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Cluster Scheme Approach to Foundational Heart Failure With Reduced Ejection Fraction Therapy

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A B S T R A C T

This review presents an evidence-based approach to heart failure with reduced ejection fraction (HFrEF), focusing on the foundational 4 drugs: renin-angiotensin-aldosterone system inhibitors/angiotensin receptor-neprilysin inhibitor, β-blockers, mineralocorticoid receptor antagonist, and sodium–glucose cotransporter-2 inhibitor. Given the benefits of the foundational 4 drugs, combined initiation of these therapies is preferable to the conventional paradigm of targeting maximally tolerated β-blockers and renin-angiotensin-aldosterone system inhibitors before adding other therapies. The conventional approach is linked to treatment gaps and delayed introduction of life-saving therapies in patients with HFrEF. The conventional approach was replaced with the cluster approach, based on large-scale randomized control trials. The cluster approach demonstrated a reduction in morbidity and mortality in patients with HFrEF.

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Introduction

Heart failure (HF) is inadequate cardiac output caused by structural or functional cardiac deformity,[1] contributing to increased mortality and morbidity of affected patients.[2] The heart's inability to pump enough blood and oxygen can result in end-organ damage.[3] HF with reduced ejection fraction (HFrEF) is the diagnosis given to patients when their left ventricular ejection fraction (LVEF) is ≤40%.[4]

Given the low ejection fraction, the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) mediate a compensatory neurohormonal reaction to boost cardiac output.[3] Initially, these systems act by increasing the myocardial contractility and heart rate; however, prolonged activation of the compensatory mechanisms becomes maladaptive, leading to myocardial hypertrophy and downregulation of the β-1 adrenergic receptor.[3]

The compensatory activation of SNS and stimulation of the RAAS result in the release of angiotensin II and aldosterone, which trigger vasoconstriction and sodium and water reabsorption, respectively.[3] In turn, the blood volume increases, resulting in distention of the cardiac chamber and subsequent release of atrial natriuretic peptides (ANP) and B-type natriuretic peptides (BNP) from the atria and ventricles.[3] The ANP and BNP counterbalance the maladaptive neurohormonal mechanisms by producing vasodilation, natriuresis, and diuresis.[3] Similarly, endothelial cells release nitric oxide, which favors vasodilation.[3] Current pharmacologic treatments for HFrEF aim to block these maladaptive neurohormonal compensatory mechanisms to attenuate or reverse their adverse remodeling effect on the myocardial muscle.[3,5]

The latest Canadian Cardiovascular Society (CCS) guideline (2021) emphasizes the importance of using the pharmacologic titration steps based on the New York Heart Association (NYHA) functional classes (Table 1)[4] and the patients' tolerability of drug therapy.[1] The aim of this review is to provide an updated and comprehensive overview of the current titration approach of pharmacotherapy in patients with HFrEF.

Conventional Approach vs Cluster Approach Strategies

Compared with conventional therapy, the cluster approach can add nearly 6 years to the life expectancy of patients with HFrEF.[6] Inadequate optimizations of the foundational 4 therapy results in clinical inertia where patients fall short of receiving evidence-based therapy.[7] In following the conventional approach, it may take 6 months to prescribe all of the recommended therapies to achieve the target doses of each drug class.[6] A delay of 6 months of therapeutic outcomes can lead to hospitalization[6] and a higher risk for mortality and morbidity.[7] Hence, it is best for practitioners to promptly implement the foundational 4 therapies when not contraindicated.[8]

On the other hand, the cluster approach ensures a concise, timely, and practical guide for treating patients with HFrEF.[9] The cluster approach emphasizes in-hospital initiation and titration because it allows close monitoring of the patients and early

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Table 1
Definition of New York Heart Association Classification

Class	Definition	Descriptor
I	No symptoms. No limitation of physical activity	Asymptomatic
II	Symptoms with ordinary activity. Comfortable at rest	Mild symptoms
III	Symptoms with less than ordinary activity	Moderate symptoms
IV	Symptoms at rest or with any minimal activity	Severe symptoms

Adapted from Ezekowitz et al.[4]

recognition of adverse effects.[10] After discharge from the hospital, the nurse practitioner (NP) or general practitioner in the clinic can use the cluster approach algorithms to expedite the process of further titration and initiation of drug therapy.[3]

The cluster-based strategy consists of 3 clusters, where each cluster represents a category of drugs with similar hemodynamic or neurohormonal effects.[3] Cluster A includes sodium–glucose cotransporter-2 inhibitor (SGLT2I) and loop diuretics. Cluster B includes angiotensin receptor-neprilysin inhibitor (ARNI) as the preferred medication instead of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) and mineralocorticoid receptor antagonists (MRAs). Cluster C includes β-blockers and ivabradine.[3]

