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Society Guidelines

CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction

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ABSTRACT

In this update of the Canadian Cardiovascular Society heart failure (HF) guidelines, we provide comprehensive recommendations and practical

RÉSUMÉ

Dans cette mise à jour des Lignes directrices de la Société canadienne de cardiologie sur l'insuffisance cardiaque (IC), nous fournissons des

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The disclosure information of the authors and reviewers is available from the CCS on their guidelines library at www.ccs.ca.

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 multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. 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. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

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tips for the pharmacologic management of patients with HF with reduced ejection fraction (HFrEF). Since the 2017 comprehensive update of the Canadian Cardiovascular Society guidelines for the management of HF, substantial new evidence has emerged that has informed the care of these patients. In particular, we focus on the role of novel pharmacologic therapies for HFrEF including angiotensin receptor-neprilysin inhibitors, sinus node inhibitors, sodium glucose transport 2 inhibitors, and soluble guanylate cyclase stimulators in conjunction with other long established HFrEF therapies. Updated recommendations are also provided in the context of the clinical setting for which each of these agents might be prescribed; the potential value of each therapy is reviewed, where relevant, for chronic HF, new onset HF, and for HF hospitalization. We define a new standard of pharmacologic care for HFrEF that incorporates 4 key therapeutic drug classes as standard therapy for most patients: an angiotensin receptor-neprilysin inhibitor (as first-line therapy or after angiotensin converting enzyme inhibitor/angiotensin receptor blocker titration); a β-blocker; a mineralocorticoid receptor antagonist; and a sodium glucose transport 2 inhibitor. Additionally, many patients with HFrEF will have clinical characteristics for which we recommended other key therapies to improve HF outcomes, including sinus node inhibitors, soluble guanylate cyclase stimulators, hydralazine/nitrates in combination, and/or digoxin. Finally, an approach to management that integrates prioritized pharmacologic with nonpharmacologic and invasive therapies after a diagnosis of HFrEF is highlighted.

recommandations complètes et des conseils pratiques pour la gestion pharmacologique des patients atteints d'IC avec une fraction d'éjection réduite (ICFER). Depuis la mise à jour complète de 2017 des Lignes directrices de la Société canadienne de cardiologie pour la prise en charge de l'IC, de nouvelles indications substantielles sont apparues au bénéfice des soins de ces patients. Nous nous concentrons en particulier sur le rôle des nouvelles thérapies pharmacologiques pour le traitement de l'ICFER, notamment les inhibiteurs des récepteurs de l'angiotensine et de la néprilysine, les inhibiteurs du nœud sinusal, les inhibiteurs du cotransporteur sodium-glucose de type 2 et les activateurs de la guanylate cyclase soluble, en conjonction avec d'autres thérapies ciblant l'ICFER et établies de longue date. Des recommandations actualisées sont également fournies dans le contexte du cadre clinique pour lequel chacune de ces molécules pourrait être prescrite ; la valeur potentielle de chaque thérapie est examinée, le cas échéant, pour une IC chronique, pour une IC apparue récemment et pour une hospitalisation pour IC. Nous définissons une nouvelle norme de soins pharmacologiques pour l'ICFER qui intègre quatre classes de médicaments thérapeutiques clés comme traitement standard pour la plupart des patients : un inhibiteur du récepteur de l'angiotensine et de la néprilysine (comme traitement de première ligne ou après titrage de l'inhibiteur de l'enzyme de conversion de l'angiotensine/inhibiteur du récepteur de l'angiotensine); un β-bloquant; un antagoniste des récepteurs des minéralocorticoïdes; et un inhibiteur du cotransporteur sodium-glucose de type 2. En outre, de nombreux patients atteints d'ICFER présenteront des caractéristiques cliniques pour lesquelles nous avons recommandé d'autres thérapies clés pour améliorer le pronostic de l'IC, notamment des inhibiteurs du nœud sinusal, des stimulateurs de guanylate cyclase soluble, l'association hydralazine/nitrates et/ou la digoxine. Enfin, une approche de traitement qui intègre des thérapies pharmacologiques prioritaires avec des thérapies non pharmacologiques et invasives après un diagnostic d'ICFER est mise en évidence.

The Canadian Cardiovascular Society (CCS) Heart Failure Guidelines Program provides guidance to clinicians, policymakers, and health systems as to the evidence supporting existing and emerging management of patients with heart failure (HF). Since the 2017 comprehensive update of the CCS guidelines for the management of HF,[1] substantial new evidence has emerged, particularly relevant to the management of patients with HF with reduced ejection fraction (HFrEF). The present CCS HF guideline update defines a contemporary standard of care for the HFrEF patient population on the basis of the totality of available evidence. This update focuses on the role of newer pharmacologic therapies for HFrEF including angiotensin receptor-neprilysin inhibitor (ARNI), sinus node inhibitor, sodium glucose transport 2 (SGLT2) inhibitor, and soluble guanylate cyclase (sGC) stimulator, in conjunction with well established and conventional HFrEF therapies. Where evidence exists, updated recommendations are provided with respect to the clinical setting in which each of these agents may be prescribed; the potential value of each therapy is reviewed, where relevant, in the setting of chronic HF, new onset HF, and for HF hospitalization. A consensus approach to management that integrates prioritized pharmacologic with nonpharmacologic and invasive therapies after a diagnosis of HFrEF is highlighted.

The scope of this guideline update is limited to key pharmacologic therapies for patients with HFrEF. A detailed description of nonpharmacologic management, including advance care planning, multidisciplinary care, remote monitoring, and diet and exercise prescription are not addressed. Management of important comorbidities including coronary disease, atrial fibrillation, functional mitral regurgitation, chronic kidney disease, diabetes, and iron deficiency have also been addressed in previous guideline updates,[1,2] although the Panel acknowledges that evidence is quickly evolving in many of these areas.

The composition and roles of the primary and secondary panels, systematic review strategy, and methods for formulating the recommendations are described at www.ccs.ca. The recommendations were developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) standards.[3] Primary panelists were responsible for writing and reviewing the document, and the secondary panelists provided critical input from provider and patient perspectives.

Standard Therapies

On the basis of new and emerging evidence for the pharmacologic treatment of HFrEF, updated treatment recommendations are provided herein. In the current era, patients with HFrEF should treated with 4 standard therapies, in the absence of contraindications, each representing a different

class of medication with unique mechanism of action. Placing a high priority on reducing cardiovascular (CV) mortality and hospitalization for HF (HHF) in most patients, these medications include: (1) an ARNI, either as first-line therapy or switching from an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB); (2) a β-blocker; (3) a mineralocorticoid receptor antagonist (MRA); and (4) an SGLT2 inhibitor. Specific recommendations for each class of therapy, including the clinical settings in which these treatments may be prescribed, are outlined in detail in the sections that follow. Beyond these standard therapies, additional medications benefit important subgroups of patients with HFrEF, and should be initiated and titrated where indicated. In particular, the role and clinical settings for prescription of ivabradine (sinus node inhibitor), vericiguat (sGC stimulator), digoxin, and hydralazine/nitrates are discussed under their respective headings. Table 1 highlights the quality of available evidence to support the use of each HFrEF therapy according to clinical setting.

A simplified, HFrEF treatment algorithm is illustrated in Figure 1. Recognizing that any such algorithm cannot address all of the nuances and multiple considerations underpinning individualized HFrEF management in the current era, the approach presented places value on pragmatic considerations for most patients. Depending on the clinical practice environment, initiation and titration of standard therapies should be embraced by nonspecialists, whereas additional pharmacologic and interventional considerations might warrant input from specialists.

It is worth noting that the algorithm in Figure 1 has been informed by best available evidence and the consensus of the Primary Panel, but to date, there is no proven superior approach to medication initiation and titration. For example, on the basis of clinical characteristics, it might be preferable to titrate doses of different classes of medications simultaneously (in-parallel approach), rather than fully titrate one medication class before initiating an additional agent (strict sequential approach). Although newer medication classes such as ARNI and SGLT2 inhibitors were evaluated in patients with high background use of β-blockers, MRAs, and ACEIs or ARBs, there is currently no Primary Panel consensus endorsing a fixed sequence for medication prescription for patients with HFrEF. There is, however, consensus that all 4 classes of therapies should be used in patients with HFrEF and detailed evidence for each specific drug class is presented in the appropriate section.

