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GUEST EDITORS' PAGE

Juggling While Dancing

The Complex Medical Management of Heart Failure With Reduced Ejection Fraction

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The management of patients with heart failure with reduced ejection fraction (HFrEF) has evolved significantly over time, and these advancements are perhaps most significant with respect to medical therapy. In addition to longstanding therapies whose survival benefit is well-established, such as beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, along with other conventional therapies such as nitrates, hydralazine, and digoxin, there now exist multiple newer agents and classes also demonstrating efficacy, including angiotensin receptor neprilysin inhibitors, sinus node inhibitors (ivabradine), sodium-glucose cotransporter-2 inhibitors (SGLT2Is), soluble guanylate cyclase stimulators (vericiguat), and cardiac myosin activators (omecamtiv mecarbil). Furthermore, older therapies such as intravenous iron supplementation have demonstrated new benefits (1), with expanded indications currently under investigation. Although these exciting developments have significantly improved the prognosis of patients with HFrEF, they have also led to a very complex therapeutic landscape that clinicians must now navigate for a disease that has always been complex and challenging (2). Furthermore, when the advancements in medical therapy are considered in the context of improvements in device therapies, treatments for valvular heart disease, advanced heart failure therapies, and remote monitoring capabilities, the challenge of optimal HFrEF management becomes even more complicated. And although the prognosis of HFrEF has significantly improved in recent years due to these advances, it should be noted that it remains a disease that is associated with a high level of risk for patient morbidity and mortality (3,4). As a result, there are multiple other investigational agents and therapeutic clinical trials that are presently in various stages of development that may further complicate the management of HFrEF in the future.

How can busy clinicians keep up with this rapidly shifting landscape to provide their patients the best therapy that modern medicine can offer? Before determining the best strategy for optimizing medical therapy for HFrEF patients in the current era, it is helpful to understand how we got here and how clinical evidence has shaped our approaches thus far. Clinical trials have historically evaluated a single new therapy's efficacy on the background of existing optimal medical therapy, and therefore clinical practice has mirrored this approach of adding a single therapy sequentially to the current standard guideline-directed medical therapy (GDMT) (4,5). Although this approach has resulted in strong evidence supporting the incremental value of newer therapies in addition to the standard GDMT regimen that was current at the time of the clinical trial, there is very little evidence comparing the efficacy of specific medical therapies head to head. This frequently translates into uncertainty in clinical practice with respect to sequence and timing of titration of medical therapy. Furthermore, enrollment criteria in clinical trials are frequently chosen to minimize competing risk of significant comorbidities rather than on the basis of biology and safety alone. Although scientifically sound for demonstrating efficacy of the therapy under study, this can also create uncertainty in clinical practice regarding potential benefit in different HFrEF population subgroups.

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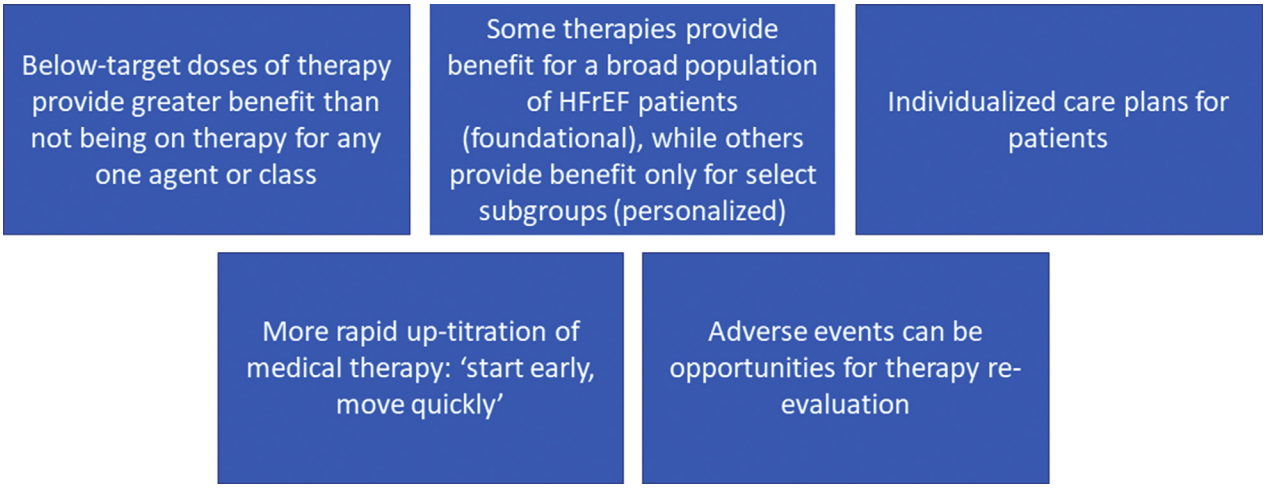
FIGURE 1 Principles for Optimization of Therapy for HFrEF



Principles for optimization of therapy for heart failure with reduced ejection fraction (HFrEF) in the current era of multiple medication classes.