To implement the cluster approach, NPs should be cognizant of the risks of starting additional HFrEF therapies before all of the foundational 4 drug classes are initiated.[3] The NP should wait at least 1 to 2 weeks before starting uptitration within each drug class to avoid adverse effects.[3] Moreover, Miller et al[3] indicated that patients with systolic blood pressure >110 mm Hg, heart rate >70 beats/min, estimated glomerular filtration rate (eGFR) >40 mL/min/1.73 m^2, and potassium ˂5.0 mmol/L can typically withstand 3 drug class changes per visit with a low risk of adverse effects. Whereas for weaker patients possibly intolerant to medication, changing a single drug class every 2 weeks is recommended.[3] Although McDonald et al[9] recommend a fast and rapid titration interval of 2 to 4 weeks to target dose or a maximally tolerated dose over 3 to 6 months, Miller et al[3] recommend a faster titration interval of 1 to 2 weeks within 3 months, suggesting rapid changes can optimize HFrEF treatment outcomes.

The Foundational Four

The developers of guideline-directed medical therapy for HFrEF evidence-based recommendations include the simultaneous use of 4 foundational medications to improve clinical outcomes and achieve maximal benefits in terms of mortality, morbidity, and quality of life.[10] These include (1) β-blockers, (2) ACEIs or ARBs, or ARNI, (3) SGLT2Is, and (4) aldosterone antagonists.[9] While the guidelines encourage clinicians to gradually uptitrate the doses of these classes to reach the maximally tolerated dose within 3 to 6 months, reaching medication optimization can take an average of 12 months.[11]

Data from the United States registries suggest that only 25% of patients with HFrEF are on optimized guideline-directed medical therapy,[12] while a large percentage of these patients do not receive the foundational 4 or receive suboptimal dosing, resulting in frequent hospitalization, poor quality of life, and sometimes death.[13] Given the high risk for mortality associated with this population, it is imperative to start the foundational 4 at the time of diagnosis.[3,9] The cluster is an evidence-based approach developed to overcome the conundrum of slow or delayed initiation of the foundational 4.[3,9] It includes the simultaneous and rapid sequence initiation and titration of the foundational 4 therapy and is linked to improved survival by achieving timely targeted or maximally tolerated doses.[7]

RAAS Inhibitors

The first drug therapy in the foundational 4 are medicines that inhibit the RAAS system, including the ACEIs, the ARBs, and the ARNI.[3] The NP may select from these 3 drug classes depending on the patient's allergies and tolerances.[3] ACEIs were the gold standard medication for HFrEF patients for the past 3 decades because of their ability to inhibit ACEs that convert angiotensin I to angiotensin II.[3] Inhibiting the release of angiotensin II reverses myocardial remodeling and fibrosis and improves survival rates.[9] Furthermore, ACEI decreases the cardiac afterload by inhibiting the degradation of bradykinin, a peptide that promotes vasodilation.[3]

Angiotensin Receptor Blockers

ARBs, on the other hand, do not cause an increase in bradykinin because they do not block ACE.[3] Instead, they are receptor antagonists that block angiotensin II type receptors.[1,3] Tia et al[14] conducted a meta-analysis of 38 randomized controlled trials. They established that the use of ACEI is associated with a reduction in all-cause mortality and cardiovascular mortality compared with ARBs, where ACEI administration reduced all-cause mortality by 11% ($P <$ .001) and cardiovascular mortality by 14% ($P <$ .001).[14] However, ARBs are recognized as an alternative to ACEI if the latter induces adverse effects of dry cough or angioedema.[14]

Angiotensin Receptor-Neprilysin Inhibitor

The ARNIs are combination products of neprilysin inhibitors, sacubitril, and valsartan (an ARB).[15] ARNI works by blocking the action of neprilysin, thus preventing the breakdown of the natriuretic peptides (atrial natriuretic peptide, brain natriuretic peptide [BNP]) and bradykinin.[3] In the 2021 CCS guideline, McDonald et al[9] recommend that it is best practice for NPs to prescribe and/or titrate ARNI during HFrEF patient hospitalizations. The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial (n = 8,399) investigated patients with NYHA functional class II to IV classification and with LVEF of ≤40% already taking HF medications to determine the efficacy of ARNI over ACEI.[16] The PARADIGM-HF trial has proven that using ARNI vs ACEI reduced recurring hospitalization and, most significantly, the risk of cardiovascular deaths in patients with chronic HF ($P <$ .001).[16] The initiation of ARNI vs ACEI also showed benefits in reducing cardiovascular (CV) deaths or HF hospitalization when started before discharge.[17,18] Therefore, it is best practice for the NPs to initiate ARNI and titrate it accordingly during hospitalization (Table 2).[7,9,19,20] ARNIs should be avoided in patients with a history of angioedema.[19]

