COMMENTARY

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Polypharmacy in Heart Failure with Reduced Ejection Fraction: Progress, Not Problem

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Heart failure affects more than 6.5 million adults in the United States[1] and carries a survival comparable to many cancers with about a 50% mortality at 5 years after diagnosis.[2] Almost half of these patients have heart failure with reduced ejection fraction (HFrEF). Medical therapy for HFrEF has evolved based on the results of landmark trials, and the current heart failure guidelines recommend multiple medications proven to increase survival and quality of life.[3-5] These include beta blockers, angiotensin-converting enzyme inhibitors (ACEis)/angiotensin II receptor blockers (ARBs) or angiotensin receptor-neprilysin inhibitors (ARNI), mineralocorticoid receptor antagonists (MRA), and most recently, sodium-glucose cotransporter-2 inhibitors (SGLT2i).[3-5] Contemporary HFrEF trials have seen a progressively increasing proportion of background therapy, especially with a larger proportion of patients taking MRA and triple therapy. This, however, is not the case in practice with even the most contemporary data showing major gaps in implementation of evidence-based medications. Although there are many reasons for this trend, a commonly perceived "problem" is polypharmacy and the presence of numerous therapeutic options.

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POLYPHARMACY IN HEART FAILURE: THE GOOD AND THE BAD

The widespread availability of life-prolonging therapies has been met with slow uptake in clinical practice, and many eligible patients are not prescribed optimal guideline-directed medical therapies (GDMT).[6] The recent introduction of ARNI and SGLT2i continues to face the same barriers of clinical inertia. The opportunity cost of failing to prescribe guideline-directed medical therapies is substantial because optimal prescription can prevent >100,000 deaths just in the United States per year.[7,8] Optimal guideline-directed medical therapy is projected to offer a 55-year-old person an additional 6 years of survival.[9]

Patients with heart failure often have other comorbidities, and the number of prescribed medications increases with age, yet the use of guideline-directed medical therapies remains low in the elderly population.[10] Most older patients hospitalized with heart failure are prescribed more than 10 medications at discharge, and this rate has increased from 41% in 2003-2006 to 68% in 2011-2014.[10] Polypharmacy is generally described as taking at least 5 medications, and it has several downsides, including increased risk for drug interactions, risk for adverse events, difficulties with adherence, and cost.[11]

With increasing availability of evidence-based options for HFrEF treatment, there is a perceived risk for increasing rates of adverse events, especially among older patients. Although this may be true, it is not universally relevant, and the alternate scenario of avoiding optimal therapy definitely poses an increased risk for worse quality of life, recurrent hospitalizations, and mortality.[3-5] Risks and benefits of polypharmacy thus need to be weighed against the risk of growing polymorbidity and its subsequent impact. We, therefore, strongly contend that the availability of multiple medications provides the clinicians and patients with potent therapeutic options and that the negative connotations around polypharmacy need to be curbed to appropriate proportion.

Patients with HFrEF may have various comorbidities, such as chronic kidney disease and orthostatic hypotension, that may prohibit their eligibility for morbidity- and mortality-reducing therapies. An example of such includes progressive renal disease in which ACEi, ARB, ARNI, or

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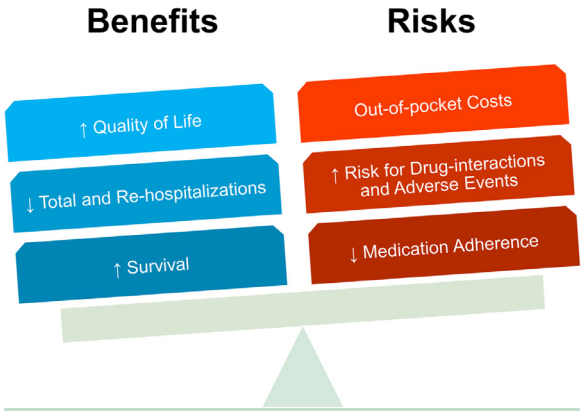

Figure Benefits and risks of polypharmacy in heart failure with reduced ejection fraction.

MRA may not be suitable; yet providers may still provide beta blockers and SGLT2i because of their cardiac or renal protective effects in HFrEF.[12] Alternatively, a patient with orthostatic hypotension may have increased adverse symptoms to beta blockers, ACEi, ARB, or ARNI[13] but may tolerate MRA and SGLT2i because of their lower hemodynamic profile.[12] Although such medication sequencing or prioritizing among certain HFrEF subtypes are lacking, the growing arsenal of HFrEF therapies warrants a tailored approach in such vulnerable subpopulations. Additionally, because there are no new pharmaceutical agents or classes in advanced stages of investigation in chronic stable HFrEF, now is the time to balance implementation of maximally prescribing existing guideline-directed medical therapies that work with minimizing patient intolerances or adverse symptoms (Figure).

The plethora of guideline-directed medical therapy choices in chronic HFrEF treatment offers new opportunities to improve outcomes through implementation and prescribing practices, as well as tailored therapies among patients likely to be intolerant to taking more than 10 medications or multiple classes. The need is clear: HFrEF affects a large proportion of the population with multiple health care workers involved in their care, and these important medications do not belong to any 1 provider or specialty. A collaborative effort among heart failure, kidney, endocrinology, pharmacy, and primary care specialists is needed to maximize the benefits of multiple guideline-directed medical therapy classes in HFrEF to optimize quality of life and survival outcomes, while minimizing adverse perceptions of misperceived risk for adverse effects of polypharmacy in HFrEF. Inappropriate polypharmacy should definitely be avoided, and polypharmacy should be tailored according to cost and tolerability related individualization. Efforts to improve adherence by instituting polypills should be evaluated (Table). But the negative rhetoric around polypharmacy needs to be carefully gauged because avoiding optimal medical therapy also has its consequences, and the consequences are likely worse than the issues with polypharmacy itself.

Table Unresolved Questions in Regard to Polypharmacy in Heart Failure with Reduced Ejection Fraction

Open Questions in Regard to Polypharmacy
Optimal sequencing of medications
Optimal matching of medications to patient profile
In-hospital guideline-directed medical therapy implementation
Efficacy of polypill
Educating and engaging patients and their families in heart failure treatment

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