
Pharmacy Benefits Management
Strategic Healthcare Group and
the Medical Advisory Panel

# The Pharmacologic Management of Chronic Heart Failure

Department of Veterans Affairs
Veterans Health Administration
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# THE PHARMACOLOGIC MANAGEMENT OF CHRONIC HEART FAILURE

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# The Medical Advisory Panel for the Pharmacy Benefits Management Strategic Healthcare Group

## Mission

The mission of the Medical Advisory Panel (MAP) for Pharmacy Benefits Management (PBM) includes the development of evidence-based pharmacologic management guidelines for improving quality and providing best-value patient care.

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# Pharmacy Benefits Management (PBM)
# Strategic Healthcare Group (SHG)

VHA's PBM-SHG has been directed by the Under Secretary for Health to coordinate the development of recommendations for the pharmacologic management of common diseases treated within the VA, establish a national level VA formulary, and to manage pharmaceutical costs, utilization, and measure outcomes as they apply to patient care. The MAP provides support and direction to the PBM staff, located in Hines, Illinois.

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# Development Process

## Summary

This consensus and evidence-based document on the pharmacologic management of patients with chronic heart failure (HF) is intended to update the April 2001 publication of the PBM-MAP The Pharmacologic Management of Congestive Heart Failure. Whenever possible, the PBM and MAP relies upon evidence-based, multidisciplinary, nationally recognized consensus statements for the basis of VA guidance. Relevant literature is reviewed and assessed with consideration given to the VA population. Draft documents are sent to the field for comments prior to being finalized.

## Development Process and Sources of Information

Development of the recommendations included reference to the following consensus document: *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.*

The algorithm and annotations are in part based on the HF recommendations developed in 1997 and updated 2001. To update this information, the literature following the publication of the 2001 document was searched (search queried articles January 2001 to November 2002). A literature search of the National Library of Medicine's MEDLINE/PubMed database and Evidence Based Medicine reviews available on OVID was conducted. The following search terms were used: heart failure, angiotensin-converting enzyme inhibitor, β-adrenergic blocker, digoxin, spironolactone, angiotensin receptor blocker, calcium channel blocker, diastolic dysfunction, side effect, clinical trial, review, meta-analysis. The literature was limited to adult human subjects and articles published in the English language. The bibliographies of articles and consensus documents were reviewed for additional relevant literature. In updating the December 2002 document, 206 abstracts and 87 articles were reviewed. Sixty-four articles were added to the update of this document, 16 of which were randomized controlled trials. In addition to randomized controlled trials of patients with a diagnosis of chronic HF, the references added to the annotations discussing recommendations for specific pharmacologic classes included 11 pertinent subgroup analyses, 6 meta-analyses of controlled trials relevant to the recommendations in the document, and 9 review articles, some that provided a comprehensive inclusion of information and others that discussed patient care considerations not addressed by clinical trials. Literature known to the PBM-MAP on medical history, physical examination, diagnosis and evaluation was also included in the document. Since publication of the December 2002 iteration, two major articles were added to the August 2003 update.

Since the publication of the 1997 document, major advances in the treatment of patients with HF have been published and were included in the 2001 update. Sections were added that discussed the positive outcomes associated with the use of β-adrenergic blockers and the use of an aldosterone antagonist in specific patients with HF. A section was also added to present the evidence and considerations in using alternative afterload reduction in patients who cannot tolerate an angiotensin-converting enzyme inhibitor. Changes from the 2001 HF guideline consist of the inclusion of recommendations from the ACC/AHA Practice Guidelines for the Evaluation and Management of HF published in 2001. The evidence rating system for this document is based on the system used by the U.S. Preventative Services Task Force and also references the grading system used in the ACC/AHA Practice Guidelines for the Evaluation and Management of HF.

## Methods to Formulate Recommendations

The literature was critically analyzed with evidence grading. The rating scale used for this document was based on the evidence rating of the U.S. Preventive Services Task Force.[1]

| Quality of Evidence | |
|---|---|
| **I** | Evidence obtained from at least one properly randomized controlled trial |
| **II-1** | Evidence obtained from well-designed controlled trials without randomization |
| **II-2** | Evidence obtained from well-designed cohort or case-control analytic studies |
| **II-3** | Evidence obtained from multiple time series studies; dramatic results in uncontrolled experiments |
| **III** | Opinions of respected authorities; descriptive studies and case reports; reports of expert committees |

| Overall Quality | |
|---|---|
| **Good** | High grade evidence (I or II-1) directly linked to health outcome |
| **Fair** | High grade evidence (I or II-1) linked to intermediate outcome or<br>Moderate grade evidence (II-2 or II-3) directly linked to health outcome |
| **Poor** | Level III evidence or no linkage of evidence to health outcome |

| Net Effect of Intervention | |
|---|---|
| **Substantial** | More than a small relative impact on a frequent condition with a substantial burden of suffering, or<br>A large impact on an infrequent condition with a significant impact on the individual patient level |
| **Moderate** | A small relative impact on a frequent condition with a substantial burden of suffering, or<br>A moderate impact on an infrequent condition with a significant impact on the individual patient level |
| **Small** | A negligible relative impact on a frequent condition with a substantial burden of suffering, or<br>A small impact on an infrequent condition with a significant impact on the individual patient level |
| **Zero or Negative** | Negative impact on patients, or<br>No relative impact on either a frequent condition with a substantial burden of suffering, or<br>An infrequent condition with a significant impact on the individual patient level |

| Strength of Recommendation | |
|---|---|
| **A** | A strong recommendation that the intervention is always indicated and acceptable |
| **B** | A recommendation that the intervention may be useful/effective |
| **C** | A recommendation that the intervention be considered |
| **D** | A recommendation that an intervention may be considered not useful/effective, or may be harmful |
| **I** | Insufficient evidence to recommend for or against; clinical judgment should be used |

[1]Harris RP, Helfand M, Woolf SH, et al. for the Methods Work Group, Third U.S. Preventive Services Task Force. Current methods of the U.S. Preventive Services Task Force. A review of the process. Am J Prev Med 2001;20(3S):21-35.

The evidence rating system used in the ACC/AHA Practice Guidelines on the Evaluation and Management of HF are included below.[2] As this is used by ACC/AHA guidelines, this format will also be included in the recommendations to assist in the application of the recommendations to clinical practice.

| Recommendation | |
|---|---|
| **Class I** | Conditions for which there is evidence and/or general agreement that a given procedure/therapy is useful and effective |
| **Class II** | Conditions for which there is conflicting evidence and/or a divergence of opinion about usefulness/efficacy of performing the procedure/therapy |
| **Class IIa** | Weight of evidence/opinion is in favor of usefulness/efficacy |
| **Class IIb** | Usefulness/efficacy is less well established by evidence/opinion |
| **Class III** | Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful |

| Level of Evidence | |
|---|---|
| **A** | Data is derived from multiple randomized clinical trials |
| **B** | Data is derived from a single randomized trial or nonrandomized studies |
| **C** | Consensus opinion of experts is the primary source of recommendation |

[2] 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

Recommendations were based on evidence published in the medical literature. Critical literature review focused on pharmacologic management of HF. The annotations that include discussion on medical history, physical examination, diagnosis and evaluation, nonpharmacologic intervention, management of concomitant cardiac conditions, and treatment of underlying causes were based on consensus and did not undergo critical literature review. Where evidence was not available, expert opinion of the MAP was used. After review and discussion by the PBM-MAP, the draft guideline was sent to experts in the field of Cardiology for review. After the Cardiologist reviewers' comments were considered and incorporated into the document where appropriate, the draft was then circulated to practicing clinicians (primarily cardiologists and primary care providers) for input on clarity and applicability.

## Use of the Document

The document is divided into four sections: Executive Summary, Algorithm, Annotations, and Appendices. The algorithm is intended to provide a systematic approach to the pharmacologic management of patients with HF. The letters within the boxes in the algorithm refer to the corresponding annotation. The annotation is further discussion of the evidence for making each recommendation. Details on drug therapy are provided to encourage the safe and effective implementation of the pharmacotherapy recommendations made in this guideline. Recommendations discussed in the annotation are referenced and graded according to the grading system outlined above. The appendices provide additional information for the clinician when considering treatment options.

The recommendations are meant to focus on the pharmacologic management of patients with HF. Other sections have been included that highlight areas such as physical examination, diagnosis, nonpharmacologic management, etc. Practitioners should refer to cardiology texts or local experts for the finer points of diagnosis and these other areas.

The purpose of the recommendations is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. This document attempts to define principles of practice that should produce high quality patient care. They are attuned to the needs of a primary care practice but are directed to providers at all levels. Care of patients with HF may occur in several clinical settings including primary care, cardiology, or by multidisciplinary HF treatment teams. Regardless of the setting in which patients with HF are cared for, the clinician is encouraged to follow these and other HF guidelines and to use clinical judgment of when to refer to a specialist. This will depend on the skill and experience of managing patients with HF, and also the resources available to the practitioner. The recommendations also serve as a basis for monitoring local, regional and national patterns of pharmacologic care.

The recommendations in this document should not be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the same results. The ultimate judgment regarding the propriety of any course of conduct must be made by the clinician in light of individual patient situations.

## Plan for Implementation

The document will be available on the PBM home page at http://www.vapbm.org or http://vaww.pbm.med.va.gov. It is recommenced that a hard copy be kept on file in the medical libraries. Distribution to all clinicians who manage patients with HF is strongly recommended. Clinicians are encouraged to have a copy of the document or a summary of key points available for reference when treating patients with HF.

A summary of key points in a pocket card version have been developed by the PBM-MAP in conjunction with the Employee Education Service and have been made available.

Continuing education programs (e.g., on-line review of guideline) have been developed.

Departmental and individual education at the facility is also encouraged.

## Referencing the Document

This document should be referenced as follows:

*The Pharmacologic Management of Chronic Heart Failure*. Washington, DC: Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel, Veterans Health Administration, Department of Veterans Affairs. December 2002; Updated August 2003. PBM-MAP Publication No. 00-0015.

## Updating the Recommendations

The PBM will review the recommendations routinely. Updating will occur as new information is made available from well-designed, scientifically valid studies and as outcome data may direct. Any member of the VA community is encouraged to recommend changes based on such evidence.

A current copy of the pharmacologic management recommendations can be obtained from the PBM home page at http://www.vapbm.org or http://vaww.pbm.med.va.gov.

# Acknowledgements*

This document was developed in consultation with members of the PBM-MAP and subject matter experts in cardiology. A draft was then forwarded to the field through the VISN Formulary Leaders for peer review. The final version was forwarded to the Director of Performance Management and the National Advisory Council for the Adoption, Development and Implementation of Clinical Practice Guidelines for approval. The following clinicians provided comments on drafts of this report. The final document incorporates reviewers' comments; however, the PBM-SHG takes full responsibility for the content of this guideline.

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* This list does not represent all the clinicians who reviewed the document, only those who agreed to be acknowledged. Reviewers of the 1997 and 2001 versions have been previously acknowledged.

## EXECUTIVE SUMMARY

1. Treatment of chronic heart failure (HF) is based upon the classification of HF into four stages by the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines: Stage A includes patients who are at high risk for developing HF, but do not have structural heart disease; Stage B are patients who do have structural damage to the heart, but have not developed symptoms; Stage C refers to patients with past or current HF symptoms and evidence of structural heart damage; and Stage D includes patients with end-stage disease, requiring special interventions. 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.

2. Goals of therapy for HF include improved symptoms, increased functional capacity, improved quality of life, slowed disease progression, decreased need for hospitalization, and prolonged survival.

3. Nonpharmacologic therapy includes abstaining from alcohol and tobacco, limiting dietary sodium, reducing weight if appropriate, and participating in exercise training programs.

4. Risk factor modification should be implemented in patients in Stage A to potentially reduce the development of HF.

5. In addition to risk factor modification, patients with HF in Stage B 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 (Grade A Recommendation, Good Overall Quality of Evidence). It is also recommended that patients with evidence of left ventricular systolic dysfunction who are without symptoms should be treated with an ACEI (Grade A Recommendation, Good Overall Quality of Evidence) and β-adrenergic blocker (Grade A Recommendation, Fair Overall Quality of Evidence).

6. Patients with HF in Stage C should also be educated on risk factor modification. Pharmacotherapy recommendations for these patients include:

    - A diuretic should be used in the treatment of patients with signs of fluid overload (Grade A Recommendation, Fair Overall Quality of Evidence).
    - All patients should be treated with an ACEI unless contraindicated or not tolerated (Grade A Recommendation, Good Overall Quality of Evidence). These agents improve HF symptoms, functional status, and quality of life, while decreasing frequency of hospitalization and mortality.
    - 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. These agents have been shown to reduce mortality and decrease the symptoms of HF (Grade A Recommendation, Good Overall Quality of Evidence).
    - Digoxin should be used in patients whose symptoms persist despite treatment with an ACEI, a β-blocker, and a diuretic. Digoxin reduces symptoms associated with HF and decreases the risk for hospitalizations due to HF but does not improve mortality (Grade A Recommendation, Good Overall Quality of Evidence).
    - An angiotensin II receptor antagonist (AIIRA) may be considered as an alternative to an ACEI in patients who are on a diuretic, β-adrenergic blocker, and usually digoxin and are unable to tolerate an ACEI due to cough or possibly, angioedema (Grade B Recommendation, Fair Overall Quality of Evidence).
    - The combination of hydralazine and isosorbide dinitrate (HYD/ISDN) may be considered as an alternative to an ACEI in patients who are on a diuretic, β-adrenergic blocker, and usually digoxin and are unable to tolerate an ACEI due to hypotension, renal insufficiency, or possibly, angioedema (Grade B Recommendation, Fair Overall Quality of Evidence).


