

# Evidence-Based Prescribing and Polypharmacy for Patients With Heart Failure

Ankeet S. Bhatt, MD, MBA; and Nitesh K. Choudhry, MD, PhD

The last decades have seen tremendous advances in drug therapies for chronic health conditions, including heart failure with reduced ejection fraction (HFrEF). Randomized clinical trials have established the efficacy of many medications, which have reduced mortality rates and averted hospitalizations for patients with heart failure. In parallel, scientific advancements have improved the ability to treat atherosclerotic cardiovascular disease, diabetes, and chronic kidney disease, among other common comorbid conditions.

Scientific progress has also had unintended consequences. To receive guideline-concordant care, persons with HFrEF must take many medications every day: a renin-angiotensin and neprilysin antagonist, a  $\beta$ -adrenergic blocker, a mineralocorticoid receptor antagonist, and a sodium-glucose cotransporter-2 (SGLT2) inhibitor. Other potentially eligible therapies may soon include a soluble guanylate cyclase inhibitor and a cardiac myosin activator. Further, patients with HFrEF have many comorbid conditions. For example, 60% of Medicare beneficiaries with heart failure have 5 or more chronic medical conditions (1), and these conditions require their own evidence-based, long-term medications.

High medication burden, often called *polypharmacy* and generally defined as needing to take 5 or more medications daily, is associated with disability (2), worsening functional status, and higher treatment-related adverse effects, including drug-drug interactions. Polypharmacy concerns generally arise from medications categorized as “potentially inappropriate.” Accordingly, many groups have supported deprescribing interventions and generated lists of medications that should be avoided, especially among very elderly patients (3). However, the adverse effects of polypharmacy may also extend to evidence-based prescribing. Independent of clinical issues, more medications mean more pills to organize, remember, and take. It also means higher out-of-pocket costs, disutility from incremental pill burden, and challenges associated with accessing medications and refills, therefore leading to decreased medication adherence (4). The result is a reduction in the benefit that these highly efficacious medications can offer. Thus, while efforts to maximize life-saving therapies should remain paramount, the complex tradeoffs between evidence-based prescribing and the real challenges encountered by patients must be acknowledged.

There are several strategies to address this problem. Solutions that make medications easier to take could help. Fixed-dose combination pills deliver multiple components of guideline-directed therapy and could reduce pill burden. Polypills have demonstrated modest benefit for atherosclerotic cardiovascular disease prevention compared with usual care (5), but their clinical equivalence to stand-alone drugs has not been established. Polypills

have been proposed for treating HFrEF, although none are commercially available (6). The hemodynamic and renal effects of these therapies may be complex and overlapping; as a result, titration using component drugs may first be necessary to confirm tolerance. Newly marketed combination medications are likely to be expensive, even if they contain agents that are available as generics. In some cases, patients may prefer individual treatments that have a lower aggregate cost when compared with more expensive polypills, though this tradeoff will need to be individually navigated.

Better data about existing medications would also help. Pharmacoepidemiologic approaches that use real-world evidence broadly applicable to patients cared for in typical care settings may serve as a good starting point. In addition, sequencing trials that explicitly evaluate different strategies for add-on therapy could identify stepwise therapeutic priorities, although these trials are challenging given the varying levels of background therapy. For example, many patients with HFrEF receive evidence-based  $\beta$ -blockade and renin-angiotensin system blockade, but the comparative benefits of a mineralocorticoid receptor antagonist or SGLT2 inhibitor as the next incremental therapy is unknown. Moreover, for patients who need a regimen change because of hemodynamic limitations, de-escalation trials with randomization to different withdrawal arms that combine clinical, adherence-based, and patient preference end points would be informative.

Generating these data will take time and will ideally be powered to explicitly test therapeutic effects within relevant patient subgroups. Regrettably, there may be little incentive for pharmaceutical manufacturers or other funders to support these studies. Accordingly, alternative approaches are available that patients and their clinicians may consider today.

First, patients with HFrEF have many comorbid conditions, including atherosclerotic cardiovascular disease, type 2 diabetes, and chronic kidney disease. Existing trials have evaluated particular drug classes across multiple disease states, allowing for possible prioritization of therapies with more than one evidence-based indication. For example, the SGLT2 inhibitors reduce cardiovascular mortality in patients with HFrEF and also attenuate decline in renal function for patients with chronic kidney disease (7). As a result, for patients with HFrEF and comorbid diabetes, chronic kidney disease, or both, SGLT2 inhibitors could be prioritized over other pharmacotherapies with a single indication. Of course, the benefits of reduced pill burden must be weighed against the cost of these newer therapies; thus, this approach may not be viable for all patients.

Second, shared decision making should explicitly acknowledge the tension between more drugs with better

outcomes and the practical realities of taking these drugs. This approach is widely used to guide choices for preference-sensitive conditions, but in patients with HFrEF, it has largely been confined to end-of-life planning in individuals with advanced disease (8). Given advances in discovery science leading to lower aggregate event rates, the incremental absolute benefit for each therapy has generally declined over time. Taking into account differing patient-specific thresholds, patients may be willing to sacrifice incremental improvements in outcomes to lessen pill burden and financial costs. However, these conversations should be framed to ensure complete understanding of the morbidity and mortality benefits that these therapies afford. In addition, most patients with HFrEF want to talk about the cost of their drugs, and simple interventions are effective for facilitating these conversations (9, 10). Therefore, creating mechanisms to prioritize shared decision making should be a central priority in ambulatory heart failure care.

In an increasingly intricate therapeutic landscape, clinicians and patients face a growing number of medication decisions. Accelerating new drug development and promoting evidence-based prescribing should undoubtedly remain a centerpiece of efforts to reduce the burden of chronic disease. However, many tradeoffs remain and may expand in the future. Along with developing and widely implementing new and effective therapies, we must recognize and address the practical implications of these advances. The approaches we propose may provide strategies to assist with these challenging therapeutic choices. They should be considered in the larger context of a need to develop a research agenda that determines how best to implement the fruits of scientific progress, that makes medications easier to take, and that prioritizes the patient-physician relationship for shared decision making.

From Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (A.S.B., N.K.C.).

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**Corresponding Author:** Niteesh K. Choudhry, Brigham and Women's Hospital and Harvard Medical School, 1620 Tremont

Street, Suite 3030, Boston, MA, 02120; e-mail, [nkchoudhry@bwh.harvard.edu](mailto:nkchoudhry@bwh.harvard.edu).

Current author addresses and author contributions are available at [Annals.org](http://Annals.org).

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**Current Author Addresses:** Dr. Bhatt: Shapiro Cardiovascular Center, 70 Francis Street, Boston, MA 02115.

Dr. Choudhry: Brigham and Women's Hospital and Harvard Medical School, 1620 Tremont Street, Suite 3030, Boston, MA, 02120.

**Author Contributions:** Administrative, technical, or logistic support: A.S. Bhatt, N.K. Choudhry.

Collection and assembly of data: N.K. Choudhry.

Conception and design: A.S. Bhatt, N.K. Choudhry.

Critical revision for important intellectual content: A.S. Bhatt, N.K. Choudhry.

Drafting of the article: A.S. Bhatt, N.K. Choudhry.

Final approval of the article: A.S. Bhatt, N.K. Choudhry.