PBM-MAP Clinical Practice Guideline for the Pharmacologic Management of **Chronic Heart Failure** in Primary Care Practice

Pharmacy Benefits Management
Strategic Healthcare Group and
Medical Advisory Panel

Veterans Health Administration
Department of Veterans Affairs
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EXECUTIVE SUMMARY

1. Treatment of chronic heart failure (HF) is based upon the four-stage classification system developed 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 improving symptoms, increasing functional capacity, improving quality of life, slowing disease progression, decreasing need for hospitalization, and prolonging survival.

3. Nonpharmacologic therapy includes abstaining from alcohol and tobacco, limiting dietary sodium, reducing weight if appropriate, exercising regularly, and influenza and pneumococcal vaccinations. Other nonpharmacologic therapies such as automatic implantable defibrillators or cardiac resynchronication therapy should be considered in appropriate patients but are beyond the scope of this document.

4. Risk factor modification and treatment of concomitant cardiac conditions and underlying causes should be implemented in patients in Stage A to potentially reduce the development of HF.

5. In addition to risk factor modification, patients in Stage B should receive post-myocardial infarction (MI) treatment with an angiotensin-converting enzyme inhibitor (ACEI) and beta-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 beta-adrenergic blocker (Grade B Recommendation, Fair Overall Quality of Evidence). An angiotensin II receptor antagonist may be prescribed in patients with a history of MI who have a reduced left ventricular ejection fraction without symptoms of HF if they are ACEI intolerant (Grade A Recommendation, Good 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 B 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. An angiotensin II receptor antagonist may be considered as an alternative to an ACEI (in patients who are on standard therapy for HF) and are unable to tolerate an ACEI (Grade A Recommendation, Good Overall Quality of Evidence).
    - A beta-adrenergic blocker that has proven to reduce mortality (i.e., bisoprolol, carvedilol, sustained release metoprolol succinate) 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).
    - Low dose of an aldosterone antagonist 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. This therapy improves symptoms (as assessed by change in NYHA functional class), decreases hospitalizations for worsening HF, and decreases mortality (Grade A Recommendation, Good Overall Quality of Evidence). An aldosterone antagonist may also be considered in patients with LVEF $\leq$ 40% in patients early post-MI on standard therapy for HF.

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- The combination of hydralazine and a nitrate should be considered, especially in African American patients with NYHA Class III or IV HF, who continue to have symptoms despite therapy with an ACEI and beta-adrenergic blocker (Grade B Recommendation, Good Overall Quality of Evidence). The combination of hydralazine and a nitrate may be considered as an alternative to an ACEI in patients who are unable to tolerate an ACEI (or angiotensin II receptor antagonist) due to hypotension, renal insufficiency, hyperkalemia, or possibly, angioedema (Grade C Recommendation, Fair Overall Quality of Evidence).
- Addition of an angiotensin II receptor antagonist to standard therapy (i.e., an ACEI and beta-adrenergic blocker) in patients with systolic HF may be considered to decrease cardiovascular death or HF hospitalizations (Grade B Recommendation, Fair Overall Quality of Evidence); although routine use of an angiotensin II receptor antagonist, ACEI, and aldosterone antagonist is not recommended.
- Digoxin can be used in patients whose symptoms persist despite treatment with an ACEI (or an angiotensin II receptor antagonist if an ACEI is not tolerated), a beta-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 B Recommendation, Fair Overall Quality of Evidence).
- Patients should receive 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, nonpharmacologic measures, and adverse effects to therapy. Patients should be scheduled for routine laboratory monitoring. The patient should also be assessed for any change in functional status or frequency of hospitalizations, and medication therapy should be optimized.

7. 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. In patients where therapeutic interventions may no longer be appropriate, discussions regarding end-of-life care should be considered. 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.

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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.