β-Blocker

The second class of medication of the foundational 4 is β-blockers, a group of drugs that inhibit the SNS activation and halt renin activities.[3] Selective β-1, such as bisoprolol and metoprolol succinate, can reverse remodeling in the left ventricle, decrease heart rate (independent of SNS inhibition), and promote nitric oxide production.[3] β-Blockers are the most beneficial agent in reducing the morbidity and mortality associated with HFrEF.[21] They reduce myocardial workload due to their effective rate-lowering action and their interference with catecholamine-related ventricular tachyarrhythmias.[22] Packer et al[22] from the European Society

Table 2
Canadian Cardiovascular Society Initial and Target Dosing for Foundational Therapies and Additional Therapies[a]

Drug Class	Specific Agent	Start Dose	Target Dose
ARNI[b]	Sacubitril-valsartan	24/26-49/51 mg bid	97/103 mg bid
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 daily; CR/XR = controlled release/extended release; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; sGC = soluble guanylate cyclase; SGLT2 = sodium-glucose transporter 2; tid = thrice daily; qid = 4 times daily.
[a] Adapted from McDonald et al.[7]
[b] Adaptad from Maddox et al[19] and McDonagh et al.[20]

of Cardiology (ESC) showed that β-blockers reduced all-cause mortality among patients with severe HF or recent decompensation by 34% to 35% demonstrated in 3 large-scale trials. On the other hand, the American College of Cardiology 2021 recommended avoiding β-blockers in patients with decompensated HF and monitoring heart rate, blood pressure, and signs of congestion during and after their administration.[19]

It is recommended that the β-blockers dose be adjusted every 2 weeks[19] (the incremental initiation and target dose are detailed in Table 2). To ensure that β-blockers are initiated safely, practitioners should ensure that patients are clinically euvolemic before starting therapy.[22] The practitioner should monitor the patient for possible fluid retention and congestion development and be prepared to start diuretics.[22] Failure to do so may result in worsening HF.[22] Following the cluster approach, it is best practice to combine β-blockers with SGLT2Is or add diuretics when needed.[22]

The NPs should be cognizant that β-blockers may take between 6 and 12 months to reach their full potential in improving LVEF.[9] Moreover, it is recommended that cardiologists initiate and monitor the effects of β-blockers in patients with NYHA class III or IV.[9] Noncardiologists can initiate and adjust β-blockers in patients with NYHA classes I or II.[9] According to a meta-analysis, 18 trials included 3,023 patients, with 1,305 treated with placebo and the remaining 1,718 with β-blockers.[23] Of these patients, 116 (9.6%) experienced hospitalizations, which was statistically significant ($P < .001$).[23]

Ezekowitz et al[4] and McDonald et al[9] CCS guidelines recommend initiating β-blockers as a first-line treatment in the foundational 4 therapies immediately after a HF diagnosis using NYHA class I to III without disruption unless contraindicated. For NYHA class IV, initiate a β-blocker once patients' symptoms have stabilized.[4,9] It is highly recommended that NPs start β-blockers in all patients with a history of myocardial infarction and an LVEF ≤40%.[9] β-Blockers should be initiated to an optimal or maximal tolerated dose (Table 2) as long as excessive bradycardia and hypotension are not a deterring factor.[9]

Mineralocorticoid Receptor Antagonist

MRA is the third drug class of the foundational 4.[9] MRA antagonizes the action of mineralocorticoid aldosterone at its receptor in the myocardium and vascular smooth muscle cells.[3] Moreover, MRAs exert antifibrotic properties by decreasing the synthesis of matrix metalloproteinases and other enzymes involved in interstitial myocardium remodeling.[3] In 2016, Berbenetz and Mrkobrada[24] conducted a systematic review and meta-analysis to examine the effectiveness of MRAs in HFrEF, focusing on cardiovascular death, all-cause mortality, and cardiac hospitalization as the main composite end points. They established that MRAs are linked to a reduction in cardiovascular death (relative risk, 0.81; 95% CI, 0.75-0.87), all-cause mortality (relative risk, 0.83; 95% CI, 0.77-0.88), and cardiac hospitalization (relative risk, 0.80; 95% CI, 0.70-0.92) in patients with HFrEF.[24]

