JACC: HEART FAILURE VOL. ■, NO. ■, 2021

PUBLISHED BY ELSEVIER

STATE-OF-THE-ART PAPER

Drug Layering in Heart Failure

Phenotype-Guided Initiation

Giuseppe M.C. Rosano, MD,[a,*] Larry A. Allen, MD,[b] Amr Abdin, MD,[c] Joann Lindenfeld, MD,[d] Eileen O'Meara, MD,[e] Carolyn S.P. Lam, MBBS, PHD,[f] Patrizio Lancellotti, MD,[g] Gianluigi Savarese, MD,[h] Stephen S. Gottlieb, MD,[i] John Teerlink, MD,[j] Jan Wintrich, MD,[c] Michael Böhm, MD[c,*]

HIGHLIGHTS

- Current HF guidelines recommend subsequent stepwise treatment initiation and up-titration.
- Most trials have been conducted in stable patients in the outpatient clinic.
- Treatments are often deferred and started in the stable outpatient.
- New trials have shown that SGLT2 inhibitors and ARN inhibitors provide early risk reduction within 30 days.
- A new approach would be to start early with evidence-based drugs.
- Patient characteristics should be determined to prioritize and up-titrate drugs early.
- Personalized drug therapy in chronic HF is advisable.

ABSTRACT

Medications with proven benefit in patients with heart failure with reduced ejection fraction are recommended, according to prospective large clinical trials, in the stable patient after careful up-titration in a strict sequential order. Although the relevance of careful clinical up-titration is unproven, there is evidence that after recompensation and shortly after hospital discharge, the rate of cardiovascular death and hospitalization is high. Clinical studies provided evidence that the onset of treatment effects is rapid, occurring within 28 days with most of these drugs used, and in in some trials, early treatment after discharge or already started in the hospital has provided benefits. Therefore, early treatment without deferring it to the stable outpatient may be useful to reduce cardiac-related events further. This expert opinion proposes treatment layering according to individual patient phenotypes involving heart rate, blood pressure, impaired renal function, and electrolyte disturbances, as well as dedicated subgroups of patients with specific requirements for treatment initiation. This complements other approaches that suggest starting sequential treatment according to the size of treatment effects of drugs, specific cardiac diseases, and patient wishes. Patient phenotyping may guide personalized drug layering in heart failure with reduced ejection fraction that provides the best outcomes, whereas pragmatic clinical trials are warranted to scrutinize the effectiveness of these approaches. (J Am Coll Cardiol HF 2021;■:■–■)

From the [a]Centre for Clinical and Basic Research, IRCCS San Raffaele Roma, Rome, Italy; [b]Division of Cardiology, University of Colorado, School of Medicine, Aurora, Colorado, USA; [c]Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Saarland University, Homburg/Saar, Germany; [d]Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA; [e]Department of Cardiology, Montreal Heart Institute, Université de Montréal, Montreal, Québec, Canada; [f]Duke-National University of Singapore and National Heart Centre Singapore, Singapore, Singapore; [g]Department of Cardiology, University Hospital of Liege, Liege, Belgium; [h]Division of Cardiology, Department of Medicine, Karolinska Institutet and Heart and Vascular Theme, Karolinska University Hospital, Stockholm, Sweden; [i]University of Maryland School of Medicine and Baltimore Veterans

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2021.06.011

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARNI = angiotensin receptor-neprilysin inhibitor

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

MRA = mineralocorticoid receptor antagonist

SGLT2 = sodium-glucose cotransporter type 2

Almost all medications with a proven prognostic benefit in heart failure (HF) with reduced ejection fraction (HFrEF) have demonstrated their efficacy in controlled placebo-controlled trials where the new drug was added on top of the pre-existing medical therapies (1-12). In a few cases, such as the PARADIGM (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor With an Angiotensin-converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) study, new and existing medications were compared head to head (13). In trials comparing new drugs with placebo on top of standard therapy, such as DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) (1), EMPEROR-Reduced (EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction) (2), VICTORIA (Vericiguat in Participants With Heart Failure With Reduced Ejection Fraction) (3), GALACTIC-HF (Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in Heart Failure) (4), and SHIFT (Systolic Heart Failure treatment with the If inhibitor ivabradine Trial) (12), adding the new drug could lead to increased complexity of treatment, and yet there has been no reassessment of the efficacy of the traditional therapy. As a consequence, the recommended order of initiation of different drug classes with prognostic benefits in the scientific guidelines often reflects the timing of discovery (14-15), rather than the efficacy or safety of the drug or the size of treatment benefit. The recommendations of existing guidelines also highlight the need for full up-titration of foundational therapies to the target (or maximally tolerated) dose before the initiation of new therapies. This approach causes delays and difficulties in the implementation of HFrEF medications, especially in highly comorbid patients already struggling with polypharmacy. Furthermore, given that risk reduction was observed early on initiation of effective medications, such as within 12 days for empagliflozin (2), 28 days for sotagliflozin (16,17), 14 days for sacubitril/valsartan (angiotensin receptor-neprilysin inhibitor [ARNI]) (13) and 20 days for ivabradine (18), and knowing that adverse events occur early after diagnosis or hospitalization, delayed initiation of new drugs may leave many patients unprotected (19).

