Circulation

ON MY MIND

Victims of Success in Failure

Carolyn S.P. Lam, MBBS, PhD
Javed Butler, MD, MPH, MBA

Multiple successful clinical trials have defined the medical treatment of heart failure (HF) with reduced ejection fraction (HFrEF). Trials in the past century established angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and mineralocorticoid receptor antagonists as the foundational therapies in HFrEF. The past decade brought more success with ivabradine, the angiotensin receptor neprilysin inhibitor (ARNI) sacubitril/valsartan, the sodium glucose cotransporter-2 inhibitors dapagliflozin and empagliflozin, as well as the soluble guanylase cyclase stimulator vericiguat. This success has led to new challenges in clinical implementation, rising costs, and high pill burdens for patients with HFrEF, who are increasingly multimorbid and elderly. An analysis of the Get With The Guidelines–HF registry showed that to be compliant with HF guidelines, ≈50% patients hospitalized with HF needed to start at least 1 new HF-related medication and a quarter needed >1 by discharge; these figures did not include medications for other comorbidities or newer therapies (data limited to before 2013).[1] Although polypharmacy is challenging, it is still superior to not having treatment options or not prescribing the best available evidence-based treatment. In fact, the availability of multiple effective medical options represents important progress for treating patients with HFrEF. However, we need to acknowledge and provide guidance for clinicians faced with decisions about how best to prioritize and sequence multiple therapies.

The traditional approach to HFrEF treatment sequencing has been informed by trials that assessed new therapies incremental to the established standard regimen at the time. For example, ACE inhibition was compared with vasodilators, and β-blockers were assessed on top of ACE inhibition. Thus, on the basis of trial protocol,[2] ARNI is currently recommended after ACE inhibition in some guidelines. Yet considering the early benefit with ARNI, are we justified in waiting before initiating the best therapy? Furthermore, the recent trials were conducted not sequentially but simultaneously and provide little opportunity to assess incremental benefit either among themselves or in combination with foundational therapy.[3,4] Thus, the add-on incremental model of serial evidence generation in HFrEF is not relevant to recent trials, leaving unanswered the question of how sodium glucose cotransporter-2 inhibitors and soluble guanylase cyclase stimulators should be prioritized and sequenced on top of ARNI, β-blockers, and mineralocorticoid receptor antagonists.

These issues are compounded when we consider the effect of any given therapy in specific subgroups of patients. Because one cannot reasonably expect a large outcomes-based randomized trial for every question and every subgroup, when is it reasonable to make clinical inferences from existing data? Despite robust evidence of superiority of ARNI compared with enalapril in the pivotal trial,[2] a call for additional evidence was pursued for new-onset HFrEF, patients naïve to ACE inhibitors, initiation in hospitalized settings, those with lower natriuretic peptide levels,

Key Words: heart failure ■ therapeutics

https://www.ahajournals.org/journal/circ

etc, without specific hypotheses that the drug would not benefit these subgroups and for which safety could have been assessed by clinical registries. Further trials mandate randomizing patients to a control arm, raising ethical questions and increasing the costs of drug development. Are these steps justifiable after convincing benefits in appropriately powered pivotal trials have been demonstrated?

Acknowledging that empirical data are, and may always be, incomplete, we should consider a more rational and best clinically applicable approach to HFrEF treatment (Figure). In this respect, with the acknowledgment that definitive data do not exist but on the basis of secondary analyses including drug effect interaction with baseline treatment, we propose that the principal goal should be to get every patient on every medication class shown to improve outcomes in HFrEF through independent mechanistic pathways, that is, targeting simultaneously the modulation of angiotensin II, norepinephrine, aldosterone, neprilysin, and sodium glucose cotransporter-2. This may be accomplished by using 4 drugs: ARNI, β-blockers, mineralocorticoid receptor antagonists, and sodium glucose cotransporter-2 inhibitors. This 4-drug combination has been suggested to increase survival by >6 years in 55-year-olds and almost 1 year in octogenarians compared with conventional therapy.[5] In specific populations, 3 additional pathways have been shown to improve outcomes: ivabradine (left ventricular ejection fraction <35%, normal sinus rhythm, and heart rate >70 bpm on optimal β-blocker therapy), hydralazine/nitrate (self-identified Blacks), and vericiguat (worsening chronic HF). The approach recognizes that tolerability, availability, costs, patient preference, and other considerations may affect choices, doses, and sequences of therapies and that not everyone will be prescribed everything.