Sodium–Glucose Cotransporter-2 Inhibitors

The last drug class of the foundational 4 is SGLT2Is.[25] Although SGLT2Is were initially studied and indicated for treating diabetes mellitus (DM) by increasing the urinary excretion rate of glucose, they have shown favorable outcomes in HFrEF patients.[3] Evidence was strong enough for a class SGLT2I recommendation in the 2021 CCS guidelines.[9] The diuretic and natriuretic action of SGLT2I are thought to be responsible for the observed cardiovascular benefits.[3,25] The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial results showed that individuals with HFrEF who received SGLT2I had a reduced risk of worsening HF or CV death ($P = .00001$) compared with placebo.[26] Additionally, SGLT2Is reduced the risk of having the first incidence of worsening HF, hospitalization for HF/urgent HF visits, and the risk of CV mortality.[26] Similarly, the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and Reduced Ejection Fraction (EMPEROR-Reduced) established low CV mortality and HF hospitalization rates, regardless of DM status, in patients who were given SGLT2I ($P < .0001$).[27] All-cause deaths and CV deaths were also lower in both landmark trials.[28] Of note, empagliflozin resulted in a 20% to 40% improvement in NYHA functional class,[27] whereas canagliflozin and dapagliflozin reduced the decline in eGFR and renal outcomes.[27,29]

SGLT2Is were highly beneficial with optimized HF background therapies.[26,27] SGLT2I seldom causes hypoglycemia unless

administered concurrently with insulin secretagogue treatment.[9] Dapagliflozin 10 mg is administered for HF management in patients with or without DM with no need for further titration.[30] Empagliflozin is also given 10 mg daily for HF management and may increase to 25 mg if being used for glycemic control.[31] Canagliflozin does not yet have an HF dosing schedule.[5] NPs should incorporate SGLT2Is as part of the standard foundational 4 therapy in HFrEF patients with or without DM (Table 2).[9] Owing to the progression of HF and renal events, particularly patients presenting with albuminuria, NPs should use SGLT2Is, such as canagliflozin or dapagliflozin, regardless of DM status.[9]

Assess for Additional Therapies

In additional to the foundational 4, the NP should consider adding additional therapies to better control HFrEF symptoms and improve clinical outcomes.

Ivabradine

Ivabradine should be added to patients with HF in sinus rhythm with heart rate ≥70 beats/min in combination with foundational therapies to prevent CV death and reduce the incidence of HF hospitalization.[9,20] Ivabradine reduces the heart rate through its selective inhibition of f-channels (I_f) in the sinus node.[32] While ivabradine is not indicated in patients with atrial fibrillation[3], it is beneficial in patients in normal sinus rhythm with contraindication to β-blockers.[19]

A systematic review and meta-analysis of 6 studies that included patients with HFrEF (LVEF ˂40%) and mean heart rate ≥70 beats/min, who were on ivabradine and β-blockers or β-blocker alone, showed a significant reduction in heart rates in the combination group compared with the β-blocker group (P ˂ .001).[33] Unlike β-blocker, ivabradine does not impact blood pressure or myocardial contractility[4,21] and should not be given to patients with advanced liver disease.[9] Ivabradine is not a substitute for a β-blocker.[19] The 2017 CCS and the 2021 American College of Cardiology guidelines recommend that NPs should make every attempt to reach the target or maximum tolerable β-blocker dosages before initiating ivabradine.[4,19]

Oral Soluble Guanylate Cyclase Stimulators

The addition of oral soluble guanylate cyclase (sGC) stimulator, such as vericiguat, increases cyclic guanylate monophosphate, thus increasing the sensitivity of endogenous sGC to nitric oxide.[34] Nitric oxide, in turn, causes relaxation of myocardial muscle and vasodilation of blood vessels,[33] thus promoting physiologic adaptation processes to limit myocardial remodeling and deterioration of HF.[9,33] In the Vericiguat Global Study in Subjects With Heart Failure With Reduced Ejection Fraction (VICTORIA) trial, the researchers enrolled 5,050 patients with chronic HF NYHA class II, III, or IV, LVEF ˂45%, and high levels of BNP or pro-BNP to determine the impact of vericiguat in reducing CV death or first HF hospitalization.[35] The results were favorable among the 2526 vericiguat group (P = .02).[34] CV death and primarily hospitalization for HF were lower in the vericiguat group than the placebo group.[35]

