TABLE 14 Important Pathophysiological Targets in Chronic, Hemodynamically Stable HFrEF and Treatments

Target	Therapy
Renin-angiotensin-aldosterone system	ARNIs/ACE inhibitors/ARBs, mineralocorticoid antagonists
Sympathetic nervous system	Beta-blockers
Natriuretic and other vasodilator peptides	Neprilysin inhibitor (ARNI)
Sodium-glucose cotransporters	SGLT1/2 and SGLT2 inhibitors
Balanced vasodilation and oxidative stress modulation	HYD/ISDN
Elevated heart rate	Beta-blocker, ivabradine
Guanylyl cyclase	Soluble guanylyl cyclase stimulators
Relief of congestion	Diuretic agents
Ventricular arrhythmias	Implantable cardioverter-defibrillators
Ventricular dyssynchrony due to conduction abnormalities	Cardiac resynchronization therapy
Mitral regurgitation	Surgical or percutaneous mitral valve repair
Reduced aerobic capacity	Aerobic exercise training

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; HFrEF = heart failure with reduced ejection fraction; HYD/ISDN = hydralazine/isosorbide dinitrate; SGLT = sodium-glucose cotransporter.

antagonists, and SGLT inhibitors are first-line medications for all populations. HYD/ISDN is also a first-line medication for self-identified African-American patients after initiating optimal doses of first-line medications. Ivabradine is a second-line medication for select populations, as is vericiguat.

Principle 2: Target doses are associated with best outcomes.

Attempt to rapidly achieve target doses of all recommended therapies in the absence of contraindications and/or intolerance. Titration should occur even if the patient appears stable or their symptoms and/or EF improve. Failure to tolerate titration should prompt consideration for referral to an advanced center.

Principle 3: Start GDMT immediately and titrate during each encounter.

Delayed initiation of GDMT is associated with never initiating GDMT.[222] The goal is to finish initiation and titration by 2 to 3 months (or sooner). Although GDMT may be added sequentially, in many cases, simultaneous start of multiple agents (or all 4) may be possible.

Principle 4: Attention to the clinical, social, and financial barriers to achieving GDMT should be prioritized.

This includes addressing bias, structural racism, and SDOH routinely during encounters. Multidisciplinary care should be targeted to the individual patient's barriers. This should be reevaluated for success at the clinic and hospital levels at routine intervals. Consider early referral to an HF team for assistance.

Principle 5: Diligent management of volume status will reduce patient symptoms.

Congestion drives symptoms and hospitalizations. If the volume status is unclear, consider performing right heart catheterization and/or referral to an HF specialist. Chronic ambulatory PAP monitoring may be considered in patients with hospitalizations in the past year who have persistent symptoms with minimal exertion.

Principle 6: Tolerability and side effects depend, in part, on how and when GDMT is prescribed.

Scenario: *Worsening kidney function or hyperkalemia.*

Available data support a survival benefit even with low doses of GDMT. Use less than target doses of an ARNI/ACE inhibitor/ARB and discontinue the mineralocorticoid antagonist if estimated creatinine clearance is <30 mL/min or serum potassium is >5.0 mEq/L, despite all efforts to address hyperkalemia. SGLT inhibitors are beneficial, even below approved creatinine clearance thresholds.

Scenario: *Symptomatic hypotension.*

Symptomatic hypotension may be due to overdiuresis, use of non-CV drugs with hemodynamic effects (eg, anticholinergic agents, treatments for prostate enlargement, others), autonomic dysfunction, or simultaneous administration of multiple HF medications. All of these should be addressed before deciding to lower doses of evidence-based therapies. After excluding other causes of hypotension, use best-tolerated doses of GDMT, accepting that less data exist for the impact of lower doses in HF management. Clinical comorbidities and clinical judgement should be used to guide which GDMTs are reduced. For persistent hypotension, consider referral to an advanced HF specialist.

Scenario: *Hypokalemia*

When possible, consider increasing the dose of mineralocorticoid antagonist (if appropriate kidney function) in lieu of adding oral potassium.

Principle 7: Primary prevention ICDs and CRT should be considered after consistent use of optimal doses of all GDMTs for at least 3 to 6 months, followed by reassessment of EF and other indications for device therapy.