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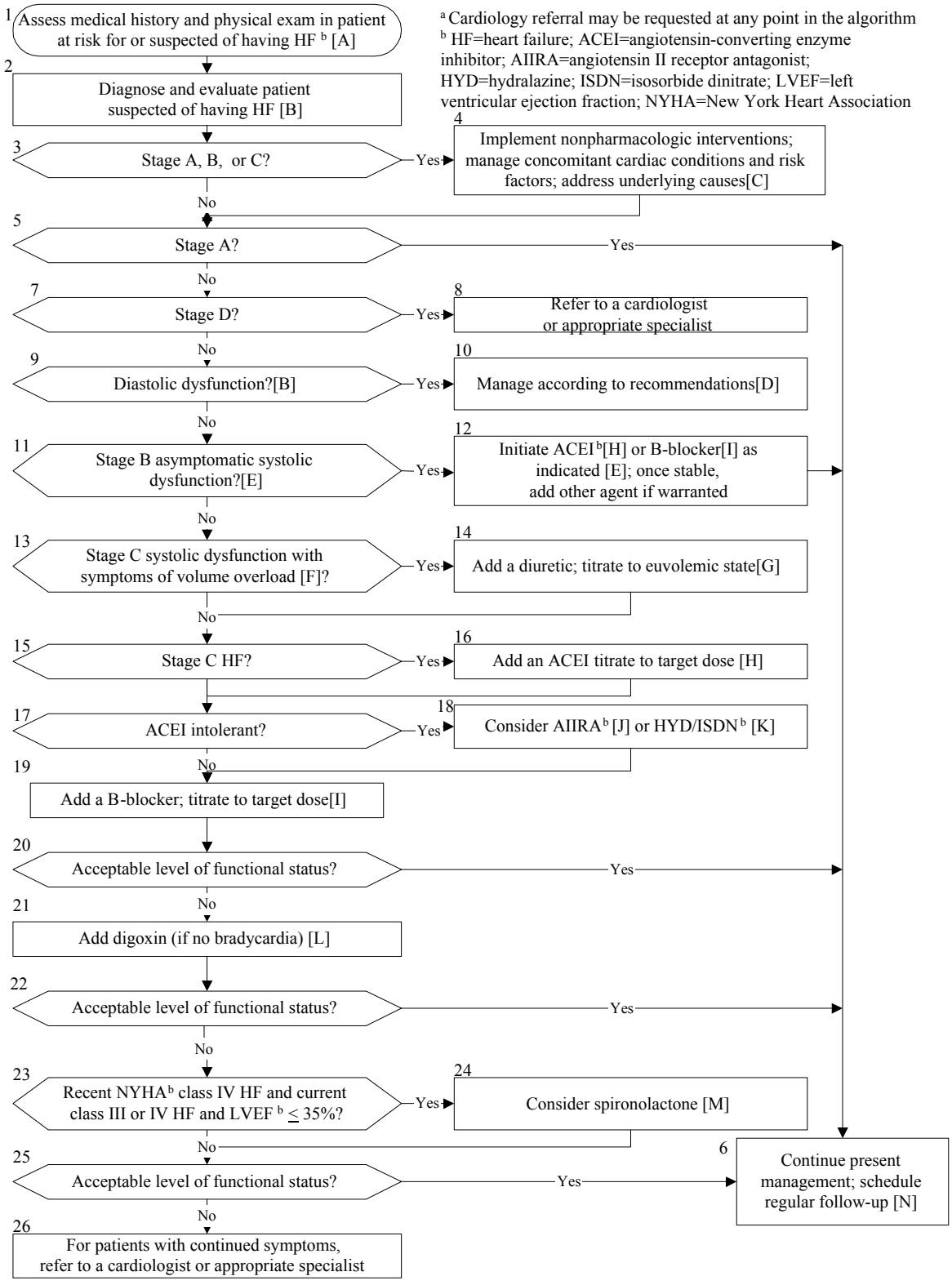
- Low dose spironolactone should be considered in patients with recent New York Heart Association (NYHA) Class IV HF and current Class III or IV symptoms and left ventricular ejection fraction (LVEF) $\leq$ 35%, provided the patient has preserved renal function and normal potassium levels (refer to Annotation M for precautions and recommended monitoring). This therapy improves symptoms (as assessed by change in NYHA functional class), decreases hospitalizations for worsening HF, and decreases mortality (Grade B Recommendation, Good Overall Quality of Evidence).

6. Patients with HF in Stage D may require special treatment interventions including mechanical circulatory support, continuous therapy with positive inotropic agents, consideration for cardiac transplantation, or hospice care. Specific recommendations are beyond the scope of this document and these patients should be referred to a HF management program that includes experts on the management of patients with refractory HF.

## Algorithm: Pharmacologic Management of Patients with Heart Failure [a]




[a] Cardiology referral may be requested at any point in the algorithm

[b] HF=heart failure; ACEI=angiotensin-converting enzyme inhibitor; AIIRA=angiotensin II receptor antagonist; HYD=hydralazine; ISDN=isosorbide dinitrate; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association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# THE PHARMACOLOGIC MANAGEMENT OF CHRONIC HEART FAILURE

## Annotations

## A. Assess Medical History and Physical Examination in a Patient at Risk for or Suspected of Having Heart Failure (HF)

OBJECTIVE

To identify patient factors associated with HF.[1-4]

ANNOTATION

Approximately 4,600,000 of the U.S. population has heart failure (HF), with 550,000 new cases each year. The prevalence of HF rises with age. There is a 5-10% annual fatality rate in patients with mild symptoms and up to 30-40% in patients with advanced disease. The 5 year mortality rate is approximately 50%.[1-3] Recent analyses of the last 50 years have shown that the incidence of HF is decreasing among women, although this does not appear to be occurring among men. Survival rates among both men and women have improved with a decrease in death risk of 12% per decade.[4] Heart failure is the leading cause of hospitalization in patients over 65 years of age. It has been estimated that $20 to 40 billion are spent for HF annually in the U.S. alone.[1-3]

The leading cause of HF due to left ventricular systolic dysfunction is coronary artery disease. Nonischemic causes include hypertension (HTN), valvular heart disease, thyroid disease, myocarditis, and alcohol consumption.[1,2]

1. Medical history

    a) Prior myocardial infarction (MI) or coronary artery disease
    b) Long standing HTN (75% of patients with HF have antecedent HTN)
    c) Valvular heart disease
    d) Diabetes
    e) Peripheral vascular disease
    f) Hypercholesterolemia
    g) Rheumatic fever
    h) Chest irradiation
    i) Exposure to antineoplastic agents (e.g., anthracyclines, trastuzumab)
    j) Alcohol and illicit drug use
    k) Exposure to sexually transmitted diseases
    l) Family history of atherosclerotic disease, cardiomyopathy, sudden death, conduction system disease and skeletal myopathies

2. Patient presentation: Patients with left ventricular (LV) dysfunction generally present in one of the following manners:

    a) Decreased exercise tolerance
    b) Fluid retention
    c) Cardiac enlargement or dysfunction noted during evaluation for a condition other than HF

3. Patient symptoms of HF:[1,5,6] Most patients will present with complaints of exercise intolerance due to dyspnea and/or fatigue. However, no symptom is sufficiently sensitive or specific for the diagnosis of HF to allow ruling in or out disease. Patients with at least one of the following symptoms are at somewhat higher likelihood of having HF. Patients can have HF and have no symptoms of the disease.

a) Shortness of breath (SOB)
b) Fatigue
c) Orthopnea
d) Paroxysmal nocturnal dyspnea (PND)
e) Dyspnea on exertion (DOE)
f) Cough
g) Edema
h) Weight gain (anorexia may be seen in advanced HF)

4. Physical examination findings of HF:[5,6] No single finding is sufficiently sensitive or specific for use alone in the diagnosis of HF. However, patients with at least one of the following signs are more likely to have HF. Patients can have HF and no signs of the condition.

a) Tachycardia
b) Increasing weight
c) Jugular venous distention (JVD) or hepatojugular reflux
d) Presence of $S_3$ (third heart sound)
e) Laterally displaced apical impulse
f) Pulmonary crackles or wheezes
g) Hepatomegaly
h) Peripheral edema

**References:**

[1] 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
[2] Agency for Health Care Policy and Research (AHCPR). Heart failure: evaluation and care of patients with left-ventricular systolic dysfunction. Clinical Practice Guideline No. 11 (AHCPR publication No. 94-0612). Rockville, MD: Agency for Health Care Policy and Research; 1994.
[3] 2000 Heart and Stroke Statistical Update. American Heart Association. http://www.americanheart.org/statistics/index.html
[4] Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002;347:1397-402.
[5] Badgett RG, Lucey CR, Mulrow CD. Can the clinical examination diagnose left-sided heart failure in adults? JAMA 1997;277:1712-9.
[6] Thomas JT, Kelly RF, Thomas SJ, et al. Utility of history, physical examination, electrocardiogram, and chest radiograph for differentiating normal from decreased systolic function in patients with heart failure. Am J Med 2002;112:437-45.

## B. Diagnose and Evaluate Patient Suspected of Having HF

OBJECTIVES

1. To distinguish between the diagnosis of HF and other conditions, such as pulmonary, hepatic, renal, hematopoetic diseases that can produce symptoms or signs suggestive of HF
2. To distinguish systolic from diastolic dysfunction
3. To evaluate the patient's functional status

ANNOTATION

Signs and symptoms of HF are nonspecific and must be distinguished from those of other conditions such as pulmonary disease, liver failure, and/or nephrotic syndrome. Heart failure due to myocardial muscle dysfunction may be characterized by systolic dysfunction, diastolic dysfunction, or both. Systolic dysfunction is generally defined as a left ventricular ejection fraction (LVEF) of < 40%.[1-3] Patients with diastolic dysfunction often have impaired ventricular relaxation and distensibility resulting in increased ventricular filling pressure (LVEDP). The ejection fraction in these patients may be normal or increased.

**Recommended Tests to Assist in the Diagnosis of HF**[1,2,4]

1. Analysis of venous blood sample for creatinine (Cr), blood urea nitrogen (BUN), serum electrolytes including calcium and magnesium, urinalysis, complete blood count, fasting lipid profile, liver function tests, thyroid stimulating hormone (TSH); consider serum iron and saturation to exclude hemochromatosis
2. Electrocardiogram to assess for prior MI, voltage criteria suggestive of left ventricular hypertrophy (LVH), cardiac rhythm
3. Chest radiography to identify signs of volume overload (pleural effusion, pulmonary edema, cardiomegaly) or pulmonary disease
4. All patients with HF should have an evaluation of left ventricular function.
   a) Before a diagnosis of HF due to diastolic dysfunction can be made, other potential causes of HF with preserved LV systolic function should be ruled out (e.g., valvular regurgitation or high-output states such as anemia or pregnancy).
   b) A diagnosis of HF due to systolic dysfunction can be made by a 2-dimensional echocardiogram with Doppler flow studies.[2-3] Testing by this method will help determine if the cause is pericardial, valvular, or myocardial. If myocardial, patients with a LVEF of < 40% are classified as having systolic dysfunction. Up to 40% of patients with a clinical diagnosis of HF have normal LVEF and no evidence of valvular disease. Most of these patients will have LV diastolic dysfunction.
   c) Other tests (e.g., radionuclide ventriculography) may be used to determine left ventricular systolic function, non-invasively. Left ventriculography (cardiac catheterization) may be indicated in selected patients to assess LV function, coronary circulation, etc. Cardiology consultation can be useful in determining the need for cardiac catheterization.
   d) The utility of measuring brain natriuretic peptide (BNP) levels has not been clearly defined although it is may be useful in the diagnosis of congestive HF. It has also been used as an indicator of morbidity and mortality in patients with HF and in the acute care setting to distinguish between dyspnea from HF vs. other etiologies.
   e) First-degree relatives of patients with idiopathic dilated cardiomyopathy may be considered for an echocardiogram and electrocardiogram.

**Classification of HF**

Different classification systems help characterize HF based on cardiac cycle (systolic, diastolic or both), and/or ventricular involvement (right, left or both). The American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines recently published recommendations for staging patients with HF based on the progression of disease (refer to Table 1).

**Table 1. ACC/AHA Guidelines for the Evaluation and Management of HF**[a]

| 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 |

[a] 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

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 (refer to Table 2).

**Table 2. NYHA Functional Classification and Objective Assessment of HF[a]**

| FUNCTIONAL CAPACITY |
|---|
| 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. |

[a] 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.

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[1] Agency for Health Care Policy and Research (AHCPR). Heart failure: evaluation and care of patients with left-ventricular systolic dysfunction. Clinical Practice Guideline No. 11 (AHCPR publication No. 94-0612). Rockville, MD: Agency for Health Care Policy and Research; 1994.
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## C. Nonpharmacologic Interventions, Management of Concomitant Cardiac Conditions and Risk Factors, and Treatment of Underlying Causes

OBJECTIVE

To provide general interventions to be recommended in patients at risk for developing HF or who have a diagnosis of HF.

ANNOTATION

Basic assessment should attempt to identify the etiology of the HF (e.g., ischemic heart disease, hypertension, thyroid dysfunction, valvular heart disease, brady and tachyarrhythmias, cardiomyopathies, infiltrative diseases or hemochromatosis), and factors that may aggravate or precipitate HF (e.g., anemia, infections, obesity, or excessive salt intake).

**General Recommendations for HF Stages A-D[1,2]**

1. Control risk factors
   a) Control HTN (refer to http://www.oqp.med.va.gov/cpg/cpg.htm, http://www.vapbm.org, or http://vaww.pbm.med.va.gov for the clinical practice guideline on the management of hypertension and other related documents)
   b) Treat hyperlipidemia (refer to http://www.oqp.med.va.gov/cpg/cpg.htm, http://www.vapbm.org, or http://vaww.pbm.med.va.gov for the clinical practice guideline on the management of dyslipidemia and other related documents)
   c) Encourage smoking cessation (refer to http://www.oqp.med.va.gov/cpg/TUC/TUC_BASE.htm for the clinical practice guideline on tobacco use cessation)
   d) Discourage alcohol consumption and illicit drug use
   e) Use of an angiotensin-converting enzyme inhibitor (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 [e.g., HTN, increased total cholesterol (> 200 mg/dl), low HDL cholesterol (≤ 35 mg/dl), cigarette smoking, documented microalbuminuria]

f) Control ventricular rate in patients with supraventricular tachyarrhythmias
g) Treat thyroid disorders
h) Treat DM (refer to http://www.oqp.med.va.gov/cpg/cpg.htm, http://www.vapbm.org, or http://vaww.pbm.med.va.gov for the clinical practice guideline on the management of diabetes and other related documents)
i) Manage atherosclerotic disease (refer to http://www.oqp.med.va.gov/cpg/cpg.htm for the clinical practice guideline on the management of ischemic heart disease and stroke)

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;[3] however, high fluid intake (e.g., > 3 liters per day) should be discouraged.

3. Weight loss if body mass index $\geq 30 kg/m^2$ (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.[2,4-8] Exercise training programs have been used in trials evaluating the effects of physical conditioning on symptoms, exercise tolerance, safety, and quality of life in patients with HF.[1,6,8] Patients should be referred to a specialist if the clinician is not comfortable designing an exercise program for the patient with HF.

5. Recommendations in selected patients
   a) In patients with HF due to systolic dysfunction and atrial fibrillation requiring rate control, a β-adrenergic blocker is preferred due to its favorable effect on patients with HF (in patients that are hemodynamically and otherwise stable). Digoxin is also commonly used. Some patients may require combination therapy with digoxin and a β-adrenergic blocker. If additional rate control is needed, referral should be made to a cardiologist with expertise in electrophysiology. Patients with atrial fibrillation and diastolic dysfunction should be treated with verapamil or diltiazem, or a β-adrenergic blocker to control the ventricular rate.[9]
   b) Warfarin anticoagulation [with a target international normalized ratio (INR) of 2.0 to 3.0] is recommended in patients with HF and atrial fibrillation or previous systemic or pulmonary thromboembolism.[1,2,10-14] The routine use of warfarin anticoagulation for HF has not been confirmed by controlled clinical trials[1,2,15] and the benefit of warfarin in patients with HF and a cardiac thrombus has not been established.[1,2,11] It is anticipated that the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial, which is a randomized comparison of warfarin, aspirin, and clopidogrel in patients with HF, will provide guidance on the use of these agents in this patient population. Arterial thromboembolism may occur in patients with HF due to systolic dysfunction as a result of the low cardiac output and poor contractility. There are no clinical trials designed to evaluate the efficacy of warfarin anticoagulation among patients with systolic dysfunction alone. Secondary data analysis supports warfarin use in these patients. Analysis of cohorts in the Studies of Left Ventricular Dysfunction (SOLVD) who received warfarin, compared to those who did not, suggests a 25% risk reduction in all-cause mortality.[16] However, a post-hoc analysis of a single study is not evidence enough to recommend anticoagulation in patients with systolic dysfunction. Patients with contraindications to warfarin (e.g., increased risk of bleeding, difficulty adhering to the medication regimen or regular INR monitoring, current alcohol abuse or falls) should receive aspirin unless contraindicated.[13,17]
   c) Reinstate sinus rhythm by chemical or electrical cardioversion in patients with acute atrial fibrillation where indicated to improve functional status. Patients should receive adequate treatment of HF prior to attempt at cardioversion.[18]
   d) Consider coronary revascularization in patients with angina or anginal equivalents or known viable myocardium with known coronary artery disease.
   e) Consultation with cardiology in patients with HF and valvular heart disease.

f) If cardiac amyloidosis is known or suspected from echocardiography or clinical grounds, further work-up and referral to a cardiologist is warranted for appropriate treatment.

g) Patients with systolic HF and concomitant HTN should be maximized on therapy with agents such as diuretics, ACEIs, and β-adrenergic blockers, or β-adrenergic blockers and nitrates in patients with concomitant angina, before adding other agents. However, in patients who are not adequately controlled on these agents, treatment with a long-acting dihydropyridine (felodipine or amlodipine) may be considered based on the following information.

