favoured over acetazolamide for maintenance treatment.

Other therapies that have been suggested in hospitalized patients include vasodilators (eg, ularitide, serelaxin, nesiritide, nitroglycerin), inodilators (eg, levosimendan, TRV027, milrinone in nonshock patients) and other variations on diuretics (eg, vasopressin antagonists); in patients with severely impaired kidney function, only the combination of hydralazine and nitrates may be considered but has not been tested in large clinical trials conducted in hospital. None of these have been successful in reducing the morbidity or mortality in patients with AHF.

Hospital admission should be an opportunity for early initiation of guideline-directed medical therapy (GDMT), especially mineralocorticoid receptor antagonists (MRA) regardless of LVEF,[12] which should be favoured over potassium supplements. Switching an angiotensin receptor blocker or angiotensin converting enzyme inhibitor to angiotensin receptor neprilysin inhibitor (ARNI) should be done early and ideally at the time of clinical presentation for those with HF and reduced ejection fraction (HfrEF; LVEF $\leq$ 40%).[11,13] The introduction of an SGLT2i should also be considered early, as soon as the patient has been stabilized, and before discharge because of the benefits of these agents on hospital readmission, regardless of LVEF.[14,15]

Risk stratification, HF pathways of care, and identifying comorbid conditions that affect care alongside dedicated teams to manage patients with AHF are currently the best treatment strategy in addition to diuretics and optimizing indicated medications.

2. The *de novo* HF phenotype

a. Characteristics and causes. Patients with *de novo* HF present with a new onset of symptoms and signs of HF without a previous diagnosis or documentation of HF or LV dysfunction,[16] regardless of the clinical setting (ambulatory or inpatient). Important differences in the clinical characteristics and outcomes of patients with *de novo* HF have been observed compared with patients with an exacerbation of chronic HF. Patients with *de novo* HF are younger and more likely to present in the context of an acute coronary syndrome. They are also less likely to have significant comorbid disease such as diabetes, chronic obstructive pulmonary disease, atrial fibrillation, and a history of vascular disease.[17] When hospitalized, patients with *de novo* HF have better dyspnea relief and lower postdischarge and 1-year mortality rates compared with patients with an acute exacerbation of their chronic HF.[17,18] Patients with *de novo* HF might also be in a favourable position to receive GDMT with the associated improvement in outcomes and reduction in rehospitalization, emphasizing the need for prompt and thorough management of this patient phenotype.[19] Like the previous phenotype, it seems reasonable to manage these patients with GDMT as early as possible and their introduction could be in pairs. For example, diuretics and MRA could be introduced first in hospitalized patients with fluid overload. For those with HFrEF, ARNI and β-blockers (BBs) should be the next modality of treatment, with SGLT2i being introduced last, but ideally before discharge.[20] A cluster scheme has been proposed, combining classes of medication with different side effects profiles (Fig. 1).[20]

In ambulatory patients with *de novo* HF, early initiation of SGLT2i might be considered, even while waiting for echocardiography to be performed to delineate whether the patient has HFrEF, because these agents are beneficial regardless of LVEF.[21,22]

b. Considerations of therapy and challenges. Irrespective of the cause of HF (whether new-onset or an exacerbation of chronic HF), guideline directed initiation/optimization of foundational HF treatment including ARNIs (angiotensin converting enzyme inhibitor/angiotensin receptor blocker), BB, MRA, and SGLT2i therapy is an essential part of HFrEF management. How these therapies are introduced in a patient naive to such treatments will depend on hemodynamic stability, BP, heart rate, and renal function. BB therapy should only be initiated when patients have no residual signs of congestion or signs of low output, particularly if treatment-naive. SGLT2i therapy can be introduced safely in patients with appropriate renal function, when I.V. therapies are stopped,[23] even when there is some mild residual congestion.[24]

Although the questions of when and how to introduce sacubitril/valsartan has been the subject of debates in the early days, its safety and efficacy in *de novo* HFrEF patients has been reported in ambulatory and hospital settings[25,26]; the subgroup with newly diagnosed HF being more likely to achieve target dose of sacubitril/valsartan at 10 weeks with fewer serious adverse reactions compared with subjects with established HF,[27] more substantial decreases in N-terminal pro hormone brain natriuretic peptide (NT-proBNP) and lower rates of rehospitalization without compromising uptitration of other GDMT. Likewise, one-third of patients enrolled in the Com**p**ar**i**son **o**f Sacubitril/Valsarta**n** Versus **E**nalapril on **E**ffect on Nt-P**r**o-Bnp in Patients Stabilized From an Acute **H**eart **F**ailure Episode (PIONEER-HF) trial had *de novo* HF and just more than half were renin angiotensin system inhibitor-naive patients.[13] Although not the primary goal of the study, an exploratory analysis of its open-label extension showed that patients who began treatment with ARNIs in-hospital had a lower incidence of subsequent HF events, including HF hospitalization (HFH) or cardiovascular mortality through the entire 12-week trial period compared with patients who were treated with ARNIs after the first 8 weeks (13.0% vs 18.1%; $P = 0.03$).[28]