TREATMENT OF THE "STABLE" PATIENT

In the majority of cases, drugs recommended in HFrEF have been tested mostly in stable patients receiving stable background therapies. These patients do not reflect the epidemiology, severity of disease, and hemodynamic stability of patients who are discharged from the hospital (20,21). Some small studies have tried to evaluate these patients (22,23) or have included them (3,4,17), but dedicated and adequately powered trials for the efficacy of HF drugs on outcomes initiated at discharge and the efficacy of their titration are lacking. Often, lifesaving medications are discontinued or down-titrated during hospitalization for decompensation, and, although prognostic, there is little evidence on how these medications should be up-titrated or initiated at discharge (24,25). Scientific guidelines provide general recommendations on up-titration without revealing clear mechanisms (14,15) because of a lack of data (26). Thus, most patients in real-world settings receive doses of lifesaving medications that are lower than the doses tested in clinical trials (27). There is no clear and definitive evidence on whether it is better to up-titrate these medications to their maximum dosage or to combine medications on the basis of their pharmacodynamic actions (eg, heart rate and blood pressure).

THE PROBLEM OF UP-TITRATION

Although post hoc analyses of clinical trials and registries have suggested lower cardiac-related event rates in patients taking higher doses of medications (27,28), these findings may have been the consequence of a selection bias. Less severely ill patients may have been able to receive higher doses of HFrEF medications and thus had a lower rate of adverse outcomes because of the lower severity of their disease. The ATLAS (Assessment of Treatment with Lisinopril and Survival) study found no difference in

Affairs Medical Center, Baltimore, Maryland, USA; and the [j]Section of Cardiology, San Francisco Veterans Affairs Medical Center, San Francisco, California, USA. *Drs Rosano and Böhm contributed equally to this work and are joint first authors.

Barry Greenberg, MD, served as Guest Editor for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 21, 2021; revised manuscript received June 8, 2021, accepted June 15, 2021.

mortality and a 12% reduction in hospitalizations in 3,793 patients with HFrEF who were allocated to receive prospectively either 37.5 or 2.5 mg daily of lisinopril after a median 47-month follow-up (29). However, the achieved final doses were closer together. Although no mortality benefit was observed in the 3,846 patients with HFrEF who were included in the HEAAL ((Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan) study and randomized to 50 or 150 mg daily of losartan (30), high-dose losartan reduced hospitalizations by 12%. Both studies reported increased side effects of hypotension, worsening renal function, and hyperkalemia with the high-dose regimen. The differences in non-randomized comparisons that do not control for factors such as renal impairment, low blood pressure, frailty, and other concomitant illnesses are much greater (28). Thus, we do not know which patients will have outcomes that are improved enough by up-titration to account for the increased risk.

There are no large, randomized studies of high-dose vs low-dose beta-blockers or mineralocorticoid antagonists (MRAs). Ouwerkerk et al (28) found that only 14% of patients received at least 50% of the predicted target dose of ACE inhibitors or angiotensin receptor blockers or beta-blockers in the combined registry data from the BIOSTAT-CHF (BIOlogy Study to TAilored Treatment in Chronic Heart Failure) study and the ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure) study, including 6,787 patients with HFrEF. These investigators found that nonuse or use of lower drug doses was associated with a greater burden of comorbidities such as renal dysfunction. After adjustment for confounding factors, the comparison between <50% of target dose of each drug and its 100% target dose demonstrated a very modest benefit of higher doses (28). Importantly, patients receiving a low-dose ACE inhibitor and beta-blocker combination had lower hospitalizations and mortality when compared with patients taking either drug alone (even at high doses). Although this study is limited by its observational design, there is no strong rationale to support dose titration of 1 medication before the initiation of another. It is also not clear whether initiation of diverse medications results in a different efficacy compared with sequential up-titration of drugs.

Not surprisingly, clear guidance on the optimal timing and sequence for the layering of HF medications is lacking both in patients with de novo HF and in patients in the postacute phase. This is of particular relevance in patients hospitalized for HF where there is a compelling indication to start at least 1 new guideline-recommended medication by discharge. In the Get With the Guideline Registry, one-fourth of patients started more than 1 medication, and 14% started 3 or more new drugs at discharge (31). The question arises whether drug initiation should start before full up-titration of pre-existing medications or whether all recommended drugs should be started together. Furthermore, implementation of therapies may vary among local health care models, and each health care system may cope differently with up-titration and staged initiation of different medications (24). In some health care systems, up-titration may be delegated to general practitioners, nurses, or pharmacists, whereas in other systems, this approach is more difficult to implement (24).