RECOMMENDATION

1. We recommend that in the absence of contraindications, patients with HFrEF be treated with combination therapy including 1 evidence-based medication from each of the following categories:
   a. ARNI (or ACEI/ARB);
   b. β-blocker;
   c. MRA; and
   d. SGLT2 inhibitor.
   (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. High value is placed on prescribing a combination of individual therapies that reduce CV mortality and HHF in well conducted randomized controlled trials. Medications such as ARNI and SGLT2 inhibitor have clinical benefits in patients treated with ACEIs or ARBs, β-blockers, and MRAs as background therapy. The complementary mechanisms of action of these agents in patients with HFrEF provides further rationale for a multidrug approach.

Preference is given to the use of pharmacotherapy in patients with established HFrEF regardless of symptom severity.

The Committee acknowledges lack of evidence favouring one particular titration strategy for guideline-directed medical therapy (GDMT) over another.

Practical tip. The approach to initiation and titration of standard therapies should be directed by clinical and other patient factors including hemodynamic status, renal function, access to medication, adherence, anticipated side effects and tolerability, and patient preference.

Practical tip. Every attempt should be made to titrate medications as soon as feasible after the diagnosis. It is reasonable to aim for titration of all standard therapies concurrently to target doses, or maximally tolerated doses, within 3-6 months from diagnosis.

Practical tip. Because of the superiority of ARNI over ACEIs or ARBs in the setting of HFrEF, prescribing ARNI as first-line therapy or before full titration of ACEIs/ARBs might facilitate more rapid optimization of GDMT.

Practical tip. If a drug with proven mortality or morbidity benefits does not appear to be tolerated (eg, low blood pressure [BP], low heart rate, or renal dysfunction), concomitant drugs (eg, diuretics) with less proven benefit should be carefully reevaluated to determine whether their dose can be reduced or the drug discontinued.

Practical tip. GDMT for HFrEF should be continued at the usual dose during acute intercurrent illness unless they are not tolerated or could potentially worsen severity of illness. Whenever possible, GDMT withheld during a hospitalization should be restarted before discharge.

Practical tip. In the event of a life-threatening complication, GDMT may be discontinued abruptly, but generally, if there is concern about their use, the dose should be decreased by one-half, and the patient should be reassessed. If the dose is reduced, the previous tolerated dose should be resumed as soon as safely possible.

Practical tip. If symptomatic hypotension persists with GDMT, consider separating the administration of the dose from the timing of other medications that could also lower BP.

RECOMMENDATION

2. We recommend preferentially use of drugs at target doses that have been proven to be beneficial in clinical trials as optimal medical therapy. If these doses cannot be achieved, the maximally tolerated dose is acceptable (Table 2; Strong Recommendation; High-Quality Evidence).

Table 1. Quality of available evidence to support the use of each HFrEF therapy according to clinical setting

HFrEF drug therapy	Quality of evidence supporting recommendation		
	Chronic ambulatory HF	New-onset HF	HF hospitalization*
Sacubitril-valsartan	High	Low	Moderate
ACEI/ARB	High	High	High†
β-blockers	High	High	High
MRAs	High	High	High†
SGLT2 inhibitors	High	N/A	N/A‡
Ivabradine	High	N/A	N/A
Vericiguat	Moderate	N/A	NA
Digoxin	Moderate	Low	Low
H-ISDN	Moderate	Low	Low

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ISDN, hydralazine and isosorbide dinitrate; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium glucose transport 2; SOLOIST-WHF, Effect of **So**tag**l**iflozin on Clinical Outcomes in Hem**o**dynam**i**cally **St**able Patients With Type 2 Diabetes Post **W**orsening **H**eart **F**ailure.

*Evidence for prescribing HFrEF therapies in the setting of HF hospitalization is derived primarily from studies in which patients had been stabilized after admission.

†Evidence for ACEI/ARB and MRA use in the setting of HF hospitalization is derived primarily from studies of high-risk post myocardial infarction patients.

‡The recent SOLOIST-WHF trial showed that sotagliflozin (an SGLT1/2 inhibitor) could be safely prescribed before discharge or shortly after discharge in patients with diabetes who were stabilized after hospitalization for heart failure. Ongoing randomized controlled trials will further evaluate the efficacy and safety of initiating SGLT2 inhibitors in a spectrum of HF patients, including those without diabetes.

ARNI

Registry data continue to identify suboptimal initiation and titration of goal-directed medical therapy in patients with ambulatory HF.[4] Thus, HHF represents an ideal time to recalibrate, and optimize the treatment plan by initiating GDMT. ARNI therapy is now a well established treatment recommendation in patients with chronic HFrEF who have been previously exposed to either ACEIs or ARBs. The multicentre, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic HFrEF (**P**rospective Comparison of **ARN**i With **A**CEi to **D**etermine **I**mpact on **G**lobal **M**ortality and Morbidity in **H**eart **F**ailure [PARADIGM-HF]) trial[5] showed superior efficacy of ARNI therapy over enalapril in chronic HF patients already receiving maximally tolerated dose of a renin-angiotensin system inhibitor (RASi). More recently, the safety and efficacy of this strategy has been explored in patients hospitalized with acute HF, including *de novo* HF, with or without previous exposure to RASi. The Comparison of Pre-discharge and Pos**t**-Discharge T**r**eatment Initiation With LCZ696 in He**a**rt Failure Patie**n**t**s** With Reduced Ejec**t**ion-Frac**t**ion Hosp**i**talized for an Acute Dec**o**mpensation Eve**n**t (TRANSITION) study[6] was an open-label multicentre randomized controlled trial of 1002 patients, which showed the safety of initiating ARNI in patients with left ventricular ejection fraction (LVEF) $\leq$ 40% admitted to hospital with decompensated HF (median 7 days from admission) compared with initiation of ARNI therapy after discharge (median 10 days from admission). There was no difference in the proportion of patients who achieved maximum dose of sacubitril-valsartan at 10 weeks of follow-up (45.4% vs 50.7%; relative risk [RR] 0.90 [95% CI 0.79-1.02] in the pre and post-discharge initiation groups, respectively). Similarly, there was no difference in the proportion of patients tolerating any dose of drug at 10 weeks with either strategy (86.0% vs 89.6%; RR, 0.96 [95% CI 0.92-1.01]). In a recent TRANSITION substudy 286 patients with *de novo* HF were compared with 705 patients with established HF and those with newly diagnosed HF were shown to be more likely to achieve target dose of sacubitril-valsartan at 10 weeks (56% vs 45%; RR, 1.30 [95% CI 1.12-1.52]; $P < 0.001$) with fewer serious adverse reactions.[7] Patients with *de novo* HFrEF who started ARNI therapy had a greater decrease in N-terminal pro hormone brain natriuretic peptide (NT-proBNP) and lower rates of rehospitalization without compromising up-titration of other guideline-directed HF therapies.

Further support for initiating ARNI as first-line HFrEF therapy in *de novo* or RASi-naive patients comes from the Com**p**ari**s**on **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,[8] and its open-label extension study.[9] In this double-blind randomized controlled trial, in-hospital initiation of sacubitril-valsartan was compared with enalapril in 881 HFrEF patients hospitalized with HF. Notably, one-third of patients enrolled did not have a history of HF and just more than half had no previous ACEI or ARB use. In-hospital initiation of sacubitril-valsartan resulted in a significantly greater proportional reduction in NT-proBNP compared with enalapril at weeks 4 and from baseline (mean time-averaged change in NT-proBNP, −46.7% vs 25.3%). This change was consistent across all subgroups, including those without previous HF and those who were RASi-naive. In the open-label extension, the clinical course of patients in the PIONEER-HF trial was evaluated for those who initiated sacubitril-valsartan treatment in-hospital as well as for those who switched from enalapril to sacubitril-valsartan treatment at week 8 of the trial protocol and were followed-up for an additional 4 weeks.[9] Among patients who continued sacubitril-valsartan for an additional 4 weeks, a further 17.2% reduction in NT-proBNP was observed; for patients who switched from enalapril to sacubitril-valsartan at week 8, a more significant 37.4% decline in NT-proBNP was seen over the following 4 weeks. Patients who started ARNI therapy in-hospital had a lower incidence of subsequent HHF or CV mortality through the entire 12-week trial period compared with patients who converted to ARNI after the first 8 weeks (13.0% vs 18.1%; $P = 0.03$). A recent additional analysis has shown that the efficacy and safety of sacubitril-valsartan is generally similar across various dose levels,[10] supporting the rationale for in-hospital initiation and continued post hospitalization use of sacubitril-valsartan broadly, including patients who might not tolerate early up-titration to target dose. Another recent analysis has shown the cost-effectiveness of this approach.[11]

Practical tip. In patients suitable for switching to an ARNI, an ACEI can be discontinued at the time of hospital admission enabling ARNI prescription at 36 hours after admission. A 36 hour wash-out period is not necessary for those receiving ARB therapy at the time of hospitalization.