First-line ARNI introduction must be considered in patients with adequate BP (systolic $>$ 100 mm Hg), stable renal function (estimated glomerular filtration rate $>$ 30 mL/min/1.73 m^2), and those in whom reliable reassessment of safety laboratory results (recheck of serum electrolytes, creatinine) can be achieved within 1 week. For most patients, especially those naive to previous renin angiotensin system inhibition therapy, starting at the lowest dose is recommended, with uptitration within 1-2 weeks as the patient tolerates. The proposed scheme of introduction of the different class of agents for the *de novo* HF phenotype is presented in Figure 2.

3. The WHF phenotype

There is not a universal definition of WHF; indeed, each published trial used its own definition and time frame, making comparisons difficult for trial results. Nevertheless, WHF is generally defined as WHF symptoms and signs requiring an

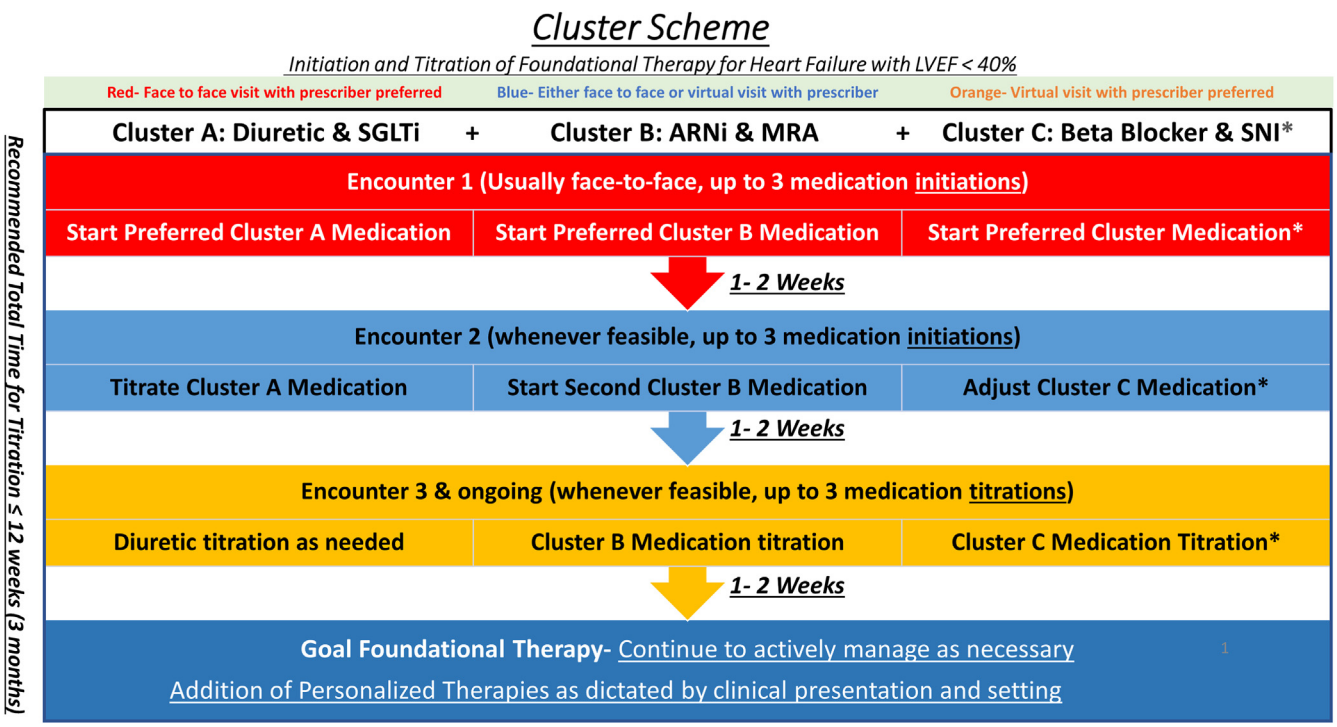

Figure 1. Initiation and titration of foundational therapy for heart failure with left ventricular ejection fraction (LVEF) ≤ 40%.[20] * Sinus node inhibitor (SNI) was the original acronym given on this figure from Miller et al.[20] The real class name: hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blockers. ARNI, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonists; SGLTi, sodium glucose cotransporter inhibitor. Reproduced from Miller et al.[20] with permission from Elsevier.