The MAP comprises practicing VA physicians from facilities across the nation:

Thomas Craig, MD
Chief Quality and Performance Officer
Office of Quality and Performance Management
Department of Veterans Affairs
Washington DC

Gregory W. Dalack, MD
Staff Psychiatrist
VA Ann Arbor Healthcare System
Vice Chair and Associate Chair for Education and Academic Affairs
Department of Psychiatry
University of Michigan

Sylvain DeLisle, MD, MBA
Associate Chief of Staff, Performance Improvement
VA Maryland HCS
Associate Professor of Medicine & Physiology
University of Maryland, School of Medicine

Thomas H. Dickinson, MD
Co-Service Line Manager, Primary Care
Brockton Division, VA Boston HCS
Clinical Instructor in Medicine
Harvard Medical School

John R. Downs, MD, FACP
Ambulatory Care
AMLD, South Texas Veterans HCS
Associate Professor of Medicine
University of Texas Health Science Center
Col, USAF (retired)

Peter A. Glassman, MBBS, MSc
Staff Physician
West Los Angeles VAMC
VA Greater Los Angeles HCS
Associate Professor
University of California, Los Angeles (UCLA)

Matthew Goetz, MD
Chief, Infectious Diseases
West Los Angeles VAMC
VA Greater Los Angeles HCS
Professor of Clinical Medicine
David Geffen School of Medicine at UCLA

Chester B. Good, MD, MPH, FACP
Chairman, Medical Advisory Panel
Staff Physician, Department of Medicine
VA Pittsburgh HCS
Associate Professor of Medicine
University of Pittsburgh

Robert C. Goodhope, MD, MBA
Chief Medical Officer
VA Outpatient Clinic
Tallahassee, FL

Robert J. Hariman, MD
Director, Cardiac Electrophysiology
Hines VA Hospital
Professor of Medicine
Loyola University School of Medicine

William Korchik, MD
Medical Director, Extended Care Center
VAMC Minneapolis
Assistant Professor of Medicine
University of Minnesota

Alexander M. Shepherd, MD, PhD, FAHA
Professor and Chief, Division of Clinical Pharmacology
Departments of Medicine and Pharmacology
University of Texas Health Science Center at San Antonio

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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.

Michael Valentino, RPh, MHSA
Chief Consultant, PBM-SHG

Virginia S. Torrise, PharmD
Deputy Chief Consultant, PBM-SHG

Joseph Canzolino, RPh
Associate Chief Consultant, PBM-SHG

Vincent Calabrese, PharmD
Assistant Chief Consultant, PBM-SHG

Fran Cunningham, PharmD
Director, Center for Medication Safety PSCI and
Program Manager Pharmacoepidemiologic/
Outcomes Research

Muriel Burk, PharmD
Clinical Pharmacy Specialist, Pharmacoepidemiologic
and Outcomes Research

Marie Sales, PharmD
Clinical Pharmacy Specialist, Pharmacoepidemiologic
and Outcomes Research

Suzanne Lenz, RPh
Pharmacist Specialist/Contract Liaison

Lucy Szudarski
Program Specialist

Lisa Torphy
Program Specialist

Janet Dailey, PharmD
Clinical Pharmacy Specialist

Elaine Furmaga, PharmD
Clinical Pharmacy Specialist

Mark Geraci, PharmD, BCOP
Clinical Pharmacy Specialist

Francine Goodman, PharmD, BCPS
Clinical Pharmacy Specialist

Cathy Kelley, PharmD
Clinical Pharmacy Specialist

Deborah Khachikian, PharmD
Clinical Pharmacy Specialist

Lisa Longo, PharmD, BCPS
Clinical Pharmacy Specialist

Todd Semla, PharmD, BCPS
Clinical Pharmacy Specialist

Kathy Tortorice, PharmD, BCPS
Clinical Pharmacy Specialist

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Alan Cohen, MD, FACP
Chief of Primary Care,
VA Central California Healthcare System

Gregg C. Fonarow, MD
Member, VA CHF QUERI Executive Committee
Professor of Cardiovascular Medicine and Science,
David Geffen School of Medicine at UCLA

