

THE PHARMACOLOGIC MANAGEMENT OF CHRONIC HEART FAILURE (HF)

Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel (PBM-MAP)

Guideline Summary

UPDATE 2003

RECOMMENDATIONS WITH THE HIGHEST EVIDENCE: The highest evidence for recommendations is A, defined as "a strong recommendation based on randomized controlled trials that the intervention is always indicated and acceptable."

Pharmacotherapy recommendations for patients with Stage B HF are as follows:

1. Patients with Stage B HF should receive post-myocardial infarction (MI) treatment with an angiotensin-converting enzyme inhibitor (ACEI) and β -adrenergic blocker, regardless of the presence of left ventricular systolic dysfunction, to prevent future development of HF and improve overall survival. [R = A]
2. It is also recommended that patients with evidence of left ventricular systolic dysfunction who are without symptoms should be treated with an ACEI and a β -blocker. [R = A]

Pharmacotherapy recommendations for patients with HF in Stage C include:

3. A diuretic should be used in the treatment of patients with signs of fluid overload. [R = A]
4. All patients should be treated with an ACEI unless contraindicated or not tolerated. [R = A]
5. A β -adrenergic blocker should be used in conjunction with an ACEI in all patients who are considered stable (i.e., minimal or no signs of fluid overload or volume depletion and not in an intensive care unit), unless contraindicated or not tolerated. [R = A]
6. Digoxin should be used in patients whose symptoms persist despite treatment with an ACEI, a β -blocker, and a diuretic. [R=A] Digoxin reduces symptoms associated with HF and decreases the risk for hospitalizations due to HF but does not improve mortality.

Actions that may not be useful/effective or may be harmful (Grade D) include:

1. Use an AIIRA instead of an ACEI in patients who are able to tolerate an ACEI [R = D]
2. Use an AIIRA before a β -adrenergic blocker in patients who are unable to tolerate an ACEI [R = D]
3. Use HYD/ISDN to reduce mortality in patients who have not been given a trial of an ACEI and/or β -adrenergic blocker [R = D]
4. Use of digoxin in patients in normal sinus rhythm who are not on an ACEI and β -adrenergic blocker [R = D]
5. Use of digoxin to improve survival in patients with HF [R = D]

EXECUTIVE SUMMARY

- Treatment of chronic heart failure (HF) is based upon the classification of HF into four stages:

DISEASE PROGRESSION
Stage A: Patients who are high risk for developing HF, but do not have structural heart disease
Stage B: Patients who have structural damage to the heart, but have not developed symptoms
Stage C: Patients with past or current HF symptoms and evidence of structural heart damage
Stage D: Patients with end-stage disease, requiring special interventions

