monotherapy for either group. Thus, the initial clinical strategy should be to use a two-drug combination first (ACEI and beta blocker; if beta blocker intolerant, then ACEI and ARB; if ACEI intolerant, then ARB and beta blocker). In symptomatic patients (NYHA class II–IV), an aldosterone antagonist should be strongly considered, but four-drug therapy should be avoided.

A recent trial called the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) tested a direct renin inhibitor, aliskiren, in addition to other heart failure medications, within a week after discharge from a hospitalization for decompensated HFrEF. No significant difference in cardiovascular death or hospitalization at 6 or 12 months was noted. Aliskiren was associated with a reduction in circulating natriuretic peptides, but any disease-modifying effect was overcome by excessive adverse events including hyperkalemia, hypotension, and renal dysfunction.

ARTERIOVENOUS VASODILATION

The combination of hydralazine and nitrates has been demonstrated to improve survival in HFrEF. Hydralazine reduces systemic vascular resistance and induces arterial vasodilatation by affecting intracellular calcium kinetics; nitrates are transformed in smooth muscle cells into nitric oxide, which stimulates cyclic guanosine monophosphate production and consequent arterial-venous vasodilation. This combination improves survival, but not to the magnitude evidenced by ACEIs or ARBs. However, in individuals with HFrEF unable to tolerate renin-angiotensin-aldosterone–based therapy for reasons such as renal insufficiency or hyperkalemia, this combination is preferred as a disease-modifying approach. A trial conducted in self-identified African Americans, the African-American Heart Failure Trial (A-Heft), studied a fixed dose of isosorbide dinitrate with hydralazine in patients with advanced symptoms of HFrEF who were receiving standard background therapy. The study demonstrated benefit in survival and hospitalization recidivism in the treatment group. Adherence to this regimen is limited by the thrice-daily dosing schedule. Table 280-2 lists the common neurohormonal and vasodilator regimens for HFrEF.

HEART RATE MODIFICATION

Ivabradine, an inhibitor of the I_f current in the sinoatrial node, slows the heart rate without a negative inotropic effect. The Systolic Heart Failure Treatment with Ivabradine Compared with Placebo Trial (SHIFT) was conducted in patients with class II or III HFrEF, a heart rate >70 beats/min, and history of hospitalization for heart failure during the previous year. Ivabradine reduced hospitalizations and the combined endpoint of cardiovascular-related death and heart failure hospitalization. The study population was not necessarily representative of North American patients with HFrEF since, with a few exceptions, most did not receive internal cardioverter-defibrillation or cardiac resynchronization therapy and 40% did not receive a mineralocorticoid receptor antagonist. Although 90% received beta blockers, only a quarter were on full doses. Whether this agent, now available outside the United States, would have been effective in patients receiving robust, guideline-recommended therapy for heart failure remains enigmatic. In the 2012 European Society of Cardiology guidelines for the treatment of heart failure, ivabradine was suggested as second-line therapy before digoxin is considered in patients who remain symptomatic after guideline-based ACEIs, beta blockers, and mineralocorticoid receptor antagonists and with residual heart rate >70 beats/min. Another group in whom potential benefit may be expected includes those unable to tolerate beta blockers.

DIGOXIN

Digitalis glycosides exert a mild inotropic effect, attenuate carotid sinus baroreceptor activity, and are sympathoinhibitory. These effects decrease serum norepinephrine levels, plasma renin levels, and possibly aldosterone levels. The DIG trial demonstrated a reduction in heart failure hospitalizations in the treatment group but no reduction in mortality or improvement in quality of life. Importantly, treatment with digoxin resulted in a higher mortality rate in women than men. Furthermore, the effects of digoxin in reducing hospitalizations were lower in women than in men. It should be noted that low doses of digoxin are sufficient to achieve any potentially beneficial outcomes, and higher doses breach the therapeutic safety index. Although digoxin levels should be checked to minimize toxicity and although dose reductions are indicated for higher levels, no adjustment is made for low levels. Generally, digoxin is now relegated as therapy for patients who remain profoundly symptomatic despite optimal neurohormonal blockade and adequate volume control.

ORAL DIURETICS

Neurohormonal activation results in avid salt and water retention. Loop diuretic agents are often required because of their increased potency,

TABLE 280-2 PHARMACOLOGIC THERAPY AND TARGET DOSES IN HEART FAILURE WITH REDUCED EJECTION FRACTION

Drug Class	Generic Drug	Mean Daily Dose in Clinical Trials (mg)	Initiation (mg)	Target Dose (mg)
Angiotensin-Converting Enzyme Inhibitors				
	Lisinopril	4.5–33	2.5–5 qd	20–35 qd
	Enalapril	17	2.5 bid	10–20 bid
	Captopril	123	6.25 tid	50 tid
	Trandolapril	N/A	0.5–1 qd	4 qd
Angiotensin Receptor Blockers				
	Losartan	129	50 qd	150 qd
	Valsartan	254	40 bid	160 bid
	Candesartan	24	4–8 qd	32 qd
Aldosterone Antagonists				
	Eplerenone	42.6	25 qd	50 qd
	Spironolactone	26	12.5–25 qd	25–50 qd
Beta Blockers				
	Metoprolol succinate CR/XL	159	12.5–25 qd	200 qd
	Carvedilol	37	3.125 bid	25–50 bid
	Bisoprolol	8.6	1.25 qd	10 qd
Arteriovenous Vasodilators				
	Hydralazine isosorbide dinitrate	270/136	37.5/20 tid	75/40 tid
	Fixed-dose hydralazine/isosorbide dinitrate	143/76	37.5/20 qid	75/40 qid