Optimizing Foundational Therapies in Patients With HFrEF

How Do We Translate These Findings Into Clinical Care?

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HIGHLIGHTS

- Clinical practice guidelines emphasize the need for guideline-directed medical therapy in patients with heart failure with reduced ejection fraction.
- Recently, international guidelines and the American College of Cardiology Expert Consensus Decision Pathway recommended quadruple therapy for these patients, including angiotensin receptor blockers/neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose co-transporter 2 inhibitors.
- Strategies to optimize use of novel therapies, achieving target doses and management of side effects and tolerability, are needed to achieve this goal.
- Future prospective studies aimed at guiding optimal implementation of quadruple therapy are needed.

SUMMARY

Given the high risk of adverse outcomes in patients with heart failure and reduced ejection fraction (HFrEF), there is an urgent need for the initiation and titration of guideline-directed medical therapy (GDMT) that can reduce the risk of morbidity and mortality. Clinical practice guidelines are now emphasizing the need for early and rapid initiation of therapies that have cardiovascular benefit. Recognizing that there are many barriers to GDMT initiation and optimization, health care providers should aim to introduce the 4 pillars of quadruple therapy now recommended by most clinical practice guidelines: angiotensin receptor-neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium–glucose co-transporter 2 inhibitors. A large proportion of patients with HFrEF do not have clinical contraindications to GDMT but are not treated with these therapies. Early initiation of low-dose combination therapy should be tolerated by most patients. However, patient-related factors such as hemodynamics, frailty, and laboratory values will need consideration for maximum tolerated GDMT. GDMT initiation in acute heart failure hospitalization represents another important avenue to improve use of GDMT. Finally, removal of therapies that do not have clear cardiovascular benefit should be considered to lower polypharmacy and reduce the risk of adverse side effects. Future prospective studies aimed at guiding optimal implementation of quadruple therapy are warranted to reduce morbidity and mortality in patients with HFrEF. (J Am Coll Cardiol Basic Trans Science 2021; ) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Heart failure with reduced ejection fraction (HFrEF) is a complex disease with worse morbidity and mortality than most cancers. Over the past 35 years, a multitude of new drug- and device-based therapies for the management of these patients have shown benefit (Figure 1) and are accordingly recommended by current practice guidelines. Although these advances have been welcomed, they have come at the expense of increasing complexity, added cost, and tolerability concerns. Given the significant co-morbidity burden among patients with HFrEF, the management of these patients has consequently become even more challenging.

Many of the recently updated HFrEF clinical practice guidelines advocate for the use of “foundational quadruple therapy”: a combination of angiotensin receptor blockers/neprilysin inhibitors (ARNIs), beta-blockers (BBs), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose co-transporter 2 inhibitors (SGLT2is). The combined use of these therapies can improve life expectancy for the average 50-year-old patient with HFrEF by a median of 6 years compared with more limited regimens. Despite robust evidence from well-conducted randomized clinical trials, these guideline-directed medical therapies (GDMTs) with established cardiovascular benefit remain significantly underutilized in clinical practice, including those that have been shown for >2 decades to benefit patients.

Such underutilization persists despite the absence of any absolute or relative contraindications or documented intolerances. In the prospective CHAMP-HF (Change the Management of Patients with Heart Failure) registry, which enrolled 3,518 patients, only 1% of the eligible patients were prescribed triple therapy; furthermore, 86% of the patients were not prescribed ARNI despite having no medical contraindication. Similar findings have been seen with the use of MRAs and SGLT2is. Notably, underutilization of GDMT is more pronounced among minorities and women. Following the discovery that the rate of heart failure (HF) hospitalization is reduced with intravenous ferric carboxymaltose in patients admitted with HF, and that cardiovascular death or HF hospitalization is lower in patients with recently worsening HF after use of vericiguat (a soluble guanylate cyclase stimulator), physicians now have multiple therapeutic strategies to leverage. If, however, these therapies continue to be underprescribed, patients will not be able to gain access to and benefit from these morbidity- and mortality-reducing therapies.