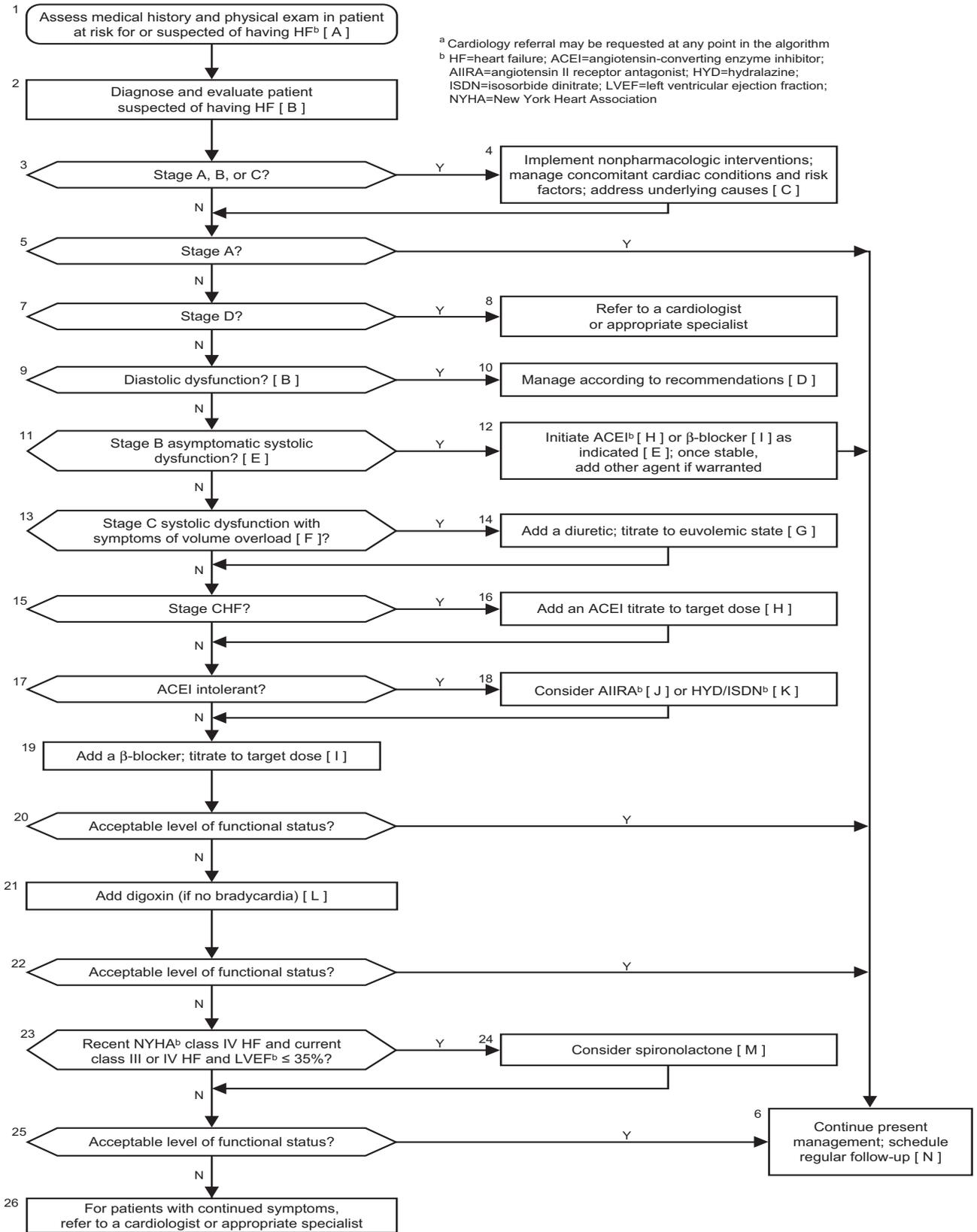
Adapted from Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). 2001. American College of Cardiology Web site. Available at: http://www.acc.org/clinical/guidelines/failure/hf_index.htm

- Nonpharmacologic therapy includes abstaining from alcohol and tobacco, limiting dietary sodium, reducing weight if appropriate, and participating in exercise training programs.
- Pharmacologic treatment has been shown to improve symptoms, increase functional capacity, improve quality of life, slow disease progression, decrease need for hospitalization, and prolong survival.
- Increase pharmacologic therapy as tolerated in an effort to achieve target doses.
- Schedule regular follow-up and assess for change in functional status.
- Referral to a cardiologist or other appropriate specialist may be requested at any point in the care of the patient. Some facilities may have interdisciplinary HF disease management clinics to provide continuity of care for patients with HF.

KEY ELEMENTS FOR PHARMACOLOGIC MANAGEMENT OF HF

- Stage A, B, or C: Implement non-pharmacologic interventions, manage concomitant cardiac conditions and risk factors, and address underlying causes; Stage D: Refer to a cardiologist or appropriate specialist.
- Stage B: Initiate angiotensin-converting enzyme inhibitor (ACEI) or β -blocker as indicated; once stable, add other agent if warranted.
- Stage C:
 - A diuretic should be used in the treatment of patients with signs of fluid overload.
 - An ACEI should be initiated and titrated to target dose as tolerated, unless contraindicated or not tolerated.
 - A β -adrenergic blocker should be used in conjunction with an ACEI in all patients with stable HF, unless contraindicated or not tolerated.
 - Digoxin should be used in patients with HF whose symptoms persist despite treatment with an ACEI, a β -blocker, and a diuretic.
 - An angiotensin II receptor antagonist (AIIIRA) may be considered as an alternative for patients who cannot tolerate an ACEI due to cough.
 - Hydralazine and isosorbide dinitrate (HYD/ISDN) may be considered in patients with contraindications to or who cannot tolerate an ACEI due to hypotension, renal insufficiency, or possibly, angioedema.
 - Low dose spironolactone should be considered in patients with recent NYHA class IV HF and current class III or IV symptoms and left ventricular ejection fraction (LVEF) $\leq 35\%$, unless contraindications exist.