DRUG LAYERING

Drug layering has rarely been systematically studied. No clear data exist on the use of diuretic therapy, and the only study that compared the order of 2 first-line therapies has been the CIBIS III (Cardiac Insufficiency Bisoprolol Study). This study showed noninferiority between bisoprolol or enalapril initiation as a first medication, but it failed to show noninferiority of starting a beta-blocker before an ACE inhibitor in patients who were caused by receive combination therapy (32). In CIBIS III, as in other beta-blocker and ACE inhibitor trials, treatment with bisoprolol or enalapril was started at a low dose (1.25 mg daily or 2.5 mg twice daily), and the drugs were progressively up-titrated at 2-week intervals. Titration was mandatory, unless prohibited because of intolerance, but it could be adjusted according to tolerability. More than 50% of patients did not tolerate full doses of either drug when given in combination. The last prescribed doses of enalapril and bisoprolol were higher according to which drug was prescribed first. In the bisoprolol-first group, the last prescribed doses of bisoprolol were significantly higher as compared with the enalapril-first group, and in the enalapril-first group, the last prescribed doses of enalapril were significantly higher as compared with the bisoprolol-first group (32). These results suggest that the historical order of clinical trials (ACE inhibitor before beta-blocker) does not equate to starting the most efficacious or best tolerated therapies first.

TOLERANCE IN HEART FAILURE PHENOTYPES

In many patients, the staged and slow initiation of drugs with hemodynamic effects reduces the possibility of side effects such as hypotension or bradycardia, which limit adherence to guideline-recommended drug therapies over time. For

instance, the simultaneous addition of renin-angiotensin-aldosterone system inhibitors and beta-blockers may have untoward effects on blood pressure, renal function, and potassium levels (33,34). However, the clinical approach of a slow, staged initiation of drugs contradicts the call for more rapid escalation of therapies to reach recommended doses within weeks of discharge. Some drugs facilitate the use of others, such as sacubitril/valsartan (35) and dapagliflozin (36), and they provide beneficial effects on renal function and hyperkalemia when used together with MRAs. Furthermore, ivabradine and beta-blockers have additive effects on heart rate reduction, and ivabradine may facilitate the up-titration of the beta-blocker (37). Indeed, the timing, order, and sequence in which HF medications should be started has never been systematically investigated.

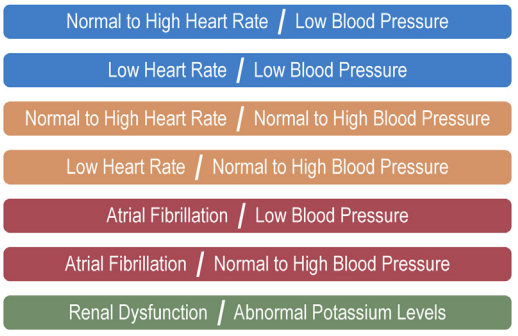
When patients are admitted with an acute exacerbation of chronic HF, beta-blockers are often reduced or discontinued because of their negative inotropic effect and their heart rate- and blood pressure-lowering effects. There is no evidence-based guidance on whether beta-blockers should be reinstated before discharge and on how to optimize doses after discharge. The OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) program suggested that the continuation of beta-blocker therapy in patients hospitalized with decompensated HF is associated with lower postdischarge mortality risk, whereas withdrawal of beta-blocker therapy is associated with worse risk and propensity-adjusted mortality (34). Similar results were reported in 2 randomized trials consistent with a meta-analysis of some smaller trials (38,39). Although these data were adjusted for confounders, these studies are limited by the knowledge that patients who discontinued beta-blockers during hospitalization were undoubtedly those with worse hemodynamic conditions and therefore at higher mortality risk (39). IMPACT-HF (Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure) was the only study to analyze when to commence beta-blockers after an acute event, and it showed no increased risk of starting these drugs at discharge; there were similar rates of mortality for patients receiving beta-blocker therapy in the hospital compared with patients who started beta-blocker therapy after discharge (40). One small randomized controlled trial showed similar mortality and readmission rates for patients who continued or discontinued beta-blocker medication during hospitalization at 3-month follow-up (41). There is clear evidence that early initiation of ACE inhibitors and MRAs is associated with a prognostic benefit. The effect was initially demonstrated by the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) for the ACE inhibitors (6) and by the EPHESUS (Eplerenone in Patients With Systolic Dysfunction After Myocardial Infarction) study for the MRAs (7).

Recently developed drugs have hemodynamic consequences that may affect titrations of other medications. Sacubitril/valsartan produces hypotension that may limit its full rapid implementation in all patients (13,42). More recently, the DAPA-HF (1) and the EMPEROR-Reduced (2) trials demonstrated a clear prognostic benefit of dapagliflozin and empagliflozin. These agents have some effect on blood pressure (43), but they are generally well tolerated in both diabetic and nondiabetic patients with HF (44,45). Vericiguat has shown some prognostic benefit in patients with worsening chronic HF, including patients in the immediate postacute phase (3). The benefit was driven by a reduction in HF hospitalization with no effect on cardiovascular mortality (3). It reduced blood pressure, but tolerance rates were not significantly lower than with placebo. Omecamtiv mecarbil, which does not affect heart rate, blood pressure, or renal function, has demonstrated a prognostic benefit in patients with HF, including those who started the drug before or immediately after hospitalization. Notably, the GALACTIC study randomized patients with a very low systolic blood pressure (≥90 mm Hg) (4).