RECOMMENDATION

3. We recommend that an ARNI be used in place of an ACEI or ARB, in patients with HFrEF, who remain symptomatic despite treatment with appropriate doses of GDMT to decrease CV death, HF hospitalizations, and symptoms (Strong Recommendation; High-Quality Evidence).
4. We recommend that patients admitted to hospital for acute decompensated HF with HFrEF should be switched to an ARNI, from an ACEI or ARB, when stabilized and before hospital discharge (Strong Recommendation; Moderate-Quality Evidence).
5. We suggest that patients admitted to hospital with a new diagnosis of HFrEF should be treated with ARNI as first-line therapy, as an alternative to either an ACEI or ARB (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. These recommendation place high value on evidence that supports the safety and efficacy of initiating ARNI therapy in hospitalized patients with or without previous RASi exposure.

Practical tip. In hospitalized and ambulatory patients with HF, without previous exposure to either an ACEI or ARB, an ARNI should be considered as first-line therapy when BP and renal function/potassium levels permit. Because a washout period is needed with ACEIs, initial therapy with this class in a hospitalized patient with HFrEF will delay the initiation of ARNI treatment.

Practical tip. ARNI might reduce diuretic requirements and diuretic dosing should be carefully evaluated when starting ARNI therapy.

Practical tip. Drug tolerability, side effects, and laboratory monitoring of ARNIs is similar to that of ACEIs or ARBs.

Practical tip. Appropriate clinical and laboratory follow-up (renal function and electrolytes) is essential after discharge to monitor for adverse events.

Practical tip. Currently, sacubitril-valsartan is the only available ARNI in Canada. Initial dosing and titration schedule should be individualized (Table 2).

ACEIs and ARBs

The benefits of GDMT for patients with HFrEF, including ACEIs and ARBs, are drawn from large randomized controlled trials of ambulatory patients. Previous guideline recommendations for ACEI/ARB therapy in patients with HFrEF reflect this evidence.[12] In contrast, recommendations regarding the role of RASi in the management of acute HF is largely consensus-based, with no good-quality evidence to support treatment recommendations in the hospitalized setting.[12] Practically, an HHF event represents an opportunity to optimize and/or reevaluate therapy including switch from an ACEI/ARB to an ARNI in eligible patients with HFrEF to improve postdischarge patient outcomes, as discussed in the previous section.

ACEI/ARB initiation and continuation during HF hospitalization. ACEIs and ARBs do not have a clear role in the early management of acute or worsening HF, because there are no robust randomized controlled trial data regarding in-hospital ACEI/ARB initiation. Observational data from the Get With The Guidelines-HF Registry showed that among 16,052 patients, those who started ACEI/ARB treatment before discharge had lower mortality and readmission rates up to 1 year.[13] Nevertheless, a significant number of patients hospitalized for HFrEF have worsening hemodynamics and/or worsening renal function, which might lead to reluctance with initiating or continuing hemodynamically active therapies.[14-16] One analysis showed that ACEI/ARB medications were reduced or discontinued because of acute kidney injury (57%), hypotension (23%), and hyperkalemia (10%); serum creatinine and systolic at admission were significant independent predictors of in-hospital dose reduction or discontinuation.[17] Although renal dysfunction was noted as the most common cause for reduction of ACEI/ARB therapy, 24% of patients had no significant in-hospital rise in creatinine level, and medication changes were made in anticipation of deteriorating renal function rather than documented change in renal function.[17]

A matched-cohort analysis of Medicare beneficiaries hospitalized for HF between 1998 and 2001 showed that patients who initiated ACEI/ARB treatment had lower 30-day readmission rates (18% vs 24%) and all-cause mortality (7% vs 14%) compared with those for whom ACEI/ARB treatment was discontinued.[18]

ACEIs/ARBs after acute myocardial infarction. It is well established that ACEIs should be administered to patients with impaired LVEF ($\leq$ 40%) or those who have experienced HF in the early phase post myocardial infarction (MI).[19-21] A systematic review[22] of 4 trials of early ACEI initiation (0-36 hours) post ST-elevation MI including more than 98,000 patients, showed a 7% relative reduction in 30-day mortality compared with placebo. Importantly, 40% of the survival benefit was seen after the first day of treatment, underscoring the value of initiating ACEI treatment early in hemodynamically stable patients.

ARBs as an alternative to ACEIs, in the context of ST-elevation MI, have been evaluated in 2 clinical trials. In the **Op**timal **T**rial **i**n **M**yocardial Infarction With the **A**ngiotensin II **A**ntagonist **L**osartan (OPTIMAAL)[23] trial, losartan failed to show either superiority or noninferiority compared with captopril for the primary end point at the 2.7-year follow-up (18% vs 16%). Conversely, in the **Val**sartan **i**n **A**cute Myocardial I**n**farc**t**ion (VALIANT) trial,[19] 14,703 patients with acute MI (0.5 and 10 days) and HF or evidence of left ventricular systolic dysfunction $\leq$ 40% were randomly assigned to valsartan alone, full-dose captopril, or both (80 mg twice daily and 50 mg 3 times daily). The primary end point of all-cause mortality was similar in the 3 groups (valsartan 19.9%, captopril 19.5%, both 19.3%), but discontinuations were more frequently seen in patients who received captopril. Therefore, valsartan, at the dosages used in the trial, represents an alternative to ACEIs.

Practical tip. ACEI intolerance describes a patient who is unable to tolerate ACEI therapy secondary to a bothersome cough (approximately 10%) or those who experience

RECOMMENDATION

6. We recommend an ACEI or ARB in those with ACEI intolerance, in patients with acute MI with HF or an LVEF < 40% post-MI to be used as soon as safely possible post-MI (Strong Recommendation; High-Quality Evidence).

angioedema (< 1%). ARB therapy is a reasonable alternative in both of these cases, however, caution should be used in patients who develop angioedema while receiving ACEI therapy because there have been case reports of patients who subsequently develop angioedema with ARB therapy. There is no significant difference in rates of hypotension, hyperkalemia, or renal dysfunction between ACEIs and ARBs to warrant substitution.

Practical tip. An increase in serum creatinine or decrease in estimated glomerular filtration rate (eGFR) of up to 30% in the absence of oliguria is not unexpected when an ACEI or ARB is introduced; if the increase stabilizes at 30%, there is no immediate need to decrease the drug dose but closer long-term monitoring might be required.

Practical tip. BP might fall when an ACEI or ARB is introduced, especially if introduced at a high dose or in combination with diuretic therapy. Check BP with the patient supine and standing to detect whether hypotension is present, which might suggest that a slower up-titration is warranted.

Practical tip. Caution is warranted in patients with marginal BP; although low-dose captopril is sometimes used to initiate an ACEI in hemodynamically tenuous patients this approach has never been tested in randomized controlled trials.

Practical tip. Longer-acting ACEIs such as perindopril or ramipril might be associated with less hypotension in patients with chronic HF, particularly in older patients.

