Advanced Heart Failure Therapies and Cardiorenal Syndrome

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Heart failure (HF) is extremely prevalent and for those with end-stage (stage D) disease, 1-year survival is only 25-50%. Several studies have captured the mortality impact of kidney disease on patients with HF, and measures of kidney function are a component of many HF risk stratification scores. The management of advanced HF complicated by cardiorenal syndrome (CRS) is challenging, and irreversible kidney failure often limits patient candidacy for advanced HF therapies, such as transplant or left ventricular assist device therapy. Thus, prompt institution of aggressive therapy is warranted in stage D HF patients with CRS to prevent irreversible kidney failure. In this chapter, we discuss the assessment and management of patients with CRS with end-stage HF. In addition to discussing medical therapy aimed at decongestion and increased cardiac inotropy, we provide a summary of temporary circulatory support devices that can be considered for those whom hospice is not desired. In all circumstances, a close collaboration between the advanced HF specialist and nephrologist is needed to achieve the best patient outcomes.

Key Words: Heart failure, Cardiorenal syndrome, LVAD, Cardiac transplant, Kidney failure

Heart failure (HF) affects over 6.5 million Americans over the age of 19 years, and the prevalence of HF is expected to increase 46% by 2030.[1,2] Several population and cohort studies have demonstrated the mortality impact of concomitant kidney dysfunction (acute and/or chronic) in HF patients with preserved ejection fraction and reduced ejection fraction.[3-10] In the subpopulation of patients with the most extreme stage of HF (stage D), the presence of kidney dysfunction often limits candidacy for advanced HF therapies, including cardiac transplant and surgically implanted mechanical circulatory support. Building on the concepts detailed in prior chapters on the pathophysiology and management of cardiorenal syndrome (CRS), this section will focus on those with advanced HF with or without various degrees of cardiogenic shock. We will review the importance of medical therapies aimed at decongestion, perfusion, and stabilizing the patient with advanced HF, as well as mechanical circulatory support options for carefully selected patients with CRS and HF.

HEART FAILURE AND PROGNOSIS

The American Heart Association and American College of Cardiology devised a classification for patients with HF, ranging from stage A (at risk for HF without structural or clinical HF) to stage D (end-stage HF)[11] (Fig 1). Those with past or current clinical HF symptoms fall into the American College of Cardiology/American Heart Association stage C HF category, while patients with recalcitrant HF despite guideline-directed therapy, biventricular pacing, and adherence to therapy fall into stage D. Kidney dysfunction is an important contributor to morbidity and mortality in those with symptomatic (stage C and D) HF, regardless of ejection fraction.

HF registries, secondary analyses of clinical trials, and cohort studies have demonstrated the important contribution of acute and/or chronic kidney dysfunction on HF mortality. The Acute Decompensated Heart Failure National Registry (ADHERE) evaluated 33,046 patient hospitalizations for HF to identify predictors of inpatient mortality.[10] The left ventricular ejection fraction (LVEF) was preserved in 46% of patients and inpatient mortality was 4.2%. A systolic blood pressure <115 mmHg, serum blood urea nitrogen (BUN) > 43 mg/dL, and/or a creatinine (Cr) > 2.75 mg/dL were found to be the strongest correlates of inpatient mortality, regardless of LVEF.[12] Patients with a BUN >43 mg/dL had a 9% mortality compared with 2.7% in those with a BUN ≤43 mg/dL. If all 3 of the aforementioned risk factors were simultaneously present in a patient, inpatient mortality averaged 22%.[12] The Studies of Left Ventricular Dysfunction (SOLVD) was a multicenter, randomized, double-blind, placebo-controlled trial evaluating the effect of the angiotensin-converting enzyme inhibitor (ACEI) enalapril on survival in patient with an LVEF <35%.[13] Ahmad *and colleagues* performed a retrospective analysis of SOLVD to further characterize the interaction between the level of kidney dysfunction and all-cause mortality in patients.[3] On multivariable analysis, reduced kidney function independently predicted death in HF (adjusted hazard ratio 1.06 per 10 mL/min/1.73 m^2 decrease in estimated glomerular filtration rate [eGFR]). Similar findings were observed in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity trial which examined the impact of the angiotensin receptor blocker (ARB) candesartan in 3 different symptomatic HF (New York Heart Association II-IV) populations: those with preserved LVEF (LVEF >40%), those with a low LVEF (LVEF <40%), and those with a low LVEF already on ACEI therapy.[14] Hillege