The new current Canadian guidelines recommend against using vericiguat in patients with systolic blood pressure ˂100 mm Hg or patients on nitrate therapy.[9,35] Patients with natriuretic peptide levels >8,000 pg/mL did not benefit from the therapy compared with patients in the lower quartile range of natriuretic peptide.[36]

Regarding safety and tolerability, vericguat appeared to be safe without severe adverse effects on renal function or electrolytes compared with the placebo.[9] Based on the VICTORIA outcomes and when vericiguat is approved by Health Canada, NPs can prescribe sGC stimulator for HFrEF patients with worsening symptoms that leads to hospitalization.[9]

Hydralazine and Nitrates

Hydralazine is a direct arterial vasodilator, and nitrates exhibit vasodilatory effects by promoting nitric oxide production.[3] Several studies reported outcomes of patients with class III or IV HF who were randomly assigned to isosorbide dinitrate plus hydralazine or placebo in addition to foundational 4 therapy for HF.[9] Hydralazine and isosorbide dinitrate (H-ISDN) compared with placebo reduced all-cause mortality, initial hospitalization for HF, and optimized the quality of life in Black patients.[9] In self-identified Black patients with HFrEF and NYHA class III to IV, the 2016 ESC, CCS 2017, and 2021 American College of Cardiology guidelines recommend H-ISDN be initiated in Black patients to reduce hospitalization for HF and CV death.[1,4,9] H-ISDN is particularly useful for those who do not respond or have adverse reactions to ACEI, ARB, or ARNI.[4,9] H-ISDN can be used in patients with a serum creatinine >220 mmol/L (2.49 mg/dL) due to renal insufficiency or experienced hyperkalemia from RAASI therapies.[4,9] Similarly, Ziaeian et al[37] found that most patients on H-ISDN had a history of renal insufficiency, hyperkalemia, or ACEI/ARB intolerance. Although H-ISDN therapy is the preferred treatment in the Black patients' subgroup, ARNI (or alternatively ACEI/ARB) must be considered and carefully introduced before adding H-ISDN.[4,9] Based on previous research and the current findings, NPs should consider the H-ISDN combination (not separately) for Black patients with HFrEF after thorough clinical assessment and consideration of foundational therapies.[9]

Oral Inotropes

Digoxin increases contractility and raises the intracellular levels of calcium by decreasing its efflux.[3] Omecamtiv mecarbil (OM) is a relatively novel drug that acts as a cardiac-specific myosin activator.[3] OM has an inotropic effect, which improves the heart's systolic function without raising its energy demand or the risks associated with increased calcium in cardiac myocytes or increasing the risk of ventricular arrhythmias.[3] Studies have shown that in individuals with HFrEF, OM treatment decreased the composite outcome of HF episodes and CV mortality.[3] No recommendations have been given at this time due to the drug's relatively small impact compared with placebo in a high-risk HF patient and the uncertainty surrounding whether OM will obtain regulatory approval in Canada.[9]

The 2016 ESC and the 2017 and 2021 CCS guidelines recommend using digoxin for patients in sinus rhythm with persistent symptoms of HF despite optimal therapy.[1,4,9] The ESC and CCS recommend using digoxin in patients who require additional rate control for atrial fibrillation despite β-blocker therapy.[1,9] Low potassium levels and renal insufficiency can increase the risk of cardiac arrhythmias with a high digoxin dose.[4,9] NPs should monitor digoxin toxicity because there is no defined maximum dose (Table 2).[9]

Sequencing Strategy

Ideally, NPs should aim to optimize each cluster during a clinic visit and initiate 1 drug class within each cluster to a maximum of 3 changes per visit.[3] Drugs within each cluster should not be initiated or titrated on the same visit to prevent exacerbated adverse effects.[3] Using the cluster approach is safer than starting all the foundational classes of 4 drugs at once.[22] Starting all 4 classes at once may increase the risk of orthostatic hypotension, hyperkalemia, and worsening eGFR.[12] Frail patients specifically may not

tolerate starting all 4 classes at once, and features such as advanced age, lower systolic blood pressure, and lower eGFR should guide which medication class within each cluster is chosen to avoid medication intolerance.[3]