β-Blockers

Since the 2017 comprehensive update of the CCS guidelines for the management of HF, no large randomized clinical trials of β-blockers in patients with HFrEF have been published. Previous landmark trials of carvedilol,[24,25] sustained-release metoprolol succinate,[26] and bisoprolol[27] have shown unequivocal reductions in mortality and hospitalization, and improvement in HF symptoms among patients with HFrEF and New York Heart Association (NYHA) functional class II-IV symptoms at baseline. In a meta-analysis of more than 10,000 patients, β-blockers prevented 3.8 deaths and were associated with 4 fewer hospitalizations per 100 patients in the first year of treatment.[28]

For patients admitted to hospital with worsening HF, β-blocker initiation, before discharge in stabilized patients, has been associated with improved short- and intermediate-term outcomes[29,30] without intolerance or extended length of hospital stay. Available evidence also strongly suggests that patients with HFrEF receiving β-blockers at the time of admission for acute HF have higher rates of death and recurrent HHF when β-blockers are not resumed before discharge.[31-34]

A recent meta-analysis of 5 observational studies and 1 randomized trial confirmed this association; β-blocker withdrawal in the setting of HHF increased the risk of in-hospital mortality (RR, 3.72 [95% CI 1.51-9.14]), mortality at 60-180 days (RR, 1.78; [95% CI 1.13-2.79]), and combined short term rehospitalization or mortality (RR, 1.84; [95% CI 1.08-3.1]).[35] The totality of available evidence suggests that β-blockers should be continued or reinitiated before discharge in those with HFrEF who are hospitalized for worsening HF, whenever clinically feasible.

In addition to including β-blockers as part of standard medical HFrEF therapy, the following recommendations on β-blocker use in HFrEF have remained unchanged from the 2017 comprehensive update of the CCS guidelines for the management of HF.

RECOMMENDATION

7. We recommend that β-blockers be initiated as soon as possible after the diagnosis of HF, including during the index hospitalization, provided that the patient is hemodynamically stable. Clinicians should not wait until hospital discharge to start β-blocker treatment in stabilized patients (Strong Recommendation; High-Quality Evidence).
8. We recommend patients with NYHA class IV symptoms be stabilized before initiation of β-blocker treatment (Strong Recommendation; High-Quality Evidence).
9. We recommend that β-blockers be initiated in all patients with an LVEF < 40% with previous MI (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. Objective improvement in cardiac function might not be apparent for 6-12 months after β-blocker initiation. The absence of LVEF recovery is not justification to stop treatment

Practical tip. Treatment of patients with NYHA class I or II symptoms can be safely initiated and titrated with a β-blocker by nonspecialist physicians.

Practical tip. Patients with NYHA class III or IV symptoms should have β-blocker therapy initiated by a specialist experienced in HF management and titrated in the setting of close follow-up, such as can be provided in a specialized clinic, if available.

Practical tip. β-Blockers should be started at low doses and increased slowly (eg, double the dose every 2-4 weeks). Transient fluid retention might occur with initiation or uptitration of β-blockers and might require assessment of diuretic dosage (eg, might consider deferring dosage reduction).

Practical tip. If concomitant reactive airways disease is present, consider using more selective β-1 blockade (eg, bisoprolol).

Practical tip. If atrioventricular (AV) block is present, consider decreasing other AV node-blocking drugs, such as digoxin or amiodarone (when appropriate). The type and

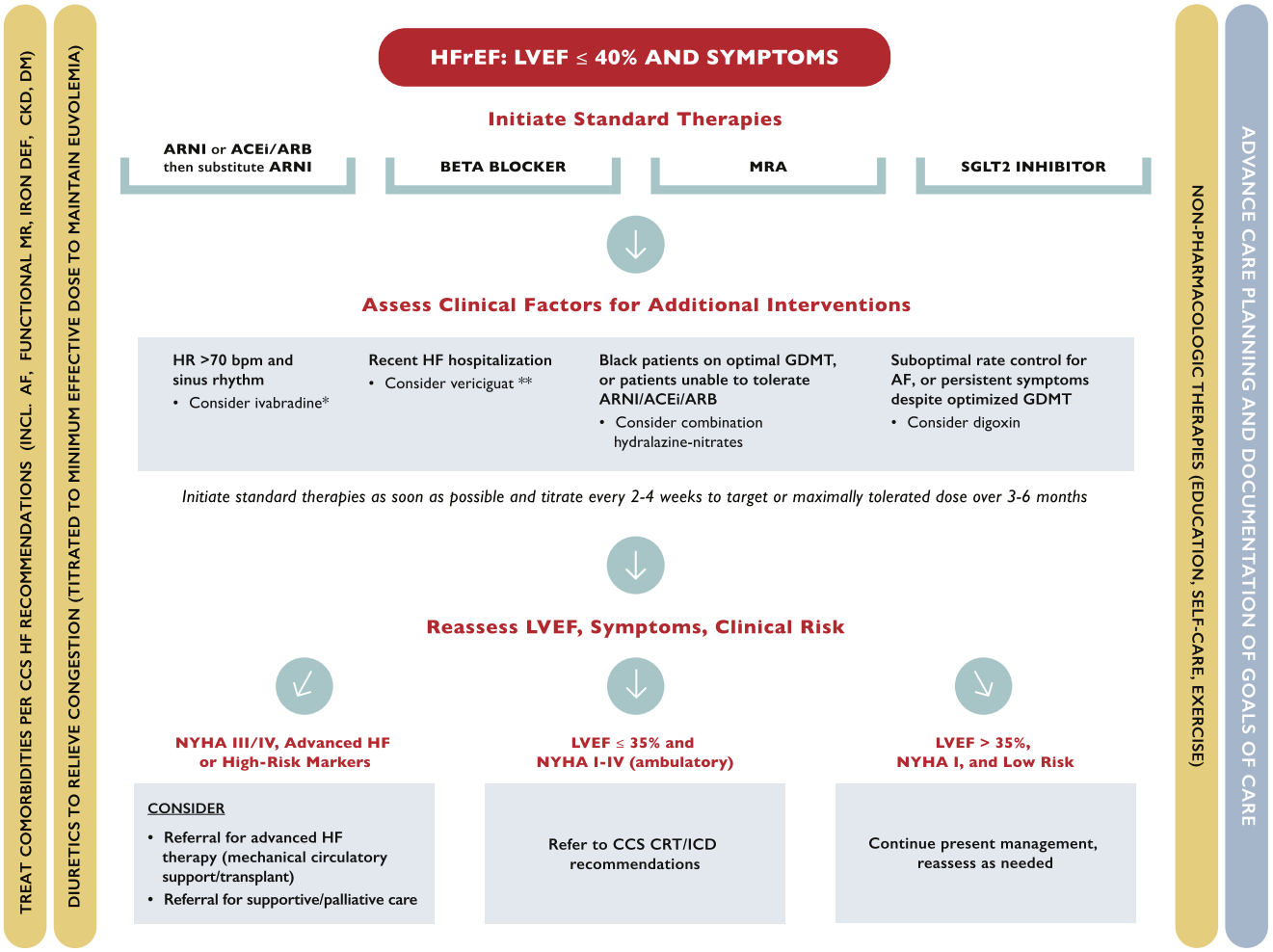

Figure 1. Simplified treatment algorithm for management of heart failure (HF) with reduced ejection fraction (HFrEF). Standard therapies are applicable to most patients with HFrEF for reducing cardiovascular mortality and hospitalization for HF. Additional, pharmacologic therapies should be individualized on the basis of clinical factors as outlined in the text. Every attempt should be made to initiate and titrate therapies with the goal of medication optimization by 3-6 months after a diagnosis of HFrEF. Throughout the patient journey, nonpharmacologic therapies should be prescribed, along with judicious use of diuretics to maintain euvolemia. Evidence also supports interventions to treat important comorbidities including iron deficiency, atrial fibrillation (AF), and functional mitral regurgitation (MR) in selected patients. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CCS, Canadian Cardiovascular Society; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SGLT, sodium glucose transport. * Health Canada has approved ivabradine for patients with HFrEF and heart rate (HR) ≥ 77 bpm in sinus rhythm. ** Vericiguat is not yet approved for use in Canada.

severity of AV block and the patient s history of arrhythmia will help guide the most appropriate treatment modifications.