Several recently published editorials and expert opinion papers indicate that the time for a change has come to implement all available drugs with different pharmacological profiles using different mechanisms rapidly because the onset of effective risk reduction occurs early (46,47). Sequencing of treatments according to trial appearance has been critically called into question (46-48), given that guidelines and some expert recommendations have followed the concept of strict sequential up-titration in stable outpatients because in this group the evidence for the majority for drugs was generated by prospective randomized trials. However, because the majority of drugs reduced adverse events in the first 30 days after treatment initiation (47,48), early treatment could further reduce events as losing patients caused by deferral of the start of treatment is avoided (47-49). Recommendations for treatment initiation can range from the size of treatment effects (47,48) to detailed judgment of specific drug mechanisms for specific diseases (50). Intolerability and potentially serious side effects are limitations of rapid initiation with several drugs in a short period of time. Therefore, comorbidities and patient characteristics also must be

taken into consideration (51). None of these concepts are contradictory, and they may complement each other. A start of rapid sequencing with beta-blockers and a sodium-glucose transporter type 2 (SGLT2) inhibitor has recently been suggested (47,48), and it has definite advantages related to tolerability and size of treatment effects (48). However, one could speculate that in individual patients with a low heart rate at baseline, the size of the treatment effect of the beta-blocker could be small, given that a significant portion of the mechanism of this drug has been suggested to result from heart rate reduction (52). It is likely that modifying restrictive models by clinical judgment of individual patients makes sense. Therefore, we would like to propose here the concept of patient phenotyping to complement algorithms on the basis of treatment effect sizes, disease-specific alterations, and adverse effects of drugs.

FIGURE 1 Patient Profiles Relevant for Drug Layering



Patient characteristics that have an impact on heart failure outcomes and limit or predispose patients to tolerability and efficacy of heart failure treatments.

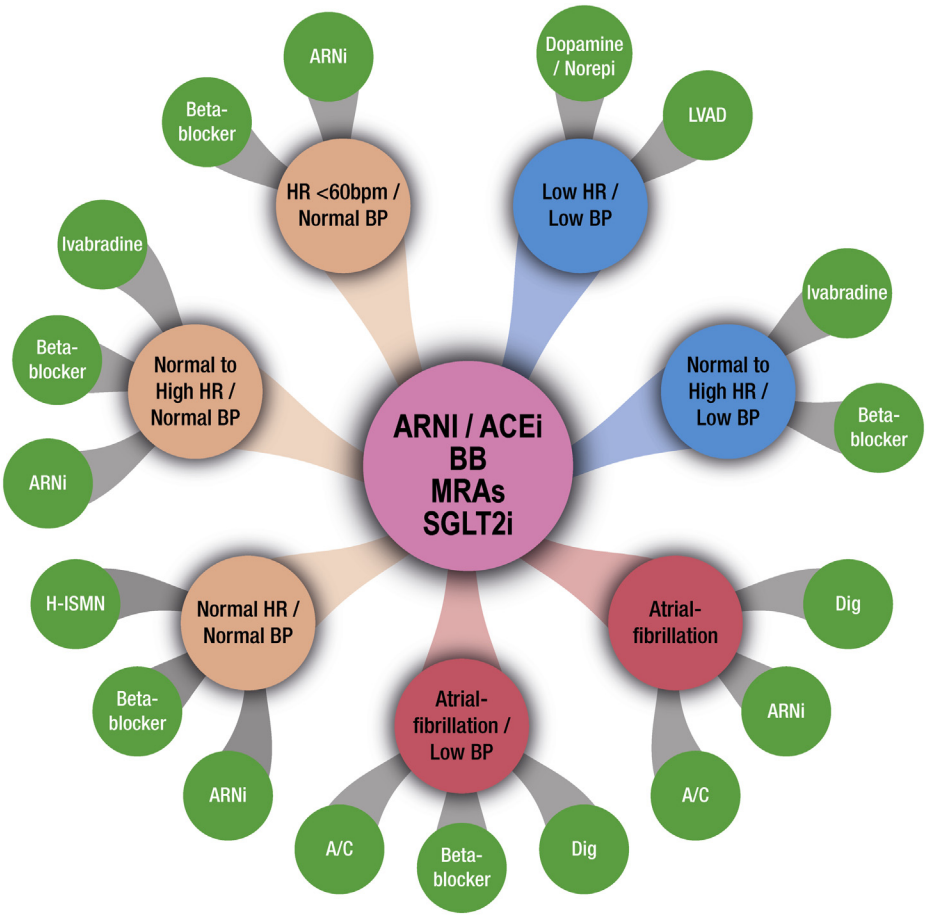
NEW THERAPEUTIC ALGORITHM ACCORDING TO PATIENT PHENOTYPE

Given that almost all drugs shown to improve prognosis influence heart rate, blood pressure, renal function, and electrolyte balance, it is appealing to consider how the implementation of these therapies may be optimized according to characteristics of individual patients. Moreover, given that there is not a compelling reason to start lifesaving medications in a stepwise fashion, it is reasonable to start drugs with proven prognostic benefit together and implement the different agents according to their pharmacodynamic effects and the patient characteristics. Such an approach may achieve more rapid escalation of HF therapies for maximal benefit for the individual patient.