In part, the slow uptake of these lifesaving therapies is due to a presumption that the pharmacologic management of patients with HFrEF should always follow a sequential format. Introduction of one therapy with up titration of doses before initiating other medications takes months, if not years, and is often associated with therapeutic hesitancy. This issue is further complicated with the more recent introduction of a fourth foundational therapy, the SGLT2i, in the regime of these patients. Therapeutic hesitancy has been similarly observed with the modification of antihyperglycemic therapies in patients with type 2 diabetes mellitus (T2DM) and established atherosclerotic cardiovascular disease. This issue is of paramount significance because: 1) optimal therapy is not provided in a large proportion of eligible patients; and 2) when it is provided, initiation of therapy is often significantly delayed. The collective trial data indicate that benefits with optimal care accrue early; thus, not providing optimal therapy, or even delaying it, exposes patients to potentially avoidable risk.

The current clinical consensus document is a product of a think tank meeting that was held on March 23, 2021, and included HF experts from across North America to discuss how to best optimize HF care. This review provides an overview of the possible approaches to therapy sequencing optimization in HFrEF. To provide more clinical relevance, approaches for GDMT optimization in common clinical scenarios are described.

**HISTORICAL CONSIDERATION OF SEQUENCING HFrEF THERAPIES**

The historical paradigm in optimizing GDMT with all 4 drug classes of the foundational quadruple therapy is to prescribe them using the specific sequence that pivotal clinical trials used in testing them. Conventionally, this involves starting with an...
angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB), followed by the add-on of a BB and then an MRA. If the patient remains symptomatic, an ARNI is introduced (switched to ACE inhibitor/ARB) before an SGLT2i is prescribed.26 Furthermore, the doses of each therapy are increased to the guideline-recommended dosing (defined as dose target in the pivotal clinical trial) or highest tolerated dose before initiating a new therapy. This traditional paradigm does not, however, take into account several important factors:27 1) most of the landmark clinical trials did not involve patients
who were already on optimized dosing of baseline HFrEF therapies at randomization; 2) this sequential algorithm tacitly assumes that a combination of low-dose therapies will not yield additive benefits; 3) the successive process may require 6 to 12 months to completely incorporate all the recommended treatments; and 4) initiation of multiple therapies upfront, specifically ARNI and SGLT2i, rather than sequentially, may facilitate stabilization of potassium and kidney function to enable initiation of MRAs in the future.

Real-world data from prospective registries around the world suggest that health care providers infrequently add GDMT and do not titrate baseline HFrEF medication doses despite the absence of clinical contraindications or circumstances in which there are no system-level barriers (eg, coverage in the US Veterans Affairs system).12-14,29 Indeed, across multiple global health systems and economies, near identical patterns of infrequent drug titration and early discontinuation of core elements of GDMT have been observed.31

**SIGNIFICANT TIME DELAY IN OPTIMIZING GDMT WITH SEQUENTIAL DOSING**

If a health care provider was to titrate the doses of an ACE inhibitor/ARB and BB in a sequential manner before the initiation of additional GDMT, it would take up to 12 months to achieve optimal dosing.27,29 However, pivotal trials have shown the achievement of early statistical significance.22,27 For example, the time to statistical significance, and by implication sustained clinical benefit, was achieved by day 28 in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial.30 Similar results have been seen in other trials, and this has triggered calls for early initiation of therapy to maximize clinical benefit.31 Of note, trials involving patients with HF and chronic kidney disease are underway to understand the safety and tolerability of dual initiation of a selective mineralocorticoid receptor modulator and SGLT2i.32

**OPTIMAL BACKGROUND THERAPY IS A HISTORICAL CONSTRUCT AND NOT BIOLOGICALLY DETERMINED**

The use of background GDMT in clinical trials was based on the conventional understanding and availability of therapies at the time and was not biologically determined. What is considered “background” or “baseline” optimal therapy has evolved over time. As an example, in CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study), which compared enalapril versus placebo in patients with HFrEF, the enrolled participants had to be on a stable background therapy of digitalis and diuretics.33 Treatment with other drugs for HF, including nitrates, prazosin, and hydralazine, was also permitted. Inasmuch as the standard “toolbox of HFrEF therapies” has changed, more contemporary trials have not included these recommendations.

Notably, the pivotal Phase III trials of foundational quadruple therapy have shown a similar magnitude of benefit with active therapy in patients regardless of the use or dosing of background therapy.34-38 These results underscore the notion that the currently recommended quadruple therapies are functionally independent and not biologically associated with each other regarding their therapeutic efficacy.