MRAs

MRA use in patients with HFrEF. Despite access to MRA therapy for the treatment of HF, and despite established guideline recommendations to initiate MRAs as part of standard therapy (along with RASi and β-blocker medications), there remains uncertainty or reluctance for widespread use. A report of the recent US CHAMP-HF registry[36] showed that MRA was used in only 33.4% of patients with HFrEF without documented contraindication. On the basis of data from the **R**andomized **Al**dactone **E**valuation **S**tudy (RALES),[37] the **E**plerenone **P**ost-Acute Myocardial Infarction **H**eart Failure **E**fficacy and **Su**rvival **S**tudy (EPHESUS),[38] and the **E**plerenone in **M**ild **P**atients **H**ospitalization **a**nd **S**urv**i**val **S**tudy in **H**eart **F**ailure (EMPHASIS-HF),[39] there are 3 clinical scenarios in which mineralocorticoid receptor antagonism in the absence of significant renal dysfunction or hyperkalemia are supported by randomized control trial evidence: (1) LVEF ≤ 35% and NYHA class III-IV symptoms; (2) post MI with signs and symptoms of acute HF and LVEF ≤ 40%, or post MI with diabetes and LVEF ≤ 40% (regardless of HF symptoms); and (3) LVEF ≤ 30% (or if LVEF 31%-35% with QRS > 130 ms), NYHA class II symptoms, and another high risk feature (eg, age > 55 years, HHF within the previous 6 months, or elevated natriuretic peptide levels).

A more generalized role for MRAs in HF management is further supported by contemporary trials that have shown a consistent benefit of newer therapies for which background treatment with MRAs has been > 50% among patients enrolled.[40,41] Moreover, in the **T**reatment **o**f **P**reserved **C**ardiac Function Heart Failure With an **A**ldosterone An**t**agonist (TOPCAT) trial HHF reduction was observed in patients with HF and LVEF ≥ 45% despite trial challenges in the population recruited,[42,43] which might lessen the reluctance to treat HF patients on the basis of reduced ejection fraction alone.

Randomized controlled trial data regarding in-hospital initiation of MRA therapy among patients with HFrEF is limited to the EPHESUS trial. However, patients with worsening HF are often admitted to hospital, creating opportunity for improving HF therapies before discharge. In the PIONEER-HF study it was noted that in patients admitted with acute decompensated HF and reduced ejection fraction, 65% had a history of HF but only 10% were receiving an MRA at the time of admission.[8]

Patients with HF have multiple comorbidities adding complexity to their care. In-patient care for any one of these medical concerns is an opportunity to enhance HF therapy. In contrast, medications are often interrupted during acute medical illness and reintroduction at maximum tolerated doses before discharge is encouraged.

In addition to including MRAs as part of standard medical HFrEF therapy, the following recommendation has been updated.

RECOMMENDATION

10. We recommend MRA treatment for patients with acute MI and LVEF ≤ 40%, and HF symptoms or diabetes, to reduce mortality, CV mortality, and hospitalization for CV events (Strong Recommendation; High-Quality Evidence).

Practical tip. MRAs recommended for patients with HFrEF include spironolactone and eplerenone.

Practical tip. MRAs should generally be avoided when eGFR is < 30 mL/min/1.73 m^2.

Practical tip. MRAs can increase serum potassium, especially during an acute dehydrating illness in which renal dysfunction can worsen. Monitoring of serum creatinine and potassium should be repeated within 1 week of initiation or dose change.

Practical tip. Temporary reduction or interruption of MRA therapy might be necessary when potassium levels are moderately (5.6-5.9 mmol/L) or severely (> 5.9 mmol/L) elevated, with a return to maximum tolerated dose when other modifiable factors are corrected and potassium levels are ≤ 5.0 mmol/L.

Practical tip. MRAs, when used for HF, have very little effect on BP.

SGLT2 inhibitors

When to start SGLT2 inhibitor treatment in patients with HFrEF. The benefits of SGLT2 inhibitors in patients with established HFrEF have been shown in 2 large clinical trials and 1 meta-analysis, with consistency of benefit regardless of diabetes status.[40,41,44] These agents should be considered as standard or foundational therapy in patients with HFrEF (Fig. 1).

The results of the **Dapa**gliflozin in Patients with **H**eart **F**ailure and Reduced Ejection Fraction (DAPA-HF) trial were described in the previous CCS HF guideline update.[2] Over a median 18-month follow-up of 4744 patients with HFrEF, treatment with dapagliflozin significantly reduced the composite primary end point of time to first worsening of HF or death from CV causes (hazard ratio [HR], 0.74 [95% CI 0.65-0.85]; $P < 0.001$), as well as HHF (HR, 0.70 [95% CI 0.59 - 0.83]) and CV death (HR, 0.82 [95% CI 0.69 - 0.98]). Importantly, 55% of patients in this trial did not have diabetes at baseline, and the effect of dapagliflozin was similar at any hemoglobin A1c level.[40] Ancillary studies have shown that benefits accrued as early as 30 days after treatment initiation.[45] Other notable substudy findings were that diuretic dose was not modified during the trial for most patients,[46] quality of life was improved,[47] and BP was reduced by an average of approximately 2 mm Hg.[48] Importantly, baseline kidney function did not modify the effect of dapagliflozin on outcomes and treatment was associated with a slower eGFR decline compared with placebo in diabetic and nondiabetic cohorts.[49]

The results of the recently published EMPEROR-Reduced trial,[41] in which empagliflozin 10 mg daily was compared with placebo in patients with symptomatic HFrEF, were concordant with those of DAPA-HF. Participants included those with an LVEF < 40% and elevated NT-proBNP levels that varied according to LVEF and atrial fibrillation status. Enrollment could occur with an eGFR as low as 20 mL/min/1.73 m^2. During a median follow-up of 16 months, the primary outcome of CV death or HHF occurred in 19.4% of participants in the empagliflozin group and in 24.7% of the placebo group (HR, 0.75 [95% CI 0.65-0.86]; $P < 0.001$); this benefit was comparable for patients with and without diabetes. The total number of HHF was lower in the empagliflozin group (HR, 0.70 [95% CI 0.58-0.85]; $P < 0.001$), as was the annual rate of decline in eGFR (−0.55 vs −2.28 mL/min/1.73 m^2 per year; $P < 0.001$).

The use of background pharmacological therapy for HFrEF was excellent in both trials. Of particular note, sacubitril-valsartan served as a RASi among approximately 11% of patients in DAPA-HF and in approximately 19% in EMPEROR-Reduced at enrollment. Cardiac resynchronization therapy (CRT) was used in 7.5% of participants in DAPA-HF and in 12% of those in EMPEROR-Reduced, whereas implantable cardioverter defibrillators (ICDs), with or without CRT, were used in 26% and 31%, respectively. There were no treatment interactions between SGLT2 inhibitor and the baseline therapies used. SGLT2 inhibitor treatment was safe with no excess in hypovolemia, hypoglycemia, or renal side effects compared with placebo.

Taken together, as shown in a meta-analysis by Zannad and colleagues, the results of these 2 landmark trials show that SGLT2 inhibitor reduces morbidity and mortality in patients with symptomatic HFrEF, whether type 2 diabetes is present or not.[44]

The recently published **Dapa**gliflozin in Patients With **C**hronic **K**idney **D**isease (DAPA-CKD) trial[50] showed that dapagliflozin, when used in addition to standard therapy, also prevents renal and CV outcomes in patient with established chronic kidney disease. Among 4304 participants, with or without type 2 diabetes, with an eGFR between 25 and 75 mL/min/1.73 m^2 and proteinuria (a urinary albumin-to-creatinine ratio of 22.6-565.6 mg/mmol) who were randomly assigned to dapagliflozin 10 mg daily or placebo, the primary composite outcome of a sustained decline in eGFR of at least 50%, end-stage kidney disease, or death from renal or CV causes was reduced by 44% (HR, 0.56 [95% CI 0.45-0.68]; $P < 0.001$). The hazard ratio for the composite of death from CV causes or HHF was 0.71 ([95% CI 0.55-0.92]; $P = 0.009$). All-cause mortality was also significantly reduced (HR, 0.69; [95% CI 0.53-0.88]; $P = 0.004$) and the safety profile of dapagliflozin was confirmed in this group.

RECOMMENDATION

11. We recommend an SGLT2 inhibitor, such as dapagliflozin or empagliflozin, be used in patients with HFrEF, with or without concomitant type 2 diabetes, to improve symptoms and quality of life and to reduce the risk of HF hospitalization and/or CV mortality (Strong Recommendation; High-Quality Evidence).
12. We recommend an SGLT2 inhibitor, such as empagliflozin, canagliflozin, or dapagliflozin be used for treatment of patients with type 2 diabetes and atherosclerotic CV disease to reduce the risk of HF hospitalization and death (Strong Recommendation; High-Quality Evidence).
13. We recommend an SGLT2 inhibitor, such as dapagliflozin, be used in patients with type 2 diabetes who are older than 50 years with additional risk factors for atherosclerotic CV disease to reduce the risk of HF hospitalization (Strong Recommendation; High-Quality Evidence).
14. We recommend SGLT2 inhibitors such as canagliflozin or dapagliflozin be used in patients with albuminuric renal disease, with or without type 2 diabetes, to reduce the risk of HF hospitalization and progression of renal disease (Strong Recommendation; High-Quality Evidence).