During the first face-to-face encounter, NPs should prescribe the preferred medications in each cluster; as such, SGLT2I, ARNI, and β-blocker should be initiated simultaneously.[3] On the second encounter within 1 to 2 weeks, NPs can see the patients face-to-face or virtually to continue SGLT2I in cluster A, start MRA in cluster B, and adjust cluster C.[3] The third visit can be a virtual visit, and NPs can add a loop diuretic as needed to achieve euvolemia and treat volume overload, titrate cluster B medication (ARNI, MRAs), and titrate cluster C (β-blockers) medication.[3] For cluster C, β-blocker can be titrated weekly for up to 2 to 3 months, and if the sinus rate remains >70 beats/min, ivabradine, a selective sinus node inhibitor, is recommended.[3] ESC noted that MRA could be initiated before ARNI if the patient cannot tolerate the hypotensive episodes of angiotensin receptor–neprilysin inhibition (eg, patients with a systolic blood pressure <100 mm Hg).[22] Furthermore, if the patient only has exposure to renin-angiotensin system inhibitors, switching to ARNI and MRA at the same time is feasible.[22] NPs should continue to manage foundational therapies, monitor patient's characteristics, and add additional therapies as needed.[3]

Adherence to the Cluster Approach

Shah et al[38] noted that patients' adherence to drug therapy, clinical improvements between clinic visits, and low hospital readmissions could be maintained by involving clinical pharmacists. Similarly, providing safe and rapid titration for HFrEF patients can be maintained while transitioning from the inpatient to outpatient environment.[10] Dixit et al[10] indicated that strategies such as telephone follow-up, education, self-management, weight monitoring, sodium restriction or dietary advice, exercise recommendations, medication review, and social and psychological support can be used to help with the implementation of the cluster approach.

Further, within 1 to 2 weeks after discharge, laboratory results, such as renal function indicators, potassium, and glucose, should be examined to assess for adverse responses to foundational therapies.[10] Similarly, BNP and N-terminal pro-BNP can be evaluated for possible rehospitalization and response to therapy.[10]

Specialized nurses and pharmacists can continue escalating foundational therapy through telehealth in liaison with the cardiologist.[10] Desai et al[39] stated that using a remote medication optimization approach enhanced initiation and titration of foundational 4 therapy to target dosage and bridged the gap between guideline-directed medical therapy guidelines and clinical application. At 3 months, 197 of 1,131 patients who were enrolled in the remote medication approach demonstrated favorable increase in baseline use of renin-angiotensin system antagonists (138 [70.1%] to 170 [86.3%]; $P < .001$) and β-blockers (152 [77.2%] to 181 [91.9%]; $P < .001$) but not MRA (51 [25.9%] to 60 [30.5%]; $P = .14$) due to its assessment difficulties.[39]

Rossignol et al[40] indicated that measuring renal function and electrolytes is based on the patient's characteristics and the clinical incidence of complications. In stable patients, serum electrolytes, creatinine, and serum urea nitrogen are regularly tested every 1 to 3 months.[11] In patients with worsening symptoms, the NPs should measure serum creatinine at each visit (or virtual). [11] Creatinine should be tested every 5 to 10 days after adding or increasing the dose of diuretic[11] and after initiation or change in ACEI, ARB, MRA, or nonsteroidal anti-inflammatory drug treatment.[11] If the patient's serum potassium is close to or >5.0 mEq/L, serum potassium should be tested every 3 to 5 days.[11] After that, within 1 to 2 days of sodium (calcium or sodium polystyrene) or calcium resonium use or initiation/change in potassium supplement therapy.[11] Howlett et al[11] recommended early serum creatinine measurements when the renal status is impacted by illness such as gastroenteritis or influenza, or after surgery.

Aside from controlling systemic hypertension, there is no agreement on which blood pressure is optimal.[11] For patients with reduced LVEF, some clinicians would seek to maintain systolic blood pressure between <110 and 120 mm Hg.[11]

Table 3
Overcoming Common Clinical Barriers to Guideline-Directed Medical Therapies Optimization[a]