Patients with HF have different clinical presentations, degrees of congestion, hemodynamic status, and renal function. Therefore, adjusting or prioritizing drugs according to the hemodynamic and renal phenotypes profile will permit personalized implementation of lifesaving medications. Furthermore, although a stepwise approach to the implementation of HF drugs can be justified in drug-naïve patients, most patients presenting with HF have often pre-existing conditions and are already taking renin-angiotensin-aldosterone system inhibitors and/or beta-blockers. The challenge is how to prioritize and choose the most adequate up-titration of drugs. Some physiological parameters should be considered as spending functions and therapies should be implemented according to the phenotypes (**Figure 1**). The most important phenotypes to consider in the implementation of HF therapy are heart rate, blood pressure, renal function, and their combinations. By using this approach, it is possible to identify 7 phenotypes in which personalized implementation and up-titration of medical therapy should be pursued.

The identification of the phenotypes should then guide the implementation of medications in individual patients with HF. The 4 classes of renin-angiotensin system antagonists, ARN inhibitors, beta-blockers, and SGLT2 inhibitors, whose lifesaving effects have been scrutinized in large, randomized, placebo-controlled trials in broad groups of patients (5-11,13), should be started in eligible patients. Because these 4 classes have been studied in broad patient groups and have demonstrated clear prognostic benefits, these drugs should be started as soon as possible according to tolerability, patient wishes, and local reimbursement and accessibility considerations. Given that the dose-response relationship is often not characterized, most physicians may start with low doses, and target doses will hardly be achieved in a short time. Therefore, dose implementation and the addition of further classes of medications should be pursued with tailored strategies (**Figure 2**). Some stable patients seen in HF clinics are already taking at least 2 or 3 drugs; in these patients, implementation of the 4 drug classes is recommended. Furthermore, many patients with de novo HF have underlying conditions and therefore are already taking 1 or 2 lifesaving medications for hypertension, diabetes, or secondary prevention or for the treatment of underlying diseases. Implementation of the 4 drug classes should be started as soon as possible after the first visit and continued and up-titrated

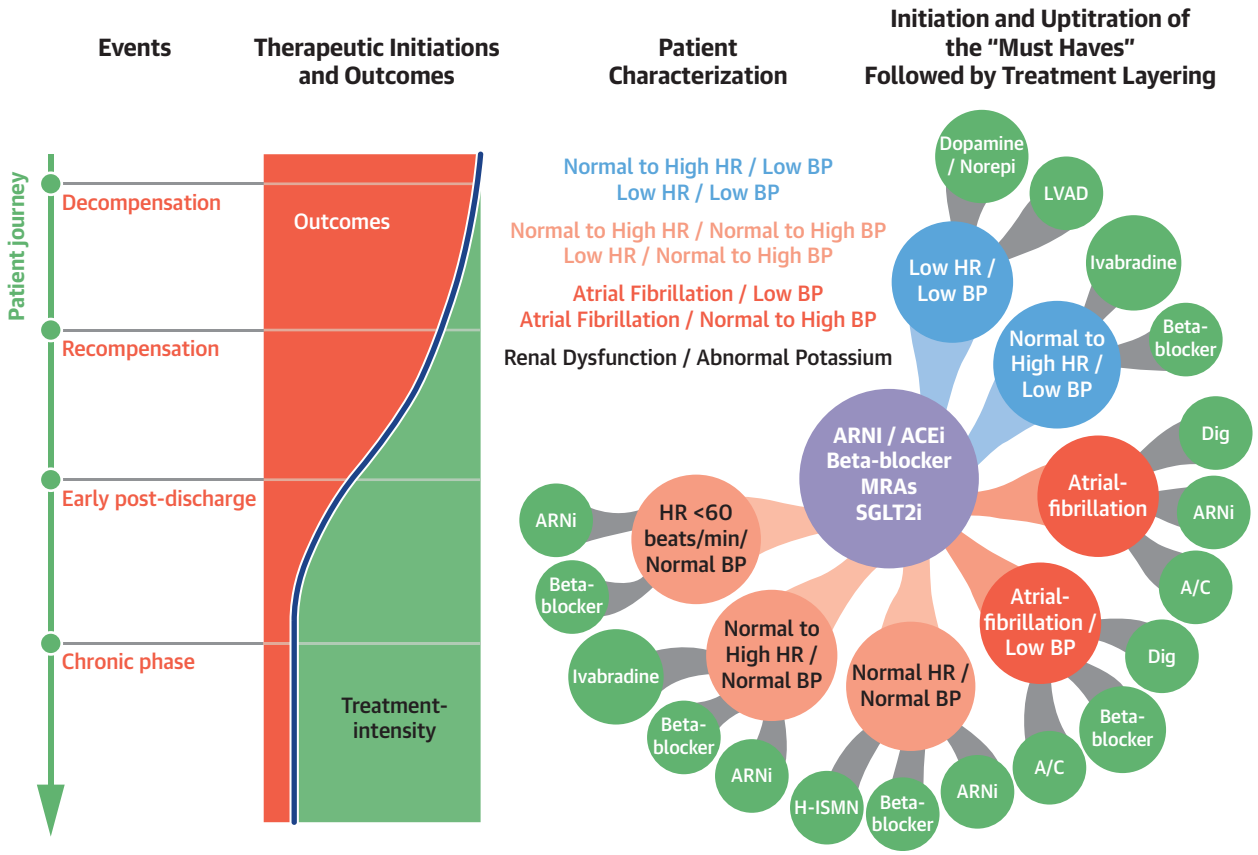
FIGURE 2 Drug Layering According to Patient Profiles