Algorithm: Pharmacologic Management of Patients with Heart Failure^a



Signs & Symptoms of Heart Failure (Annotation A)

Symptoms	Signs
Shortness of breath (SOB)	Tachycardia
Cough	Increasing weight
Orthopnea	Jugular venous distention (JVD) or hepatojugular reflux
Paroxysmal nocturnal dyspnea (PND)	Presence of S ₃ (third heart sound)
Dyspnea on exertion (DOE)	Laterally displaced apical impulse
Edema	Pulmonary crackles or wheezes
Fatigue	Hepatomegaly
Weight gain (anorexia may be seen in advanced HF)	Peripheral edema

It is the intent of the ACC/AHA recommendations to be used in conjunction with the New York Heart Association (NYHA) functional classification that estimates the severity of disease based on patient symptoms.

NYHA Functional Classification (Annotation B)

Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or angina.
Class II: Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
Class IV: Unable to carry on any physical activity without discomfort. Symptoms are present at rest. With any physical activity, symptoms increase.

Adapted from the Criteria Committee of the American Heart Association. 1994 revisions to the classification of functional capacity and objective assessment of patients with disease of the heart. Circulation 1994;90:644-5.

Recommendations for Nonpharmacologic Therapy, Management of Concomitant Cardiac Conditions and Risk Factors, and Treatment of Underlying Causes (Annotation C)

1. Control risk factors
 - a) Control hypertension (HTN)
 - b) Treat hyperlipidemia
 - c) Encourage smoking cessation
 - d) Discourage alcohol consumption and illicit drug use
 - e) Use of an ACEI in patients with a history of coronary artery disease, peripheral vascular disease, or stroke; or DM plus at least one additional cardiovascular risk factor
 - f) Control ventricular rate in patients with supraventricular tachyarrhythmias
 - g) Treat thyroid disorders
 - h) Treat diabetes mellitus (DM)
 - i) Manage atherosclerotic disease
2. To maintain fluid balance
 - a) Restrict daily sodium intake to 2 to 3 grams per day (1 gram sodium = 2.5 grams salt).
 - b) Daily weight measurements to assess for fluid retention.
 - c) Fluid restriction is generally needed only to correct a clinically important hyponatremia rather than being a generalized treatment for HF; however, high fluid intake (e.g., > 3 liters per day) should be discouraged.
3. Weight loss if body mass index ≥ 30 kg/m² (obesity) after adjustment for fluid retention.
4. Moderate exercise (in conjunction with drug therapy) to improve physical conditioning in patients with stable HF, Stage C. Patients should be referred to a specialist if the clinician is not comfortable designing an exercise program for the patient with HF.