Values and preferences. These recommendations place weight on the results from large randomized, placebo-controlled trials that consistently showed a benefit of SGLT2 inhibitor treatment on HF prevention and treatment among patients with and without type 2 diabetes.

Practical tip. In EMPEROR-Reduced and DAPA-HF, SGLT2 inhibitor treatment was initiated in addition to maximally tolerated GDMT. However, recognizing the significant residual risk of patients with HFrEF despite GDMT and the benefits associated with dapagliflozin and empagliflozin, it would be reasonable to start this class of therapy early in the disease course for eligible patients.

Practical tip. EMPEROR-Reduced excluded patients with an eGFR < 20 mL/min/1.73 m^2 and DAPA-HF excluded patients with an eGFR < 30 mL/min/1.73 m^2. Data supporting the use of these agents in patients with HFrEF and eGFR < 30 mL/min/1.73 m^2 are very limited.

Practical tip. The Canadian Heart Failure Society (CHFS) has published Practical Approach to SGLT2 Inhibitors for Treatment of Cardiovascular Disease, which includes contraindications, cautions, drug initiation, special considerations, and sick day management tips.[51]

Additional Practical Tips related to SGLT2 inhibitor prescription from the previous 2020 HF guideline update[2] remain relevant and are included as follows:

Practical tip. SGLT2 inhibitors are currently contraindicated for patients with type 1 diabetes.

Practical tip. The most common adverse effect of this class of medications are genital mycotic infections (GMIs). Women (10%-15% risk), those with previous GMIs, and uncircumcised men are at highest risk. Typically, GMIs can be managed with antifungal drugs and do not require discontinuation of therapy.

Practical tip. SGLT2 inhibitor use might result in temporary reduction of eGFR up to 15%, which generally resolves within 1-3 months. SGLT2 inhibitors have also been associated with acute kidney injury and increased monitoring is warranted in those at risk.

Practical tip. SGLT2 inhibitors rarely cause hypoglycemia in the absence of concomitant insulin and/or secretagogue therapy. Background therapies might need to be adjusted to prevent hypoglycemia.

Practical tip. SGLT2 inhibitors should be held in the setting of concomitant dehydrating illness as part of Sick Day management. Patients should be educated on Sick Day management.

Practical tip. These agents have been associated with diabetic ketoacidosis (incidence 0.1%). Patients might present with normal or only modestly elevated blood glucose level (< 14 mmol/L). On rare occasions, SGLT2 inhibitors might be associated with normal anion gap acidosis, which is best detected with measurement of serum ketones. Nonspecific symptoms associated with diabetic ketoacidosis include: shortness of breath, nausea, vomiting, abdominal pain, confusion, anorexia, excessive thirst, and lethargy.

Practical tip. Careful attention to volume status is required when SGLT2 inhibitors, ARNIs, and loop diuretics are used in combination because of their concomitant effects to promote diuresis.

Sinus Node Inhibition

Resting heart rate independently predicts CV events, including HHF and death.[52-54] Studies have shown that the effect of elevated heart rate on outcomes becomes apparent within 30 days of discharge from hospital.[55] In systematic reviews it has been postulated that a major contributor to the benefits of β-blocker therapy in patients with HFrEF might be their rate-lowering effect.[56-58]

Ivabradine selectively inhibits the depolarizing I_f current in the sinus node. It thus requires sinus rhythm to provide its pharmacological effect. In contrast to β-blockers, ivabradine decreases heart rate without lowering BP or myocardial contractility.[59] The

Systolic **H**eart Failure Treatment With the I_f Inhibitor Ivabradine **T**rial (SHIFT) trial addressed the use of ivabradine in ambulatory patients with chronic symptomatic HFrEF.[60] The SHIFT trial design, inclusion criteria, and results have been discussed previously in the 2017 comprehensive guideline update.[1] In this trial, there was an 18% reduction in the primary outcome of CV death or HHF favouring ivabradine compared with placebo, which was largely driven by a reduction in HHF (relative risk reduction, 26%). In the prespecified subgroup of patients with resting heart rate > 77 bpm, ivabradine exerted a greater effect on outcome reduction including the primary end point (HR, 0.76 [95% CI 0.68-0.85]; $P < 0.0001$), all-cause mortality (HR, 0.83 [95% CI 0.72-0.96]; $P = 0.0109$), and CV mortality (HR, 0.83 [95% CI 0.71-0.97]; $P = 0.0166$).[61] In the 685 patients not taking β-blockers at baseline, ivabradine reduced the primary end point with a HR of 0.68 (95% CI 0.52-0.88).

Studies have shown that most titration of β-blockade occurs early in the course of treatment, with most of the heart rate reduction occurring at < 50% of target dose.[62,63] With further titration, there is a diminishing effect on heart rate, leaving approximately 10%-15% of patients with residual heart rate > 70 bpm after β-blocker titration.[64,65] Beyond chronic ambulatory HF, small studies have shown that the additional use of ivabradine with a β-blocker is safe and well tolerated in hospital settings.[66-69]

RECOMMENDATION

15. We recommend that ivabradine be used for patients with HFrEF and symptoms despite treatment with GDMT, a resting heart rate ≥ 70 bpm, and sinus rhythm for the prevention of CV death and HF hospitalization (Strong Recommendation; High-Quality Evidence).

Values and preferences. High value is placed on reducing the risk of CV death and HHF when ivabradine is used as adjunctive therapy with standard HF medication treatments in a selected HFrEF population. Differing criteria for heart rate eligibility have been approved by various regulatory authorities ranging from 70-77 bpm, although the trial entry criteria was 70 bpm.

Practical tip. Ivabradine has no direct effect on BP, myocardial contractility, or renal function and as such is well tolerated in patients who are unable to initiate or titrate β-blockers for these reasons.

Practical tip. Ivabradine may be considered for patients with either stable or decompensated chronic HFrEF who are intolerant of β-blockers, with a resting heart rate in sinus rhythm of > 70 bpm.

Practical tip. Typical reductions in resting sinus heart rate after treatment with β-blockers range from 10-15 bpm, with little change (< 5 bpm) between low and high doses. This consideration might assist in the decision to use further medications for sinus heart rate control.

Practical tip. Ivabradine is well tolerated in older adults and can be initiated at 2.5 mg twice daily.

Practical tip. Ivabradine should be avoided in patients with advanced liver disease.

sGC stimulators

Worsening HF and HHF portend a poor prognosis and are associated with increased risk of mortality and recurrent hospitalization. The initial posthospitalization phase is the highest risk period for adverse events and represents an opportunity for the clinician to optimize HF care.[70] Pharmacological therapies targeted at this vulnerable phase of the patient journey as a strategy to improve longer-term outcomes have been evaluated in recent clinical trials.[71,72]

sGC stimulators, such as vericiguat, directly enhance cyclic guanylate monophosphate (GMP) production and also enhance endogenous sGC sensitivity to nitric oxide. This results in a cascade of adaptive effects on the heart, blood vessels, and kidneys, providing the physiological rationale for their use in patients with HF.

In the **Veri**ci**gua**t Gl**o**bal Study in Subjects With Heart Failure With **R**educed Ejec**ti**on Fr**a**ction (VICTORIA) trial the efficacy and safety of vericiguat compared with standard of care was evaluated in patients with advanced functional symptoms, an LVEF < 45% and a worsening HF event characterized by HHF or elevated natriuretic peptide levels.[71] Notably, patients with an eGFR < 15 mL/min/m^2 and systolic BP of < 100 mm Hg were excluded. Study participants receiving optimal guideline-based HF therapies were randomized to placebo or vericiguat and followed for an average of 11.8 months. The primary combined end point of CV death or first HHF was significantly lower (HR, 0.90 [95% CI 0.82-0.98]; $P = 0.019$) in the vericiguat group and this was driven primarily by a reduction in hospitalization rather than CV death. Of note, the secondary end point of total HHF was also decreased in the vericiguat group (HR, 0.91 [95% CI 0.84-0.99]; $P = 0.023$). From a safety perspective, there was more hypotension in the vericiguat group but this did not contribute to renal dysfunction, despite the relatively low eGFR cutoff for enrollment.