Suggested treatment layering in heart failure patients. After initiation of the "must haves" (renin-angiotensin-aldosterone system inhibitors, mineralocorticoid receptor antagonists [MRAs], sodium-glucose transporter type 2 inhibitors [SGLT2i], and angiotensin receptor blockers and neprilysin inhibitors [ARNI]). These drugs should be up-titrated according to patient profile, and other drugs should be initiated according to patient characteristics, thus leading to a more personalized approach for treatment. Renal dysfunction or abnormal potassium should be addressed by dose adaptations according to the pharmacologic characteristics of all drugs. This should be considered in every compartment of drug layering with all drugs available. Other drugs for subclasses are ivabradine for patients with a heart rate (HR) ≥70 beats/min and dopamine/norepinephrine (Norepi) for patients with severe heart failure. A left ventricular assist device (LVAD), digoxin (Dig), and anticoagulation (A/C) are recommended for prevention of thromboembolic complications in atrial fibrillation according to individual risk. Isosorbide mononitrate (H-ISMN) may be useful for relieving congestion and is effective in African Americans. BB = beta-blocker; BP = blood pressure.

according to patient characteristics and guideline recommendations (49). In particular, after recent decompensation, applied medication burden is low according to the number of drugs and doses (28-33). Therefore, closely after an adverse event, in particular in patients with de novo HF (25), undertreatment occurs despite high rates of hospitalization and cardiovascular death (**Central Illustration**, left). Patients with de novo HF who are naïve to HFrEF therapies will need more careful implementation of the medications, whereas patients with known HF can be either switched to more effective medications (ARN inhibitors in patients taking ACE inhibitors) or administered additional medications. Either at discharge or when clinically appropriate, patients should receive ARN inhibitors or ACE inhibitors, beta-blockers, MRAs, and SGLT2 inhibitors. ARN inhibitors can be implemented according to patient characteristics and local guidelines, which are continuously updated (26). Up-titration to an appropriate and tolerated dose should be done at any time. Limitations of up-titration should be controlled by

CENTRAL ILLUSTRATION **Treatment Layering According to Patient Characterization Alone: Patient Journey**



Rosano, G.M.C. et al. J Am Coll Cardiol HF. 2021;■(■):■–■.

Patients during decompensation and recompensation, as well as in the early postdischarge period, are less intensively treated while outcome rates are high **(left)**. After initiation and up-titration of the "must haves," patient characterization according to heart rate, blood pressure, atrial fibrillation, renal dysfunction, and potassium levels may provide a guide to initiate and up-titrate treatments as early as possible. A/C = anticoagulation; ACEI = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; BP = blood pressure; dig = digoxin; H-ISMN = hydralazine isosorbide mononitrate; HR = heart rate; LVAD = left ventricular assist device; MRA = mineralocorticoid receptor antagonist; Norepi = norepinephrine; SGLT2i = sodium-glucose cotransporter type 2 inhibitor.

monitoring the estimated glomerular filtration rate and potassium levels according to recommendations for specific classes of drugs.

Figure 2 suggests a therapeutic algorithm that adheres to the recommendations of the major guidelines but enables physicians to implement medications according to patient characteristics. This should be flexibly handled and should take into consideration that clinical phenotypes of patients may regularly change over time. Cost issues and patient preferences need to be considered. The goal is for patients to receive as many disease-modifying treatments as soon as possible because studies have shown an incremental progressive benefit of intensive combination treatments (53,54).

CONCLUSIONS

Implementation of medical therapy in patients with HFrEF is often challenging because patient characteristics, including their physiological parameters and comorbidities, limit up-titration of lifesaving medications. Patient access to drugs also may be limited by availability, cost issues, and prescription policies, with specific problems in individual regions of the world (55). Patient phenotyping may guide personalization of drug therapy to provide patients with tailored therapy while using all drug classes proven effective in improving prognosis. Future HF guidelines should re-evaluate the treatment algorithms for patients with HFrEF to enable rapid implementation

of all HF medications in therapy. In the future, pragmatic clinical studies will be needed to identify the best strategy for implementation of medications in clinical practice, given that the implementation of current multidrug HFrEF therapy may increase life expectancy up to 8.4 years (54).