Charles Hoesch, MD
Medical Director, Perry Point VAMC
VA Maryland Healthcare System

David Parra, PharmD, BCPS
Clinical Pharmacy Specialist in Cardiology,
West Palm Beach VAMC
Clinical Assistant Professor,
Department of Experimental and Clinical Pharmacology
University of Minnesota College of Pharmacy

Eugene S. Smith, III, MD
Acting Chief of Cardiology,
Central ArkansasVeterans Healthcare System
Associate Professor of Medicine, Division of Cardiology
University of Arkansas for Medical Sciences

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

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ABBREVIATIONS

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
BPH	Benign prostatic hyperplasia
BUN	Blood urea nitrogen
CCB	Calcium channel blocker
CI	95% confidence interval
Cr	Creatinine
CrCl	Creatinine clearance
DM	Diabetes mellitus
DOE	Dyspnea on exertion
HCTZ	Hydrochlorothiazide
HF	Heart failure
HFSA	Heart Failure Society of America
HTN	Hypertension
INR	International normalization ratio
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)
TZD	Thiazolidinedione

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INTRODUCTION

THE PHARMACOLOGIC MANAGEMENT OF CHRONIC HEART FAILURE

Approximately 5 million patients in the United States have heart failure (HF), with 550,000 new cases diagnosed each year.[1,2] The prevalence of HF increases with age, with nearly 5% of patients seen at Veterans Affairs (VA) Medical Centers having a primary diagnosis of HF. According to a recent report from the American Heart Association, 80% of men and 70% of women with a diagnosis of HF who are less than 65 years of age will die within 8 years. In addition, the one year mortality rate was reported as 20%.[2] Hospitalizations for HF have increased,[1,2] accounting for 6.5 million hospital days annually.[1] Heart failure was also reported to be the main reason for 12 to 15 million clinic visits each year.[1] The VA provides care for approximately 240,000 veterans with HF, with over 42,000 of these patients being hospitalized during Fiscal Year (FY) 2005 with a primary diagnosis of HF. It has been estimated that the cost for HF in 2006 is $29.6 billion in the United States alone.[1]

The pharmacologic treatment of HF has advanced significantly over the years, with clinical research establishing the benefit of drug therapy in preventing morbidity and mortality in patients with this condition.[1] The clinical outcomes and resulting economic benefits of drug therapy have also been documented in the clinical practice setting.[3] With HF being such a prevalent disease, especially among the older patient population, and with it a high rate of morbidity and mortality, it is prudent that evidence-based therapy and associated clinical practice guidelines be utilized to improve patient outcomes.[4,5]

Since the beginning of fiscal year (FY) 2003, the VA Office of Quality and Performance has implemented performance measures evaluating the treatment of HF with the angiotensin-converting enzyme inhibitors (ACEIs), including data on the angiotensin II receptor antagonists as part of the measure in FY2005. After annual chart review of approximately 3,000 veterans, the External Peer Review Program reported that nearly 90% of these veterans with HF were prescribed an ACEI or angiotensin II receptor antagonist (refer to http://vaww.pdw.med.va.gov/pdwframe.asp for details on the indicators and updated results).

Utilization of beta-adrenergic blockers and renin-angiotensin-aldosterone inhibitors have continued to increase in veteran patients with HF (refer to the Figure); although use of these drug classes in combination is less than optimal. Continued efforts to optimize evidence-based therapy should be encouraged.

These clinical practice guidelines for the management of patients with HF focus on the pharmacologic treatment of the disease. The clinician is referred to the American College of Cardiology/American Heart Association (ACC/AHA) Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult[1] and other medical literature and cardiology experts for the overall management of patients with HF.