Intention to treat subgroup analysis of the combined primary end point showed that vericiguat provided benefit across most clinically relevant subgroups with exception of those with very high NT-proBNP values at baseline (> 8000 pg/mL).[73]

RECOMMENDATION

16. We recommend that vericiguat, an oral sGC stimulator, be considered in addition to optimal HF therapies for HFrEF patients with worsening symptoms and HHF in the past 6 months, to reduce the risk of subsequent HF hospitalization (Conditional Recommendation; Moderate-Quality Evidence).

Values and preferences. This recommendation places value on the use of an additional medication to reduce the risk of HHF in a high-risk patient population that experiences high rates of hospitalization and mortality despite the relatively modest relative benefits observed in the VICTORIA trial.

A conditional recommendation is provided because vericiguat has not yet been approved for this indication in Canada.

Table 2. Standard therapies and their initial and optimal dose targets for patients with HFrEF

Drug class	Specific agent	Start dose	Target dose
ARNI	Sacubitril-valsartan	50-100 mg BID (dose rounded)	200 mg BID (dose rounded)
ACEI	Enalapril	1.25-2.5 mg BID	10 mg BID/20 mg BID (NYHA IV)
	Lisinopril	2.5-5 mg daily	20-35 mg daily
	Perindopril	2-4 mg daily	4-8 mg daily
	Ramipril	1.25-2.5 mg BID	5 mg BID
	Trandolapril	1-2 mg daily	4 mg daily
ARB	Candesartan	4-8 mg daily	32 mg daily
	Valsartan	40 mg BID	160 mg BID
β-Blocker	Carvedilol	3.125 mg BID	25 mg BID/50 mg BID (> 85 kg)
	Bisoprolol	1.25 mg daily	10 mg daily
	Metoprolol (CR/XL)	12.2-25 mg daily	200 mg daily
MRA	Spironolactone	12.5 mg daily	25-50 mg daily
	Eplerenone	25 mg daily	50 mg daily
SGLT2 inhibitor	Dapagliflozin	10 mg daily	10 mg daily
	Empagliflozin	10 mg daily	10-25 mg daily
	Canagliflozin	100 mg daily	100-300 mg daily
Sinus node inhibitor	Ivabradine	2.5-5 mg BID	7.5 mg BID
sGC stimulator	Vericiguat	2.5 mg daily	10 mg daily
Vasodilator	Hydralazine and isosorbide dinitrate	10-37.5 mg TID/10-20 mg TID	75-100 mg TID or QID/40 mg TID
Cardiac glycosides	Digoxin	0.0625-0.125 mg daily	Not applicable: monitor for toxicity

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BID, twice per day; CR/XL, controlled release/extended release; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; QID, 4 times per day; sGC, soluble guanylate cyclase; SGLT, sodium glucose transport; TID, 3 times per day.

Practical tip. Subgroup analysis from the VICTORIA trial suggests that clinical response to vericiguat might be attenuated in patients with very elevated natriuretic peptide levels.

Digoxin

The **D**igitalis **I**nvestigation **G**roup (DIG) trial enrolled 6800 patients with HF and a LVEF ≤ 45%. The primary end point was mortality, and the mean follow-up was 37 months. Patients were randomized to digoxin (median dose, 0.25 mg/d) or placebo. Fifty-four percent of participants had NYHA class II symptoms and 94% were treated with an ACEI. There was no difference in all-cause mortality between groups. There were fewer patients hospitalized for worsening HF in the digoxin group. Suspected digoxin toxicity was higher in the digoxin group.[74]

RECOMMENDATION

17. We suggest digoxin be considered in patients with HFrEF and atrial fibrillation, with poor control of ventricular rate and/or persistent symptoms despite optimally tolerated β-blocker therapy, or when β-blockers are not tolerated, in the setting of chronic HF, new onset HF, or HF hospitalization (Weak Recommendation; Low-Quality Evidence).
18. We suggest digoxin be considered in patients with HFrEF in sinus rhythm who continue to have moderate to severe symptoms despite appropriate doses of GDMT to relieve symptoms and reduce hospitalizations (Weak Recommendation; Moderate-Quality Evidence).

Values and preferences. These recommendations place a high value on the understanding that the role of cardiac glycosides in patients with HFrEF remains controversial in light of evolving contemporary HF therapy.

A subsequent systematic review of 13 studies (which included the DIG trial) showed similar results. None of these studies provide meaningful insight into the relative benefit, or harm, of digoxin in light of contemporary HFrEF therapy. There has been substantial use of digoxin as background therapy in the current era of HFrEF landmark trials with no apparent change in outcomes stratified according to baseline digoxin use.[75]

Practical tip. Serum concentrations of digoxin < 1.2 ng/mL are associated with less treatment-related morbidity. Nonetheless, routine digoxin levels are not required other than to assess for digoxin toxicity. Digoxin levels should not be used to guide chronic therapy and titrating to digoxin levels has not been tested in clinical trials

Practical tip. Digoxin can cause atrial and ventricular arrhythmias particularly in the presence of hypokalemia and/or worsening renal function and levels should be monitored accordingly.

Practical tip. In patients receiving digoxin, serum potassium and creatinine should be measured with increases in digoxin or diuretic dose, the additional use or discontinuation of an interacting drug, or during a dehydrating illness, to reduce the risk of digoxin toxicity. Patients with reduced or fluctuating renal function, older patients, those with low body weight, and women are at increased risk of digoxin toxicity and might require more frequent monitoring including digoxin levels.

Practical tip. Among hospitalized older patients with HFrEF who are receiving guideline-directed medical therapies, discontinuation of preadmission digoxin therapy might have deleterious effects.[76]

Hydralazine and isosorbide dinitrate

The combination of hydralazine and isosorbide dinitrate (H-ISDN) has had a role in the management of HFrEF since the 1980s. The first large-scale trial of this therapy predated

landmark studies of RASi and β-blockers. In **V**asodilator in **He**art **F**ailure **T**rial (V-HeFT) the effect of H-ISDN, prazosin, and placebo were compared in an HFrEF patient population. Mortality was reduced among patients treated with H-ISDN with a relative risk reduction of 34% at 2 years ($P = 0.028$).[77] Compared with enalapril, treatment with H-ISDN provided less mortality reduction after a mean of 2.5 years (32.8% vs 38.2%; $P = 0.016$) and no difference in hospitalizations.[78]

In the **A**frican-American **He**art **F**ailure **T**rial (A-HeFT), H-ISDN was investigated as used in addition to optimal therapy in self-identified black patients with HFrEF and NYHA class III/IV symptoms. Black patients were specifically evaluated in this trial because they are known to have reduced activity of the renin-angiotensin system. A total of 1050 black patients were randomized to H-ISDN or placebo, in addition to standard of care, and followed for a mean of 10 months. The study was terminated early because of higher mortality in the placebo group. The primary outcome was a weighted score, but individual components of the outcome showed a difference favouring H-ISDN for all-cause mortality, first HHF, and change in quality of life score.[79]

RECOMMENDATION

19. We recommend that H-ISDN be considered for treatment of patients with HFrEF who are unable to tolerate an ACEI, ARB, or ARNI because of hyperkalemia, renal dysfunction, or other contraindications, in the following settings:
    i. Chronic HF (Strong Recommendation, Moderate-Quality Evidence);
    ii. New-onset HF (Weak Recommendation, Low-Quality Evidence); and
    iii. HF hospitalization (Weak Recommendation, Low-Quality Evidence).
20. We recommend that H-ISDN treatment be considered in addition to standard GDMT at appropriate doses for black patients with HFrEF and advanced symptoms (Strong Recommendation; Moderate-Quality Evidence).

Values and preferences. There is limited high-quality clinical trial evidence in the modern era on which to base an H-ISDN recommendation. Adverse effects related to H-ISDN are frequent, limit up-titration, and lead to discontinuation in a significant proportion of patients. Every effort should be made to use ARNI (or alternatively ACEI/ARB) therapy including initiating at a low dose and/or rechallenging patients who have experienced adverse events/intolerability before changing to H-ISDN.