To date, CIBIS (Cardiac Insufficiency Bisoprolol Study III) is one of the very few “sequencing” trials. Specifically, CIBIS III compared a bisoprolol-first then enalapril strategy versus an enalapril-first then bisoprolol strategy.39 A total of 1,010 patients were randomized to treatment, and no one strategy was superior, suggesting that either approach was reasonable. Although this cannot be extrapolated to other types of sequencing studies involving more contemporary therapies, thus far there is limited evidence that a rigid sequence approach is optimal or superior when considering the initiation of GDMT in patients with HFrEF.

**FALSE ASSUMPTION THAT TRIALS HAVE OPTIMAL USE OF BACKGROUND GDMT**

Although randomized controlled trials generally have inclusion criteria that mandate patients should be on “optimally tolerated GDMT,” it cannot be assumed that all patients in the landmark trials were on every GDMT or that these therapies were being used at the maximally recommended therapeutic doses. As recently highlighted, the use of background therapy in Phase III studies of HFrEF trials has been extremely heterogeneous.34 For instance, the background use of BB was 3% in CONSENSUS,40 8% in SOLVD (Studies of Left Ventricular Dysfunction),41 and 11% in RALES (Randomized Aldactone Evaluation Study).42 Among the more contemporary trials, the use of MRA was 52% in the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial,8 71.3% in EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction),10 and 71% in the DAPA-HF trial.9 Furthermore, ARNI use was 10.4% in the DAPA-HF trial and 19.4% in EMPEROR-Reduced.10 Therefore, the assumption that clinicians should only initiate
foundational therapies after background therapies have been started and titrated to maximal doses is not consistent with the cohorts of these paradigm-changing clinical trials.

**LOW DOSES OF GDMT HAVE THERAPEUTIC EFFICACY**

An additional fallacy is the assumption that only maximal doses of GDMT have therapeutic benefit, and newer therapies should only be prescribed once the maximal doses are achieved. Closer examination of the baseline trial data suggests that the vast majority of trial participants never received optimal doses of the active drug. For example, only 64% of the MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure) participants eventually met the target trial dose of metoprolol, and only 60.2% of the EMPHASIS-HF (Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms) cohort achieved the target dose of eplerenone. Indeed, there is a paucity of evidence supporting the notion that higher versus lower doses of GDMT robustly improves outcomes; that said, the evidence for greater benefit of higher doses of GDMT is seen with BBs, in which higher doses seem to reduce the risk of death and HF hospitalizations compared with lower doses.

Two key randomized trials come to mind when high-dose versus low-dose ACE inhibitors/ARBs are considered. The first is low- versus high-dose lisinopril in the ATLAS (Assessment of Treatment with Lisinopril and Survival) trial. When comparing the low-dose (2.5 mg to 5.0 mg daily) versus the high-dose (32.5 mg to 35 mg daily) group, there was no difference in mortality, although there was a 24% lower risk of HF hospitalization in the latter group. Although discontinuation rates were similar between the 2 arms, dizziness and renal insufficiency were observed more frequently in the high-dose group. The second trial is the HEAAL (High-Dose Versus Low-Dose Losartan on Clinical Outcomes in Patients with Heart Failure) study. HEAAL participants were randomized to receive either a high-dose (150 mg) or a low-dose (50 mg) losartan regimen. Although no difference in the risk of death was observed, there was a 13% reduction in the risk of HF hospitalization in the high-dose group. Furthermore, the impact of dose on outcomes in male and female subjects requires further clarification because post hoc analyses of HEAAL and ATLAS suggest that lower doses may be acceptable in female subjects to achieve outcome benefit.

There have also been no dedicated trials of high-versus low-dose MRA therapies, and the pivotal MRA trials have shown that low-dose spironolactone and eplerenone (compared with placebo) still had benefit in reducing the risk of adverse outcomes. However, in a post hoc analysis of the EMPHASIS-HF trial, low-dose eplerenone (vs placebo) was revealed to exert a similar magnitude of benefit compared with the higher dose of eplerenone in reducing the risk of adverse HF outcomes.

In the PARADIGM-HF trial, participants may have needed dose reduction at some point during the trial, thereby allowing some assessment of impact of dose on outcome. Overall, the magnitude of benefit with low-, moderate-, or high-dose sacubitril/valsartan relative to enalapril doses was similar. Although there was no direct comparison of low versus high ARNI dose, the findings suggest that ARNIs offer advantages over ACE inhibitors across the dosing ranges. SGLT2is benefit from not requiring any dose adjustments in HF. The collective trial evidence to date supports the view that up titration of ACE inhibitor/ARB, BB, MRA, and ARNI doses may not be necessary to achieve reductions in outcomes, and that initiation of additional foundational GDMT on low-dose background therapies represents an evidence-based strategy to reduce morbidity and mortality in patients with HFREF.