Summary

This consensus and evidence-based document on the pharmacologic management of patients with chronic HF is intended to update the August 2003 publication of the PBM-MAP The Pharmacologic Management of Chronic Heart Failure. Whenever possible, the PBM and MAP rely 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, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis 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 (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). American College of Cardiology Web site. Available at: http://www.acc.org/clinical/guidelines/failure/index.pdf.*

To update the August 2003 PBM-MAP guideline "The Pharmacologic Management of Chronic Heart Failure", a literature search of the National Library of Medicine's MEDLINE/PubMed database and Evidence Based Medicine reviews available on OVID was conducted. Preference was given to randomized controlled trials, meta-analyses, and systematic reviews. The following search terms were used: heart failure, angiotensin-converting enzyme inhibitor, beta-adrenergic blocker, digoxin, spironolactone, angiotensin receptor blocker, aldosterone antagonist, hydralazine, isosorbide dinitrate, diastolic dysfunction, 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 2006 document, 208 abstracts and 144 articles were reviewed. One hundred thirty-seven articles were added to the update of the 2006 document, 49 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 or HF in general included 67 pertinent subgroup or retrospective evaluations, 9 meta-analyses or systematic reviews of controlled trials relevant to the recommendations in the document, 5 case reports and 7 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, consensus statements and clinical practice guidelines were also included in the document. Major changes to the 2006 update include addition of pertinent medical evidence published since the last iteration of the document including data with the angiotensin II receptor antagonists, isosorbide dinitrate and hydralazine, the aldosterone antagonists, and a comparison of an ACEI versus a beta-adrenergic blocker as initial therapy. The treatment algorithm has been revised to reflect the recommended place in therapy of these drug classes based on this information. The document has been reformatted as per other VA/DoD clinical practice guidelines. In addition, relevant data from long-term outcome trials in patients with chronic HF due to systolic dysfunction have been compiled in the Appendix.

Methods to Formulate Recommendations

The literature was critically analyzed and evidence was graded using a standardized format. 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. The rating scale of the U.S. Preventive Services Task Force is summarized in Tables 1 to 5.[6]

Table 1	Quality of Evidence (QE)
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

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

Table 3	Net Effect of Intervention
Substantial	More than a small relative impact on a frequent condition with a substantial burden of suffering, or 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 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 A small impact on an infrequent condition with a significant impact on the individual patient level
Zero or Negative	Negative impact on patients, or No relative impact on either a frequent condition with a substantial burden of suffering, or An infrequent condition with a significant impact on the individual patient level

Table 4	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

Table 5	Grade for Strength of Recommendation			
Overall Quality of Evidence	**Net benefit of intervention**			
	Substantial	**Moderate**	**Small**	**Zero or Negative**
I	A	B	C	D
II	B	B	C	D
III	I	I	I	D

The evidence rating system used in the ACC/AHA Practice Guidelines on the Evaluation and Management of HF are included below.[1] As this is used by ACC/AHA guidelines, this format will also be included in the recommendations in the text to assist in the application of the recommendations to clinical practice.

Table 6	ACC/AHA Class of Recommendation
Class	**Recommendation**
I	Conditions for which there is evidence and/or general agreement that a given procedure/therapy is useful and effective
II	Conditions for which there is conflicting evidence and/or a divergence of opinion about usefulness/efficacy of performing the procedure/therapy
IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
IIb	Usefulness/efficacy is less well established by evidence/opinion
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

Table 7	ACC/AHA Level of Evidence
A	Data is derived from multiple randomized clinical trials or meta-analyses
B	Data is derived from a single randomized trial or nonrandomized studies
C	Consensus opinion of experts is the primary source of recommendation

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 and cardiology expert reviewers were 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 annotations on pharmacotherapy 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 comprehensive clinical practice guideline on HF, 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 www.pbm.va.gov or http://vaww.pbm.va.gov as well as the VA Office of Quality and Performance at www.oqp.med.va.gov. It is recommended 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.

Continuing education programs will be developed.

Departmental and individual education at the facility is also encouraged.