intensification of therapy[29,30]; several studies showed that even just an increase in oral diuretics is associated with increased risk of short-term events. So WHF can be a spectrum of increased oral diuretics, outpatient I.V. diuretics, unscheduled clinic visit, visit to emergency room, or admission. It is difficult to ascertain the exact epidemiology of WHF because of these varying published definitions, but WHF accounts for anywhere from 5% to 42% of HF admissions. The most common causes of worsening of chronic HFare ischemia, arrhythmias, valvular dysfunction, systemic or pulmonary hypertension, volume overload or fluid retention, high-output conditions (infection, anemia, thyrotoxicosis), drugs (nonsteroidal anti-inflammatory drugs, cyclo-oxygenase inhibitors, thiazolidinediones), and HF medication change (decrease in diuretics, patient's noncompliance, etc).

Patients hospitalized with WHF are at high risk for adverse outcomes postdischarge, with high readmission rates (0.7 per patient at 30 days and 2.0 at 24 months postworsening event). These patients also exhibited a rapid decline in survival starting soon after a WHF event, with almost 30% of the patients not being alive within 2 years.[31] Although only a few trials specifically targeted patients with WHF (see The WHF phenotype), a first step is to optimize GDMT and see this hospital admission as an opportunity to improve care. The **O**rganized **P**rogram **t**o **I**nitiate Lifesaving Treat**m**ent **i**n Hospitali**z**ed Patients With **H**eart **F**ailure (OPTIMIZE-HF)[32] registry evaluated the relationship between use of carvedilol and early clinical outcomes in patients discharged while receiving BBs (93.3%) 60 and 90 days after discharge, compared with those not receiving BB therapy at discharge (30.4%).[33] Predischarge use of carvedilol was well tolerated with high rates of continued therapy at follow-up and was associated with a significant reduction in mortality at 90 days (hazard ratio [HR], 0.46; $P \leq 0.01$) and the combination of mortality or rehospitalization (odds ratio, 0.71; $P = 0.02$) compared with the group without BBs at discharge. More recently, the PIONEER-HF trial discussed previously, showed the safety and benefit of introducing/switching to an ARNI compared with enalapril, with significant reduction of NT-proBNP[13] and subsequent clinical events.[28]

Despite the high event rate, developing new therapies for these patients has been challenging, in part because of the lack of reliable surrogate markers to predict future risk. Only 4 trials have enrolled patients with WHF.

In patients with diabetes hospitalized for HF, the Effect of **So**tagli**flo**zin on Cardi**o**va**s**cular Events in Patients With **T**ype 2 Diabetes Post **W**orsening **H**eart **F**ailure (SOLOIST-WHF) trial showed a reduction in cardiovascular events (HR, 0.67; 95% confidence interval [CI], 0.52-0.85; $P < 0.01$) of the combined SGLT2i and sodium glucose cotransporter-1 inhibitor sotaglifozin[23] (50% initiated after discharge), but this agent is not available commercially. More recently, the **Emp**agliflozin 10 mg Compared to Placebo, Initiated in Patients Hospitalised for Ac**u**te Heart Fai**l**ure (de Novo or Decompensated Chronic HF) Who Have Been **S**tabili**s**ed (EMPULSE) trial[14,15] showed that the SGLT2i empagliflozin was beneficial at reducing the composite of death, number of HF events, time to first HF event, and change in **K**ansas **C**ity **C**ardiomyopathy **Q**uestionnaire-**T**otal **S**ymptom **S**core (KCCQ-TSS) from baseline to 90 days among 530 acute decompensated HF patients, regardless of ejection fraction (median LVEF of 31%) or diabetes status. Clinical stability