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Allen has received grants from the American Heart Association, the National Institutes of Health, and the Patient-Centered Outcomes Research Institute; and consulting fees from Abbott, ACI Clinical, Amgen, Boston Scientific, Cytokinetics, and Novartis. Dr Abdin has received speaker honoraria from Novartis; and travel grants from Biotronik, Medtronic, and Novartis. Dr Lindenfeld has received grant funding from AstraZeneca, Sensible Medical, Volumetrix; and personal fees from Abbott, AstraZeneca, Boehringer Ingelheim, Boston Scientific, CVRx, Edwards Lifesciences, Impulse Dynamics, and VWave. Dr Lam has received research support from AstraZeneca, Bayer, Boston Scientific; and Roche Diagnostics; consultancy fees from service on the advisory board, steering committee, or executive committee of Actelion, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Cytokinetics, Darma Inc, Us2.ai, Janssen Research & Development LLC, Medscape, Merck, Novartis, Novo Nordisk, Radcliffe Group Ltd, Roche Diagnostics, Sanofi, and WebMD Global LLC; and holds a position as cofounder and nonexecutive director of Us2.ai. Dr Savarese has received grants from Boston Scientific (outside the submitted work), Vifor, Boehringer Ingelheim, AstraZeneca, and Novartis; nonfinancial support from Boehringer Ingelheim; and personal fees from Vifor and the Societá Prodotti Antibiotici, AstraZeneca, Roche, Servier, GENESIS, Cytokinetics, and Medtronic. Dr Gottlieb has received grants from Pfizer, Cytokinetics, and Amgen; and consulting for Cytokinetics. Dr Böhm has received support from the Deutsche Forschungsgemeinschaft (German Research Foundation; TTR 219, project number 322900939); and has fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Servier, Medtronic, Vifor, and Novartis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Michael Böhm, Kardiologie, Angiologie und Internistische Intensivmedizin, Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Saarland University, Kirrberger Strasse 1, 66421 Homburg/Saar, Germany. E-mail: michael.boehm@uks.eu.

REFERENCES

1. McMurray JJV, Solomon SD, Inzucchi SE, et al, DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008.

2. Packer M, Anker SD, Butler J, et al, EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383:1413–1424.

3. Armstrong PW, Pieske B, Anstrom KJ, et al, VICTORIA Study Group. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2020;382:1883–1893.

4. Teerlink JR, Diaz R, Felker GM, et al, GALACTIC-HF Investigators. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. *N Engl J Med*. 2021;384:105–116.

5. SOLVD Investigators, Yusuf S, Pitt B, et al. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med*. 1992;327:685–691.

6. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*. 1987;316:1429–1435.

7. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999;353:9–13.

8. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353:2001–2007.

9. Flather MD, Shibata MC, Coats AJS, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J*. 2005;26:215–225.

10. McMurray JJV, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet*. 2003;362:767–771.

11. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709–717.

12. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010;376:875–885.

13. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004.

14. Seferovic PM, Ponikowski P, Anker SD, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2019;21:1169–1186.

15. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol*. 2017;70(6):776–803.

16. Bhatt DL, Szarek M, Pitt B, et al, SCORED Investigators. Sotagliflozin in patients with diabetes and chronic kidney disease. *N Engl J Med*. 2021;384:129–139.

17. Bhatt DL, Szarek M, Steg PG, et al, SOLOIST-WHF Trial Investigators. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;384:117–128.

18. Komajda M, Tavazzi L, Swedberg K, et al, SHIFT Investigators. Chronic exposure to ivabradine reduces readmissions in the vulnerable phase after hospitalization for worsening systolic heart failure: a post-hoc analysis of SHIFT. *Eur J Heart Fail*. 2016;18:1182–1189.

19. Greene SJ, Fonarow GC, Vaduganathan M, Khan SS, Butler J, Gheorghiade M. The vulnerable phase after hospitalization for heart failure. *Nat Rev Cardiol*. 2015;12:220–229.

20. Chioncel O, Lainscak M, Seferovic PM, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2017;19:1574–1585.

21. Chioncel O, Mebazaa A, Harjola VP, et al, ESC Heart Failure Long-Term Registry Investigators. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2017;19:1242–1254.

22. Velazquez EJ, Morrow DA, DeVore AD, et al, PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med*. 2019;380:539–548.

23. Butler J, Anstrom KJ, Felker GM, et al, National Heart Lung and Blood Institute Heart Failure Clinical Research Network. Efficacy and safety of spironolactone in acute heart failure: the ATHENA-HF randomized clinical trial. *JAMA Cardiol*. 2017;2:950–958.

24. Crespo-Leiro MG, Anker SD, Maggioni AP, et al, Heart Failure Association (HFA) of the European Society of Cardiology (ESC). European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail*. 2016;18:613–625.

25. Maggioni AP, Anker SD, Dahlström U, et al, Heart Failure Association of the ESC. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2013;15:1173–1784.

26. Writing Committee, Maddox TM, Januzzi Jr. JL, et al. 2021 Update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2021;77:772–810.

27. Marti CN, Fonarow GC, Anker SD, et al. Medication dosing for heart failure with reduced ejection fraction – opportunities and challenges. *Eur J Heart Fail*. 2019;21:286–296.

28. Ouwerkerk W, Teng TH, Tromp J, et al. Effects of combined renin-angiotensin-aldosterone system inhibitor and beta-blocker treatment on outcomes in heart failure with reduced ejection fraction: insights from BIOSTAT-CHF and ASIAN-HF registries. *Eur J Heart Fail*. 2020;22:1472–1482.

29. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation*. 1999;100:2312–2318.