Specific Recommendations for Oral Medications Used in the Treatment of HF

Diuretic	Dose Range	Comments/Cautions
<u>Loop diuretic</u> Furosemide Bumetanide Torsemide	range = 20-400 ^a mg/d range = 0.5-10 mg/d range = 10-200 mg/d	<ul style="list-style-type: none"> • Loop diuretics are more effective than thiazide diuretics in patients with severe volume overload • Usually administered once daily unless higher doses (e.g., furosemide > 160 mg/d) are needed, then more frequent daily dosing should be considered • Effective in patients with CrCl < 30 mL/min
<u>Thiazide diuretic</u> Hydrochlorothiazide (HCTZ) Chlorthalidone	range = 12.5-50 mg/d range = 12.5-50 mg/d	<ul style="list-style-type: none"> • Lose effectiveness in patients with CrCl < 30 mL/min; change to loop diuretic • Monitor serum K⁺ at 1 to 2 weeks after initiating therapy or changing dose, then every few months; more frequently if patient is also on digoxin or has demonstrated hypokalemia • Add potassium supplement or low dose potassium-sparing diuretic^b if the patient becomes hypokalemic (serum K⁺ < 4.0 mEq/L) • Use cautiously in poorly controlled DM, symptomatic benign prostatic hyperplasia, or in patients with increased risk of volume depletion
<u>Thiazide-related</u> Indapamide Metolazone^c Zaroxolyn [®] Mykrox [®]	range = 2.5-5 mg/d range = 5-20 ^a mg/d ^d range = 0.5-1 mg/d ^d	<ul style="list-style-type: none"> • Reserve indapamide for patients with CrCl < 25 mL/min • Reserve metolazone for intermittent use as an adjunct to loop diuretics for diuresis in patients with HF or in patients with CrCl < 25 mL/min; thiazide/loop combinations are also effective and are less expensive
ACEI (Annotation H)	Initial dose (Target doses ^e)	Comments/Cautions
Captopril^f	6.25-12.5 mg tid (50 mg tid)	<ul style="list-style-type: none"> • Start with lower or less frequent doses in patients with renal insufficiency
Enalapril	2.5 mg bid (10-20 mg bid)	<ul style="list-style-type: none"> • CrCl < 30 mL/min, initial dose 2.5 mg qd
Fosinopril	5-10 mg qd (20-40 mg bid)	<ul style="list-style-type: none"> • Start with 5 mg qd if moderate to severe renal failure
Lisinopril	2.5-5 mg qd (20-40 mg qd)	<ul style="list-style-type: none"> • CrCl < 30 mL/min, initial dose 2.5 mg qd
Also refer to PBM-MAP Criteria for use of ramipril, available at www.vapbm.org or http://vaww.pbm.med.va.gov		<p style="text-align: center;"><u>Contraindications to all ACEI</u></p> <ul style="list-style-type: none"> • History of angioedema or other documented hypersensitivity to an ACEI; Bilateral renal artery stenosis or renal artery stenosis in a solitary kidney; Symptomatic hypotension; Pregnancy; Serum potassium > 5.5 mEq/L that cannot be reduced

Specific Recommendations for Oral Medications Used in the Treatment of HF

β -Blocker (Annotation I)	Dose Range	Comments/Cautions
Cardioselective Metoprolol XL⁹ Bisoprolol α & β antagonist Carvedilol^h	Initial 12.5-25 mg qd; double dose every 2 wks to target dose 200 mg qd (or as tolerated) Initial 1.25 mg qd; increase by 1.25 mg q wk until 5 mg qd, then increase by 2.5 mg q 4 wks to target 10 mg qd Initial 3.125 mg bid, (patients \geq 85 kg may be titrated to 50 mg bid); titrate at minimum of q 2 wks to target 25-50 mg bid	<ul style="list-style-type: none"> • Agents listed are those with positive outcomes in systolic dysfunction • Cardioselectivity is dose related • Caution should be used when using β-adrenergic blockers in patients with systolic dysfunction • Low initial doses should be implemented • Use slow gradual increases in the dosage • Effects are generally seen in 3-12 months • Do not use in patients with bronchospastic disease, symptomatic bradycardia, or advanced heart block without a pacemaker • Should not be abruptly discontinued • Carvedilol should be given with food to reduce the incidence of orthostatic hypotension; consider separating the ACEI, adjusting dose of diuretic, or temporary ACEI dose reduction if dizziness occurs
AIIIRA (Annotation J)	Dose Range	Comments/Cautions
Candesartan	4-32 mg divided qd-bid	<ul style="list-style-type: none"> • All AIIIRAs are contraindicated in 2nd and 3rd trimesters pregnancy due to potential neonatal/fetal morbidity and death • Use AIIIRAs with caution in patients with renal artery stenosis • Initiate losartan at 25 mg and use telmisartan with caution in patients with hepatic impairment • Consider lower doses in patients with intravascular volume depletion • An AIIIRA should be used with caution, if at all, in patients who have previously experienced angioedema with an ACEI
Eprosartan	400-800 mg divided qd-bid	
Irbesartan	75-300 mg qd	
Losartan	25-100 mg divided qd-bid	
Olmesartan	5-40 mg qd	
Telmisartan	20-80 mg qd	
Valsartan	80-320 mg qd (Val-HeFT divided bid)	
Drug (Annotation K)	Dose Range	Comments/Cautions
Hydralazine	Initial= 75 mg/d (3-4 divided doses); Range= 75-300 mg/d (3-4 divided doses); (ave. dose V-HeFT II 200 mg/d)	<ul style="list-style-type: none"> • Monitor adverse effects: dizziness, headache, lupus-like syndrome, nausea, tachycardia, postural hypotension • Advise patient to take with food
Isosorbide dinitrate	Initial= 30 mg/d (3 divided doses); Range= 30-160 mg/d (3 divided doses); (ave. dose V-HeFT II 100 mg/d)	<ul style="list-style-type: none"> • Monitor adverse effects: flushing, headache, postural hypotension, rash • May cause an increase in ocular pressure; caution with presence of glaucoma