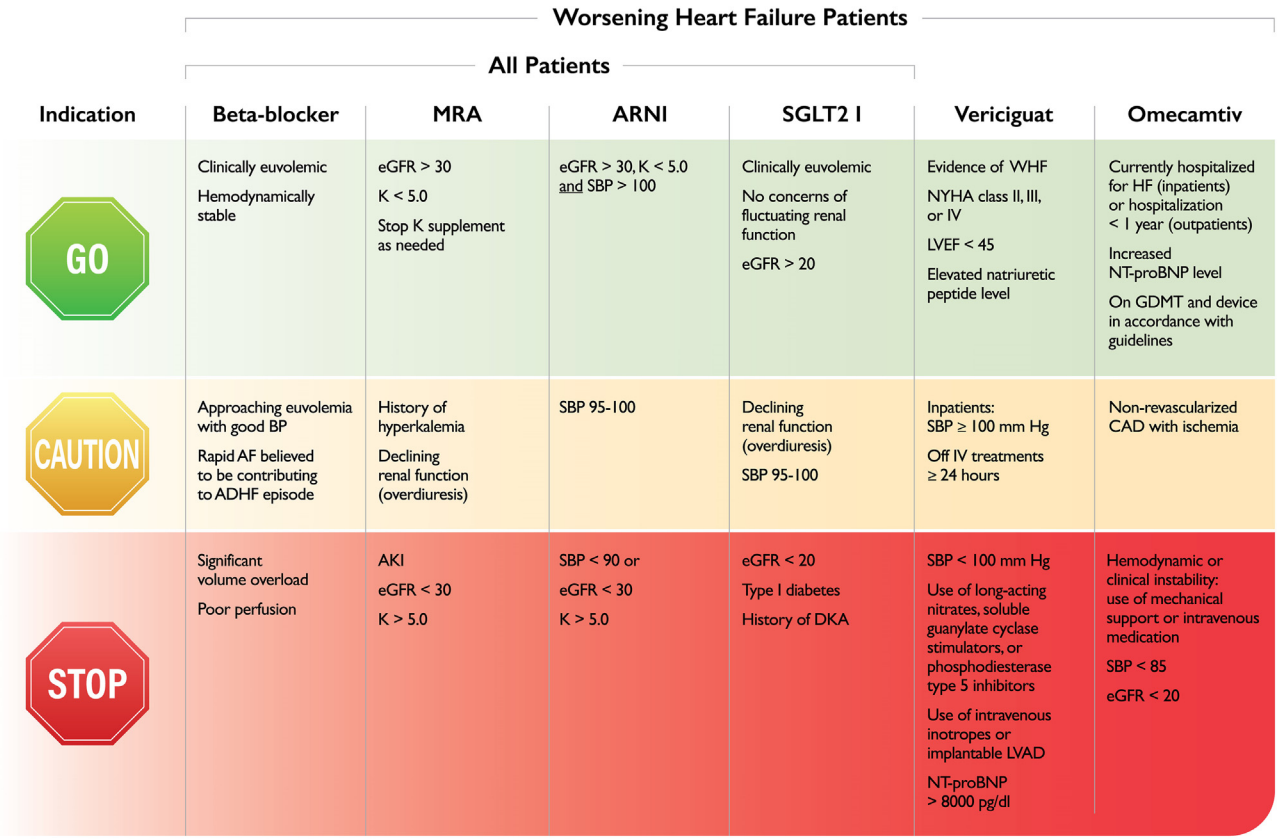

Figure 2. Heart failure (HF) practical tips for initiation of quadruple therapy in patients with HF with reduced ejection fraction (left ventricular ejection fraction [LVEF] ≤ 40%). Framed section (**right**): patients with WHF practical tips, in addition to the 4 pillars. Note: omecamtiv is not currently available in Canada. ADHF, acute decompensated heart failure; AF, atrial fibrillation; AKI, acute kidney injury; ARNI, angiotensin receptor neprilysin inhibitor; BP, blood pressure; CAD, coronary artery disease; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; I.V., intravenous; LVAD, left ventricular assist device; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro hormone brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SGLT2 I, sodium glucose cotransporter-2 inhibitor; WHF, worsening heart failure.

was defined as SBP ≥ 100 mm Hg and no symptoms of hypotension within 6 hours, no increase in I.V. diuretic or nitrate dose within 6 hours, and no I.V. inotropic drugs within 24 hours. In addition, HF was confirmed by elevated NT-proBNP ≥ 1600 pg/mL or brain natriuretic peptide ≥ 400 pg/mL during hospitalization or within 72 hours before admission. The clinical benefit occurred at a rate of 53.9% in the empagliflozin group compared with 39.7% in the placebo group ($P < 0.01$). There was no evidence for treatment interaction among various tested subgroups and the benefit of empagliflozin was independent of symptomatic impairment at baseline. Taken together, these small trials support the early initiation of SGLT2i, a class of drugs with benefits that have been shown in ambulatory patients regardless of diabetes and ejection fraction.

In the **Veri**ciguat **Glo**bal Study in Subjects With Heart Failure With **R**educed Ejec**t**ion Fr**a**ction (VICTORIA) trial, the effect of vericiguat, which directly and selectively stimulates the soluble guanylate cyclase to increase cyclic guanosine monophosphate production even in low nitric oxide conditions such as HF, was evaluated. They enrolled 5050 patients with AHF who were receiving GDMT, randomized either as inpatient or outpatient but must have met criteria for clinical stability (eg, SBP ≥ 100 mm Hg, no I.V. treatments for ≥ 24 hours), and showed a decrease of cardiovascular death or HFH (HR, 0.90; 95% CI, 0.82-0.98; $P = 0.02$) after a median follow-up of 10.8 months, despite most patients receiving recommended GDMT.[2] The effect on renal function and BP is minimal and this agent should be considered in patients with a current or recent WHF despite GDMT.