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and colleagues performed a secondary analysis of the combined cohorts (2680 North American patients) to further assess the prognostic value of the eGFR. Compared with HF patients with an eGFR >60 mL/min per 1.73 m^2, the adjusted risk of death was 50% and 91% higher in those with an eGFR of 45-60 and < 45 mL/min per 1.73 m^2, respectively. The prognostic value of eGFR for predicting mortality was noted in both the preserved and reduced LVEF groups. Finally, the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness trial[15,16] was a prospective, randomized study comparing the use of pulmonary artery (PA) catheter-guided therapy to clinical assessment alone in 433 patients with an LVEF ≤30% and advanced HF symptoms. A post hoc analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness trial was performed to further characterize the cardiorenal interactions in the HF population.[17] On adjusted analysis, impaired baseline (hazard ratio 1.25) and discharge (hazard ratio 1.28) eGFR, but not worsening kidney function, were associated with worse outcomes (death and/or rehospitalization) at 6 months. PA catheter-guided therapy did not impact 6-month survival, rehospitalization, length of stay, or the development of worsening kidney function in either those with (eGFR <60 mL/min) or without baseline kidney dysfunction. While a previous history of hypertension and diabetes predicted the development of worsening kidney function while inpatient, the use of intravenous vasodilator and loop diuretic dosage did not, suggesting that intrinsic kidney disease may have played a larger role in the negative prognosis.[17]

CLINICAL SUMMARY

- Acute or chronic kidney failure correlates with worse survival in patients with heart failure, irrespective of patient ejection fraction.
- In heart failure patients with cardiorenal syndrome without evidence of shock, vasodilators and diuretics, but not inotropes, are first-line therapies.
- Cardiogenic shock phenotypes often differ based on cardiomyopathy etiology; patients with shock warrant urgent stabilization with inotropes, vasopressors, and/or temporary mechanical circulatory support.
- Patients with evidence of shock often have concomitant systemic inflammatory response syndrome with microcirculatory dysfunction and improvements in kidney function can lag behind gains achieved in cardiac output with shock management.

In addition to the clinical trials outlined previously, several risk models have been developed for prognostication of mortality in HF patients with preserved ejection fraction and preserved ejection fraction.[5-9] The Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) score is one of the more robust HF risk scores.[7] The MAGGIC model was devised using data from 39,372 patients enrolled into 30 different cohort studies, and it can be used to estimate an individual's probability of dying within 1 and 3 years. Patients in the MAGGIC cohort had both reduced and preserved LVEF, and average mortality was 40% over a median follow-up of 2.5 years. The MAGGIC cohort is composed of 13 predictors of mortality (including age, LVEF, HF medication use, blood pressure), and serum creatinine is one of the strongest predictors (rate ratio for mortality 1.039 per 10 μmol/L Cr). The model has also been independently validated and demonstrated very good accuracy (C index 0.74) for mortality discrimination in HF.[18]

MANAGEMENT OF ADVANCED HEART FAILURE AND CARDIORENAL SYNDROME

In the subpopulation of patients with stage D HF, there are 4 options for management: medical therapy with diuretics and/or inotropes, mechanical circulatory support, transplant, or hospice. For many, especially those who are older or with major comorbidities including end-stage kidney failure, palliative care and/or hospice care may be the best care recommendation. However, the decision on the optimal HF management strategy for some is often unclear until appropriate cardiac support and decongestion are achieved to demonstrate if improvements in end-organ function can be achieved. This is particularly true of those patients with acute kidney dysfunction from HF (CRS type I) and those with acute worsening of chronic kidney disease due to cardiac insufficiency (CRS type II).

Categorization of patients based on volume and perfusion statuses is critical. Some patients may suffer mainly from volume overload without severe reductions in cardiac output ("warm and wet") and others may be more profoundly "low flow" with ("cold and wet") or without volume elevation ("cold and dry"). While LVEF can provide an estimate of cardiac function, LVEF is not synonymous with cardiac output, and cardiac output is not always synonymous with end-organ perfusion. Thus, even patients with preserved LVEF can have reduced cardiac output because of reduced stroke volumes in the setting of a small left ventricular (LV) chamber or restrictive filling. These features can be seen in patients with advanced hypertrophic cardiomyopathy, critical aortic stenosis, cardiac amyloidosis, and other restrictive or constrictive myopathies. In addition, elevated right-sided cardiac filling pressures can lead to renal venous congestion and reduced kidney perfusion. Patients with pulmonary hypertension, congenital heart disease, and other maladies provoking right ventricular (RV) failure can display this phenotype. When volume status and cardiac output are in doubt, right heart catheterization should be performed.

Cardiac congestion increases myocardial wall stress, which increases cardiac oxygen consumption and reduces cardiac efficiency. In the normal heart, the LV is capable of increasing contractile force and stroke volume when exposed to increased preload, a principle described by the Frank-Starling curve (Fig 2A).[19-21] In patients with HF, the Frank-Starling curve flattens, and more preload