is also associated with increased arrhythmia, hypotension, and no beneficial effects on hard outcomes. Inotropic agents are currently indicated as bridge therapy (to either left ventricular assist device support or to transplant) or as selectively applied palliation in end-stage heart failure.

Novel inotropic agents that leverage the concept of myofilament calcium sensitization rather than increasing intracellular calcium levels have been introduced. *Levosimendan* is a calcium sensitizer that provides inotropic activity, but also possesses phosphodiesterase-3 inhibition properties that are vasodilators in action. This makes the drug unsuitable in states of low output in the setting of hypotension. Two trials, the second Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy (REVIVE II) and Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE), have tested this agent in ADHF. SURVIVE compared levosimendan with dobutamine, and despite an initial reduction in circulating B-type natriuretic peptide levels in the levosimendan group compared with patients in the dobutamine group, this drug did not reduce all-cause mortality at 180 days or affect any secondary clinical outcomes. The second trial compared levosimendan against traditional noninotropic therapy and found a modest improvement in symptoms with worsened short-term mortality and ventricular arrhythmias. Another drug that functions as a selective myosin activator, *omecamtiv mecarbil*, prolongs the ejection period and increases fractional shortening. Distinctively, the force of contraction is not increased, and as such, this agent does not increase myocardial oxygen demand. In a 600-patient trial called ATOMIC-HF (A Trial of Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure), this agent showed improvement in dyspnea scores in the highest dose cohort, but not across all enrolled patients. How this agent performs in broader populations remains uncertain. Other inotropic agents that increase myocardial calcium sensitivity through mechanisms that reduce cTnI phosphorylation or inhibit protein kinase A are being developed. (Table 280-1 depicts typical inotropic, vasodilator, and diuretic drugs used in ADHF.)

NEUROHORMONAL ANTAGONISTS

Other trials testing unique agents have yielded disappointing results in the situation of ADHF. The Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) trial of selective adenosine antagonism and the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial of an oral selective vasopressin-2 antagonist in ADHF were both negative with respect to hard outcomes.

In patients who fail to respond adequately to medical therapy, mechanical assist devices may be required. This is covered in more detail in Chap. 281.

HEART FAILURE WITH REDUCED EJECTION FRACTION

The past 50 years have witnessed great strides in the management of HFrEF. The treatment of symptomatic heart failure that evolved from a renocentric (diuretics) and hemodynamic therapy model

TABLE 280-1 INTRAVENOUS THERAPY IN ACUTE DECOMPENSATED HEART FAILURE

Drug Class	Generic Drug	Usual Dosing	Special Caution	Comments
Inotropic therapy				Use in hypotension, end-organ hypoperfusion, or shock states
	Dobutamine	2–20 μg/kg per min	Increased myocardial oxygen demand, arrhythmia	Short acting, an advantage; variable efficacy in presence of beta blockers (requires higher doses); clinical tolerance to prolonged infusions; concerns with hypersensitivity carditis (rare)
	Milrinone	0.375–0.75 μg/kg per min	Hypotension, arrhythmia	Decrease dose in renal insufficiency; avoid initial bolus; effectiveness retained in presence of beta blockers
	Levosimendan	0.1 μg/kg per min, range, 0.05–0.2 μg/kg per min	Hypotension, arrhythmia	Long acting; should not be used in presence of low blood pressure; similar effectiveness as dobutamine but effectiveness retained in presence of beta blockers
	Omecamtiv Mecarbil	N/A	*In trials	Increases contractility without increasing myocardial oxygen demand; in confirmatory trials
Vasodilators				Use in presence of pulmonary congestion for rapid relief of dyspnea, in presence of a preserved blood pressure
	Nitroglycerine	10–20 μg/min, increase up to 200 μg/min	Headache, flushing, tolerance	Most common vasodilator but often underdosed; effective in higher doses
	Nesiritide	Bolus 2 μg/kg and infusion at 0.01 μg/kg per min	Hypotension	Decrease in blood pressure may reduce renal perfusion pressure; bolus may be avoided since it increases hypotension predilection
	Nitroprusside	0.3 μg/kg per min titrated to 5 μg/kg per min	Thiocyanate toxicity in renal insufficiency (>72 hours)	Requires arterial line placement for titration for precise blood pressure management and prevention of hypotension
	Serelaxin	N/A (tested at 30 μg/kg per d)	Baseline blood pressure should be >125 mmHg	Not widely commercially available; undergoing confirmatory trials
Diuretics				First line of therapy in volume overload with congestion; may use bolus or continuous dosing; initial low dose (1× home dose) or high dose (2.5 × home dose) equally effective with higher risk of renal worsening with higher dose
	Furosemide	20–240 mg daily	Monitor for electrolyte loss	In severe congestion, use intravenously and consider continuous infusion (not trial supported)
	Torsemide	10–100 mg daily	Monitor for electrolyte loss	High bioavailability, can be given orally; anecdotally more effective in advanced heart failure states if furosemide less bioavailable (due to gut congestion)
	Bumetanide	0.5–5 mg daily	Monitor for electrolyte loss	Can be used orally; intermediate bioavailability
	Adjuvant diuretics for augmentation	n/a	Metolazone, chlorthalidone, spironolactone, acetazolamide	Acetazolamide is useful in presence of alkalosis; metolazone given in 2.5- to 10-mg doses; causes severe electrolyte imbalance; spironolactone is useful in presence of severe hypokalemia and normal renal function