Last, the selective cardiac myosin activator omecamtiv mecarbil has been shown to improve cardiac function in patients with HFrEF. Its effect on cardiovascular outcomes was studied in the **G**lobal **A**pproach to **L**owering **A**dverse **C**ardiac Outcomes **T**hrough **I**mproving **C**ontractility in **H**eart **F**ailure (GALACTIC-HF) trial,[34] which randomized 8256 HFrEF patients (inpatients and outpatients) to receive omecamtiv mecarbil (using pharmacokinetic-guided doses of 25 mg, 37.5 mg, or 50 mg twice daily) or placebo, in addition to standard HF therapy. They showed a reduction in the composite of a first HF event or cardiovascular death (HR, 0.92; 95% CI, 0.86-0.99; $P = 0.03$) compared with placebo during a median of 21.8 months, but no significant difference in the change from baseline on the KCCQ-TSS. Therefore, this agent should be considered in patients with WHF.[34]

WHF is a challenging condition to treat, because many comorbidities might limit our ability to implement GDMT, such as chronic kidney disease, frailty, and low BP. Therefore,

treatment needs to be individualized in accordance with each patient's response to therapy. Other HF therapies should also be sought for the WHF patient, such as ivabradine, hydralazine, and nitrates combination, cardiac resynchronization, and other interventions described in the HF guidelines.[4] Many options are being developed, but mostly for patients with HFrEF except MRA and SGLT2i. To improve outcomes, one potential solution might be to intervene earlier and potentially avert this HFH. Anderson et al. reported that acutely hospitalized patients with HF consulted a physician multiple times before their incident HFH, particularly in the month before (adjusted rate ratio [RR], 1.28; 95% CI, 1.25-1.31; $P < 0.01$) compared with matched chronic obstructive pulmonary disease controls and 75% compared with stable HF patients (RR, 1.75; 95% CI, 1.71-1.79; $P < 0.01$).[35] These health care contacts could represent missed opportunities to diagnose HF and provide optimal medical therapy in an ambulatory setting and prevent hospitalizations for HF. Finally, considerations for advanced HF therapies, mainly mechanical circulatory support and heart transplantation, are addressed in the next section. The proposed scheme of introduction of the different classes of agents for the patients with WHF phenotype is presented in Figure 2 (lower panel).

4. The HF patient with cardiorenal phenotype

Most patients with AHF present with signs and symptoms of volume overload, necessitating the relief of clinical congestion as a primary goal. Although patient-specific circumstances vary, recent studies suggest 4-8 kg of weight loss during a typical hospitalization, although reduction of cardiac filling pressures and clinical congestion associates most closely with prognosis.[36] Fortunately, most patients rapidly improve with I.V. diuretic therapy. However, approximately 20% of inpatients fail to improve after they are initially stabilized. These patients are more challenging to treat, experience longer length of stay, and have typically more comorbidities such as chronic kidney disease. Several patient and treatment factors should be considered in these cases, and a stepwise approach, as outlined below might be of help. It might not be possible to fully decongest such patients without complications of therapy, and a degree of "permissive overload" might be necessary, keeping in mind that it would be associated with worse prognosis.

a. Identifying the cardiorenal HF phenotype. In the absence of a unified definition of clinical improvement in AHF, one might reasonably take known and favourable prognostic patient response to therapy, together with absence of complications. Thus, systematic standard daily assessment of each patient, including signs and symptoms, oxygen requirements, weight loss, urine output, electrolytes, and creatinine should be obtained and documented for future comparison.

A major hallmark of this phenotype is the presence of CRS,[37] in which cardiac and renal disease coexist, and although it is common, the CRS remains vaguely defined. Acute kidney injury (AKI; increase in serum creatinine > 26 μmol/L or 1.5 times baseline serum creatinine coupled with < 0.5 mL/kg/h urine output for at least 6 hours) is a specific syndrome requiring careful assessment, frequently specialist consultation, and close follow-up. It is associated with worse in-hospital and outpatient outcomes. Although escalation of diuretics might prove useful in this setting, worsening AKI might also result, necessitating decision with respect to renal replacement therapy and goals of care.

b. Management of the decompensated cardiorenal HF phenotype. A detailed review of this topic is beyond the scope of this CPU but can be found elsewhere.[38] Practical management of these patients can be achieved using a stepwise approach.