The negative inotropic properties of the calcium channel blockers (CCBs) may cause deleterious effects in patients with HF due to systolic dysfunction. Studies have looked at the use of the long-acting dihydropyridines, felodipine and amlodipine, in patients with systolic dysfunction. Note that neither amlodipine nor felodipine have approval by the Food and Drug Administration for use in patients with HF and should be used with caution in patients with this diagnosis.

The Prospective Randomized Amlodipine Survival Evaluation (PRAISE) evaluated patients with NYHA class IIIB or IV with a LVEF of < 30%, who remained symptomatic despite treatment with digoxin, diuretics, and an ACEI. There were 571 patients who received amlodipine up to 10mg qd compared to 582 patients on placebo. The average follow-up was 13.8 months (range 6-33). There was no significant difference in the primary endpoint between groups which was the combined risk of death and major cardiovascular hospitalizations. There was a trend toward amlodipine to decrease all-cause mortality (p=0.07). Subgroup analysis showed that amlodipine significantly decreased the risk of death from all causes in patients with HF due to nonischemic dilated cardiomyopathy, without a difference in patients with ischemic dilated cardiomyopathy.[19] This result was not considered *a priori* end-point. The survival benefit of amlodipine in patients with nonischemic dilated cardiomyopathy found in the original PRAISE trial was not confirmed in PRAISE-2.[20]

The third Vasodilator Heart Failure Trial (V-HeFT III) included patients with NYHA class II or III HF with a LVEF of 18-42% who remained symptomatic despite treatment with digoxin, diuretics, and an ACEI. There were 224 patients who received felodipine at a maximum dose of 5mg bid compared to 226 patients on placebo. The average follow-up was 18 months (range 3-39). The primary endpoint of the study was the effect of treatment on exercise tolerance. There was no significant difference between groups in death from all causes, worsening HF, or number of hospitalizations. This study was not sufficiently powered to demonstrate that felodipine did not alter mortality, however. Exercise tolerance and quality of life significantly improved with felodipine at 27 months.[21]

Clinical experts have stated that only trials with amlodipine and felodipine have provided long-term safety data in patients with HF.[2] The evidence with amlodipine suggests that this agent does not adversely affect survival in patients with systolic HF. Felodipine or amlodipine may be considered for the treatment of hypertension and/or angina in patients with HF due to systolic dysfunction.[22,23] The PBM-MAP Criteria for Use of the Long-Acting Dihydropyridine Calcium Antagonists can be found at http://www.vapbm.org or http://vaww.pbm.med.va.gov.

6. Medications to avoid

a) Anti-arrhythmic agents, other than β-adrenergic blockers, are not recommended to suppress asymptomatic ventricular arrhythmia or ectopy. Class I anti-arrhythmic agents have been shown to increase the risk of sudden death in patients with HF. Of the class III agents, treatment with amiodarone or dofetilide does not appear to increase the risk of death in patients with HF.[24-27] Patients with ventricular arrhythmias should be referred to a cardiologist with expertise in electrophysiology for individualized treatment.

b) Most CCBs (except felodipine and amlodipine) should not be used in patients with systolic dysfunction (refer to 5.g above).

c) Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided;[1,2,28,29] alternative anti-inflammatory agents may be used (e.g., non-acetylated salicylates)

d) Antineoplastic agents such as anthracyclines or trastuzumab may lead to the development of HF and should be avoided, if possible.

e) Conventional wisdom has been that digoxin and CCBs should be avoided in patients with amyloid cardiomyopathy.[30,31] However, this point is controversial[32] and supported by only weak published evidence. Several case reports suggest a sensitivity to digoxin,[33-38] however one prospective autopsy study found no association.[39] Digoxin can be useful in controlling rapid ventricular response to atrial fibrillation and might be useful, especially in early stages of systolic dysfunction caused by amyloid cardiomyopathy.[32] The data supporting a CCB sensitivity is based on case reports for nifedipine[40,41] and verapamil.[42] Both these drugs can exacerbate chronic systolic dysfunction independent of etiology. We can find no case reports of other CCBs to suggest sensitivity to them. The following recommendations are based on review of available evidence:

   i) Avoid verapamil, diltiazem, and nifedipine in systolic dysfunction of all etiologies.

   ii) If digoxin is necessary in a patient with known or suspected amyloid cardiomyopathy (e.g., to control ventricular response to atrial fibrillation), it should be used very cautiously with careful monitoring for evidence of cardiac toxicity.

   iii) Use digoxin in severe cases of known or suspected amyloid cardiomyopathy only in close consultation with a cardiologist and after carefully weighing the potential risks and benefits.

   iv) Use felodipine or amlodipine only according to prescribing guidelines. Monitor patients with known or suspected amyloid cardiomyopathy very closely when using any CCB.

   v) Consider using other agents for diastolic dysfunction before resorting to a CCB in patients with known or suspected amyloid cardiomyopathy.

7. Additional recommendations

a) Unless contraindicated, influenza vaccination should be offered every fall.

b) Pneumococcal immunizations should be provided at diagnosis if not previously vaccinated. If initial vaccination was at age less than 65 years, revaccinate at age 65 or 5 years after initial immunization, whichever is later.

c) Patients and their families or caregivers should receive education on HF, dietary restrictions, drug therapy and importance of adherence to the medication regimen, symptoms associated with worsening HF and what to do if they occur, and prognosis.

d) Patients should be followed closely by a clinician competent in caring for patients with HF. Care of patients with HF may occur in several clinical settings including primary care, cardiology, or by multidisciplinary HF treatment teams. Regardless of the setting in which patients with HF are cared for, the clinician is encouraged to follow these and other HF guidelines and to use clinical judgement of when to refer to a specialist. This will depend on the skill and experience of managing patients with HF, and also the resources available to the practitioner. Interdisciplinary HF disease management clinics have improved patient outcomes[43] including fewer HF events, achievement of higher ACEI[44]and β-adrenergic blocker use and doses,[45] and lower mortality.[44]

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## D. Pharmacologic Management of HF Due to Diastolic Dysfunction

OBJECTIVE

To discuss pharmacologic recommendations for patients with HF due to diastolic dysfunction.

ANNOTATION

In diastolic dysfunction the systolic function of the left ventricle is preserved. The defect of ventricular function lies in the reduced LV compliance and difficulty in passive filling. Increased LVEDP can result in pulmonary congestion indistinguishable clinically from LV systolic dysfunction.

Compared to HF due to systolic dysfunction, there is a paucity of data from randomized trials about the pharmacologic management of patients with diastolic dysfunction.[1-13] Since questions remain regarding the optimal treatment of patients with diastolic dysfunction, it is recommended that these patients be treated in conjunction with a cardiologist.

General principles of lowering blood pressure, treating myocardial ischemia, slowing atrioventricular (AV) conduction, controlling central blood volume, and providing anticoagulation for patients with atrial fibrillation apply to these patients as well as to patients with systolic dysfunction.[1]

The main goal of therapy is to improve symptoms by lowering the filling pressures of the left ventricle without significantly reducing cardiac output. Agents that decrease heart rate can be helpful by increasing diastolic filling time.

**Pharmacologic recommendations of HF due to diastolic dysfunction:**

| Strength of Recommendation and Evidence Rating | Overall Quality | Net Effect | References | ACC/AHA Recommendations | Evidence Level |
|---|---|---|---|---|---|
| **Grade A (always indicated and acceptable):** | | | | | |
| Control blood pressure | Good | Substantial | 1 | Class I | A |
| **Grade B (may be useful/ effective):** | | | | | |
| Judicious use of diuretics in patients with symptoms of volume overload | Poor | Moderate | 4-7 | Class I | C |
| Use drugs that control ventricular rate in patients with atrial fibrillation | Poor | Moderate | 1 | Class I | C |
| **Grade C (may be considered):** | | | | | |
| Digoxin improves symptoms and reduces hospitalizations in patients with diastolic dysfunction in the absence of atrial fibrillation | Poor | Moderate | 2,3 | Class IIb | C |
| Use β-adrenergic blockers, CCBs, ACEI, AIIRAs in patients with controlled blood pressure who continue to have symptoms | Poor | Small | 1, 5, 6, 8-12 | Class IIb | C |
| Use nitrates in patients with diastolic dysfunction as a result of coronary artery disease | Poor | Small | 4-7, 13 | NA | NA |
| **Grade D (may not be useful/ effective; possibly harmful):** | | | | | |
| None | | | | | |
| **Grade I (insufficient evidence to recommend for or against):** | | | | | |
| None | | | | | |

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## E. Interventions in Patients With Asymptomatic Left Ventricular Systolic Dysfunction

OBJECTIVE

To provide recommendations for patients with asymptomatic left ventricular systolic dysfunction (Stage B).

ANNOTATION

The management goals for patients with asymptomatic systolic dysfunction are to initiate therapy in an effort to prevent the development of HF.[1] These recommendations are divided into the following patient groups.

### Patients With an Acute, Recent, or History of MI

Prescribing an ACEI in patients with an acute[2] or recent MI[3] and evidence of left ventricular systolic dysfunction may reduce mortality and slow the progression to symptomatic heart failure.[4-7] In the Survival and Ventricular Enlargement (SAVE),[4] Acute Infarction Ramipril Efficacy (AIRE),[5,6] and Trandolapril Cardiac Evaluation (TRACE)[7] trials, patients with a recent MI and evidence of HF experienced a significant decrease in all-cause mortality and risk of developing severe heart failure when treated with an ACEI compared to placebo. Treatment with an ACEI in patients recently recovered from an MI can decrease the risk of reinfarction and death in patients with evidence of HF at the time of the infarction.[5] Patients with a history of MI without reduced LVEF may also benefit from treatment with an ACEI. [8]

The use of a β-adrenergic blocker in patients with asymptomatic left ventricular systolic dysfunction post-MI reduces the risk of cardiovascular morbidity and mortality.[9-12] In the Carvedilol Post-Infarct Survival

Control in LV Dysfunction (CAPRICORN) trial that randomized 1959 patients with a LVEF ≤ 40% post-MI to carvedilol or placebo, there was not a statistically significant difference in the primary endpoint of all-cause mortality or hospital admission for cardiovascular problems (originally a prespecified secondary endpoint). The original primary endpoint of all-cause mortality (changed to co-primary endpoint due to inadequate sample size and power) was lower (but not statistically significant based on $\alpha$=0.005 for all-cause mortality alone) in patients on carvedilol compared to placebo [hazard ratio 0.77 (0.60-0.98), P=0.03].[13] Although the results of this study did not achieve statistical significance (thought to be due to trial design), the endpoints were lower in patients treated with carvedilol. Taking this into account with results of other trials, there still appears to be a benefit of using a β-adrenergic blocker in patients with asymptomatic left ventricular systolic dysfunction post-MI.

Combination therapy with a β-adrenergic blocker and an ACEI may also be beneficial in patients with left ventricular systolic dysfunction post-MI.[14-16]

Future results of clinical trials should provide data as to the potential benefit of the AIIRAs in patients with a recent MI.[17,18]

**Patients With Asymptomatic Left Ventricular Dysfunction**

In the Studies of Left Ventricular Dysfunction (SOLVD) Prevention trial, patients with asymptomatic left ventricular dysfunction treated with an ACEI experienced a significant reduction in the combined risk of death and hospitalization for HF by 20% compared to placebo. However, there was no significant decrease in all-cause mortality alone in the ACEI group.[19] The benefit of an ACEI in men compared to women with HF was recently evaluated. According to a subgroup analysis of trials including treatment of patients with asymptomatic LV dysfunction, there did not appear to be a clear benefit of ACEI in women, with a relative risk of 0.96 (95% CI 0.75-1.22). It was concluded that further investigation is warranted before making a definitive recommendation on the use of ACEIs in women with asymptomatic left ventricular dysfunction.[20] While the benefit, to the extent that one exists, remains to be quantified, an ACEI should still be considered standard therapy given the current level of data overall.

Although the benefit of β-adrenergic blockers in patients with asymptomatic HF (not in the post-MI setting) has not been critically evaluated, current recommendations include use of a β-adrenergic blocker in this patient population.[1,12-14]

Digoxin is currently recommended in patients with symptomatic HF to improve clinical status and decrease the risk of hospitalization due to HF (refer to Annotation L).[21] Since there is not a significant reduction in disease progression or mortality, digoxin is not recommended in patients with asymptomatic left ventricular dysfunction.[1]


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**Pharmacologic recommendations for patients with asymptomatic systolic dysfunction:**

| Strength of Recommendation and Evidence Rating | Overall Quality | Net Effect | References | ACC/AHA Recommendations | Evidence Level |
|---|---|---|---|---|---|
| **Grade A (always indicated and acceptable):** | | | | | |
| ACEI in patients with acute, recent, or history of MI, regardless of LVEF | Good | Substantial | 1-8 | Class I | A |
| ACEI in patients with reduced LVEF, whether or not history of MI | Good | Substantial | 1,19 | Class I | B |
| β-adrenergic blocker in patients with acute, recent, or history of MI, regardless of LVEF | Good | Substantial | 1,9-14 | Class I | A |
| β-adrenergic blocker in patients with reduced LVEF, whether or not history of MI | Fair | Substantial | 1,10-14 | Class I | B |
| **Grade B (may be useful/ effective):** | | | | | |
| None | | | | | |
| **Grade C (may be considered):** | | | | | |
| None | | | | | |
| **Grade D (may not be useful/ effective; possibly harmful):** | | | | | |
| Digoxin in patients with asymptomatic left ventricular dysfunction in sinus rhythm | Poor | Zero | 1,21 | Class III | C |
| **Grade I (insufficient evidence to recommend for or against):** | | | | | |
| None | | | | | |

## References:


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## F. Systolic Dysfunction and Assessment for Symptoms of Volume Overload

OBJECTIVE

To provide recommendations for initial therapy in patients with a diagnosis of systolic HF who exhibit symptoms of volume overload.

ANNOTATION

The goals of treating patients with HF due to systolic dysfunction are to improve the patient's symptoms and quality of life, and to reduce the risk of morbidity and mortality by slowing the progression of disease. Patient's symptoms are often related to volume overload.

Symptoms of volume overload include ankle swelling, weight gain, fatigue, orthopnea, PND, DOE, SOB at rest and nocturnal cough. The signs of volume overload are pulmonary crackles, third heart sound, cardiomegaly, JVD, hepatojugular reflux, hepatomegaly, ascites, dependent edema (presacral, flank, lower extremity), tachypnea, tachycardia, and pulmonary edema.

Chest radiography is useful to identify signs of volume overload (pleural effusion, pulmonary edema, cardiomegaly).

A diuretic is recommended in patients with HF who exhibit signs or symptoms of volume overload.[1] (refer to Annotation G)

**References:**

[1] 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

## G. Diuretic Therapy

OBJECTIVE

To provide recommendations for the appropriate use of diuretics in patients with a diagnosis of systolic HF (for a discussion on the use of aldosterone antagonists in HF, refer to Annotation M).