A nonstepped approach can be considered as in other disciplines such as cancer in which multiple therapeutic options are considered on "equal ground" and the best available option (or combination) is selected for individual patients, starting all rather than introducing each class in a stepwise fashion over months or years. Considering the high risk of patients with HFrEF, it stands to reason that the sooner all pathways are modulated, the better. The overarching rationale is that all attempts should be made to modulate all relevant pathways and that, when there is compromised blood pressure or renal function, it is best to treat with smaller doses of drugs affecting all relevant pathways before maximizing doses of 1 class of drugs at the expense of not giving another. Of course, if patients can tolerate it, doses of all classes of therapies should be maximized.

We acknowledge the large philosophical dilemma we now face as victims of our own success in HF: Do we follow the sequencing in trials (which can take months, and maximizing 1 agent may preclude use of another), or do we accept that these classes of medications work differently and all should be introduced as quickly as

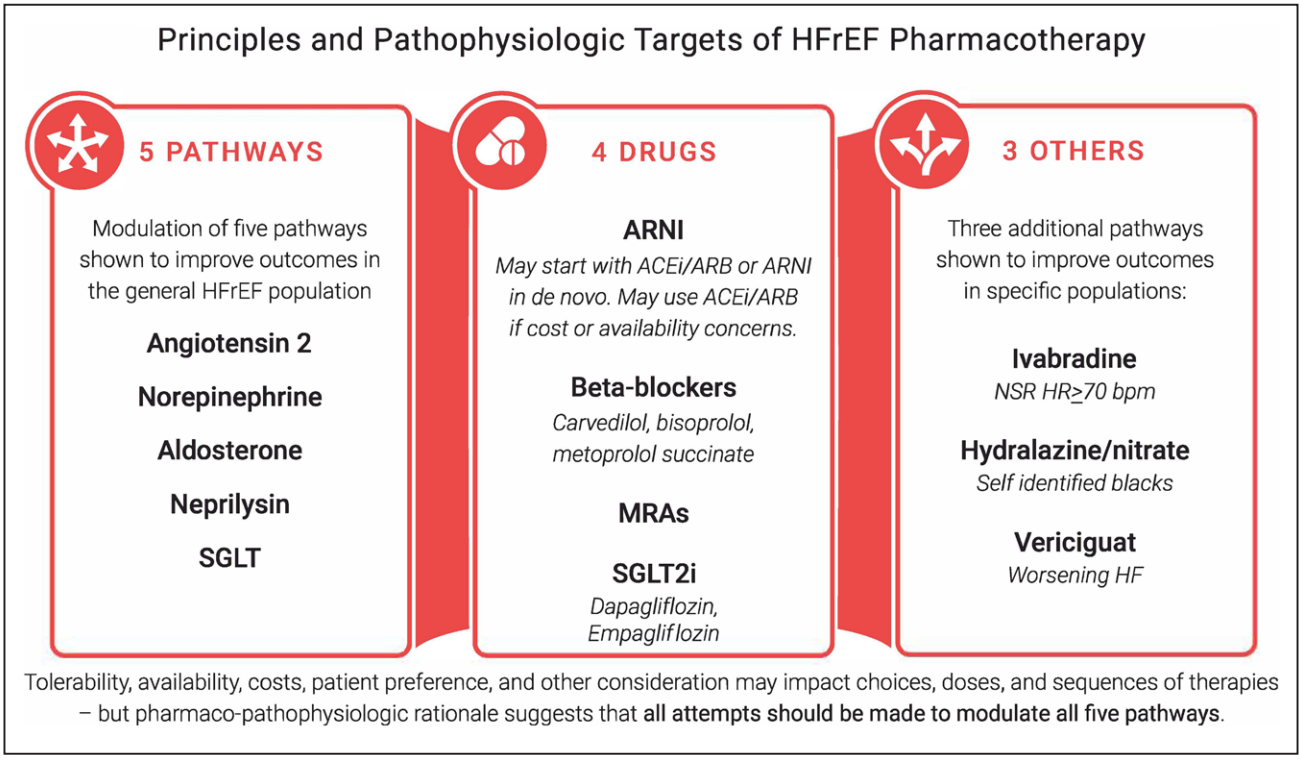

Figure. Principles and target of heart failure (HF) with reduced ejection fraction (HFrEF) pharmacotherapy.
ACEi/ARB indicates angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; HR, heart rate; MRA, mineralocorticoid receptor antagonist; NSR, normal sinus rhythm; SGLT, sodium glucose cotransporter; and SGLT2i, sodium glucose cotransporter-2 inhibitor.

possible? We strongly encourage the perspective that the new foundational therapy for HFrEF should be defined as modulation of 5 pathways by 4 drugs, that lower doses of all drug classes are preferable to target dose of 1 class at the expense of another, and that all pathways should be modulated as soon as possible while simultaneously keeping patient safety in mind.

We anticipate that an evidence-based empiricist perspective is at odds with this rational clinical approach. We certainly advocate for continued evidence generation for questions for which we do not have data and for implementation science. However, the absence of evidence should not impede the application of best clinical judgment now.

ARTICLE INFORMATION

Correspondence

