

TABLE 5-4 MEDICATIONS USED AND APPROVED FOR HEART FAILURE

DRUG	INITIAL DOSES	MAXIMUM DOSES	MEAN DOSES ACHIEVED IN CLINICAL TRIALS*
ANGIOTENSIN-CONVERTING ENZYME INHIBITORS			
Captopril	6.25 mg tid	50 mg tid	122.7 mg/day (421)
Enalapril	2.5 mg bid	10 to 20 mg bid	16.6 mg/day (412)
Fosinopril	5 to 10 mg qd	40 mg qd	—
Lisinopril	2.5 to 5 mg qd	20 to 40 mg qd	32.5 to 35.0 mg/day (444)
Perindopril	2 mg qd	8 to 16 mg qd	—
Quinapril	5 mg bid	20 mg bid	—
Ramipril	1.25 to 2.5 mg qd	10 mg qd	—
Trandolapril	1 mg qd	4 mg qd	—
ANGIOTENSIN-RECEPTOR BLOCKERS			
Candesartan	4 to 8 mg qd	32 mg qd	24 mg/day (419)
Losartan	25 to 50 mg qd	50 to 150 mg qd	129 mg/day (420)
Valsartan	20 to 40 mg bid	160 mg bid	254 mg/day (109)
ALDOSTERONE ANTAGONISTS			
Spironolactone	12.5 to 25 mg qd	25 mg qd or bid	26 mg/day (424)
Eplerenone	25 mg qd	50 mg qd	42.6 mg/day (445)
β-BLOCKERS			
Bisoprolol	1.25 mg qd	10 mg qd	8.6 mg/day (118)
Carvedilol	3.125 mg bid	50 mg bid	37 mg/day (446)
Carvedilol CR	10 mg qd	80 mg qd	—
Metoprolol succinate extended release (metoprolol CR/XL)	12.5 to 25 mg qd	200 mg qd	159 mg/day (447)
HYDRALAZINE AND ISOSORBIDE DINITRATE			
Fixed dose combination (423)	37.5 mg hydralazine and 20 mg isosorbide dinitrate tid	75 mg hydralazine and 40 mg isosorbide dinitrate tid	≈175 mg hydralazine/90 mg isosorbide dinitrate qd
Hydralazine and isosorbide dinitrate (448)	Hydralazine, 25 to 50 mg tid or qid, and isosorbide dinitrate, 20 to 30 mg tid or qid	Hydralazine, 300 mg qd in divided doses, and isosorbide dinitrate, 120 mg qd in divided doses	—

Modified from Yancy CW, Jessup M, Bozkurt B, et al: 2013 ACCF/AHA guidelines for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 62:e147–e239, 2013.

*Number of patients enrolled is given in parentheses.

Carvedilol is the least β -selective of the three drugs, and bisoprolol and metoprolol succinate are much more β_1 -selective. Carvedilol is also an antioxidant and an α -blocker, which may result in lowered blood pressure and improved endothelial function and may be beneficial in patients with HF. Compared with bisoprolol or metoprolol, carvedilol can cause hypotension and may cause more bronchospasm in patients with underlying lung disease. According to the American College of Cardiology and American Heart Association (ACC/AHA) 2013 HF guidelines, use of one of the three β -blockers proven to reduce mortality (i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate) is recommended for all patients with current or prior symptoms of HFrEF (LVEF <40%), unless contraindicated, to reduce morbidity and mortality.

Aldosterone Receptor Antagonists

After initiating first-line therapy with ACE inhibitors and β -blockers, the next class of beneficial agents is aldosterone receptor antagonists. Two agents studied are spironolactone and eplerenone. Aldosterone receptor antagonists are weak diuretics and have important antifibrotic properties. Use of aldosterone receptor antagonists is a class I indication according to the ACC/AHA 2013 HF guidelines, and they are recommended for patients with NYHA class II through IV HF and who have an LVEF of 35% or less, unless otherwise contraindicated, to reduce morbidity and mortality. The landmark Randomized Aldactone Evaluation Study (RALES), which evaluated spironolactone in

patients with NYHA class III or IV HF with an EF less than 35% demonstrated a 30% relative risk reduction for death from progressive HF and sudden death from cardiac causes. Eplerenone was studied in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial, which evaluated patients with NYHA class II symptoms and found a relative risk reduction of 37% for the primary end point of death and hospital readmissions.

Hydralazine and Nitrates

Hydralazine in combination with oral nitrates has reduced mortality rates for African American patients with ongoing symptomatic HF after institution of the three regimens previously described (i.e., ACE inhibitors or ARBs, β -blockers, and aldosterone receptor antagonists). This combination provides an alternative for patients who are ACE inhibitor intolerant or may require additional therapy for blood pressure control. Although this drug combination has not proved to be efficacious in non-African Americans, all patients who cannot tolerate ACE inhibitors or ARBs may use this regimen.

The ACC/AHA HF guidelines class I recommendation states that the combination of hydralazine and isosorbide dinitrate can be used to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III through IV HFrEF receiving optimal therapy with ACE inhibitors and β -blockers, unless contraindicated. The class IIa recommendation states that a combination of hydralazine and