Step 1: Re-confirm volume status. Determination of intravascular fluid volume might be challenging. In the event of inadequate diuresis, it is critical to confirm that clinical congestion exists. More than 20% of patients with AHF might present with discordant right- and left-sided filling pressures.[39] This is particularly important in patients with relatively high right-sided filling pressures, where further diuresis might precipitate low cardiac output and AKI, or alternatively improve renal function without adversely affecting cardiac output. Also, patients with elevated left filling pressure in the absence of peripheral congestion would benefit from vasodilators rather than excessive diuresis that could precipitate AKI. Hence, disproportional elevation of right ventricular or LV filling pressures requires careful attention to diuretic responsiveness.

Recent studies suggest diagnostic aids, such as the chest radiograph or point-of-care ultrasound with which right-sided (inferior vena cava or jugular venous pressure diameter) and left-sided (pulmonary B lines, pleural effusions) filling pressures might be estimated. Comprehensive 2-dimensional echocardiography may also be used to estimate LV and pulmonary artery pressures. Invasive measurement of right-sided pressures might be necessary and in small, single-centre studies have been shown to change therapeutic decisions, even compared with highly experienced HF practitioners, and improved outcomes.[40]

Step 2: Mitigate iatrogenic and patient contributions. Several concomitant therapies might contribute to inadequate decongestion. Inadvertent administration of solute (via I.V. infusions) and use of agents that promote volume retention in patients with AHF should be stopped, if possible, along with medications typically avoided in this population. It is also important to acknowledge that extreme salt restriction (< 1500 mmol per 24 hours) and water restriction (< 1200 mL per 24 hours) have not been shown to improve decongestion, and in several studies have been associated with worse patient outcomes.[41] Many patients with AHF experience water and salt craving and will self-administer increased levels. Clues to this behaviour include multiple fluid containers at the bedside, delivered food with high salt content to the patient (instead of hospital diet), frequent patient absences from the ward, especially during mealtimes, and large discrepancies between fluid intake/output balance and daily weights/clinical assessment. Measurement of urinary sodium excretion (lack of weight loss despite serum sodium > 50 meq/L on spot urine) might be useful. One way to mitigate this behaviour is to allow a less restrictive

intake restriction of a maximum of 2 L/d in patients without hyponatremia.

It is critically important to identify and address other comorbid conditions such as concomitant infection, anemia, iron deficiency, hepatic dysfunction, thyroid disease, concomitant cardiac ischemia, valve disease, or poor lung function, which otherwise might lead to refractory HF.

Step 3: Escalation of diuretic therapy. Nearly all admitted patients with AHF exhibit some degree of diuretic resistance and require increased doses to diurese adequately. In general, chronic HF patients will require 2 times the usual dose of home diuretic given intravenously whereas newly diagnosed patients will require a lesser dose, such as 40 mg furosemide equivalent. In general, a stepped approach to diuretic therapy is strongly suggested, beginning with doubling of the loop diuretic dose, followed by the additional use of a second, typically thiazide diuretic, while monitoring for complications of therapy (hyponatremia, hypokalemia).[42-44] Several additional options are also available to the clinician for add-on therapy, none of which are proven superior to any other. They include the additional use of thiazide diuretic, use of a vasopressin inhibitor (tolvaptan) or carbonic anhydrase inhibitor (acetazolamide; see ADVOR trial described previously, which was not performed specifically in cardiorenal patients, however). The additional use of MRA might also potentiate the loop diuretic while introducing the GDMT (spironolactone, eplerenone). Use of these agents will often result in additional 2-3 L of diuresis. When goals are met, deescalation may be undertaken as per CCS guidelines recommendations.[45] Many clinicians report increased urine output after an infusion of loop diuretic instead of bolus injections. Although this strategy appears as safe as bolus injections, clinical superiority has not been shown.[46]

Step 4: Consideration of other therapies. Selected patients with low-output HF might benefit from I.V. vasodilation therapy as a means to tailored therapy, lower systemic vascular resistance, and improve cardiac output. This afterload reduction strategy is probably underutilized because it has been shown to improve outcomes in small studies from experienced centres.[40] However, caution must be used to avoid excessive hypotension, which will impair renal perfusion pressure and potentially lead to AKI. The **R**enal **O**ptimization **S**trategies **E**valuation (ROSE) AHF trial was conducted in participants with AHF and renal dysfunction and showed that neither low-dose dopamine nor low-dose nesiritide enhanced decongestion or improved renal function when used in addition to diuretic therapy.[47] Whether differences in the vasodilator used or the absence of invasive hemodynamic monitoring in the ROSE AHF trial can explain the apparent discrepancy in the results of these trials is unknown.