ANNOTATION

Diuretics act by inhibiting sodium or chloride reabsorption in the renal tubules. The loop diuretics exert their effects more proximally and are therefore the most potent of the diuretics. The diuretics primarily differ in their duration of action (e.g., furosemide 6 hours, hydrochlorothiazide 6-12 hours, metolazone 12-24 hours). As HF progresses, a delay in absorption may be a contributing factor to the need for increasing diuretic doses in some patients.[1-4]

There have been no long-term controlled clinical trials evaluating the effectiveness of loop or thiazide diuretic therapy in patients with HF.[1] Short-term and intermediate length studies have demonstrated that diuretics can decrease the signs and symptoms of fluid retention, and improve cardiac conduction and exercise tolerance.[1,5-8] The majority of patients enrolled in long-term trials demonstrating a decreased morbidity or mortality with ACEI or β-adrenergic blocker therapy, were also receiving a diuretic.[1]

Some patients with HF may experience a recurrence of symptoms if diuretic therapy is withdrawn.[9] In one trial the risk of requiring reinstitution of diuretic therapy was 36% in patients in the withdrawal group compared with controls.[10] A LVEF $\leq$ 27%, diuretic dose greater than 40mg of furosemide daily, or a history of HTN were independent risk factors for early reinstitution of diuretic therapy.[11]

Patients with HF may have symptoms that interfere with their daily activities and, therefore, impact on their quality of life. A diuretic should be used for preload reduction in patients with HF and current or previous signs or symptoms of volume overload (e.g., orthopnea, PND, DOE, or edema).[1,9] Patients with symptoms of fluid overload benefit from treatment with a diuretic in conjunction with an ACEI and β-adrenergic blocker,[1] and possibly digoxin.[12]

Loop diuretics are most commonly used for patients with HF and volume overload. They are effective in patients with renal insufficiency or creatinine clearance (CrCl) < 30 mL/min, whereas the effectiveness of thiazides are diminished in patients with CrCl < 30 mL/min.[1,13] Edema resistant to large doses of loop diuretics may intermittently require combined diuretic therapy (e.g., adding metolazone or thiazide at low doses two to three times per week or more frequently if needed, one hour prior to a loop diuretic), or intravenous diuretics.[1,12-18] The use of combination diuretics increases the risk of electrolyte imbalances and overdiuresis leading to prerenal azotemia. Therefore, combination diuretic therapy requires close monitoring.

Monitoring parameters with diuretics include the following:[1,13]

1. Weight: (initially 1 - 2 pound weight loss per day until "ideal weight" achieved); weight loss may be greater during the first few days when significant edema is present; obtain daily weights
2. Signs or symptoms of volume depletion: weakness, dizziness, decreased urine output, symptomatic hypotension, orthostatic hypotension
3. Serum potassium ($K^+$), BUN or Cr (and serum BUN/Cr ratio); consider magnesium (especially if high doses diuretic used), sodium, calcium, bicarbonate, uric acid, glucose as indicated. Use of an ACEI (or AIIRA) and/or spironolactone may offset potential diuretic-induced hypokalemia, minimizing the need for potassium or potassium-sparing diuretics.
4. Diuretic dosage may require adjustment if hypotension or decrease in renal function occurs. Avoid excessive diuresis, which could also limit ACEI dosage due to hypotension or renal dysfunction.


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**Table 3. Diuretic Therapy [a-b]**

| DRUG ((**Bold** = National Formulary item) | DOSE RANGE | COMMENTS/CAUTIONS |
|---|---|---|
| **Loop diuretics**<br>**Furosemide**<br><br>**Bumetanide**<br><br>**Ethacrynic acid**<br><br>Torsemide | range = 20-400[c] mg/d (see comments)<br>range = 0.5-10mg/d<br><br>range = 50-400mg/d<br><br>range = 10-200 mg/d | • Loop diuretics are more effective than thiazide diuretics in patients with severe volume overload<br>• Usually administered once daily unless higher doses (e.g., furosemide > 160mg/d) are needed, then more frequent daily dosing should be considered[19,20]<br>• Effective in patients with CrCl < 30 mL/min<br>• Ethacrynic acid may be used in patients with sulfonamide sensitivity |
| **Thiazide diuretics**<br>**Hydrochlorothiazide** (HCTZ)<br><br>**Chlorthalidone** | range= 12.5-50 mg/d<br><br>range = 12.5-50 mg/d | • Thiazides lose effectiveness in patients with CrCl < 30 mL/min<br>• 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<br>• Add potassium supplement or low dose potassium-sparing diuretic[d] if the patient becomes hypokalemic (serum $K^+$ < 4.0 mEq/L)<br>• Use cautiously in poorly controlled DM, symptomatic benign prostatic hyperplasia, or in patients with increased risk of volume depletion |
| **Thiazide-related**<br>**Indapamide**<br><br>**Metolazone**[e]<br>*Zaroxolyn®*<br>*Mykrox®* | range = 2.5-5 mg/d<br><br>range = 5-20[f] mg/d<br>range = 0.5-1[f] mg/d | • Reserve indapamide for patients with CrCl < 25 mL/min<br>• 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 |

[a] Adapted from Hebel SK, ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc., January 2000.
[b] Adapted from 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.
[c] Higher doses have been effective and tolerated
[d] Unless patients have persistent hypokalemia or are being treated with low dose spironolactone for severe HF (refer to Annotation M), potassium-sparing diuretics should not be used in combination with ACEI (refer to Appendix B for common diuretic drug interactions)
[e] The brand names of metolazone are not bioequivalent, therefore doses vary
[f] Intermittent use recommended once the response of the patient is stabilized

**Pharmacologic recommendations for diuretic therapy in patients with HF:**

| Strength of Recommendation and Evidence Rating | Overall Quality | Net Effect | References | ACC/AHA Recommendations | Evidence Level |
|---|---|---|---|---|---|
| **Grade A (always indicated and acceptable):** | | | | | |
| Use loop diuretic in patients with evidence of fluid overload | Fair | Moderate | 1,5-9 | Class I | A |
| **Grade B (may be useful/ effective):** | | | | | |
| Use combination of loop diuretic and either thiazide or metolazone in patients refractory to loop diuretic | Fair | Moderate | 1,12-18 | NA | NA |
| **Grade C (may be considered):** | | | | | |
| None | | | | | |
| **Grade D (may not be useful/ effective; possibly harmful):** | | | | | |
| None | | | | | |
| **Grade I (insufficient evidence to recommend for or against):** | | | | | |
| None | | | | | |

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## H. Angiotensin-Converting Enzyme Inhibitors

OBJECTIVE

To provide recommendations for the appropriate use of ACEIs in patients with a diagnosis of systolic HF.

ANNOTATION

Angiotensin-converting enzyme (ACE) is responsible for converting angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor and it stimulates aldosterone secretion, which leads to increased sodium and water retention. By inhibiting this enzyme, ACEIs ultimately reduce the vasoconstriction associated with angiotensin II and decrease the sodium and water retention associated with aldosterone. ACE is structurally similar to kininase II, so it may also inhibit the breakdown of bradykinin, a vasodilator. The importance of ACE's effect on kinin-mediated prostaglandin synthesis in the management of patients with HF is not yet known, but it may be as important as angiotensin suppression.[1,2]

In addition to improving HF symptoms and functional status,[1-9] treatment with an ACEI has been shown to decrease the frequency of hospitalization and mortality rate.[10-14]

In the Captopril-Digoxin Multicenter Trial, patients with mild to moderate HF were randomized to placebo or captopril in addition to treatment with diuretics for 6 months. Patients on captopril experienced significant improvement in exercise tolerance and decreased frequency of hospital or emergency care for worsening HF.[10]

Patients with mild to moderate HF who received enalapril for an average of 41 months in the SOLVD Treatment Trial had a significant decrease of 16% in all-cause mortality (CI 0.05 to 0.26, P=0.0036; ARR 4.55%; NNT=22.0) and a 26% decreased risk of death or hospitalizations for HF compared to patients on placebo.[11]

The Vasodilator Heart Failure Trial (V-HeFT) II showed that patients with mild to moderate HF who received enalapril for an average of 2.5 years experienced a significant decrease of 28% (P=0.016) in the risk of death at 2 years compared to patients on the combination hydralazine and isosorbide dinitrate (HYD/ISDN) (ARR 5.41%; NNT=18.5).[12]

The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) evaluated treatment with enalapril for 6 months compared to placebo in patients with NYHA class IV HF. There was not a significant benefit in the combined risk of death and hospitalizations for HF in patients on enalapril. Treatment with enalapril significantly decreased all-cause mortality at 6 months (RR 0.40, P=0.002; ARR 17.67%; NNT=5.7).[13]

The possibility of racial differences in response to therapy has been seen in a subanalysis of V-HeFT and V-HeFT II, where white patients did not experience the same mortality benefit as black patients on HYD/ISDN. In V-HeFT II, white patients on an ACEI experienced a decrease in mortality compared to treatment with HYD/ISDN, whereas black patients did not.[15] When matched cohorts of white patients were compared to black patients on an ACEI enrolled in the SOLVD Treatment Trial, white patients experienced a decreased risk for hospitalizations due to HF which was not seen in the cohort of black patients.[16] Based on a pooled relative risk analysis, there was no evidence that mortality differed substantially with an estimate for white patients of 0.89 (95% CI 0.82-0.97) and 0.89 (85% CI 0.74-1.06) for black patients.[17] Further trials will need to be conducted to determine if recommended therapy for HF needs to be modified based on patient demographics.

It is recommended that an ACEI should be offered to all patients with reduced left ventricular systolic dysfunction unless the patient has specific contraindications:[1,2,18,19]

1. A history of angioedema or other documented hypersensitivity to an ACEI[20]
2. Bilateral renal artery stenosis or renal artery stenosis in a solitary kidney
3. Pregnancy
4. Serum potassium > 5.5 mEq/L that cannot be reduced
5. Symptomatic hypotension

Before initiating therapy, patients should first be assessed for adequate volume status. If the patient is on a potassium-sparing diuretic when an ACEI is begun, close monitoring of potassium is recommended. Alternatively, the potassium-sparing diuretic may be stopped while titrating the ACEI and re-started later, if hypokalemic, with subsequent close monitoring of potassium.

Patients at high risk of first dose hypotension (e.g., advanced age, volume depletion, diuretic use, severe left ventricular dysfunction, initial systolic blood pressure < 100 mm Hg, or serum sodium < 135 mEq/L) should be given a small dose (i.e., 6.25-12.5 mg) of a short acting ACEI (captopril) and monitored for 2 hours.[19] Significant hypotension may signal the need for reducing the dosage of diuretics or other blood pressure lowering agents.

Patients started on an ACEI should be evaluated within 1 to 2 weeks to monitor blood pressure, serum potassium and creatinine; more frequent monitoring may be warranted depending on the severity of the patient's condition.

Doses should initially be low and then titrated upward over several weeks to the maximum dose tolerated, with the target doses based on those used in large scale clinical trials (refer to Table 3).[19] Despite the overwhelming evidence in favor of treating HF patients with ACEIs and that a large majority of patients are able to tolerate high doses,[19] these agents are often underutilized, and frequently at low doses,[20] although this may depend on the clinical setting.[21]

There appears to be a dose response benefit as shown in the Assessment of Treatment with Lisinopril and Survival (ATLAS) study. In this study, patients with NYHA class II-IV HF on maximal doses of lisinopril (average of 33.2 $\pm$ 5.4mg daily) experienced a significant 12% decrease in the risk of death or hospitalization for any reason and 24% fewer hospitalizations for HF, compared to patients receiving lower doses (average of 4.5 $\pm$ 1.1 mg daily). There was also a nonsignificant 8% lower risk of death in the high dose compared to the low dose treatment group. The authors observed that the decrease in risk with the high dose compared to the low dose group in the ATLAS study was approximately half that seen with target doses of an ACEI compared to placebo in other trials. This suggests that even patients on suboptimal doses will derive benefit, although not as great as patients receiving higher doses. This is important to realize since other factors may preclude a patient from achieving target doses.[24] In another trial, patients on high doses of an ACEI (enalapril 20mg/d) had a decreased risk of HF hospitalizations compared to patients on medium and lower doses (enalapril 10mg/d and 5mg/d, respectively). There was no difference between doses in symptoms or mortality.[25] There was also no difference in NYHA class, LVEF, or mortality in a trial of patients on standard (17.9 $\pm$ 4.3mg/d) compared to high (42 $\pm$ 19.3mg/d) doses of enalapril.[26]

Due to the strong evidence for the beneficial effects of ACEIs in patients with HF, every effort should be made to adjust the dosage before a patient is documented as intolerant. Dosage should be modified if the patient develops any of the following:[23]

1. While creatinine often increases (usually < 25%) after initiation of an ACEI, clinically significant decline in renal function (suggested by a change in serum Cr concentration of at least 0.5 mg/dL) should be investigated. Consultation with a nephrologist should be considered for persistent deteriorations in renal function that cannot be explained or corrected.
2. Hyperkalemia (potassium > 5.5 mEq/L), after other causes have been excluded
3. If patient cannot tolerate ACEI due to symptomatic hypotension, consider referral to a cardiologist for assistance in titrating the ACEI dosage
4. The cough associated with an ACEI has been described as dry, nonproductive, persistent, beginning with a tickling sensation, and often worse at night. The onset is usually within the first week of ACEI therapy and continues throughout treatment, resolving within a few days to 4 weeks after the ACEI is discontinued. The cough is not usually dose-dependent, although in some instances it may be eliminated with a reduction in dose. In addition, fosinopril may be considered in patients who experience cough on another ACEI.[27-29] Since therapy with an ACEI has proven valuable, it is important to consider alternative diagnoses (e.g, asthma, chronic obstructive pulmonary disease, allergic rhinitis, upper respiratory tract infection, heart failure, gastroesophageal reflux disease) before a diagnosis of ACEI-induced cough is made. If the cough is not bothersome, the benefits of continuing the ACEI should be discussed with the patient.

Special considerations with ACEI use:[19]

1. The dose of an ACEI needs to be individualized with special consideration to age, indication, renal function, concomitant medication and/or diseases
2. Prior to initiating ACEIs, obtain baseline serum potassium, Cr, and BUN; ACEIs should be used cautiously in patients with serum Cr > 3mg/dL
3. Patients should be monitored and follow-up laboratory tests obtained within 1 to 2 weeks (or sooner if worsening renal function); patients at high risk for hypotension should be seen sooner or can be instructed on home blood pressure monitoring
4. In patients taking diuretics, symptomatic hypotension may occur following initiation of an ACEI; if the diuretic cannot be discontinued, consider a lower starting dose of an ACEI

5. Lower initial doses should be considered in HF patients, doses then should be titrated to maximum tolerated dose
6. Lower doses should be administered for hemodynamically stable post-MI patients
7. Captopril doses greater than 150 mg per day are generally not necessary and are associated with an increased risk of neutropenia or rash and should be used with caution if felt to be clinically justified
8. For most ACEIs, the dose should be reduced in renal dysfunction
9. Avoid concomitant use with potassium-sparing medications and NSAIDs whenever possible; use with caution with spironolactone. NSAIDs used in conjunction with an ACEI may worsen renal function and contribute to hyperkalemia (refer to Appendix B for common drug interactions)
10. There is some controversy as to whether use of aspirin decreases the cardiovascular benefit of an ACEI when used concomitantly. Some of the beneficial effects of ACEIs are thought to be due to inhibiting the breakdown of bradykinin, which in turn, increases the production of vasodilatory prostaglandins. Aspirin, which blocks cyclooxygenase, may therefore interfere with the full benefit of an ACEI by inhibiting vasodilatory prostaglandin synthesis.[30,31] Much of the discussion was prompted from the publication of retrospective analyses of data from large trials evaluating the benefits of treatment with an ACEI.[32,33] A cohort analysis of SOLVD found that treatment with an antiplatelet agent (e.g., aspirin or dipyridamole) was associated with a reduction in all-cause mortality and a decrease in the risk of death or hospital admission for HF. In contrast, this association was not apparent in patients treated with an ACEI who were on an antiplatelet agent at baseline, and patients on an ACEI did not experience a reduction in all-cause mortality as did patients randomized to enalapril who were not on an antiplatelet agent. There was a reduction in the combined risk of death or hospital admission for HF in patients on an ACEI and antiplatelet agent.[32] In an analysis of CONSENSUS II in patients with acute MI, those in the ACEI treatment group who were taking aspirin at baseline experienced a lower mortality benefit than patients who were on an ACEI without aspirin.[33] It is difficult to determine the clinical significance of these results given the retrospective nature of the analyses and the potential contribution of differences in the groups at baseline.[30-33] Given the benefit of aspirin in patients with coronary artery disease, there is insufficient evidence to warrant a change in the current recommendations in patients with coronary artery disease and HF. Ongoing prospective evaluations of warfarin or antiplatelet therapy in patients with HF may provide additional information in order to determine the most appropriate therapy for patients in whom an antiplatelet agent and ACEI are indicated.