Practical tip. Renal dysfunction warranting a trial of H-ISDN includes those who have a significant change in creatinine from baseline with ACEI/ARB/ARNI therapy that persists despite modification of dose, rechallenge, and/or removal of other potentially nephrotoxic agents. It may also be considered in those with a serum creatinine > 220 mmol/L who experience significant worsening in renal function with the use of ACEI/ARB/ARNI therapy, or if the risk of these agents (eg, potential for worsening renal function requiring renal replacement therapy) is thought to outweigh benefits.

Practical tip. A trial of H-ISDN might be warranted in patients with persistent hyperkalemia (K > 5.5 mmol/L) despite dietary intervention, dose reduction of ACEI/ARB/ARNI, and removal of other agents known to increase potassium levels.

Practical tip. Nitrates alone might be useful to relieve orthopnea, paroxysmal nocturnal dyspnea, exercise-induced dyspnea, or angina in patients when used as tablet, spray, or transdermal patch, but continuous (ie, around the clock) use should generally be avoided because most patients will develop tolerance. It should be noted that use of nitrates or hydralazine alone has not been shown to improve HF outcomes.

Referral for ICD and CRT

When to refer for ICD/CRT in the current era of medical therapy for HFrEF

The decision regarding when and if an ICD should be implanted must include evaluation of the short- and long-term risks of sudden death due to a ventricular arrhythmia and death from nonarrhythmic causes. This is often a complex assessment and must integrate many factors including the presence of ischemic heart disease, burden of scar, frailty, advancing dementia, comorbidities, and adequacy of background medical therapy. In addition to ICD considerations, CRT further improves mortality and reduces HHF in patients with HFrEF and dyssynchrony, particularly those with QRS > 150 ms.[1]

Most trials that have shown a mortality reduction for primary prevention ICD implantation or CRT were conducted in an era when conventional HFrEF therapy included β-blockers, RASi with ACEIs and ARBs, and MRAs. In the past decade, HFrEF therapies such as sacubitril-valsartan,[5] ivabradine,[60] SGLT2 inhibitor,[40,41] and vericiguat[71] have also shown a reduction in CV death and worsening HF events in patients with HFrEF. In part, this might be because of the beneficial effects of these agents on ventricular function. For example, in the echocardiography substudy of the SHIFT trial (discussed previously), among the 411 patients who had paired baseline and 8-month follow-up echocardiography data, there was an increase in LVEF of 2.4% (SD, 7.7) in ivabradine-treated patients compared with a decrease of 0.1% (SD, 8.0%) in the placebo group ($P < 0.001$).[80] Similarly, patients with NYHA II-IV symptoms and LVEF < 40% who were switched from an ACEI/ARB to an ARNI in the open-label, single-arm Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure (PROVE-HF) study, there was an increase in LVEF by 4.9% (range, 4.5%-5.3%) at 6 months and 8.8% (range, 8.3%-9.3%) at 12 months.[81] In a meta-analysis of 9 studies including 707 patients with HFrEF, the LVEF increased by 4.9% (range, 4.13%-5.65%) after patients were switched to treatment with an ARNI.[82] Because of the demonstrated benefits of current HFrEF therapies to improve LVEF over time, it seems prudent to ensure that GDMT has been optimized before implanting primary prevention ICDs and CRT. However, it must be emphasized that there are no randomized controlled trial data

on the risk/benefit of ICD implantation and CRT before vs after the initiation of newer HFrEF therapies. Every attempt should be made to initiate and titrate GDMT as quickly as feasible to avoid delays in referring suitable patients with persistently reduced LVEF for device therapy.

RECOMMENDATION

21. We recommend that after a diagnosis of HFrEF, standard medical therapy should be initiated and titrated to target or maximally tolerated doses with a repeat assessment of LVEF before referral for ICD or CRT (Strong Recommendation; Moderate-Quality Evidence).

Practical tip. Reassessment of ejection fraction should be performed 3 months after the achievement of target or maximally tolerated doses of GDMT.

Practical tip. An assessment of arrhythmic and non-arrhythmic sudden cardiac death (SCD) risk should be performed to estimate the risk/benefit of ICD implantation or CRT.

Practical tip. Specific HF therapies might contribute to improvements in LVEF and should be considered before referral for ICD implantation or CRT:

- For eligible patients, switching to ARNI therapy should be considered before referral for ICD or CRT.
- Additional use of ivabradine, where otherwise indicated after β-blocker optimization, should be considered before referral for ICD implantation or CRT.

Practical tip. Referral for ICD implantation or CRT should not be unduly delayed if timely titration of pharmacologic therapies is infeasible or impractical.

Areas of Uncertainty and Evolving Evidence

The CCS HF Guidelines Panel identified a number of unresolved questions relevant for the management of patients with HFrEF. For the purposes of this guideline update, systematic evidence reviews were limited in scope to the therapies and settings discussed herein. However, on the basis of emerging evidence, some additional considerations are worth noting, and further research will likely inform future guidelines.

1. Should ARNIs be prescribed in the setting of HF after MI?

The **P**rospective **AR**NI vs **A**CE Inhibitor Trial to **D**etermine **S**uperiority in Reducing Heart Failure **E**vents After **MI** (PARADISE-MI; NCT02924727) trial has completed enrollment and will compare sacubitril-valsartan with ramipril treatment early after high-risk MI (12 hours to 7 days) with respect to the composite end point of CV death, HHF, or urgent outpatient HF visit.

2. Should SGLT2 inhibitor treatment be initiated during an HHF episode in patients with HFrEF?

In the recently published **So**tag**l**iflozin on Clinical Outcomes in Hem**o**dynam**i**cally **St**able Patients With Type 2 Diabetes POST **W**orsening **H**eart **F**ailure (SOLOIST-WHF) trial,[83] sotagliflozin (a combined sodium glucose transport 1/SGLT2 inhibitor) was compared with placebo in 1222 patients with diabetes who were admitted to hospital with worsening HF. The medication was prescribed before discharge or shortly after discharge when hemodynamic stability was achieved. Sotagliflozin significantly reduced the risk of achieving the primary end point of CV death, HHF, or urgent visit for HF (51.0 vs 76.3 events per 100 patient-years; HR, 0.67 [95% CI 0.52-0.85]). Ongoing trials will further evaluate the efficacy and safety of initiating SGLT2 inhibitors in a spectrum of hospitalized HF patients, regardless of diabetes status (**Dapa**gliflozin and Effect on Cardiovascular Events in **Ac**u**t**e **H**eart **F**ailure -**T**hrombolysis **i**n **M**yocardial **I**nfarction 68 [DAPA ACT HF-TIMI 68; NCT04363697] and A Multicentre, Randomised, Double-blind, 90-day Superiority Trial to Evaluate the Effect on Clinical Benefit, Safety and Tolerability of Once Daily Oral **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**tabilise**d** [EMPULSE; NCT04157751]) trial.

3. Do myosin activators (myotropes) have a role in managing patients with HFrEF?

Omecamtiv mecarbil (OM) is a myosin activator that enhances systolic function in patients with HFrEF by augmenting actin-myosin interaction in the sarcomere.[84] 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), OM was compared with placebo in 8256 patients with HFrEF and worsening symptoms (either currently hospitalized or hospitalized within the past year).[72] Dosing was adjusted according to study drug level, and the primary end point was a composite of HHF or urgent HF visit or CV death. Compared with placebo, OM reduced incidence of the primary outcome over 22 months of follow-up (37.0% vs 39.1%; HR, 0.92 [95% CI 0.85-0.99]). It is unclear whether there are important subgroups of patients (such as those with severely depressed LVEF) that might derive greater benefit from OM. Because of the relatively modest effect of this drug compared with placebo in a high-risk HF population, and uncertainty around whether OM will receive regulatory approval in Canada, no recommendations have been made at this time.

Conclusion

This CCS HF guideline update heralds a shift in the clinical approach to management of patients with HFrEF and will likely have significant practice implications. Although many areas of uncertainty remain and there is continued need for evidence to inform our approach to best practice, it is clear that knowledge translation strategies and change management will be essential to ensure that patients with HFrEF, regardless of practice setting, consistently receive the new standard for optimal medical therapy as outlined in this update.

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