**INITIATION OF MULTIPLE THERAPIES UPFRONT FACILITATES GDMT OPTIMIZATION LATER**

A post hoc analysis of the PARADIGM-HF trial suggested that sacubitril/valsartan, compared with enalapril, did not lead to greater discontinuation of other GDMTs over time and may facilitate initiation and sustained use of MRAs due to stabilization of kidney function and potassium. Similar results have been identified in the EMPEROR-Reduced trial, in which empagliflozin, compared with placebo, was associated with a reduced risk of MRA discontinuation over time. These results suggest that earlier use of ARNIs and SGLT2is may provide a solution to enable further initiation, titration, and sustained use of MRA over time.

**COST-EFFECTIVENESS OF FOUNDATIONAL THERAPIES**

Although there are upfront costs in the utilization of foundational therapies, numerous analyses have reported the global cost-effectiveness of leveraging these medications. Several elements of foundational therapy are now generic (eg, BB, MRA), thereby minimizing cost burden to patients. Furthermore, ARNIs have been shown to be associated with significant cost savings to health care systems, even in
patients in whom the therapy is initiated de novo (ie, before the use of ACE inhibitors/ARBs).\textsuperscript{53,57} The vast majority of data on the system-level cost-effectiveness of SGLT2is come from the T2DM literature.\textsuperscript{54} However, emerging data from the DAPA-HF trial from 2 independent analyses show that dapagliflozin is cost-effective when used in patients with HFpEF regardless of presence of T2DM.\textsuperscript{56} Such results highlight the need for widespread system-level initiatives to utilize foundational therapies.

**CURRENT STRATEGIES TO INITIATE AND TITRATE HFpEF THERAPIES**

The focus on sequential therapy initiation is likely a critical reason for therapy underutilization in people with HFpEF. Updated clinical consensus documents and practice guidelines are now moving away from recommendations of strict sequencing of therapies to more rapid initiation of therapies (Table 1). Updated clinical practice guidelines acknowledge that there is limited evidence to guide optimal sequencing, rapid initiation, and titration of GDMT in patients with HFpEF.\textsuperscript{7,44} However, there are several newer strategies that have been proposed which aim to overcome some of the challenges that occur when following the conventional paradigm (Table 2).

1. McMurray and Packer\textsuperscript{27} advocate for a 3-step rapid initiation method for stable outpatients. This approach starts with the initiation of a BB and an SGLT2i. This is to be followed by the subsequent initiation of an ARNI in 1 to 2 weeks, and then an MRA within an additional 1 to 2 weeks. Dose titration should be attempted once all foundational therapies have occurred. The authors recognize that the latter 2 steps can be re-ordered or changed depending on patient-specific circumstances, including therapies at baseline and therapy tolerability.

2. Clinical consensus guidelines such as those created by the European Society of Cardiology highlight the needed for individualized patient profiling to identify the optimal approach to initiate and titrate HF-specific GDMT.\textsuperscript{55} Such recommendations were echoed by a recent publication by Miller et al\textsuperscript{59} in which a patient-centric or “cluster”-based approach was highlighted as a strategy to optimize GDMT. In general, patients are considered within the lens of 3 general phenotypes depending on the clinical scenario: volume overload, normo-hypertensive, or increased heart rate. In patients with volume overload, an SGLT2i (given their diuretic-like properties) with a diuretic should be initiated. In those who are normo-hypertensive, an ARNI plus an MRA at low doses should be considered. In patients with an increased heart rate, a BB plus a sinust node inhibitor (ivabradine) should be considered. Once therapy from one cluster has been initiated, the therapy classes from the other clusters can be added within 2 to 4 weeks, therefore achieving low doses of all the classes within 3 to 6 weeks.

3. Greene et al\textsuperscript{60} recommend near-simultaneous initiation of low doses of all 4 classes of quadruple therapy. This should occur within 1 week, followed by gradual up titration depending on patient factors and therapy tolerability. Furthermore, if a patient is hospitalized and in stable condition, every attempt should be made to initiate GDMT and increase the doses of pre-existing therapies.