**Table 4. ACE Inhibitors[a-b]**

| **Drug** (**Bold** = National Formulary item) | **Usual initial dose for HF (Usual target doses[c])** | **Usual initial dose for other indications[d] (Usual target doses[c])** | **Renal adjustment** |
|---|---|---|---|
| **Captopril[e]** | 6.25-12.5 mg tid<br>(50 mg tid) | **LVD Post-MI**<br>12.5 mg tid<br>(25-50 mg tid) | Start with lower or less frequent doses in patients with renal insufficiency |
| **Enalapril** | 2.5 mg bid<br>(10-20mg bid) | **ALVD[f]**<br>2.5 mg bid<br>(10mg bid) | CrCl < 30 mL/min, initial dose 2.5mg qd |
| **Fosinopril** | 5-10 mg qd<br>(20-40 mg qd) | | Start with 5mg qd if moderate to severe renal failure |
| **Lisinopril** | 2.5-5 mg qd<br>(20-40 mg qd) | **Post-MI**<br>5 mg initially<br>5 mg in 24 hours<br>10 mg 48 hours<br>(10-20 mg qd) | CrCl < 30 mL/min, initial dose 2.5mg qd |

[a] Adapted from Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc., June 2001.
[b] Adapted from 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.
[c] 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
[d] Approved by the U.S. Food and Drug Administration or per clinical trials
[e] One hour before meals, on an empty stomach
[f] ALVD = asymptomatic left ventricular dysfunction

**Pharmacologic recommendations for ACEIs in patients with HF:**

| Strength of Recommendation And Evidence Rating | Overall Quality | Net Effect | References | ACC/AHA Recommendations | Evidence Level |
|---|---|---|---|---|---|
| **Grade A (always indicated and acceptable):** | | | | | |
| Use maximally tolerated doses of ACEIs to improve symptoms and mortality and reduce hospitalizations in patients with HF | Good | Substantial | 1-13 | Class I | A |
| Even lower-dose ACEIs will reduce mortality if target dosage is not tolerated | Good | Moderate | 23-25 | NA | NA |
| **Grade B (may be useful/ effective):** | | | | | |
| None | | | | | |
| **Grade C (may be considered):** | | | | | |
| None | | | | | |
| **Grade D (may not be useful/ effective; possibly harmful):** | | | | | |
| None | | | | | |
| **Grade I (insufficient evidence to recommend for or against):** | | | | | |
| None | | | | | |

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## I. β-Adrenergic Blockers

OBJECTIVE

To provide recommendations for the appropriate use of β-adrenergic blockers in patients with a diagnosis of systolic HF.

ANNOTATION

Activation of the sympathetic nervous system (SNS) is one of the proposed compensatory mechanisms to maintain circulation in the presence of left ventricular dysfunction. However, activation of the SNS can result in β-receptor down-regulation, LVH, cardiotoxic effects, and arrhythmia. It is thought that one or more of these effects may contribute to HF progression.[1-2] Therefore, using a β-adrenergic blocker in a patient with HF due to systolic dysfunction could potentially negate some of these adverse effects on the heart. Until recently, the use of β-adrenergic blockers has been considered contraindicated in patients with HF due to the recognized negative inotropic effects of these agents.

Numerous trials have shown the beneficial effects of β-adrenergic blockers in reducing symptoms, hospitalization, and progression of disease in patients with HF due to systolic dysfunction.[2-17] However, more recent evidence has demonstrated a significant reduction in mortality with the use of β-adrenergic blockers in this patient population[11-17] (Table 5). The β-adrenergic blockers that have been studied for chronic HF and have demonstrated a clear reduction in mortality include bisoprolol, carvedilol and metoprolol. Other β-adrenergic blockers may have similar benefit, however definitive studies evaluating other β-adrenergic blockers are lacking. Patients with stable HF due to systolic dysfunction, with appropriate volume control and adequate afterload reduction, should receive therapy with a β-adrenergic blocker unless contraindicated.[2]

One trial in patients with advanced HF did not show a statistically significant improvement in mortality as was seen in the COPERNICUS trial. The Beta-Blocker Evaluation of Survival Trial (BEST) evaluated 2708 patients with NYHA class III (92%) or IV (8%) HF and a LVEF ≤ 35% who were randomized to placebo or bucindolol (not available in the U.S.). Patients were excluded if their systolic BP was < 80 mm

Hg or HR < 50 bpm. According to the authors, the trial was discontinued after a mean follow-up of 2 years due to the evidence from BEST and other trials that β-adrenergic blockers are beneficial in patients with HF. Upon termination of BEST, there was not a significant difference in the primary endpoint of mortality between the two groups of patients (adjusted P=0.13). The secondary endpoint of cardiovascular death was lower in patients on bucindolol (P=0.04). There were a decreased proportion of patients with HF related hospitalizations (P<0.001) and with the combined endpoint of death or heart transplant (P=0.04). After subgroup analysis, there was a significant survival benefit in nonblack patients (P=0.01) but not in black patients (P=0.27). There was also a trend toward improved survival in patients with less severe HF (P=0.05 in patients with LVEF > 20%). The authors stated that due to the small number of patients with NYHA class IV HF, definitive conclusions could not be made in these patients.[18]

In a subgroup analysis of MERIT-HF, 795 patients with NYHA class III or IV HF with a LVEF < 25% who received placebo or metoprolol XL were compared. Similar to COPERNICUS, the mean baseline LVEF was 19.1% and the annual mortality for patients in the placebo group was 19%. Patients randomized to metoprolol XL experienced a decreased risk of total mortality (39%, P=0.0086), death due to worsening HF (55%, P=0.015), hospitalization due to worsening HF (45%, P<0.0001), and combined all-cause mortality or all-cause hospitalization (29%, P=0.0012) compared to placebo.[19]

In another post hoc analysis of MERIT-HF, the beneficial effects on morbidity and mortality with metoprolol XL were also seen in the subgroup of 898 women, including 183 women with stable severe HF.[20]

The difference in response in black compared to nonblack patients in BEST is contrary to findings from a retrospective comparison of patients enrolled in the U.S. Carvedilol Heart Failure Study where the benefit of carvedilol was not statistically significantly different between black and nonblack patients.[21] A recent meta-analysis by the U.S. Department of Health and Human Services reported the estimate of pooled random-effects of the relative risk for mortality in black patients to be 0.67 (95% CI 0.39-1.16) compared to 0.63 (95% CI 0.52-0.77) for white patients. Results were similar for the pooled estimates from the hazard ratio analysis. The evidence report to address the potential difference in mortality of β-adrenergic blockers depending on race concluded that black patients should derive the same benefits as white patients when treated with bisoprolol, carvedilol, or metoprolol (the results of BEST were not included in the pooled analysis).[22]

The question of whether to use a selective beta-adrenergic blocker (e.g., bisoprolol or metoprolol) versus a non-selective agent with alpha-adrenergic blocking and antioxidant effects (e.g., carvedilol) remains controversial.[23-26] Although the Carvedilol Or Metoprolol European Trial (COMET) demonstrated a statistically significant improvement in survival with carvedilol compared to immediate-release metoprolol (metoprolol tartrate), it is unknown whether there is a difference between carvedilol and immediate-release metoprolol or metoprolol XL (metoprolol succinate) when prescribed at the recommended target doses. Since metoprolol XL was not available at the time of enrollment in COMET, immediate-release metoprolol was selected as the comparator to carvedilol, at doses that were expected to result in comparable β-blockade. Much of the discussion about the results of COMET includes the difference in target dose and effect on resting heart rate. The dose of carvedilol used in COMET achieved a similar reduction in heart rate as seen in U.S. Carvedilol (i.e., 13 beats per minute). The mean dose of immediate-release metoprolol used in COMET was less than the mean dose in the Metoprolol in Dilated Cardiomyopathy (MDC) trial (i.e., 85 vs. 108mg/d), and resulted in less of a decrease in heart rate (i.e., 11.7 vs. 15 beats per minute). The mean dose in MERIT-HF was 159mg/d and achieved a reduction in heart rate of 14 beats per minute.[3,11-13,26,27] Whether these factors had an influence on the results is unknown. Very few trials with β-adrenergic blockers that are available in the U.S. other than bisoprolol, carvedilol, or metoprolol have been published. It is therefore unknown if treatment with other β-adrenergic blockers would provide the same benefits as seen with the agents that have demonstrated a reduction in mortality in patients with heart failure.


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The majority of patients included in the β-adrenergic blocker trials received therapy with an ACEI. Survival benefit in the ACEI trials ranged from 12 to 33%, which was mainly a result of reduction in deaths from worsening HF. Meta-analyses of the β-adrenergic blocker trials show a reduction in mortality of approximately 30 to 35%.[28-31] It is felt that the use of an ACEI and β-adrenergic blocker in patients with HF is synergistic[32] and should be used in combination whenever possible.[2]

**Table 5. β-Adrenergic Blockers in Patients with Systolic HF**

| TRIAL | METHODS | RESULTS | COMMENTS |
|---|---|---|---|
| MERIT-HF[11]<br><br>R, DB, PC | 3991 pts; mean age 63.9 yrs<br>Sx HF; 62% ischemic etiology<br>NYHA class: 41% II, 56% III, 3.4% IV<br>Mean EF: 28%<br>F/U: mean 12 months<br>Metoprolol (mean 159 mg/d)<br>Addnl tx: ACEI, diuretics, 2/3 digoxin<br>PEP: all-cause mortality | Metoprolol ↓ PEP 34% (P=0.00009), ARR 3.6%; 41% ↓ sudden death, 49% ↓ death from worsening HF | Study stopped early because of mortality benefit<br>NNT (PEP)=27.8 |
| CIBIS II[12]<br><br>R, DB, PC | 2647 pts; mean age 61 (22-80) yrs<br>50% CAD<br>NYHA class: 83% III, 17% IV<br>Mean EF: 27.5%<br>F/U: mean 1.3 yrs<br>Bisoprolol (majority 10mg/d)<br>Addnl tx: ACEI, diuretics, 53% digoxin<br>PEP: all-cause mortality | Bisoprolol ↓ PEP 34% (P<0.0001), ARR 5.5%; ↓ hosp, CV deaths, sudden death | Trial stopped early due to improved survival;<br>subgroup analysis, class IV did not benefit as much, but not sig different<br>NNT (PEP)=18.2 |
| US Carvedilol[13] (Survival)<br><br>R, DB, PC | 1094 pts; mean age 58 yrs<br>ischemic or nonischemic etiology<br>NYHA class: majority II and III<br>Mean EF: 23%<br>Median F/U: 6.5 months<br>Carvedilol mean 45 ± 27mg/d<br>Addnl tx: ACEI, loop diuretic, digoxin<br>PEP: death or hosp due to CV reasons | Carvedilol 38% ↓ combined death or CV hosp (P<0.001), ARR 8.8%; 65% ↓ risk of death (P<0.001), ARR 4.6%; 27% ↓ risk CV hosp (P=0.036) | Trial stopped early due to sig improved survival with carvedilol<br>NNT (PEP)=11.4;<br>NNT (death)=21.7 |
| COPERNICUS[14,15]<br><br>R, DB, PC | 2289 pts; mean age 63 yrs<br>ischemic or nonischemic etiology<br>Severe HF (≥ 2 months dyspnea/fatigue at rest or minimal exertion, EF < 25%)<br>Mean EF: 19.9%<br>Median F/U: 10.4 months<br>Carvedilol (mean 37 mg/d)<br>Addnl tx: ACEI/AIIRA, diuretic, digoxin<br>PEP: all-cause mortality | Carvedilol ↓ PEP 35% (P=0.0014), ARR 5.5%; 24% ↓ risk combined death or hosp (P<0.001)[14]<br>27% ↓ risk combination death or CV hospitalization (P=0.00002); 31% ↓ risk combination death or HF hospitalization (P=0.000004)[15] | Trial stopped early due to sig improved survival with carvedilol. Annual placebo mortality of 19.7% per patient year of follow-up.<br>NNT (PEP): 18.2 |
| COMET[26]<br><br>R, DB, PG | 3029 pts; mean age 62yrs<br>Sx HF, previous CV admission w/in past 2 yrs<br>> 50% ischemic etiology<br>NYHA class: 48-49% II, 47-48% III, 3-4% IV<br>Mean EF: 26%<br>Median F/U: 58 months<br>Carvedilol (mean 41.8 ± 14.6mg/d)<br>Metoprolol IR (mean 85 ± 28.9mg/d)<br>Addnl tx: ACEI, diuretic<br>PEP: all-cause mortality | Carvedilol ↓ PEP 17% vs. metoprolol (P=0.017), ARR 5.6%<br>Composite all-cause mortality or all-cause hosp (P=0.122) | 78% metoprolol 50mg bid (target dose)<br>75% carvedilol 25mg bid (target dose)<br>NNT(PEP): 17.7 |

ACEI=angiotensin-converting enzyme inhibitor; Addnl tx=additional treatment; ARR=absolute risk reduction; AIIRA=angiotensin II receptor antagonist; CAD=coronary artery disease; CV=cardiovascular; DB=double-blind; EF=ejection fraction; F/U=follow-up; HF=heart failure; hosp=hospitalizations; NNT=number needed to treat; PC=placebo-controlled; PEP=primary endpoint; Pts=patients; R=randomized; sig=significantly; Sx=symptoms; yrs=years

Caution should be exercised when initiating these agents in patients with HF. Initial dosages should be low and titrated upward slowly and as tolerated. Patients can become transiently worse with each dosage increase. Since patients may experience fluid retention during initiation, daily weights are recommended with corresponding adjustments in diuretic dose. Some patients may also experience fatigue or weakness that may resolve after several weeks or require dosage adjustments. Another factor that may contribute to a need for a delay in titration is a low heart rate.[33] Clinicians who do not have experience with β-adrenergic blockers in patients with HF should consult with a cardiologist. It is important that patients with HF on a β-adrenergic blocker are titrated carefully to a target dose as used in clinical trials (refer to Table 6) or as tolerated.

Factors that appear to contribute to a beneficial response are selection of patients who are clinically stable (i.e, not hospitalized in intensive care, no or minimal evidence of volume overload or depletion, no recent treatment with intravenous positive inotropic agents) when therapy starts, a low initial dosage, a gradual increase in the dosage (2 week intervals), and an adequate duration of treatment (3-12 months before effects are seen).

β-adrenergic blockers should not be used in patients with bronchospastic disease, symptomatic bradycardia, or advanced heart block without a pacemaker. Caution should be used in patients with asymptomatic bradycardia with a HR of less than 60 bpm.[2] If the patient is on digoxin with a HR of less than 60 bpm, reconsider digoxin in favor of the benefits of a β-adrenergic blocker, or consider referral to a cardiologist for adjustment in therapy. It should be noted that patients with DM or chronic obstructive pulmonary disease were not excluded from the clinical trials.[2,11-13,34]

Common drug interactions are listed in Appendix B.