Inotropic therapy may be used as either a palliative option to improve symptoms, even for outpatients, or if advanced HF therapies are being considered, as a bridge to a more definitive treatment option. In either case, use of these therapies is highly dependent on clear starting and stopping rules. However, it is important to recognize early when patients with this phenotype are in cardiogenic shock, by measuring serum blood lactate levels.[48] The choice of the inotropic agent is nowadays less controversial as in the **Do**butamine Compa**re**d to **Mi**lrinone (DOREMI) trial,[49] which was conducted in 192 cardiogenic shock patients and showed similar effects of milrinone and dobutamine on a wide composite end point including all-cause in-hospital death, resuscitated cardiac arrest, cardiac transplantation/mechanical circulatory support, nonfatal myocardial infarction, stroke or transient ischemic attack, or AKI requiring renal replacement therapy (milrinone [49%] and dobutamine [54%]; relative risk, 0.90; 95% CI, 0.69 -1.19; $P = 0.47$).[49] This high mortality of cardiogenic shock patients has remained unchanged for 3 decades, potentially because early recognition of shock is still suboptimal, especially in patients with acute decompensated heart failure.

Also, single-centre studies have reported that administration of small boluses of hypertonic saline (100 mL of 3% NaCl over 30-60 minutes or 150 mL 3% NaCl to be given over 30 minutes (300 mL/h)[50] followed by I.V. loop diuretic might increase urine output and fluid loss. Peripheral and central ultrafiltration have been shown to be highly effective in removing fluid, although they have not been shown to preserve renal function or improve clinical outcomes.[43,51] In highly selected patients, these options might be considered. Removal of loculated fluid collections, such as relief of pleural effusion or paracentesis might offer short-term relief of symptoms and are typically limited for this use.

Some patients with the cardiorenal phenotype who are not responding to therapy due to low output might benefit from referral for evaluation for advanced HF therapies, because they have very high short-term risk. Regardless of the situation, a simple acronym can be used as a reminder of when the clinician should consider referral to an advanced HF centre: I NEED HELP (Fig. 3).[52]

Finally, selected patients might benefit for consideration of transcatheter valvular intervention in patients with severe mitral functional regurgitation[53] or tricuspid insufficiency[33]; although these trials did not specifically enroll hospitalized patients with the cardiorenal phenotype, it is not infrequent that progression of valvular disease leads to refractory HF that can be sometimes safely be alleviated with such interventions.[3]

5. The frail HF phenotype

Frailty is a syndrome characterized by progressive loss of physiological reserve resulting in decreased energy, decreased physical activity, and reduced cognitive ability, and is associated with increased morbidity and mortality. In the FRAIL-HF prospective observational cohort study, 70.2% of 450 patients older than 70 years admitted with HF (mean age, 80 $\pm$ 6 years) fulfilled the criteria for frailty.[54] The frailty phenotype in the HF population is challenging for management because of increased falls risk from multimorbidity and polypharmacy, reduced health care access due to limited mobility, problems with self-care, frequent hospitalizations, and decreased quality of life.[55] Medication therapy in these patients should be individualized, with shared decision-making between prescribers and patients, in the setting in which multiple comorbidities might further limit life span and lead to complex medication regimens.[56]

GDMT used in the treatment of HF have BP- and/or HR-lowering effects, which might be difficult to tolerate for those who are unsteady in their movement or prone to falls. Doses of GDMT achieved in these patients will often be lower than

