280 Heart Failure: Management

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Distinctive phenotypes of presentation with diverse management targets exemplify the vast syndrome of heart failure. These range from chronic heart failure with reduced ejection fraction (HFrEF) or heart failure with preserved ejection fraction (HFpEF), acute decompensated heart failure (ADHF), and advanced heart failure. Early management evolved from symptom control to disease-modifying therapy in HFrEF with the advent of renin-angiotensin-aldosterone system (RAAS)–directed therapy, beta receptor antagonists, mineralocorticoid receptor antagonists, cardiac resynchronization therapy, and implantable cardio-defibrillators. However, similar advances have been elusive in the syndromes of HFpEF and ADHF, which have remained devoid of convincing therapeutic advances to alter their natural history. In advanced heart failure, a stage of disease typically encountered in HFrEF, the patient remains markedly symptomatic with demonstrated refractoriness or inability to tolerate full-dose neurohormonal antagonism, often requires escalating doses of diuretics, and exhibits persistent hyponatremia and renal insufficiency with frequent episodes of heart failure decompensation requiring recurrent hospitalizations. Such individuals are at the highest risk of sudden or progressive pump failure–related deaths (Chap. 281). In contrast, early-stage asymptomatic left ventricular dysfunction is amenable to preventive care, and its natural history is modifiable by neurohormonal antagonism (not further discussed).

HEART FAILURE WITH PRESERVED EJECTION FRACTION

GENERAL PRINCIPLES

Therapeutic targets in HFpEF include control of congestion, stabilization of heart rate and blood pressure, and efforts at improving exercise tolerance. Addressing surrogate targets, such as regression of ventricular hypertrophy in hypertensive heart disease, and use of lusitropic agents, such as calcium channel blockers and beta receptor antagonists, have been disappointing. Experience has demonstrated that lowering blood pressure alleviates symptoms more effectively than targeted therapy with specific agents.

CLINICAL TRIALS IN HFpEF

The Candesartan in Heart Failure—Assessment of Mortality and Morbidity (CHARM) Preserved study showed a statistically significant reduction in hospitalizations but no difference in all-cause mortality in patients with HFpEF who were treated with the angiotensin receptor blocker (ARB), candesartan. Similarly, the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial demonstrated no differences in meaningful endpoints in such patients treated with irbesartan. An earlier analysis of a subset of the Digitalis Investigation Group (DIG) trial found no role for digoxin in the treatment of HFpEF. In the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) trial of nebivolol, a vasodilating beta blocker, the subgroup of elderly patients with prior hospitalization and HFpEF did not appear to benefit in terms of all-cause or cardiovascular mortality. Much smaller mechanistic studies in the elderly with the angiotensin-converting enzyme inhibitor (ACEI) enalapril showed no effect on peak exercise oxygen consumption, 6-minute walk distance, aortic distensibility, left ventricular mass, or peripheral neurohormone expression.

NOVEL TARGETS

A small trial demonstrated that the phosphodiesterase-5 inhibitor *sildenafil* improved filling pressures and right ventricular function in a cohort of HFpEF patients with pulmonary venous hypertension. This finding led to the phase II trial, Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX), in HFpEF patients (left ventricular ejection fraction [LVEF] >50%) with New York Heart Association (NYHA) functional class II or III symptoms, who received sildenafil at 20 mg three times daily for 3 months, followed by 60 mg three times daily for another 3 months, compared with a placebo. There was no improvement in functional capacity, quality of life, or other clinical and surrogate parameters. Conceptually targeting myocardial fibrosis in HFpEF, the large-scale Aldosterone Antagonist Therapy in Adults with Preserved Ejection Fraction Congestive Heart Failure (TOPCAT) trial has been completed. This trial demonstrated no improvement in the primary composite end-point, but did show a secondary signal of benefit on HF hospitalizations, counterbalanced, however, by an increase in adverse effects, particularly hyperkalemia. However, pessimism has been generated by the negative outcome of the Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-DHF) study wherein *spironolactone* improved echocardiographic indices of diastolic dysfunction but failed to improve exercise capacity, symptoms, or quality-of-life measures. A unique molecule that hybridizes an *ARB with an endopeptidase inhibitor*, LCZ696, increases the generation of myocardial cyclic guanosine 3′,5′-monophosphate, enhances myocardial relaxation, and reduces ventricular hypertrophy. This dual blocker has been shown to reduce circulating natriuretic peptides and reduce left atrial size to a significantly greater extent than valsartan alone in patients with HFpEF.

CLINICAL PEARLS

Even as efforts to control hypertension in HFpEF are critical, evaluation for and correction of underlying ischemia may be beneficial. Appropriate identification and treatment of sleep-disordered breathing should be strongly considered. Excessive decrease in preload with vasodilators may lead to underfilling the ventricle and subsequent hypotension and syncope. Some investigators have suggested that the exercise intolerance in HFpEF is a manifestation of chronotropic insufficiency and that such aberrations could be corrected with use of rate responsive pacemakers, but this remains an inadequately investigated contention (Fig. 280-1).

ACUTE DECOMPENSATED HEART FAILURE

GENERAL PRINCIPLES

ADHF is a heterogeneous clinical syndrome most often resulting in need for hospitalization due to confluence of interrelated abnormalities of decreased cardiac performance, renal dysfunction, and alterations in vascular compliance. Admission with a diagnosis of ADHF is associated with excessive morbidity and mortality, with nearly half of these patients readmitted for management within 6 months, and a high short-term (5–8% in-hospital) and long-term mortality (20% at 1 year). Importantly, long-term aggregate outcomes remain poor, with a combined incidence of cardiovascular deaths, heart failure hospitalizations, myocardial infarction, strokes, or sudden death reaching 50% at 12 months after hospitalization. The management of these patients has remained difficult and principally revolves around volume control and decrease of vascular impedance while maintaining attention to end-organ perfusion (coronary and renal).

The first principle of management of these patients is to identify and tackle known precipitants of decompensation. Identification and management of medication nonadherence and use of prescribed medicines such as nonsteroidal anti-inflammatory drugs, cold and flu preparations with cardiac stimulants, and herbal preparations, including licorice, ginseng, and ma huang (an herbal form of ephedrine now banned in most places), are required. Active infection and overt or covert pulmonary thromboembolism should be sought, identified, and treated when clinical clues suggest such direction. When possible, arrhythmias should be corrected by controlling heart rate or restoring sinus rhythm in patients with poorly tolerated rapid atrial fibrillation and by correcting ongoing ischemia with coronary revascularization or by correcting offenders such as ongoing bleeding in demand-related ischemia. A parallel step in management involves stabilization of hemodynamics in those with instability. The routine use of a pulmonary artery catheter is not recommended and should be restricted to those who respond poorly to diuresis or experience hypotension or signs and symptoms suggestive of a low cardiac output where therapeutic targets are unclear. Analysis of in-hospital registries has identified several