**Table 6. β-Adrenergic Blockers[a,b]**

| DRUG (**Bold** = National Formulary item) | DOSE RANGE | COMMENTS/CAUTIONS |
|---|---|---|
| *β-adrenergic blockers with positive outcomes in systolic dysfunction[b]* | | |
| **Cardioselective**<br><br>**Metoprolol XL[c]**<br><br>Bisoprolol<br><br>**α & β antagonist**<br>**Carvedilol[d]** | <br><br>Initial dose 12.5-25mg qd; double dose every 2 weeks to target dose 200mg qd (or highest dose tolerated)<br><br>Initial dose 1.25mg qd; increase by 1.25mg q week until 5mg qd, then increase by 2.5mg every 4 weeks to target dose 10mg qd<br><br>Initial dose 3.125mg bid; titrate at minimum of every 2 weeks to target 25mg bid (patients ≥ 85 kg may be titrated to 50mg bid with caution) | • Cardioselectivity is dose related<br>• Caution should be used when using β-adrenergic blockers in patients with systolic dysfunction<br>• Low initial doses should be implemented<br>• Use slow gradual increases in the dosage<br>• Effects are generally seen in 3-12 months<br>• Carvedilol should be given with food to reduce the incidence of orthostatic hypotension<br>• Consider separating the ACEI, adjusting dose of diuretic, or temporary ACEI dose reduction if dizziness occurs<br>• Should not be abruptly discontinued |

[a] Adapted from Beta-adrenergic blocking agents. In: Hebel SK, ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc., July 2001.
[b] Refer to PBM-MAP Recommendations for use of β-adrenergic blockers in VA patients with HF, available at www.vapbm.org or http://vaww.pbm.med.va.gov
[c] FDA approved for the treatment of stable, NYHA class II or III HF
[d] FDA approved for the treatment of mild to severe HF


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**Pharmacologic recommendations for β-adrenergic blockers in patients with HF:**

| Strength of Recommendation and Evidence Rating | Overall Quality | Net Effect | References | ACC/AHA Recommendations | Evidence Level |
|---|---|---|---|---|---|
| **Grade A (always indicated and acceptable):** | | | | | |
| Use a β-adrenergic blocker in patients with stable HF (Stage C) on standard therapy | Good | Substantial | 11-17 | Class I | A |
| **Grade B (may be useful/ effective):** | | | | | |
| None | | | | | |
| **Grade C (may be considered):** | | | | | |
| None | | | | | |
| **Grade D (may not be useful/ effective; possibly harmful):** | | | | | |
| None | | | | | |
| **Grade I (insufficient evidence to recommend for or against):** | | | | | |
| None | | | | | |

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## J. Angiotensin II Receptor Antagonists (AIIRAs)

OBJECTIVE

To provide recommendations for the appropriate use of AIIRAs (also referred to as ARBs) in patients with a diagnosis of systolic HF.

ANNOTATION

ACEIs reduce levels of angiotensin II, a potent vasoconstrictor, and inhibit the breakdown of bradykinin, a vasodilator. Production of angiotensin II also occurs through alternative pathways. The AIIRAs, on the other hand, selectively block the angiotensin II type1 receptor so that the effects of angiotensin II are blocked regardless of how it is produced. The AIIRAs do not inhibit the angiotensin II type 2 receptor which is thought to have beneficial effects such as vasodilation and inhibition of proliferative and hypertrophic responses.[1] The AIIRAs do not affect bradykinin, which is thought to be responsible for the cough that occurs in up to 39% of patients taking an ACEI. The incidence of cough in patients treated with an AIIRA is similar to that with placebo. The contribution of bradykinin to the favorable results of the ACEI trials in HF patients is unknown, but may be as important as suppression of angiotensin.

In the ELITE (Evaluation of Losartan in the Elderly) Study, the AIIRA losartan was compared to an ACEI, captopril, in 722 patients with NYHA class II to IV HF and LVEF < 40%. Patients were randomized to losartan (up to 50mg) once daily or captopril (up to 50mg) three times daily for 48 weeks. Seventy-five percent of patients in the losartan group and 71% of patients in the captopril group received target doses. The majority of patients were prescribed diuretics and 55% were taking digoxin at the time of study enrollment. The primary endpoint of the study was the effect of treatment on serum Cr ($\geq$ 0.3mg/dL increase). There was no difference between treatment groups in the rise in serum creatinine during continued treatment. Death and/or hospitalization for HF occurred in 9.4% of patients on losartan and 13.2% on captopril (32% risk reduction, P=0.075). These results were primarily due to a 46% decrease in all-cause mortality in patients on losartan compared to patients on captopril (P=0.035), primarily due to a reduction in sudden cardiac death. The two treatment groups did not differ in the frequency of hospital admission for HF. NYHA functional class improved significantly and similarly compared to baseline for both groups. More patients in the captopril group (20.8%) withdrew from the study due to adverse events

compared to patients in the losartan group (12.2%). Cough was reported in 3.8% of patients taking captopril compared to 0% in losartan treated patients.[2] The favorable mortality rate in the losartan group was not hypothesized *a priori*. Therefore, replication of the results was attempted in ELITE II.

ELITE II enrolled 3,152 HF patients to evaluate the effects of losartan 50mg once daily compared to captopril 50mg three times daily on overall mortality and cardiac events (sudden cardiac death or resuscitated cardiac arrest). There was no significant difference in all-cause mortality between the treatment groups (17.7% on losartan vs. 15.9% on captopril, P=0.16). There was no difference between the groups in sudden death or resuscitated cardiac arrest, or hospital admissions. However, this was a superiority trial not designed to detect equivalence between groups. Therefore, losartan and captopril cannot be concluded to be the same. Patients receiving captopril had significantly more adverse effects resulting in discontinuation of the drug than patients on losartan (P<0.001).[3]

The RESOLVD Pilot Study compared candesartan, enalapril, and the combination of the two agents in 768 patients with NYHA class II to IV HF with a LVEF < 40%. Patients were placed on candesartan (4, 8, or 16mg), candesartan (4 or 8mg) plus enalapril (20mg), or enalapril (20mg) for 43 weeks. The primary endpoints were exercise tolerance, ventricular function, quality of life, neurohormone levels, and tolerability. There was no significant difference between the treatment groups in results of the six-minute walk test, NYHA functional class, or quality of life. There was a trend toward an increase in ejection fraction, although not significant, in the patients treated with candesartan and enalapril compared to patients on candesartan or enalapril. End-diastolic and end-systolic volumes increased less with combination therapy compared with patients on candesartan or enalapril alone. There appeared to be a benefit of combination therapy on the patient's neurohormonal profile.[4] Although not powered to evaluate morbidity and mortality, another analysis suggested that there might be an increase in HF hospitalizations in the patients receiving candesartan by 3-way group comparison.[5]

More recently, the results of the Val-HeFT (Valsartan Heart Failure Treatment) study were published. The trial included 5,010 patients with NYHA class II (62%), III (36%), or IV (2%) HF on standard therapy (diuretics: 85%; ACEI: 93%; β-adrenergic blockers: 35%; and digoxin 67%). Baseline LVEF was 27%. Patients were randomized to therapy with either valsartan (40mg twice daily, titrated to a target of 160mg twice daily) or placebo. Mean follow-up was 23 months. The two primary endpoints were mortality and the combined endpoint of mortality and morbidity (i.e., cardiac arrest with resuscitation, HF hospitalization, or intravenous inotropic agents or vasodilators for over 4 hours). Overall mortality was similar, occurring in 19.7% of patients in the valsartan group and 19.4% of patients on placebo (P=0.80). The combined primary endpoint occurred in 28.8% and 32.1% of patients on valsartan and placebo, respectively (RR 0.87 CI 0.77-0.97, P=0.009; ARR 3.3%; NNT=30.3). This included a reduction in hospitalizations for HF (13.8% valsartan vs. 18.2% placebo; ARR 4.4%; NNT=22.7). However, death from any cause (as first event) was higher in patients on valsartan compared to patients receiving placebo (14.2% vs. 12.6%, respectively). According to a subgroup analysis, there was an increased risk of mortality (P=0.009) and a trend toward an increased risk of combined morbidity and mortality (P=0.10) in patients receiving valsartan in conjunction with an ACEI and β-adrenergic blocker. Patients who were not on an ACEI or β-adrenergic blocker experienced a significant reduction in mortality (P=0.012). Patients on valsartan but not on an ACEI (with or without a β-adrenergic blocker) had a lower risk of death (RR 0.67, CI 0.42-1.06) and a lower risk of the combined endpoint (RR 0.56, CI 0.39-0.81).[6] A subanalysis of the 366 patients in Val-HeFT who were not on an ACEI was recently published. In these patients there was a 33% decrease in all-cause mortality (P=0.017) and a 53% decrease in combined morbidity and mortality (P<0.001). The authors conclude that valsartan is an appropriate alternative in patients who are unable to tolerate and ACEI for the treatment of HF.[7]

The AIIRAs have yet to be shown to be equivalent or superior to the ACEIs in patients with HF. According to a recent meta-analysis of 12,469 patients, the AIIRAs were not found to be superior to an ACEI in reducing mortality or hospitalizations. There was a trend toward improved mortality and hospitalizations with an AIIRA compared to placebo in patients not on an ACEI, and the combination of an AIIRA and ACEI significantly reduced the risk of hospitalizations compared to patients on an ACEI alone.[8] In a previous meta-analysis of 1,896 patients, losartan contributed to a mortality benefit compared to a

control group of either placebo or an ACEI, but this meta-analysis did not include the more recent outcome trials with an AIIRA in patients with HF.[9]

An AIIRA should not be considered unless a patient is unable to tolerate an ACEI due to uncontrolled cough (or with caution in patients with history of angioedema; refer to discussion below).[10] The benefit of an AIIRA in combination with an ACEI is still to be determined.[11] Since the benefits of an ACEI in conjunction with a β-adrenergic blocker is well-defined and there may be a detrimental effect in patients on an AIIRA with an ACEI and β-adrenergic blocker, an AIIRA should not be used unless the patient is intolerant to an ACEI or unable to take a β-adrenergic blocker. Additional information on the role of an AIIRA in patients with HF may be determined with the results of CHARM (candesartan in HF-assessment of reduction in mortality and morbidity).[12]

The incidence of cough is estimated to be anywhere from 0 to 39% in patients treated with an ACEI.[13] In SOLVD, cough was reported in 37% of patients treated with enalapril compared to 31% of patients randomized to placebo.[14] In V-HeFT II, 37% of patients on enalapril complained of cough compared to 29% receiving HYD/ISDN.[15] The incidence of cough associated with the AIIRAs is similar to placebo (2.6 to 3.4% vs. 1.5 to 3.3%).[12] In the ELITE Study, 3.8% of patients on an ACEI withdrew from the study due to complaints of cough compared to 0% of patients treated with an AIIRA.[2] Use of an AIIRA can be considered in patients who are unable to tolerate treatment with an ACEI due to cough, although there is a slight chance that patients may develop a cough with an AIIRA.[16]

The incidence of angioedema in patients taking ACEIs is approximately 0.1-1.2 %.[13] It has been reported that black American patients have an increased relative risk of 4.5 of angioedema associated with use of an ACEI compared to white patients.[17] There are at least 20 published case reports of angioedema in patients treated with an AIIRA. In over one-third of these cases, the patients previously experienced angioedema with an ACEI.[13, 18-26] Almost 100 cases have been reported to the Therapeutic Goods Administration of Australia as of April 2001. Therefore, if an AIIRA is considered appropriate in a patient who has previously experienced angioedema, it should be used with caution.[18, 27]

The angiotensin II receptor antagonists, like the ACEIs, decrease release of aldosterone from the adrenal cortex, which can lead to potassium reabsorption. It is unclear at this time if treatment with an AIIRA would be an appropriate alternative in patients who develop hyperkalemia on an ACEI. In SOLVD, hyperkalemia with potassium levels greater than 5.5 mmol/L was reported in 6.4% of patients on enalapril compared to 2.5% of patients on placebo.[14] In the ELITE Study, an increase in serum potassium of $\geq$ 0.5 mmol/L above baseline was observed in 22.7% patients receiving captopril compared to 18.8% of patients on losartan.[2] The proportion of patients with potassium levels $\geq$ 5.5 mmol/L did not differ significantly among the treatment groups in the RESOLVD Pilot Study.[4] The VAL-K Study Group reported that the change in serum potassium was not significantly different in patients on lisinopril compared to valsartan with mild renal insufficiency. In patients with moderate renal insufficiency with a GFR $\leq$ 60mL/min/1.73 $m^2$, there was a significant increase of 0.28 mEq/L (P=0.04) above baseline (4.6 mEq/L). The increase of 0.12 mEq/L seen with valsartan in this subgroup was not significant (P=0.1).[28] Therefore, if use of a diuretic is contraindicated or is not effective in reducing hyperkalemia, an AIIRA may be considered instead of an ACEI, under close monitoring, in patients with moderate renal insufficiency who develop hyperkalemia on an ACEI.

Patients receiving an AIIRA in conjunction with potassium supplements or potassium-sparing diuretics (including spironolactone) may result in an increased potassium level. Other clinically significant drug interactions with the AIIRAs are listed in Appendix B.

**Table 7. Angiotensin II Receptor Antagonists[a-c]**

| DRUG | DOSE RANGE | COMMENTS/CAUTIONS |
|---|---|---|
| Candesartan<br>4, 8, 16, 32mg tablets | 4-32mg<br>divided qd-bid | • All AIIRAs are contraindicated in 2nd and 3rd trimesters pregnancy due to potential neonatal/fetal morbidity and death<br>• Consider lower doses in patients with intravascular volume depletion<br>• Use AIIRAs with caution in patients with renal artery stenosis<br>• Initiate losartan at 25mg and use telmisartan with caution in patients with hepatic impairment |
| Eprosartan<br>400, 600mg tablets | 400-800mg<br>divided qd-bid | |
| Irbesartan<br>75, 150, 300mg tablets | 75-300mg qd | |
| Losartan<br>25, 50, 100mg tablets | 25-100mg<br>divided qd-bid | |
| Olmesartan<br>5, 20, 40mg tablets | 5-40mg qd | |
| Telmisartan<br>40, 80mg tablets | 20-80mg qd | |
| Valsartan<br>80, 160, 320mg tablets | 80-320mg qd (divided bid in Val-HeFT) | |

[a] Adapted from McEvoy GK, ed. American Hospital Formulary Service Drug Information, Bethesda, MD:American Society of Health-System Pharmacists, Inc., 2000.
[b] Adapted from Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc., July 2002.
[c] Refer to PBM-MAP AIIRA Criteria for Use in Veteran Patients, available at www.vapbm.org or http://vaww.pbm.med.va.gov

**Pharmacologic recommendations for AIIRAs in patients with HF:**

| Strength of Recommendation and Evidence Rating | Overall Quality | Net Effect | References | ACC/AHA Recommendations | Evidence Level |
|---|---|---|---|---|---|
| **Grade A (always indicated and acceptable):** | | | | | |
| None | | | | | |
| **Grade B (may be useful/ effective):** | | | | | |
| Use an AIIRA in patients on standard therapy who cannot tolerate an ACEI due to cough and possibly, angioedema | Fair | Moderate | 2-10 | Class IIa | A |
| **Grade C (may be considered):** | | | | | |
| Use an AIIRA in addition to an ACEI in patients with HF, if not on a β-adrenergic blocker | Fair | Moderate | 6,8,10,11 | Class IIb | B |
| **Grade D (may not be useful/ effective; possibly harmful):** | | | | | |
| Use an AIIRA instead of an ACEI in patients who are able to tolerate an ACEI | Fair | Negative | 2-6,8-10 | Class III | B |
| Use an AIIRA before a β-adrenergic blocker in patients who are unable to tolerate an ACEI | Fair | Negative | 6,10 | Class III | A |
| **Grade I (insufficient evidence to recommend for or against):** | | | | | |
| None | | | | | |

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## K. Hydralazine/Isosorbide Dinitrate

OBJECTIVE

To provide recommendations for the appropriate use of HYD/ISDN in patients with a diagnosis of systolic HF.