**TABLE 1** Current Clinical Consensus and Clinical Practice Guideline Recommendations on Sequencing

| 2021 European Society of Cardiology (preview presented at European Society of Cardiology Heart Failure 2021 congress) | Quadruple Therapy | Recommendation |
|---|---|---|
| Defined as ARNI (or ACE inhibitor/ARB), BB, MRA, and SGLT2i | Recommended for all eligible patients with HFpEF to reduce the risk of mortality |

| 2021 American College of Cardiology Expert Consensus Pathway\textsuperscript{3} | For patients with newly diagnosed stage C HFpEF, a BB, ACE inhibitor/ARB/ARNI should be started in any order | Each agent should be uptitrated to maximally tolerated or target dose. Initiation of a BB is better tolerated when patients are “dry” and an ACE inhibitor/ARB/ARNI when patients are “wet” |
|---|---|---|
| After initiation of BB and angiotensin antagonist, addition of an MRA should be considered with close monitoring of electrolytes | Standard (quadruple) therapies are applicable to most patients with HFpEF for reducing cardiovascular mortality and hospitalization for HF | It might be preferable to titrate doses of different classes of GDMT medications simultaneously (“in-parallel” approach), rather than fully titrate 1 medication class before initiating an additional agent (“strict sequential” approach) |
| SGLT2i should also be considered for HFpEF with NYHA functional class II-IV | Every attempt should be made to initiate and titrate therapies with the goal of medication optimization by 3-6 months after a diagnosis of HFpEF |

| 2021 Canadian Cardiovascular Society\textsuperscript{4} | Standard (quadruple) therapies are applicable to most patients with HFpEF for reducing cardiovascular mortality and hospitalization for HF |

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ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor/neprilysin inhibitor; BB = beta-blocker; GDMT = guideline-directed medical therapy; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; SGLT2i = sodium-glucose co-transporter 2 inhibitor.
These recommendations have several intersecting themes (Table 2). The first consideration is that these therapies reduce morbidity and mortality very rapidly after initiation, thus emphasizing the need to add multiple classes of therapy in rapid succession. Further, each therapy has a treatment effect that is independent of dose or prior initiation of other therapies. In addition, low doses of each of the pillars of the quadruple therapies have additive therapeutic efficacy; initiating low doses of all 4 categories of quadruple therapies should be prioritized over strict sequencing and dose escalation as recommended by the historical therapy paradigm. Finally, most recommendations for rapid therapy sequencing suggest that all therapy classes, in the absence of any contraindications, should be initiated within 4 weeks of identification of HFrEF.

### LEVERAGING HOSPITALIZATIONS TO TITRATE THERAPIES

Although the rapid initiation proposals predominantly focus on the outpatient setting, the hospital setting is a critical time to initiate and optimize therapies. It has been clearly shown across multiple HFrEF studies that therapies prescribed at discharge are rarely modified, titrated, or optimized up to 1 year after discharge. The CONNECT-HF (Care Optimization Through Patient and Hospital Engagement Clinical Trial for Heart Failure) study was conducted at 161 sites with 5,647 patients who were admitted with HF. Participants were randomized to clinician education, audit, and feedback of HF quality of care. The study showed no improvement in use of GDMT over time or clinical outcomes in patients discharged from hospital with HF. Few changes occurred in ambulatory care after hospital discharge, leading to the conclusion that health care providers should aim to leverage the hospitalization period to initiate GDMT, which seems to be a feasible approach across specialty types (Supplemental Ref. 2).

### REAL-WORLD SCENARIOS

Although each patient with HFrEF is unique and deserves a patient-centric approach to therapy optimization, a large proportion of patients have few medical contraindications to GDMT. The following represents 3 clinical scenarios whereby rapid GDMT optimization can occur.

#### CHRONIC STABLE HFrEF. Patients with chronic stable HFrEF have a high burden of co-morbidities, including T2DM and chronic kidney disease (Supplemental Ref. 3). Here, a rapid titration strategy recommended by Greene et al can be considered, with discontinuation of any ACE inhibitor/ARB and starting an ARNI and an SGLT2i. Future titration to higher doses of ARNI can occur during follow-up.