Carolyn S.P. Lam, MBBS, PhD, National Heart Centre Singapore, 5 Hospital Dr, Singapore 169609; or Javed Butler, MD, MPH, MBA, University of Mississippi Medical Center, 2500 State St, Jackson, MS 39216. Email carolyn.lam@duke-nus.edu.sg or jbutler4@umc.edu

Affiliations

National Heart Centre Singapore (C.S.P.L.). Duke-National University of Singapore (C.S.P.L.). University of Mississippi Medical Center, Jackson (J.B.).

Disclosures

Dr Lam is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has served as a consultant to or on the Advisory Board/ Steering Committee/ Executive Committee for Abbott Diagnostics, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Biofourmis, Boehringer Ingelheim, Boston Scientific, Corvia Medical, Cytokinetics, Darma Inc, Eko.ai Pte Ltd, JanaCare, Janssen Research & Development LLC, Medtronic, Menarini Group, Merck, MyoKardia, Novartis, Novo Nordisk, Radcliffe Group Ltd, Roche Diagnostics, Stealth BioTherapeutics, The Corpus, Vifor Pharma, and WebMD Global LLC; and serves as cofounder and nonexecutive director of EKo.ai Pte Ltd. Dr Butler has served as a consultant to Abbott, Adrenomed, Amgen, Applied Therapeutics, Array, AstraZeneca, Bayer, BerlinCures, Boehringer Ingelheim, Cardior, CVRx, Foundry, G3 Pharma, Imbria, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Roche, Sanofi, Sequana Medical, V-Wave Limited, and Vifor.

REFERENCES

1. Allen LA, Fonarow GC, Liang L, Schulte PJ, Masoudi FA, Rumsfeld JS, Ho PM, Eapen ZJ, Hernandez AF, Heidenreich PA, 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. doi: 10.1161/CIRCULATIONAHA.115.014281
2. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, et al; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004. doi: 10.1056/NEJMoa1409077
3. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, 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. doi: 10.1056/NEJMoa1911303
4. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, Lam CSP, Ponikowski P, Voors AA, Jia G, et al; VICTORIA Study Group. Vericiguat in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2020;382:1883–1893. doi: 10.1056/NEJMoa1915928
5. Vaduganathan M, Claggett B, Jhund PS, Cunningham HW, Ferreira JP, Zannad F, Packer M, Fonarow GC, McMurray JJJV, Solomon SD. 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;396:121–123. doi:10.1016/S0140-6736(20)30748-0.