Barrier to Optimization	First-Line Strategy	Second-Line Strategy
Acute kidney injury	• Reduce dose or hold RAAS-I/ARNI. Retrial once renal function improves • Reduce diuretic dose to the lowest dose required to maintain euvolemia	• Switch RAAS-I/ARNI to combination of hydralazine/nitrate only after multiple failed trial
Hyperkalemia	• Remove potassium supplementation • Consider addition of potassium-binders and low potassium diet • Add SGLT2I • Retrial with ARNI (instead of ACEI or ARB)	• Reduce or hold doses of RAAS-I/ARNI or MRA. Retrial one at a time • Switch RAAS-I/ARNI to combination of hydralazine/nitrate only after multiple failed trial
Symptomatic hypotension	• Reduce or remove medications that lower BP and are not guideline recommended • Stagger doses of foundational therapy that lower BP (eg, morning and evening doses) • Reduce foundational therapy dose based on symptoms of hypotension, not BP parameters alone • Reduce diuretic dose to the lowest dose to required maintain euvolemia	• Prioritize β-blocker dosage • Switch carvedilol to metoprolol succinate • Reduce dosage of RAAS-I/ARNI • Switch ARNI to ACEI/ARB and retrial with ARNI in future • Reduce SGLT2I dose and retrial at regular dose in future
Adherence	• Medication reminders (eg, pillboxes, smartphone apps, medication logs). Use once daily medications	• Postdischarge telehealth. • Refer to HF-specific medication titration clinics
Cost/insurance	• Submit prior authorization requests early in hospitalization • Assess patient willingness and ability to pay and prescribe more affordable medications, if necessary	• Periodically reassess availability of new/higher cost medications • Perform institution-specific cost-effectiveness analysis

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; BP = blood pressure; HF = heart failure; MRA = mineralocorticoid receptor antagonist; RAAS-I = renin-angiotensin-aldosterone system inhibitor; SBP = systolic blood pressure; SGLT2I = sodium–glucose cotransporter-2 inhibitor.

[a] Adapted from Dixit et al.[10]