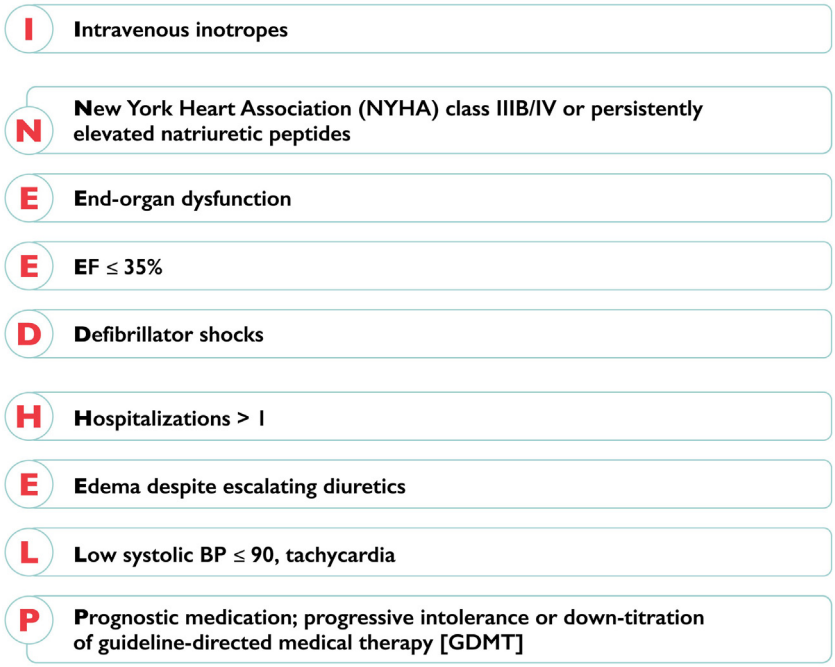

Figure 3. Referral to heart failure specialist—I NEED HELP. The "I NEED HELP" acronym incorporates all risk factors that have been proven to increase all-cause mortality in heart failure patients. The level of renal and liver dysfunction, and the extent of natriuretic peptide increase and diuretic dose that would raise red flags and trigger referral is not well defined. As such, precise cutoffs for alarm are not listed for these continuous variables. BP, blood pressure; EF, ejection fraction; NYHA, New York Heart Association. Modified from Yancy et al.[52] with permission from Elsevier.

the target doses used in clinical trials, as well as those tolerated by younger patients.[56] Strategies to help mitigate hypotension and risk of falls include initiating medications at small doses and titrating very slowly as tolerated (every 2-4 weeks) and separating administration times of the various medications by at least several hours apart such that the peak antihypertensive effects do not all overlap simultaneously. Certain medications in the different GDMT classes might be less tolerated hemodynamically vs other drugs from the same class, such as carvedilol, which has α-1 receptor antagonism, and ARNIs which are associated with significant hypotension. All patients with frailty should be instructed on how to carefully change positions from supine to standing to minimize symptoms of orthostasis. Changing the chronology of administration of drugs might also be useful, favouring those with higher vasodilatory effects at bedtime and separating the timing of administration of the different classes (morning, lunch, supper, and bedtime).

Including a pharmacist as a member of the multidisciplinary HF team is beneficial because of the issues with polypharmacy and medication adherence that is common in this population. Medications such as eplerenone and ivabradine are substrates of cytochrome P450 3A4, and many β-blockers are substrates of cytochrome P450 2D6, and so inhibitors and inducers of these enzymes can increase the risk for side effects or decrease efficacy of these medications, respectively. Carvedilol is an inhibitor of P-glycoprotein and might increase the serum concentrations of other medications that are substrates. Ivabradine can prolong the QT interval and can increase risk of torsade de pointes if combined with other QT-prolonging drugs. Encouraging patients to fill all their prescriptions at the same pharmacy will facilitate pharmacists to better identify these and other clinically significant drug interactions. Clinical pharmacists can also help to improve medication adherence by providing education to patients regarding their medications, monitoring refill dates, and dispensing medications in compliance packaging. Furthermore, they are instrumental in optimizing GDMT in a multidisciplinary setting.[6]

Last, frailty can sometimes be reversed with physiotherapy, occupational therapy, and nutrition; therefore, referral for cardiac rehabilitation should be considered. Altogether they might be key to prevent HF-driven cachexia, clinical deterioration, and ultimately autonomy loss.

The **Rehab**ilitation Therapy in Older Acute **H**eart **F**ailure Patients (REHAB-HF) trial randomized 349 geriatric patients hospitalized because of acute decompensated HF. They were subjected to a timely, personalized, and progressive rehabilitation program, which comprised multiple physical function domains. The intervention group exhibited a significantly greater improvement in physical function compared with the standard care group. Notably, all patients had severely compromised physical function at baseline, with 97% of them being frail or prefrail. The intervention group maintained an 82% retention rate with good adherence to the sessions (67%). The Short Physical Performance Battery score at 3 months improved more in the intervention than in the control group, (8.3 ± 0.2 and 6.9 ± 0.2, respectively; mean difference between groups: 1.5; 95% CI, 0.9-2.0; $P < 0.001$). At 6 months, there was no difference in rates of rehospitalization for any cause (1.18 and 1.28 for the intervention and control groups respectively; RR, 0.93; 95% CI, 0.66-1.19).[57]

Conclusions

HF is a complex clinical syndrome, with multiple phenotypic patient presentations. Identifying these varying HF patients is critically important for the subsequent tailoring of therapies to improve their presenting symptoms, their other associated morbidities, and ultimately their life span with an acceptable quality of life. Because not all patients with HF are created alike, it is equally important to understand which of the available therapeutic armamentarium can provide efficacious outcomes with respect to HF symptoms and myocardial function, and so in the event that the patient with HF has a phenotype that is recalcitrant to its therapeutic options, be they pharmacological or nonpharmacological, these patients with HF can be considered for advanced therapeutic options when indicated. This CPU is designed to be used in conjunction with the CCS-Canadian Heart Failure Society guidelines with the intent to provide a clinical context for practical applicability.

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CCS Disclaimer

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