#### ACUTE DECOMPENSTATED HF WITH KNOWN HFrEF. Frequently, the inpatient admission for acute HF

| Details | Timeline | Advantages | Disadvantages |
|---------|----------|------------|---------------|
| Packer and McMurray<sup>27</sup> | Initiate BB and SGLT2i upfront, followed by ARNI then MRA | Four weeks to achieve initiation of GDMT | Focus on tolerability without initiating multiple medications that can induce hypotension or acute kidney injury | Coverage of therapies such as SGLT2i and ARNI may be predicated on being symptomatic on baseline HF therapies such as an ACE inhibitor, MRA, and BB |
| Miller et al<sup>52</sup> | Cluster phenotype-based approach; if volume overloaded, add SGLT2i; if hypertensive add ARNI/MRA; if higher heart rate, add and titrate BB and SNI | 3-6 weeks of therapy initiation followed by dose titration | Based on patient clinical characteristics that may enhance tolerability | Needs multiple patient visits or touchpoints; drug coverage may predicate a sequential approach to therapy initiation |
| Greene et al<sup>60</sup> | Rapid initiation of low doses of all categories of foundational quadruple therapy within 1 week | Dose titration across 1 month | Enables rapid initiation of GDMT upfront, which may optimize clinical benefit | If a patient has a side effect, unclear which therapy is the culprit; drug coverage may predicate a sequential approach to therapy initiation |

SNI—sinus node inhibitor; other abbreviations as in Table 1.
represents an optimal time to initiate and titrate GDMT. As previously described, what patients are prescribed within the hospital setting will be unchanged despite frequent evaluations in the outpatient setting. The vast majority of patients admitted with acute HF will be on an ACE inhibitor/ARB and a BB (Supplemental Ref. 6), and therefore optimization can build on these 2 foundational therapies (Figure 2B). Current data suggest that initiation of an ARNI and potentially an SGLT2i remains relatively safe when done in the inpatient environment. Data from the PIONEER-HF (Comparison of Sacubitril/Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) trial identified that sacubitril/valsartan, compared with enalapril, significantly reduced N-terminal pro-B-type natriuretic peptide levels and recurrent HF hospitalization (Supplemental Ref. 7). There was no difference in rates of hypotension, hyperkalemia, or acute kidney injury with sacubitril/valsartan. As recommended by McMurray and Packer, the patient should be prioritized for switching the valsartan to ARNI (eg, sacubitril/valsartan at 24/26 mg orally twice a day) and adding spironolactone at 12.5 mg orally daily. There is no need to delay the initiation of an ARNI because the patient was on an ARB. The SGLT1/2 inhibitor sotagliflozin exhibited a reduction in the risk of total worsening HF events and cardiovascular death in patients with acute HF and T2DM (Supplemental Ref. 8,9). Ongoing trials are evaluating the safety and efficacy of SGLT2i among patients with acute HF both with and without T2DM (Supplemental Ref. 10,11). Therapies that do not have clear cardiovascular morbidity and mortality benefit, such as calcium-channel blockers, could be discontinued to prioritize GDMT with cardiovascular mortality benefit. This approach may help to further address the issues around polypharmacy and to prevent future hypotension. Laboratory investigations,

**FIGURE 2** Titration Strategies by Clinical Scenario in Patients With HF and Reduced Ejection Fraction

(A) Chronic stable heart failure and reduced ejection fraction; (B) acute heart failure; (C) de novo non-ischemic heart failure with reduced ejection fraction. This figure displays the time points at which each medication in the quadruple therapy regimen should be initiated and titrated in patients with acute, chronic, and de novo heart failure and reduced ejection fraction (HFrEF). Other abbreviations as in Figure 1.
including kidney function and electrolytes, can be conducted, if possible, within 4 weeks as an outpatient. Upon discharge, vericiguat starting at 2.5 mg orally per day can also be initiated.20

**STABLE OUTPATIENT WITH DE NOVO NONISCHEMIC HFrEF.** Among patients, with de novo nonischemic HFrEF, rapid and sequential initiation of low-dose therapies in multiple classes of quadruple therapy should be considered (Figure 2C). In this case, low-dose ARNI (eg, 24/26 mg orally twice a day), BB (eg, bisoprolol 2.5 mg orally daily), and spironolactone (12.5 mg orally once daily) can be initiated. Given that the potassium levels were borderline elevated, early patient follow-up within 2 weeks to check laboratory values, blood pressure, and heart rate should occur. If stable, the patient should be started on an SGLT2i with follow-up bloodwork to check renal function and electrolytes within 2 weeks. Furthermore, ongoing evaluation for assessment of further device therapies (eg, implantable cardioverter-defibrillators or cardiac resynchronization therapy) should commence.

