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Heart Failure Drug Therapy: New Treatments, New Guidelines

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In recent years, several new medications have proven useful in reducing heart failure–related morbidity and mortality. The result is a broader therapeutic armamentarium to treat both heart failure with reduced ejection fraction (HFrEF; left ventricular ejection fraction [LVEF] <40%) and heart failure with preserved ejection fraction (HFpEF; LVEF >50%).

Current Limitations

As pharmacological treatment of heart failure increases in complexity and cost, it has become more challenging for clinicians and patients to initiate and maintain treatment with the multitude of medications shown to reduce the morbidity and mortality associated with heart failure. In addition, the clinical time required to titrate these medications to the optimal target doses identified by clinical trials has proven to be another barrier to optimal pharmacologic intervention. Data suggest that guideline-directed medical therapy (GDMT) remains underprescribed, leaving patients at risk for disease progression and negative outcomes.[1] This review describes a contemporary pharmacologic approach to treating both HFrEF and HFpEF (Fig. 1).

Recent Developments

Two recent guidance documents emphasize an evidence-based approach to managing heart failure, including practical considerations for medical therapy and the urgency of initiating GDMT.[2,3] No longer is it acceptable to delay initiating or titrating heart failure medications. Instead, it is recommended that therapy for patients with newly

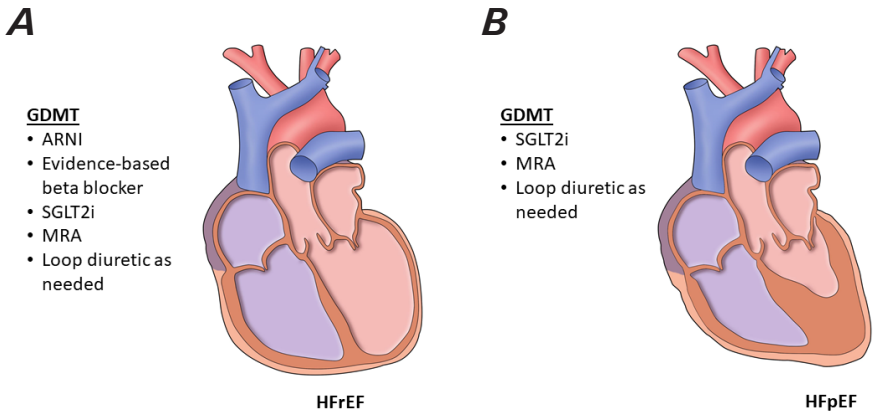

Fig. 1 *Illustration presents contemporary guideline-directed medical therapies (GDMTs) for **A**) heart failure with reduced ejection fraction (HFrEF) and **B**) heart failure with preserved ejection fraction (HFpEF).*

ARNI, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor

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diagnosed heart failure be intensified every 1 to 4 weeks, with the goal of ensuring optimal treatment within 3 to 4 months. These new recommendations emphasize the importance of frequent, active follow-up and dynamic clinical assessment to ensure that patients receive the multiple different classes of morbidity- and mortality-reducing agents at the maximally tolerated or trial-supported doses. Patients with HFrEF who respond clinically to GDMT should be reassessed to evaluate cardiac structure and function and to guide referral for implantable cardioverter-defibrillator or cardiac resynchronization therapy, if indicated. Patients for whom GDMT is not effective or not tolerable; who have residual New York Heart Association functional class III to IV symptoms, end-organ dysfunction, or hypotension; or who require frequent hospitalization should be referred to a heart failure specialist to be considered for advanced therapies or inclusion in a clinical trial.

A contemporary, guideline-directed medical regimen for patients with HFrEF should preferentially include an angiotensin receptor–neprilysin inhibitor (ARNI; ie, sacubitril-valsartan), a β-blocker shown to be effective for HFrEF (eg, carvedilol, sustained-release metoprolol, or bisoprolol), and the lowest dose of loop diuretic needed to maintain euvolemia. In addition, patients with preserved renal function and a normal serum potassium level should receive a mineralocorticoid receptor antagonist (MRA) such as spironolactone, provided that the patient is willing to return for follow-up measurements of serum electrolytes and renal function.

There is a growing and compelling body of evidence from clinical trials that a sodium-glucose cotransporter-2 inhibitor (SGLT2i) consistently reduces heart failure–related hospitalizations and mortality in patients with HFrEF. These benefits are seen in individuals with and without diabetes.[4] The SGLT2i should be used with caution in patients with an estimated glomerular filtration rate of less than 20 to 30 mL/min. The combination of hydralazine and nitrates in African American patients treated with standard therapy reduces the rate of the combined end point of mortality, first heart failure hospitalization, and worsening quality of life.[5]

Packer and McMurray[6] have proposed an approach for implementing HFrEF GDMT on the basis of early outcome benefits, advocating use of a β-blocker and an SGLT2i as first-line therapy and then adding an ARNI and an MRA within 4 weeks. They propose using the ensuing 2 to 3 months to titrate dosing to align with the dosages found to be most efficacious in clinical trials. Tromp and colleagues[7] recently described the relative benefits of varying combinations of HFrEF treatments. Patients treated with sacubitril-valsartan, a β-blocker, an MRA, and an SGLT2i had a 60% relative reduction in all-cause mortality and a 64% reduction in the combined end point of cardiovascular mortality and heart failure hospitalization.

The evidence base for HFpEF medical therapy is much less robust. The Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial studied the utility of spironolactone in treating HFpEF.[8] Although the trial did not show a significant reduction in the rate of cardiovascular death, aborted cardiac arrest, or heart failure hospitalization in the treatment arm, the results were skewed by the cohort of patients enrolled in Eastern Europe, who had a markedly lower mortality rate than the patients from the Americas. When the analysis was limited to patients enrolled in the Americas, spironolactone had a significant impact on the primary end point.[9] Another HFpEF pivotal trial, the EMPEROR-Preserved trial, examined the efficacy of the SGLT2i empagliflozin.[10] This trial enrolled nearly 6,000 patients, and those who received empagliflozin had a 21% relative risk reduction in the end point of heart failure hospitalization and cardiovascular death compared with that with placebo. In addition to the above-mentioned disease-modifying treatments, loop diuretics are essential for maintaining euvolemia, although lower doses may be needed as a result of the diuretic effects of both spironolactone and empagliflozin.

Future Directions

In summary, evidence is accumulating in support of GDMT for both HFrEF and HFpEF. Patients with an LVEF less than 40% should receive an ARNI, a β-blocker, an SGLT2i, and an MRA. Those with an LVEF greater than 50% should be treated with an MRA and an SGLT2i. In addition, both groups of patients likely require a loop diuretic. Therapy should be initiated and titrated urgently because these therapies favorably alter the course of the disease. Failure to start GDMT expeditiously in patients with heart failure increases their risk of morbidity and mortality.

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