ANNOTATION

Patients with contraindications to or who cannot tolerate an ACEI present a dilemma since ACEIs are the preferred agents for afterload reduction.[1,2] While no studies have specifically addressed the combination of HYD/ISDN in patients with HF who cannot tolerate ACEIs, treatment with HYD/ISDN has been shown to reduce mortality by two years compared to placebo (risk reduction 34%, CI 0.04 to 0.54, P<0.028; ARR 5.29%; NNT=18.9).[3] A similar mortality rate was found in another study in HF patients (majority with NYHA class II or III HF) treated with HYD/ISDN compared with an ACEI, although mortality after two years was lower in patients treated with an ACEI compared with patients on HYD/ISDN (risk reduction 28.2%, P=0.016; ARR 7.0%; NNT=14.3).[4] As discussed in Annotation H, there may be racial differences in response to therapy with the ACEIs where black patients may not derive as much benefit as seen in white patients. The opposite may occur with HYD/ISDN, where there has been a greater benefit in black patients compared to white patients.[5,6] It is unknown at this time if recommendations for HF therapy should be modified based on these findings.

Peripheral vasodilators such as HYD (arterial vasodilator) and ISDN (venodilator) can produce favorable hemodynamic effects in patients with HF. Although the benefit of HYD/ISDN in combination with an ACEI and/or a β-adrenergic blocker has not been evaluated, this combination may be considered in patients who do not achieve adequate response with standard therapy.[1]

Side-effects such as headache, tachycardia, flushing, hypotension, and edema, as well as dosing frequency, preclude the use of this regimen in as many as one third of patients. Other adverse effects reported with hydralazine include rash, arthralgia, and other lupus-like symptoms. Common drug interactions are listed in Appendix B.

**Table 8. Use of HYD/ISDN in Patients with Systolic Dysfunction[a,b]**

| DRUG (**Bold** = National Formulary item) | DOSE RANGE | COMMENTS/CAUTIONS |
|---|---|---|
| **Hydralazine** (HYD) | initial= 75 mg/d (in 3-4 divided doses) range= 75-300 mg/d (in 3-4 divided doses) (average dose V-HeFT II was 200 mg/d[4]) | • Monitor adverse effects: dizziness, headache, lupus-like syndrome, nausea, tachycardia, postural hypotension<br>• Advise patient to take with food |
| **Isosorbide dinitrate** (ISDN) | initial= 30 mg/d (in 3 divided doses) range=30-160mg/d (in 3 divided doses) (average dose V-HeFT II was 100 mg/d[4]) | • Monitor adverse effects: flushing, headache, postural hypotension, rash<br>• May cause an increase in ocular pressure; caution with presence of glaucoma |

[a] Adapted from Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc., January 2000.
[b] Adapted from 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.

**Pharmacologic recommendations for HYD/ISDN in patients with HF:**

| Strength of Recommendation And Evidence Rating | Overall Quality | Net Effect | References | ACC/AHA Recommendations | Evidence Level |
|---|---|---|---|---|---|
| **Grade A (always indicated and acceptable):** | | | | | |
| None | | | | | |
| **Grade B (may be useful/ effective):** | | | | | |
| Use HYD/ISDN (in patients on standard therapy) in patients intolerant to ACEIs, especially for those with hypotension, renal insufficiency, and possibly angioedema on an ACEI | Fair | Moderate | 1-4 | Class IIa | B |
| **Grade C (may be considered):** | | | | | |
| Use HYD/ISDN in patients already taking an ACEI and β-adrenergic blocker | Poor | Small | 3,4 | Class IIb | B |
| **Grade D (may not be useful/ effective; possibly harmful):** | | | | | |
| Use HYD/ISDN to reduce mortality in patients who have not been given a trial of an ACEI and/or β-adrenergic blocker | Fair | Negative | 1-4 | NA | NA |
| **Grade I (insufficient evidence to recommend for or against):** | | | | | |
| None | | | | | |

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## L. Digoxin

OBJECTIVE

To provide recommendations for the appropriate use of digoxin in patients with a diagnosis of systolic HF.

ANNOTATION

Digoxin is thought to be beneficial in patients with systolic HF through inhibition of sodium-potassium adenosine triphosphatase resulting in increased contractility of the heart and reduced activation of the neurohormonal system.[1] The use of agents with positive inotropic activity as the mainstay of therapy for HF has decreased over the years. This has primarily been due to the increased mortality associated with some of the agents in this class. Digoxin continues to have a role in the treatment of patients with HF by improving patient symptoms and decreasing hospitalizations and not adversely affecting survival.[2,3]

According to a meta-analysis, treatment with digoxin in patients with HF due to systolic dysfunction can reduce the incidence of clinical deterioration by 12% compared to patients on placebo.[4] The Randomized Assessment of (the effect of) Digoxin on Inhibitors of the Angiotensin-Converting Enzyme (RADIANCE) Study evaluated 178 patients with NYHA class II or III HF stabilized on digoxin, diuretics, and an ACEI. Patients were randomized to continuation of treatment or withdrawal of digoxin therapy for 12 weeks. Patients who were withdrawn from digoxin experienced worsening HF ($P<0.001$) and a decreased exercise tolerance ($P=0.033$), worsening NYHA class ($P=0.019$), decreased quality of life ($P=0.04$) and LVEF ($P=0.001$; digoxin $0.27 \pm 0.01$ and $0.26 \pm 0.01$ compared to placebo $0.30 \pm 0.01$ and $0.26 \pm 0.01$, before and after treatment, respectively).[5] The Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin (PROVED) trial was a study evaluating 88 patients with NYHA class II or III HF on digoxin and diuretics and the effect of digoxin withdrawal or continuation of therapy. Patients who had digoxin withdrawn experienced a worsening of maximum exercise performance, a higher percentage of treatment failures, and a decreased time to treatment failure.[6]

These trials demonstrate the benefit of digoxin in reducing symptoms associated with mild to moderate HF. The Digitalis Investigators Group (DIG) trial evaluated the benefit of digoxin on survival. This trial enrolled 6,800 patients on diuretics and an ACEI who were randomized to receive digoxin or placebo for a mean of 37 months. The results showed that treatment with digoxin significantly decreased the risk for hospitalizations due to HF by 28%, although there was no significant reduction in mortality with digoxin treatment.[2] In a recent post hoc analysis of the DIG trial, a decrease in the rate of cardiovascular deaths and deaths from worsening HF was found in the men (n=5281), but not in the women who were treated with digoxin (n=1519). The death rate in women on digoxin was higher than women randomized to placebo (33.1% vs. 28.9%, respectively; P=0.078). There was a decrease in hospitalizations for worsening HF in women on digoxin compared to women on placebo (30.2% vs. 34.4%, respectively; P=0.079). Due to these findings, the authors suggest that the role of digoxin in women be reevaluated.[7] Others suggest that a

lower dose with a resultant serum concentration < 1ng/ml be used as there was a significant difference in the digoxin concentration (random measurement in approximately one-third of patients at 1 month) that may have accounted for the difference in outcome (0.9ng/ml in women vs. 0.8ng/ml in men; P=0.007).[7,8]

Digoxin is recommended in patients with symptomatic HF, without bradycardia, to improve clinical status and thereby decrease the risk of hospitalization due to HF. Treatment is usually initiated in conjunction with a diuretic, ACEI, and β-adrenergic blocker since these latter two classes of agents have been shown to improve survival in patients with HF.[1] If there is no symptomatic improvement after one to two months of therapy, the risk vs. benefit of continued digoxin therapy should be considered. Digoxin is the drug of choice to control rapid ventricular response in patients with systolic dysfunction and atrial fibrillation.[1]

Loading doses are not necessary for patients in normal sinus rhythm. The most commonly prescribed dose of digoxin is 0.125-0.25mg/day. Initial dosing should be conservative (e.g., 0.125mg qd or qod) especially for patients with reduced CrCl, decreased weight and/or decreased muscle mass. The utility of monitoring serum digoxin levels to assess efficacy has not been established.[1] Subgroup analysis from the DIG trial as well as in the Prospective Randomized Milrinone Survival Evaluation (PROMISE) trials showed that higher concentrations (even within the therapeutic range) were associated with an increased risk of mortality.[9-12] In both the RADIANCE and PROVED trials, the mean digoxin serum concentration was 1.2 ng/ml and in the DIG trial, the mean serum digoxin level was 0.8 ng/ml at 12 months.[5,6,10,12] In a meta-analysis of the PROVED and RADIANCE trials, the clinical efficacy (e.g., worsening HF, change in LVEF, treadmill time) of low (0.5-0.9ng/ml), moderate (0.9-1.2ng/ml), and high (>1.2ng/ml) serum digoxin concentrations were compared. There was no relationship between the endpoints and the three groups. The authors concluded that lower levels may therefore provide similar outcomes without the risk of detrimental effects seen with higher levels[13] although levels are not typically drawn unless monitoring for toxicity.

In general, trough (or a minimum of 6 hours post dose due to distribution) serum digoxin levels should be monitored if any of the following occurs:[14]

1. HF worsens or renal function deteriorates
2. Signs of toxicity develop (e.g., confusion, nausea, vomiting, abdominal pain, diarrhea, anorexia, fatigue, arrhythmias, visual disturbances)
3. Dose adjustments are made
4. Additional medications are added that affect the serum digoxin concentration (e.g., quinidine, verapamil, amiodarone, antibiotics, anticholinergics) (refer to Appendix B)

**Pharmacologic recommendations for digoxin in patients with HF:**

| Strength of Recommendation And Evidence Rating | Overall Quality | Net Effect | References | ACC/AHA Recommendations | Evidence Level |
|---|---|---|---|---|---|
| **Grade A (always indicated and acceptable):** | | | | | |
| Use digoxin to improve functional status and reduce frequency of hospitalizations if continued symptoms on a diuretic and ACEI | Good | Moderate | 1-8 | Class I | A |
| **Grade B (may be useful/ effective):** | | | | | |
| None | | | | | |
| **Grade C (may be considered):** | | | | | |
| None | | | | | |
| **Grade D (may not be useful/ effective; possibly harmful):** | | | | | |
| Use digoxin in patients in normal sinus rhythm who are not on an ACEI and β-adrenergic blocker | Good | Negative | 1-8 | NA | NA |
| Use digoxin to improve survival in patients with HF | Good | Zero | 2,3 | NA | NA |
| **Grade I (insufficient evidence to recommend for or against):** | | | | | |
| None | | | | | |

**References:**

[1] 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
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## M. Aldosterone Antagonists

OBJECTIVE

To provide recommendations for the appropriate use of aldosterone antagonists in patients with a diagnosis of systolic HF.

ANNOTATION

Aldosterone antagonists (e.g., spironolactone) competitively inhibit the effects of aldosterone. One of the proposed mechanisms for benefit of using ACEIs in patients with HF is that of suppression of production of aldosterone. Additional therapy with an aldosterone antagonist was originally felt not to be necessary and could cause an increase in the risk of hyperkalemia due to potential for potassium retention if aldosterone is decreased. Evidence has shown that addition of an aldosterone antagonist may be beneficial in patients with severe HF (recent NYHA class IV HF and current class III or IV symptoms and LVEF $\leq$ 35%), even in patients already receiving an ACEI.[1, 2] This suggests that therapy with an ACEI may not achieve long-term suppression of aldosterone production. There is insufficient evidence to make a recommendation as to the use of aldosterone antagonists in patients with mild to moderate HF.

These recommendations are based on a study that enrolled 1663 patients with severe class IV HF within the last 6 months (and class III or IV at time of enrollment), a LVEF $\leq$ 35% within the last 6 months, and treated with conventional therapy (95% ACEI, 100% loop diuretic, 75% digoxin). In addition, 11% of patients were on a β-adrenergic blocker. Patients were randomized to spironolactone 25mg once daily or placebo. The primary endpoint was to evaluate all-cause mortality. After a mean follow-up of 24 months, the trial was discontinued early due to a 30% reduction in the risk of death due to progressive HF and sudden death of a cardiac cause in patients in the spironolactone group (RR 0.70, 95% CI 0.60-0.82, P<0.001; ARR 11.4%; NNT=8.8). Patients on spironolactone also had a 35% decrease in hospitalizations due to worsening HF (P<0.001) and experienced a significant improvement in symptoms (P<0.001) resulting in some patients dropping into a lower NYHA class.[2]

These are highly complex patients with a high mortality rate and should be cared for by a multidisciplinary HF team including a primary care provider in consultation with a cardiologist. The risk vs. benefit of using spironolactone in these patients needs to be determined. Spironolactone may contribute to serious hyperkalemia if not used properly in patients with HF.[4]

In addition to gastrointestinal side effects, aldosterone antagonists can cause gynecomastia, hyperkalemia, and menstrual irregularities. In the study, gynecomastia or breast pain was reported in 10% of male patients in the spironolactone group. The incidence of hyperkalemia was not significant. However, it should be noted that patients with serum creatinine > 2.5 mg/dL and serum potassium > 5.0 mmol/L were excluded from the study and patients were not taking other potassium-sparing diuretics. Hyperkalemia occurs more frequently in patients receiving potassium supplements and in patients with renal insufficiency. Use of potassium supplements with spironolactone should be avoided unless hypokalemia develops. Spironolactone should be used with caution in patients with renal insufficiency; patients should be scheduled for follow-up electrolytes and renal function after initiation and dose adjustments. Spironolactone should also be used with caution in patients receiving ACEIs due to the potential for hyperkalemia; potassium should be monitored closely in these patients.[3] Serum potassium should be monitored at 1 week and every 4 weeks for the first 3 months, then every 3 months for the first year and every 6 months thereafter.[2,4] More frequent monitoring may be indicated in patients on concomitant medications that may increase potassium levels, with renal insufficiency or DM, who are of advanced age, experiencing worsening HF or conditions that may contribute to dehydration.[5,6] If the potassium increases to > 5.4 mmol/L, the dose of spironolactone should be reduced. If serious hyperkalemia develops, spironolactone should be discontinued.[1]

The initial dose of spironolactone used was 25mg once daily. The dose was decreased to 25mg every other day in patients exhibiting hyperkalemia. The dose was increased to 50mg once daily at 8 weeks in patients who had signs or symptoms of worsening HF and did not have hyperkalemia. Patients receiving 50mg spironolactone should have their serum potassium measured one week after the dose was increased, and then follow-up as described above.[4] Refer to Appendix B for common drug interactions.

**Pharmacologic recommendations for spironolactone in patients with HF:**

| Strength of Recommendation and Evidence Rating | Overall Quality | Net Effect | References | ACC/AHA Recommendations | Evidence Level |
|---|---|---|---|---|---|
| **Grade A (always indicated and acceptable):** | | | | | |
| None | | | | | |
| **Grade B (may be useful/ effective):** | | | | | |
| Low dose (12.5 to 25mg/d) spironolactone in patients with severe HF (recent NYHA class IV HF and current class III or IV symptoms), provided the potassium is normal (< 5 mmol/L) and renal function adequate (serum Cr ≤ 2.5 mg/dL) | Good | Substantial | 1,2 | Class IIa | B |
| **Grade C (may be considered):** | | | | | |
| None | | | | | |
| **Grade D (may not be useful/ effective; possibly harmful):** | | | | | |
| None | | | | | |
| **Grade I (insufficient evidence to recommend for or against):** | | | | | |
| None | | | | | |

## References:

[1] 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

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## N. Continue Present Management and Schedule Regular Follow-up

OBJECTIVE

To provide recommendations for appropriate follow-up of patients with a diagnosis of systolic HF.

ANNOTATION

Patients should be scheduled for regular follow-up in order to provide the most effective care. At each encounter, an inquiry should be made as to the patient's adherence to the medication regimen and nonpharmacologic measures, and adverse effects to therapy. The patient should also be assessed for any change in functional status.