Even before the current era, optimization of HFrEF medical therapy has long been challenging in clinical practice. It has been well-documented that even in the more regimented environment of clinical trials, achievement of target doses of background GDMT is rarely achieved (4,6–9). Recommendations towards optimal strategies around timing, frequency, and choice of agent for up-titration from consensus guideline documents have been limited, although more recent publications have attempted to address this challenge more directly (4,10,11). Programs that have been developed to guide and facilitate medical therapy optimization have yielded variable results with respect to adherence and improvement in patient outcomes (12). There are several factors that can complicate optimization of HFrEF medical therapy, including those related to patient factors, clinician factors, and system factors. Perhaps one of the most important is the time required to do this effectively. Beyond the challenges involved in choosing the next step when up-titrating therapy, explaining the importance of this to the patient and monitoring tolerance can strain busy clinicians, even those working in dedicated heart failure clinics. There are multiple factors and variables that need consideration when evaluating medication tolerance and therapeutic response, including symptoms, vital signs and physical examination findings, and serum and imaging markers, among others, and the frequency and interpretation of monitoring often needs to be individualized accounting for comorbid conditions, adding to the complexity. Cost, insurance coverage, and availability of newer therapies, in addition to patient attitudes toward polypharmacy and monitoring frequency, may also present further challenges (13). Recent data on statin prescription even suggests that time of day of a clinic appointment may influence prescribing behavior (14). These and other factors can lead to wide treatment disparities among HFrEF patients, including those based upon sex, race and ethnicity, socioeconomic status, and geography. These challenges all conspire toward a therapeutic inertia for up-titration of HFrEF medical therapy, particularly for patients who are perceived as stable by either themselves and/or their treating clinicians (15,16).

What can be done to meet this increasingly complex challenge? There is an urgent need for more data to support an evidence-based approach to optimizing HFrEF medical therapy. Such data can be collected from a variety of different sources depending on specific objectives and questions being addressed. Prospective clinical trials designed to examine titration approaches and strategies, including those based upon implementation science methodologies, can provide robust data to guide clinical practice and can tailor inclusion criteria to be broad or focused on specific HFrEF subgroups such as those with a de novo diagnosis or with advanced renal dysfunction. However, adequately powered clinical trials can be costly to design and implement and the lead time before findings can be translated into clinical practice can be lengthy, with a risk of further evolution of the therapeutic landscape

occurring in the process. Other traditional sources of patient data such as subgroup analysis from completed clinical trials and registry data can be helpful but have well-recognized methodologic limitations and may lack the granularity of collected data elements to support specific recommendations that can influence clinical practice patterns. For example, standardized data collection on medication intolerance or individualized decisions about dosage adjustments and timing can be challenging to capture, especially for larger multicenter cohorts (8). The rise of advanced analytical tools to interrogate electronic health records, including technologies such as machine-learning and artificial intelligence, may be particularly well-suited to examine, test, and importantly, validate approaches for optimizing HFrEF medical therapy (17). The statistical power of these approaches for analyzing large and complex data sets may provide advantages over other techniques and may reduce the lead time between analysis and integration into clinical practice. In addition to further data and research, expert cardiovascular and heart failure medical societies should prioritize the topic of HFrEF medical therapy optimization approaches with respect to education, advocacy, guidance, and recommendations directed at those in clinical practice as best they are able to ensure it remains an important area of focus.

What can clinicians do as we wait for more data and recommendations to arrive? Despite significant knowledge gaps, there are important conclusions that can still be drawn from existing data and studies (**Figure 1**). Among them is that below-target doses of therapy are recognized to provide greater benefit than not being on therapy for any one agent or class (4). For example, lower doses of multiple therapies are more efficacious then target doses of one therapy at the cost of not receiving another. Another is the recognition that some therapies provide benefit for a broad population of HFrEF patients, whereas others provide benefit to more select subgroups. For example, beta-blockers are recognized to confer survival benefit for all HFrEF patients, whereas only those intolerant of beta-blockers or with persistently elevated resting heart rates derive benefit from ivabradine. This approach has led to new categories of agents being created to aid clinicians in prioritizing their initiation, labeling medications as either foundational therapies (beta-blockers, angiotensin receptor neprilysin inhibitors or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, SGLT2Is, mineralocorticoid receptor antagonists) or personalized therapies (ivabradine, vericiguat, hydralazine, and nitrates) based upon their indication criteria (4,5,18). Other strategies that clinicians can use include creation of an individualized care plan for patients, complete with target medication classes and doses, and a titration schedule. Engaging patients early in their disease course regarding goals of treatment can improve adherence. Care plans that clearly describe therapeutic targets and parameters for up-titration can facilitate greater autonomy for nursing-led decision-making, which in turn can enhance efficiency. A concept that is also gaining more acceptance is more rapid up-titration of medical therapy, with shorter time periods between dosage adjustments and making more than one change at a time. Although such a "start early, move quickly" approach to medical therapy optimization may need to be individualized depending on patient factors, improved capabilities and wider acceptance of remote monitoring can facilitate this strategy and improve the likelihood of success. And although adverse events such as decompensations, hospitalizations, and implantable defibrillator therapies can be difficult setbacks for patients, they can also represent opportunities for re-evaluation and updating of their medical therapies or planning for more advanced therapies.

The exciting advancements in HFrEF medical therapies have created new opportunities to improve patient's survival and quality of life but have also led to challenges for clinicians facing an increasingly complicated number of choices and decisions for optimizing their care. A framework for guiding the complex decision-making involved in selecting HFrEF medications and doses that accounts for both the universal aspects of HFrEF pathophysiology and the individualized nature of this complex clinical syndrome is needed. Ongoing clinical research, including in the field implementation science, will hopefully lead to more evidence to support development of formal recommendations and guidelines in this challenging area. In the meantime, clinicians can take proactive steps, such as locally developed treatment algorithms and care plans, to ensure their patients are receiving the best medical care possible.

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