dopamine; however, subsequent studies demonstrated a lack of long-term clinical improvement in the treatment of AHF. Meta-analysis data have demonstrated improved urine output but no significant difference in change in creatinine, rehospitalization, or mortality with low-dose dobutamine used in various clinical scenarios.[149] As discussed, the ROSE-AHF trial showed no difference in the coprimary end points of cumulative urine volume and change in serum CysC at 72 hours or any effect on the secondary end points reflective of decongestion, renal function, or clinical outcomes when a 72-hour infusion of low-dose dopamine was compared with placebo in patients with AHF.[116] Post hoc analysis demonstrated a differential effect on 72-hour cumulative urine volume in favor of dopamine in patients with LVEF ≤40% (*P*=0.029) compared with nesiritide in patients with LVEF >40% (*P*=0.001) but no differential effect in change in CysC (*P*=0.66), suggesting a worse clinical effect of low-dose dopamine in patients with HFpEF.[150] Other novel inotropes such as levosimendan (calcium-sensitizing agent and potassium channel modulator) and omecamptiv mecarbil (cardiac myosin activators) have limited data in the context of CRS.

Although progress has been made in the field of inotrope and vasodilator therapy, its long-term efficacy in the treatment of AHF and type 1 CRS is yet to be demonstrated.

RAAS Inhibition in Chronic CRS

Angiotensin-Converting Enzyme Inhibitors/ARBs

Although the importance of RAAS inhibition in slowing CKD progression is well established, there is a paucity of data on clinically relevant long-term renal end points in trials on RAAS inhibition in HF. Given the known hemodynamic (and potentially reversible) effects of angiotensin blockade, interpreting fluctuations in serum creatinine as meaningful renal end points in the context of the use of angiotensin-converting enzyme (ACE) inhibitors and ARBs poses challenges in clinical practice. The benefits of ACE inhibitors in patients with HF and renal impairment have been demonstrated in observational data[151,152] and post hoc analyses of randomized controlled trials (RCTs). These studies pertain specifically to the presence of preexisting renal impairment (type 2 or 4 CRS) in outpatient studies with HF, not to acutely decompensated subjects with CRS.

CONSENSUS demonstrated a marked reduction in HF-associated mortality and symptom burden and was characterized by a doubling of serum creatinine in 11% of subjects taking enalapril compared with those taking placebo[153] However, trends in serum creatinine rise were predominantly early and returned to within 30% of baseline values in most subjects, consistent with the known hemodynamic effects of ACE inhibitors, with the effect of concomitant diuretic use and hypotension being independent predictors of doubling of serum creatinine.[21] SOLVD (Study of Left Ventricular Dysfunction) reiterated the benefits of enalapril for HF symptoms and hospitalization reduction (LVEF <35%, serum creatinine <2.5 mg/dL) in a much larger population compared with CONSENSUS (2569 versus 253 subjects).[154] The enalapril group in SOLVD showed a 33% higher likelihood of a serum creatinine rise of >0.5 mg/dL, but no data on progression of CKD, ESKD, or doubling of creatinine were reported. A post hoc analysis of SOLVD with HF and CKD demonstrated the mortality benefits even in subjects with higher degrees of CKD.[155] The overall incidence of hyperkalemia was 6% overall with enalapril, correlating with the severity of renal dysfunction.[156] However, in a meta-analysis of 5 placebo-controlled RCTs of ACE inhibitors in HF by Flather et al,[157] drug discontinuation was rarely necessary despite higher rates of AKI in the treatment arms versus placebo in most cases. A meta-analysis of 8 trials looking at the use of RAAS inhibition in KT demonstrated a higher risk of hyperkalemia (relative risk [RR], 2.44 [95% CI, 1.53–3.9]).[158] The strength of evidence of ACE inhibitors in HF with predialytic CKD is not established given the lack of inclusion of these patients in RCTs for HF. Hospitalization and safety reporting data from the ongoing multicenter randomized controlled STOP-ACEi trial (Trial of Angiotensin-Converting Enzyme Inhibitor/Angiotensin Receptor Blocker Withdrawal in Advanced Renal Disease; ISRCTN62869767) will shed light on the consequences of ACE inhibitors in advanced CKD and related cardiorenal outcomes. Although data on ARBs in CKD and HF specifically are sparse, in a propensity score analysis of 1665 patients with HF (EF <45%) and eGFR <60 mL/min per 1.73 m^2, treatment with an ACE inhibitor or ARB was associated with significant reductions in all-cause mortality (HR, 0.68 [95% CI, 0.74–0.996]; *P*=0.04)[159] (Tables 4 and 5). The addition of ARBs to ACE inhibitors has been discouraged because of the increased risk of adverse events.[176]

Neprilysin/Renin-Angiotensin Inhibitors

Trials that looked at outcomes with the combination of renin angiotensin system blocker/neprilysin inhibition (sacubitril/valsartan and omapatrilat) provided an excellent opportunity to study the combined approach to RAAS blockade and vasodilator versus RAAS blockade alone. A recent meta-analysis analyzed data from 3 trials in HFrEF that compared combined neprilysin/RAAS inhibition with RAAS inhibition alone and included the following: IMPRESS (Inhibition of Metallo Protease by Omapatrilat in a Randomized Exercise and Symptoms Study of Heart Failure; n=573), OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events trial; n=5770), and PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; n=8399).[177] The composite outcome of death or HHF was reduced numerically in patients receiving