**STRATEGIES TO ANTICIPANT GDMT-RELATED ADVERSE EVENTS**

Health care providers are frequently concerned with the potential of acute kidney injury, hypotension, and hyperkalemia after the initiation and titration of GDMT in patients with HFrEF (Table 3) (Supplemental Ref. 12). However, many of these issues can be anticipated. In cases of chronic kidney disease, it should be expected that the eGFR will decrease after initiation of a renin-angiotensin system inhibitor, ARNI (Supplemental Ref. 13), or SGLT2i (Supplemental Ref. 14). This action occurs because of a reduction in glomerular filtration through a drop in glomerular pressure. In terms of SGLT2i compared with other antihyperglycemic therapies in patients with chronic kidney disease, there is no increased risk of acute kidney injury on therapy initiation (Supplemental Refs. 15,16). As previously described in the landmark MRA in HFrEF trials, continuation of MRAs in patients with serum potassium levels up to 5.6 mmol/L provided mortality benefit.34 Accordingly, health care providers should continue to pursue strategies to lower serum potassium levels, such as using potassium binders while attempting to continue MRA therapies. Furthermore, clinical consensus suggests that practitioners may consider novel potassium binders, such as patiromer and sodium zirconium cyclosilicate to enable the uptitration of ARNIs/ACE inhibitors/ARBs and MRAs if hyperkalemia persists.3 (Supplemental Ref. 17).

With SGLT2i, there may be an increased risk of mycotic genital infections but not urinary tract infections. Patients should be counseled on adequate genital hygiene; if a

| TABLE 3 Anticipated Drug-Related Side Effects and Mitigation Strategies |
|-----------------------------|-----------------------------|-----------------------------|
| **Clinical Parameters to Initiate and Titrate** | **Follow-up Laboratory and Clinical Parameters (Within 2-4 Weeks of Initiation)** | **When to Consider Reducing Dose or Discontinuing** |
| ARNI/ACE inhibitor/ARB | SBP >100 mm Hg, eGFR >30 mL/min/1.73 m² | Symptoms of postural hypotension, serum creatinine, serum potassium |
| | K+ >5.4 mmol/L | Symptomatic postural hypotension, K+ >5.4 mmol/L, serum increase creatinine >30% within 4 weeks of initiating |
| BB | HR >60 beats/min, SBP >100 mm Hg | No laboratory parameters needed. Heart rate and SBP |
| | | HR <50 beats/min (without PP), symptomatic postural hypotension |
| MRA | SBP >100 mm Hg, eGFR >30 mL/min/1.73 m², K+ >5.4 mmol/L | Symptoms of postural hypotension, serum creatinine, serum potassium |
| | | Symptomatic postural hypotension, K+ >5.5 mmol/L, increase in serum creatinine >30% within 4 weeks of initiating |
| SGLT2i | SBP >100 mm Hg, eGFR >25 mL/min/1.73 m² | Symptoms of postural hypotension, serum creatinine, glycemic control (if diabetic), serum/urine ketones and lactate (if presenting in acute decompensation), genital mycotic infection |
| | | Symptomatic postural hypotension, increase in serum creatinine >30% within 4 weeks of initiating, development of ketones or elevated lactate if patient presenting acutely decompensated |

| **Strategies to Mitigate Adverse Side Effects** |
|-----------------------------------------------|
| Recognize that early rise in serum creatinine is an anticipated effect of drug. Discontinue antihypertensive medications without cardiovascular benefit (eg, calcium-channel blockers). Can also consider novel potassium binders such as patiromer and sodium zirconium cyclosilicate to enable the uptitration of ARNI/ACE inhibitor/ARB and MRA if hyperkalemia persists. |
| Discontinue antihypertensive medications without cardiovascular benefit (eg, calcium-channel blockers). |
| Recognize that early rise in serum creatinine is an anticipated effect of drug; proper genital hygiene; if genital mycotic infection develops, consider treating with a single oral dose of fluconazole 150 mg. Counsel patient to temporarily hold SGLT2i if acutely unwell (eg, viral illness, dehydration); stop SGLT2i 2-3 days before procedure or surgery. |

**CRT** = cardiac resynchronization therapy; **eGFR** = estimated glomerular filtration rate; **HR** = heart rate; **ICD** = implantable cardioverter-defibrillator; **K+** = potassium; **SBP** = systolic blood pressure; other abbreviations as in Table 1.
genital mycotic infection does occur, treatment with a single dose of oral fluconazole 150 mg can be considered (Supplemental Ref. 12). In addition, SGLT2is increase the risk of nonhyperglycemic diabetic ketoacidosis in some patients. Patients should be counseled on temporarily discontinuing the drug if they develop acute illness that can cause limited oral intake. Therapies can be adequately restarted when there is resumption of oral intake.