Patients should also be scheduled for routine monitoring of electrolytes and renal function. Evaluation of the patient's serum potassium is important due to the influence of medications on this parameter. There is the potential for hypokalemia with diuretics that may lead to toxicity in a patient receiving digoxin. The ACEIs, AIIRAs, and spironolactone may all increase potassium, leading to potential toxicity.[1]

Adherence to the medication regimen is often not optimal[2,3] and may lead to clinical deterioration in patients with HF.[4] Patients need to be educated on the importance of adherence to the medication regimen in order to derive the benefits of decreased morbidity and mortality. The reason for not taking a medication as prescribed should be investigated. If it is a result of an adverse effect, the dosage of the medication can be adjusted or another class of medication considered.

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, activity, adherence, and the signs and symptoms of recurrent HF. If patients and/or caregivers are cognizant of the signs and symptoms of recurrent HF, they may have the opportunity to present to the healthcare practitioner before the patient's condition deteriorates.[5] Patients and caregivers should also be educated on the patient's prognosis for function and survival. Treatment options, a living will, and advanced directives should be discussed with the patient and caregiver in response to different events that may occur. The availability of hospice care should also be discussed. Continuity of care is important for the patient's overall care and for the implementation of the patient's request for end of life care.[1]

Some facilities may have interdisciplinary HF disease management clinics to provide continuity of care and improve outcomes for patients with HF.[1,6-12]

**References:**

[1] 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
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**APPENDIX A. Acronym List**

| | |
|---|---|
| AIIRA (also ARB) | Angiotensin II receptor antagonist (also referred to as angiotensin receptor blocker) |
| ACC/AHA | American College of Cardiology/American Heart Association |
| ACEI | Angiotensin-converting enzyme inhibitor |
| ARR | Absolute risk reduction |
| AV | Atrioventricular |
| BNP | Brain natriuretic peptide |
| BUN | Blood urea nitrogen |
| CCB | Calcium channel blocker |
| CI | 95% confidence interval |
| Cr | Creatininee |
| CrCl | Creatinine clearance |
| DM | Diabetes mellitus |
| DOE | Dyspnea on exertion |
| HCTZ | Hydrochlorothiazide |
| HF | Heart failure |
| HTN | Hypertension |
| HYD | Hydralazine |
| INR | International normalized ration |
| ISDN | Isosorbide dinitrate |
| JVD | Jugular venous distention |
| $K^+$ | Potassium |
| LV | Left ventricular |
| LVEF | Left ventricular ejection fraction |
| LVEDP | Left ventricular end diastolic pressure |
| LVH | Left ventricular hypertrophy |
| MI | Myocardial infarction |
| NNT | Number needed to treat |
| NSAID | Non-steroidal anti-inflammatory drug |
| NYHA | New York Heart Association |
| PND | Paroxysmal nocturnal dyspnea |
| RR | Relative risk |
| SNS | Sympathetic nervous system |
| SOB | Shortness of breath |
| TSH | Thyroid-stimulating hormone (thyrotropin) |


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## Appendix B. Common Drug Interactions with Agents Used in HF [a-e]

**Bold =** serious drug interaction; *Italics* = moderate; Regular = minor

| DRUG CLASS | INTERACTING DRUG | DESCRIPTION |
|---|---|---|
| **DIURETICS** | | |
| | *ACEI* | ↑ hypotensive effect in the presence of intensive diuretic therapy due to sodium depletion and hypovolemia; at low doses this combination may be used synergistically |
| | Bile Acid Resins | ↓ absorption of all diuretics; take diuretics 1 hour prior or 4 hours after bile acid resin |
| | *Digoxin* | Loop and thiazide diuretics may induce hypokalemia which may ↑ risk of digitalis toxicity |
| | **Lithium** | With thiazides, a compensatory ↑ in proximal tubule reabsorption of sodium occurs, which results in ↑ lithium reabsorption (reduce lithium dose by 50%); furosemide appears to have little effect in most people |
| | NSAIDs | NSAIDs ↓ antihypertensive effect when used with thiazides due to inhibition of PG synthesis resulting in ↓ GFR, ↓ sodium and water excretion, and vasoconstriction |
| | *Oral hypoglycemics* | Thiazides may ↓ hypoglycemic effects of sulfonylureas possibly due to ↓ insulin sensitivity, ↓ insulin secretion or ↓ in $K^+$; clinical significance unclear |
| | $K^+$preparations, ACEI, NSAIDs | $K^+$sparing diuretics used concomitantly may ↑ $K^+$ serum levels |
| **ACEIs** | | |
| | **Allopurinol** | Isolated case reports with allopurinol and captopril or enalapril may have caused predisposition to hypersensitivity reactions (e.g., Stevens Johnson Syndrome, anaphylaxis, skin eruptions, fever, arthralgias) |
| | *Lithium* | ↑ toxicity; suggested mechanism is ACEI-induced sodium depletion resulting in ↑ reabsorption |
| | *NSAIDs* | NSAIDs ↓ antihypertensive effects due to inhibition of PG synthesis resulting in ↓ GFR, ↓ sodium and water excretion, and vasoconstriction |
| | $K^+$ preparations $K^+$-sparing diuretics | Concomitant therapy may ↑ $K^+$ serum levels |
| **AIIRAs** | | |
| | Cimetidine | Coadministration led to an ↑ of about 18% in the AUC of losartan, but did not affect the pharmacokinetics of its active metabolite |
| | **Digoxin** | See digoxin for description of drug interaction |
| | Fluconazole | Inhibits CYP2C9 resulting in reduced concentration of losartan's active metabolite |
| | Phenobarbital | Coadministration led to a reduction of about 20% in the AUC of losartan and that of its active metabolite |

[a] Adapted from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). Arch Intern Med 1997;157:2413-46.

[b] Hebel SK, ed. Drug Facts and Comparisons, St. Louis: Facts and Comparisons Inc., 1999.

[c] Mignat C, Unger T. ACE inhibitors. Drug interactions of clinical significance. Drug Safety 1995 May 12(5):334-47.

[d] Hansten PD, Horn JR eds. Drug Interactions Analysis and Management, Vancouver: Applied Therapeutics, Inc., 1999.

[e] AUC=area under the curve; CV=cardiovascular; CYP=cytochrome P-450 enzyme system; GFR=glomerular filtration rate; PG=prostaglandin

**Bold =** serious drug interaction; *Italics* = moderate; Regular = minor

| | | |
|---|---|---|
| **β-ADRENERGIC BLOCKERS** | | |
| | *Cimetidine* | Hypotension and bradycardia have been reported with propranolol and metoprolol when used with cimetidine due to ↑ serum levels of β-adrenergic blockers that undergo hepatic metabolism |
| | *Diltiazem*<br>*Verapamil* | Combination may potentiate the pharmacologic effects of β-adrenergic blockers; additive effects on cardiac conduction |
| | **Epinephrine** | Noncardioselective agents may ↑ the pressor response resulting in ↑ in HTN/ bradycardia |
| | *Lidocaine* | ↑ toxicity due to reduced hepatic metabolism of lidocaine |
| | *NSAIDs* | NSAIDs ↓ antihypertensive effect due to inhibition of PG synthesis resulting in ↓ GFR, ↓ sodium and water excretion, and vasoconstriction |
| | *Neuroleptics* | Some β-adrenergic blockers and neuroleptics (chlorpromazine/ thioridazine) may ↑ the plasma concentrations of one another; monitor for enhanced effects of both drugs |
| | *Oral hypoglycemics* | With noncardioselective agents, ↓ hypoglycemic action may occur due to possible inhibition of insulin secretion and also mask symptoms of hypoglycemia; clinical significance is unclear |
| | *Prazosin* | ↑ postural hypotension due to ↓ compensatory CV response |
| | *Propafenone* | ↑ hypotensive effect has been seen with propranolol and metoprolol due to inhibition of metabolic clearance; HF and nightmares have been reported |
| | *Rifampin* | May enhance the hepatic metabolism of propranolol and metoprolol; enzyme induction effect may resolve after a 3-4 week washout period |
| | *Theophylline* | ↑ serum concentration in a dose-dependent manner has been seen with propranolol |
| **CCBs** | | |
| | *Carbamazepine* | ↑ toxicity has been noted with verapamil and diltiazem due to ↓ metabolism of carbamazepine; may be more significant with verapamil. Felodipine bioavailability may be ↓, making it difficult to achieve therapeutic felodipine concentrations |
| | *Cimetidine* | Metabolism has been ↓ especially with verapamil, diltiazem, nifedipine |
| | *Cyclosporin* | Blood concentrations have ↑ with verapamil, diltiazem and nicardipine; renal toxicity has been reported |
| | *Digoxin* | Verapamil, diltiazem, bepridil, and nisoldipine have ↑ digoxin levels by 20-70% |
| | *Lithium* | Combination with verapamil or diltiazem may result in neurotoxicity that may occur without attendant ↑ in serum level |
| | **Lovastatin** | Diltiazem produces marked ↑ lovastatin concentrations through inhibition of CYP3A4, therefore potential for ↑ toxicity; verapamil likely to produce similar changes; simvastatin also likely to be affected; specific interaction studies have not been performed with atorvastatin or cerivastatin |
| | *Quinidine* | Verapamil inhibits metabolism of quinidine leading to ↑ toxicity; nifedipine appears to ↓ blood concentrations |
| | *Theophylline* | Inhibition of hepatic metabolism with verapamil may lead to ↑ serum levels |

[a] Adapted from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). Arch Intern Med 1997;157:2413-46.

[b] Hebel SK, ed. Drug Facts and Comparisons, St. Louis: Facts and Comparisons Inc., 1999.

[c] Mignat C, Unger T. ACE inhibitors. Drug interactions of clinical significance. Drug Safety 1995 May 12(5):334-47.

[d] Hansten PD, Horn JR eds. Drug Interactions Analysis and Management, Vancouver: Applied Therapeutics, Inc., 1999.

[e] AUC=area under the curve; CV=cardiovascular; CYP=cytochrome P-450 enzyme system; GFR=glomerular filtration rate; PG=prostaglandin


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**Bold =** serious drug interaction; *Italics* = moderate; Regular = minor

| | | |
|---|---|---|
| **DIGOXIN** | | |
| | *Amiodarone* | ↑ serum digoxin concentrations; may need to decrease digoxin dose by ~ 50%; monitor for digoxin toxicity (i.e., anorexia, nausea, fatigue, vomiting, diarrhea, visual disturbances, confusion, ventricular tachycardia); effects may be delayed up to 7 days |
| | *Cyclosporine* | ↑ serum digoxin concentrations; may need dose ↓ ~ 50%; monitor for toxicity (i.e. anorexia, nausea, vomiting, diarrhea, fatigue, visual disturbances, confusion, and ventricular tachycardia) |
| | *Diuretics* | ↑ risk of digitalis toxicity due to diuretic induced hypokalemia |
| | **Quinidine** | ↑ serum digoxin concentrations; may need dose ↓ ~ 50%; monitor for toxicity (i.e. anorexia, nausea, vomiting, diarrhea, fatigue, visual disturbances, confusion, and ventricular tachycardia); effects may be delayed up to 7 days |
| | Spironolactone | Renal excretion of digoxin may be reduced; false increases in plasma digoxin concentrations may occur depending on the assay method used |
| | **Telmisartan** | May increase digoxin peak plasma concentrations (49%) and in trough concentrations (20%); monitor digoxin levels when starting, adjusting, or discontinuing therapy with telmisartan |
| | **Verapamil** | ↑ digoxin serum concentrations on average ~70%; dose related; may need to ↓ dose be at least 50%; monitor for toxicity (i.e. anorexia, nausea, vomiting, diarrhea, fatigue, visual disturbances, confusion, and ventricular tachycardia); effects may be delayed up to 7 days |
| **SPIRONOLACTONE** | | |
| | Digoxin | See digoxin for description of drug interaction |
| | **Mitotane** | Spironolactone may antagonize the activity of mitotane; avoid concomitant use |
| | **Potassium, other potassium-sparing diuretics,** *ACEI, NSAIDs* | Coadministration may result in hyperkalemia |
| **VASODILATORS** | | |
| Hydralazine | *Indomethacin* | ↓ antihypertensive effect of hydralazine due to PG synthesis inhibition |
| | Propranolol<br>Metoprolol | Serum levels of propranolol or metoprolol may be ↑ with hydralazine use; clinical significance unknown |

[a] Adapted from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). Arch Intern Med 1997;157:2413-46.
[b] Hebel SK, ed. Drug Facts and Comparisons, St. Louis: Facts and Comparisons Inc., 1999.
[c] Mignat C, Unger T. ACE inhibitors. Drug interactions of clinical significance. Drug Safety 1995 May 12(5):334-47.
[d] Hansten PD, Horn JR eds. Drug Interactions Analysis and Management, Vancouver: Applied Therapeutics, Inc., 1999.
[e] AUC=area under the curve; CV=cardiovascular; CYP=cytochrome P-450 enzyme system; GFR=glomerular filtration rate; PG=prostaglandin

## Appendix C. Selected Costs for HF Drug Therapy

For current prices, refer to www.vapbm.org

| DRUG (**BOLD** = National Formulary item) | DOSE[a] | FEDERAL SUPPLY SCHEDULE (FSS) COST/MONTH |
|---|---|---|
| ACE INHIBITORS | | |
| **Captopril** | 50 mg tid | $ 1.57 |
| **Enalapril** | 10 mg bid | $ 1.68 |
| **Fosinopril** | 20-40 mg qd | $ 4.50 |
| **Lisinopril** | 20-40 mg qd | $ 4.20 |
| BETA BLOCKERS | | |
| ***Cardioselective*** | | |
| Bisoprolol | 10 mg qd | $19.48 |
| **Metoprolol** | 100 mg bid | $ 1.42 |
| **Metoprolol XL**[b] | 200mg qd | $29.43 |
| ***α & β Blocking Agents*** | | |
| **Carvedilol**[b] | 25 mg bid | $56.83 |
| COMBINATION THERAPY | | |
| **Hydralazine** | 75 mg tid | $ 1.71 |
| **Isosorbide dinitrate** | 40 mg tid | $11.56 |
| DIURETICS | | |
| ***Thiazides*** | | |
| **Hydrochlorothiazide** | 25 mg qd | $ .23 |
| **Chlorthalidone** | 50 mg qd | $ 1.07 |
| ***Thiazide-Related*** | | |
| **Indapamide** | 2.5 mg qd | $ .71 |
| **Metolazone** | | |
| Zaroxolyn ® | 5 mg qd | $ 9.33 |
| Mykrox ® | 0.5 mg qd | $13.90 |
| ***Loop Diuretics*** | | |
| **Furosemide** | 40 mg qd | $ .64 |
| **Bumetanide** | 2 mg qd | $ 2.82 |
| *Aldosterone Antagonist* | | |
| **Spironolactone** | 25 mg qd | $ .82 |
| POSITIVE INOTROPE | | |
| **Digoxin** (Lanoxin®) | 0.25 mg qd | $ .61 |
| AIIRAS[b] | | |
| Candesartan | 16 mg qd | $19.70 |
| Eprosartan | 600mg qd | $21.70 |
| Irbesartan | 150 mg qd | $22.84 |
| Losartan | 50 mg qd | $22.06 |
| Olmesartan | 20mg qd | $14.47 |
| Telmisartan | 40 mg qd | $15.08 |
| Valsartan | 160 mg bid[c] | $41.82 |
| CALCIUM CHANNEL BLOCKERS | | |
| ***Long-acting Dihydropyridines*** | | |
| **Felodipine** | 10 mg qd | $13.50 |
| **Amlodipine**[b] | 10 mg qd | $34.04 |

[a] Usual doses; does not reflect equivalent doses
[b] Refer to PBM-MAP Criteria for Use at www.vapbm.org or http://vaww.pbm.med.va.gov
[c] bid dosing used in Val-HeFT