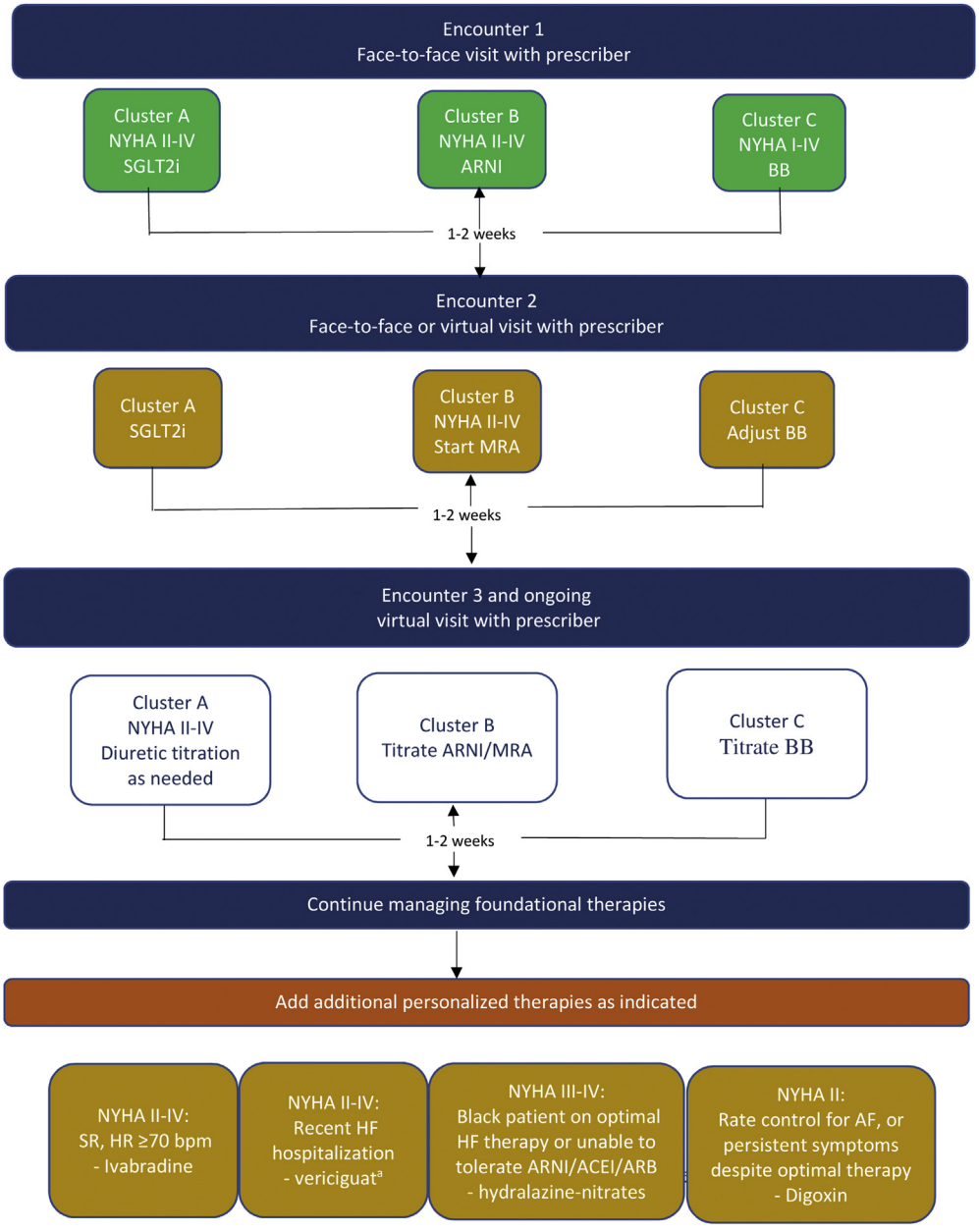

Figure. Simplified medication sequencing algorithm for heart failure with reduced ejection fraction. [a]Vericiguat is not yet approved by Health Canada. Adapted from Miller et al[3] and McDonald et al.[9] *AF = atrial fibrillation; ARNI = angiotensin receptor neprilysin inhibitor; BB = β-blocker; HF = heart failure; HR = heart rate; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; SGLT2i = sodium–-glucose cotransport-2 inhibitor; SR = sinus rhythm.*

Certain clinical barriers to foundational therapies that can hinder optimal HF management are presented in (Table 3).[10] Medications provided at discharge are adhered to and continued in the outpatient setting.[10] Further adherence strategies for medical optimization include pillboxes, smartphone apps, medications logs, and referral to HF-specific medication titration clinics.[10] A simplified HFrEF medication sequencing algorithm is illustrated in the Figure.

Lengthy or repeated attempts to titrate β-blockers without result should be avoided before starting sinus node inhibitor.[9] All foundational 4 classes must be initiated before adding personalized medications and before dose titration.[3] Personalized therapies are given to benefit certain subgroups of patients with HFrEF.[3] Furthermore, the mentioned cluster scheme was designed with the understanding that patients require personalized therapies based on parameters such as tolerability, medical history, vital signs, and so on.[3] Therefore, personalized therapies alone cannot improve all-cause mortality.[3] For instance, ivabradine can only improve mortality if the patient's heart rate is >77 beats/min despite the maximal tolerated β-blockade.[3] Similarly, digoxin can be used for atrial fibrillation or ongoing symptoms despite optimal therapy.[9] Hydralazine nitrates are proven to be beneficial in self-identified Black ethnicity on foundational therapy or intolerant of ACE/ARB/ARNI.[3] Vericiguat has shown benefit in recent HF hospitalization and elevated natriuretic peptide.[3]

The NP should attempt to initiate or titrate 1 medication class within each cluster at every clinical encounter, to a maximum of 3.[3] The purpose of each clinical visit is to start or titrate 1 drug class within each cluster. For instance, practitioners cannot titrate ARNI and MRA simultaneously because they are in a similar cluster.[3] The

NP prescription practices of choosing medication from a particular cluster should be guided by the patient and laboratory characteristics.[3] The NP can alternate between medication classes within a cluster in the absence of a preferred choice.[3] The NP should attempt to schedule a meeting with the patient every 1 to 2 weeks, if possible, with a goal of full foundational therapy titration within 12 weeks.[3] The NP should wait at least 2 weeks before attempting titration within each medication to improve tolerance and mitigate adverse effects.[3] Intolerance of a medication initiation/titration not related to volume depletion should stop further changes in that class until other foundational therapy titration is achieved.[3] The NP should avoid multiple attempts to titrate a particular medication class before adjusting the other cluster classes.[3]

Although there is some preferability in sequencing order of HFrEF drugs; for example, starting only with ARNI or combined with SGLT2I as a first step, followed by simultaneous treatment of β-blocker and MRA as a second step, ESC noted it is unwise to debate the subtle differences.[22] Instead, practitioners should aim to initiate the 4 foundational drugs within a few weeks.[22] The in-hospital environment showed significant benefits and an opportunity to initiate and titrate HFrEF therapy.[3]

Conclusion

The NP should focus on initiating the foundational 4 drug classes as soon as HFrEF is diagnosed. Mortality and morbidity are reduced when 4 foundational drug classes therapy are initiated within 4 weeks; thus, the rate of medication titration should not exceed 3 months (12 weeks) when possible. It is critical to initiate 1 medication from each cluster at each visit and uptitrate simultaneously. Initiating medications from the same cluster is not recommended within the same visit. In the absence of a preferred choice within a cluster, uptitrate each at alternating visits. The NP can make up to 3 changes per visit based on their assessment of the patient's symptoms, vital signs, and renal function. The cluster approach to HFrEF therapy titration can guide NPs to improve morbidity and mortality in this high-risk patient population.

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