30. Konstam MA, Neaton JD, Dickstein K, et al, HEAAL Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet*. 2009;374:1840–1848.

31. Allen LA, Fonarow GC, Liang L, et al, American Heart Association's Get With The Guidelines Heart Failure (GWTG-HF) Investigators. Medication initiation burden required to comply with heart failure guideline recommendations and hospital quality measures. *Circulation*. 2015;132:1347–1353.

32. Willenheimer R, van Veldhuisen DJ, Silke B, et al, CIBIS III Investigators. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. *Circulation*. 2005;112:2426–2435.

33. Khattab M, Parwani P, Abbas M, et al. Utilization of guideline-directed medical therapy in patients with de novo heart failure with reduced ejection fraction: a Veterans Affairs study. *J Family Med Prim Care*. 2020;9:3065–3069.

34. Fonarow GC, Stough WG, Abraham WT, et al, OPTIMIZE-HF Investigators and Hospitals. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. *J Am Coll Cardiol*. 2007;50:768–777.

35. Desai AS, Vardeny O, Claggett B, et al. Reduced risk of hyperkalemia during treatment of heart failure with mineralocorticoid receptor antagonists by use of sacubitril/valsartan compared with enalapril: a secondary analysis of the PARADIGM-HF trial. *JAMA Cardiol*. 2017;2:79–85.

36. Shen L, Kristensen SL, Bengtsson O, et al. Dapagliflozin in HFrEF patients treated with mineralocorticoid receptor antagonists: an analysis of DAPA-HF. *J Am Coll Cardiol HF*. 2021;9:254–264.

37. Bocchi EA, Böhm M, Borer JS, et al, SHIFT investigators. Effect of combining ivabradine and β-blockers: focus on the use of carvedilol in the SHIFT population. *Cardiology*. 2015;131:218–224.

38. Böhm M, Link A, Cai D, et al. Beneficial association of β-blocker therapy on recovery from severe acute heart failure treatment: data from the Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support trial. *Crit Care Med*. 2011;39:940–944.

39. Prins KW, Neill JM, Tyler JO, Eckman PM, Duval S. Effects of beta-blocker withdrawal in acute decompensated heart failure: a systematic review and meta-analysis. *J Am Coll Cardiol HF*. 2015;3(8):647–653.

40. Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiade M, IMPACT-HF Investigators and Coordinators. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. *J Am Coll Cardiol*. 2004;43:1534–1541.

41. Jondeau G, Neuder Y, Eicher JC, et al, B-CONVINCED Investigators. B-CONVINCED: Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode. *Eur Heart J*. 2009;30:2186–2192.

42. Böhm M, Young R, Jhund PS, et al. Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced ejection fraction: results from PARADIGM-HF. *Eur Heart J*. 2017;38:1132–1143.

43. Serenelli M, Böhm M, Inzucchi SE, et al. Effect of dapagliflozin according to baseline systolic blood pressure in the Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial (DAPA-HF). *Eur Heart. J*. 2020;41:3402–3418.

44. Petrie MC, Verma S, Docherty KF, et al. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. *JAMA*. 2020;323:1353–1368.

45. Anker SD, Butler J, Filippatos G, et al. Effect of Empagliflozin on cardiovascular and renal outcomes in patients with heart failure by baseline diabetes status: results from the EMPEROR-Reduced Trial. *Circulation*. 2021;143:337–349.

46. Lam CSP, Butler J. Victims of success in failure. *Circulation*. 2020;142(12):1129–1131.

47. McMurray JJV, Packer M. How should we sequence the treatments for heart failure and a reduced ejection fraction?: A redefinition of evidence-based medicine. *Circulation*. 2021;143(9):875–877. https://doi.org/10.1161/CIRCULATIONAHA.120.052926

48. Packer M, McMurray JJV. Rapid evidence-based sequencing of foundational drugs for heart failure and a reduced ejection fraction. *Eur J Heart Fail*. 2021;23(6):882–894.

49. Greene SJ, Butler J, Fonarow GC. Simultaneous or rapid sequence initiation of quadruple medical therapy for heart failure-optimizing therapy with the need for speed. *JAMA Cardiol*. 2021;6(7):743–744.

50. Bhatt AS, Abraham WT, Lindenfeld J, et al. Treatment of HF in an era of multiple therapies: Statement from the HF Collaboratory. *J Am Coll Cardiol HF*. 2021;9(1):1–12. https://doi.org/10.1016/j.jchf.2020.10.014

51. Rosano GMC, Moura B, Metra M, et al. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2021;23(6):872–881.

52. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med*. 2009;150(11):784–794.

53. Komajda M, Böhm M, Borer JS, et al. Incremental benefit of drug therapies for chronic heart failure with reduced ejection fraction: a network meta-analysis. *Eur J Heart Fail*. 2018;20:1315–1322.

54. Vaduganathan M, Claggett BL, Jhund PS, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet*. 2020;396:121–128.

55. Psotka MA, Fiuzat M, Solomon SD, Chauhan C, et al. Challenges and potential improvements to patient access to pharmaceuticals: examples from cardiology. *Circulation*. 2020;142(8):790–798.

KEY WORDS drugs, heart failure treatments, medical treatment, prognosis