**KNOWLEDGE GAPS AND LIMITATIONS**

The aforementioned recommendations must be placed within the context of several knowledge gaps in the current literature. The patient profiles highlighted in our discussion represent commonly seen clinical scenarios, and we present one approach to initiation and titration to achieve optimal use of GDMT; however, it should be acknowledged that there are no specific contemporary randomized trials that have shown the safety and efficacy of any one titration strategy over another. Furthermore, as we bridge the gap between our understanding of the basic biology of HFrEF and the mechanisms of actions of the foundational therapies, we may enable more precision targeting of therapies to individual patients, rather than treating them as aggregates of a clinical profile (Supplemental Ref. 18). The expanding use of artificial intelligence in identifying who may optimally respond to foundational therapies also represents an emerging and expanding area of exploration (Supplemental Refs. 19,20).

Expanding on precision therapies is the concept of precision dosing; as an example, there is a growing understanding that there are likely sex-based
differences in responses to dosing of some of the foundational therapies. Future dosing studies are needed to enable targeting of specific therapies and specific dosing to an individual patient. Furthermore, during the inpatient setting, although we have recommended a strategy of low-dose initiation of foundation therapies with subsequent uptitration over time, we recognize that there is limited titration of medication in the postdischarge setting; future quality improvement studies and educational programs will be needed to empower health care providers to titrate doses upon a patient’s discharge from hospital.

Within the EMPEROR-REDUCED and DAPA-HF clinical trials, enrollment criteria involved background optimal therapy, including ARNI/ACE inhibitors/ARBs, BBs, and MRAs; however, the population enrolled large enough subsets of patients without those therapies to support the assertions that benefits of SGLT2 inhibitor treatment are independent of the previous therapies. However, there was no heterogeneity of trial results with interaction testing based on baseline therapies; therefore, although the therapies have independent benefit, there is likely additive benefit of being on multiple agents of foundational therapies. However, future studies evaluating head-to-head comparison of foundational therapies may provide greater insight into the optimal use of HFrEF therapies.

There are additional patient-centric concerns regarding the cost related to these therapies that must be considered. The burden of pre-approval and copay may put many newer therapies out of reach for many patients with HFrEF. Because several foundational therapies are generic and as others approach patent expiry, however, cost considerations can hopefully be reduced in a significant number of patients. In addition to costs, patients themselves can be hesitant to initiate more therapies due to perceived risk of side effects and pill burden. Future quality improvement programs focusing on understanding patient-centric concerns and barriers to HFrEF GDMT are needed.

CONCLUSIONS

Given the high risk of adverse outcomes in patients with HFrEF and that a large proportion of these patients who do not have clinical contraindications to GDMT are not yet on these therapies, there is an urgent need to encourage the initiation and titration of GDMT to reduce morbidity and mortality. The more recently updated clinical practice guidelines now emphasize the importance of early and rapid initiation of drugs that have cardiovascular benefit(s) with the caveat that these decisions should be shared and personalized according to patient values and preferences, baseline medications, and laboratory values (Central Illustration). Removal of therapies that do not have clear cardiovascular benefit should be considered to prevent polypharmacy and reduce risk of adverse side effects. Anticipation of a drop in eGFR and a rise in potassium levels can help guide frequency of follow-up and repeat laboratory investigations. Recognizing that many barriers to GDMT initiation and optimizations exist, health care providers should aim to introduce the 4 pillars of the quadruple therapy now recommended by most clinical practice guidelines. Although implementation of other therapies is important, additional work on ensuring expanded access to quadruple therapies is critical to ensure that all eligible patients with HFrEF have access to lifesaving GDMT. Future prospective studies aimed at guiding optimal implementation of quadruple therapy are needed to reduce the morbidity and mortality in patients with HFrEF.

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**APPENDIX** For supplemental references, please see the online version of this paper.