Specific Recommendations for Oral Medications Used in the Treatment of HF

Drug	Dose Range	Comments/Cautions
Digoxin (Annotation L)	Initial = 0.125 mg qd-qod Usual maintenance 0.125-0.25 mg/day	Trough serum digoxin levels should be monitored if: <ul style="list-style-type: none"> • HF worsens or renal function deteriorates • Signs of toxicity develop (e.g., confusion, nausea, vomiting, abdominal pain, diarrhea, anorexia, fatigue, arrhythmias, visual disturbances) • Dose adjustments are made • Medications added that affect digoxin concentration (e.g., quinidine, verapamil, amiodarone, antibiotics, anticholinergics)
Spironolactone (Annotation M)	Initial = 25 mg qd Range = 25 mg qod- 50 mg qd	<ul style="list-style-type: none"> • Potential side effects include gastrointestinal, gynecomastia, hyperkalemia, menstrual irregularities • Hyperkalemia occurs more frequently in patients on K⁺ supplements and patients with renal insufficiency • K⁺ supplements should be avoided with spironolactone unless hypokalemia develops • Use with caution in patients with renal insufficiency • Schedule follow-up electrolytes (check K⁺ q 4 wks for first 3 months, then q 3 months for first yr and then q 6 months) and renal function after initiation and dose adjustments • Use with caution in patients receiving ACEIs due to the potential for hyperkalemia

Bold = National Formulary item

Adapted from Hebel SK, ed. *Drug Facts and Comparisons*, St. Louis, Missouri: Facts and Comparisons Inc., 2000; *Heart failure: Management of patients with left ventricular systolic dysfunction. Clinical Practice Guideline, No. 11*. Rockville, MD. U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 94-0613; McEvoy GK, ed. *American Hospital Formulary Service Drug Information*, Bethesda, MD: American Society of Health-System Pharmacists, Inc., 2002.

^a Higher doses have been effective and tolerated

^b Unless patients have persistent hypokalemia or are being treated with low dose spironolactone for severe HF (Annotation M), potassium-sparing diuretics should not be used in combination with ACEI (Appendix 1)

^c The brand names of metolazone are not bioequivalent, therefore doses vary

^d Intermittent use recommended once the response of the patient is stabilized

^e Target doses for HF were derived from major trials and AHCPR guidelines. Excluding captopril and enalapril, doses for HF reflect doses used to increase exercise tolerance in HF patients

^f One hour before meals, on an empty stomach

^g FDA approved for the treatment of stable, NYHA class II or III HF

^h Carvedilol is FDA approved for the treatment of mild-moderate HF stabilized on standard therapy

PATIENT EDUCATION AND FOLLOW-UP (ANNOTATION N)

- Proper education of patients and their family is imperative so that they may have an understanding of the cause of HF, prognosis, therapy, dietary restrictions, risk factor modification, activity, adherence, and the signs and symptoms of recurrent HF.
- Nonpharmacologic therapy including abstaining from alcohol and tobacco, limiting dietary sodium, reducing weight if appropriate, and participating in exercise training programs should be discussed with the patient.
- Instruct patient and/or caregiver on daily weight measurements to assess for fluid retention.
- Inquiry should be made as to the patient's adherence to the medication regimen and nonpharmacologic measures, and adverse effects to therapy.
- Patients should be scheduled for regular follow-up and assessed for change in functional status.
- Some facilities may have interdisciplinary HF disease management clinics to provide continuity of care for patients with HF