Referencing the Document

This document should be referenced as follows:

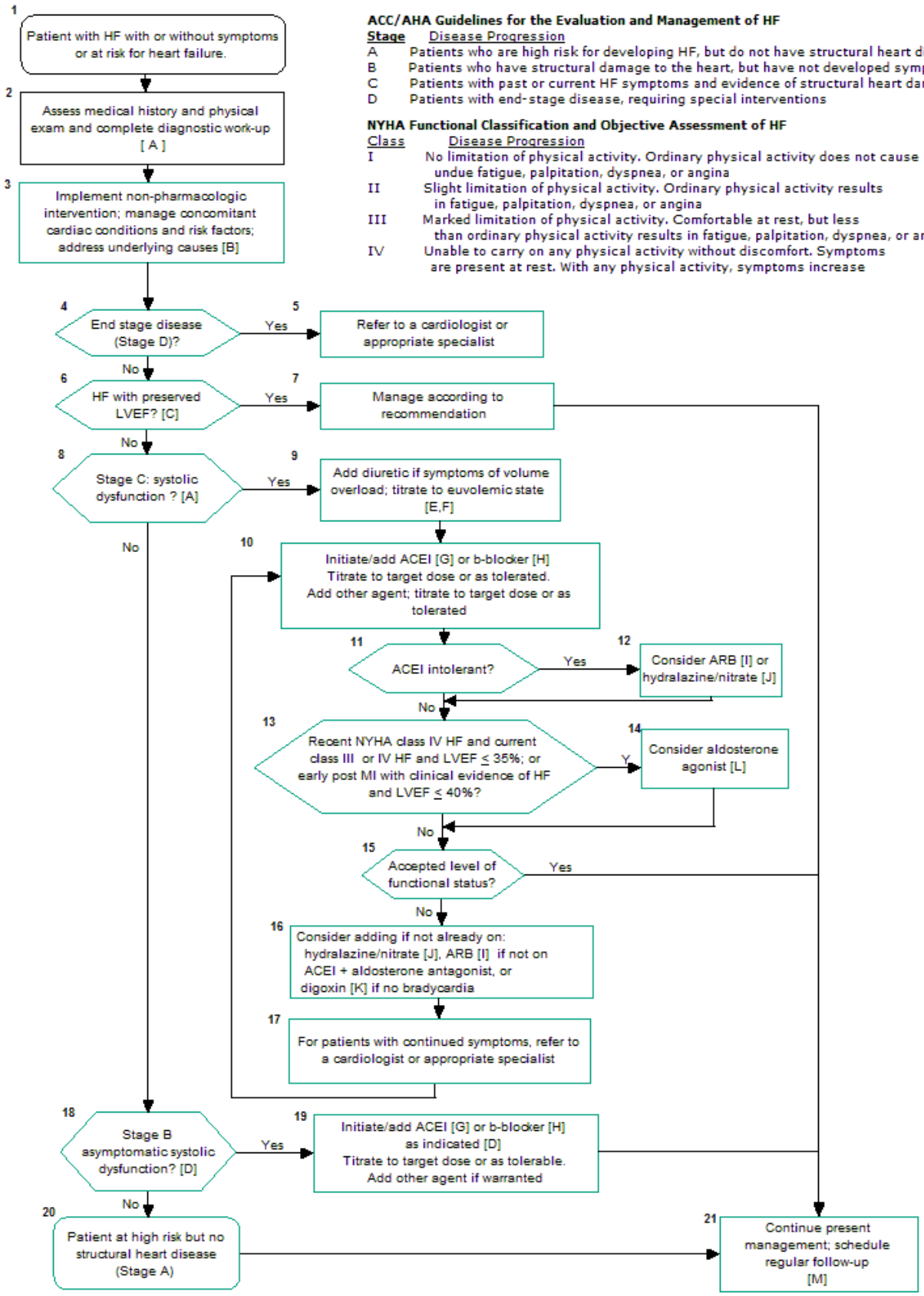
The Pharmacologic Management of Chronic Heart Failure. Washington, DC: Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel, Veterans Health Administration, Department of Veterans Affairs. September 2007 Update. PBM-MAP Publication No. 00-0015.

Updating the Guideline

The PBM will review the guideline 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 guideline can be obtained from the PBM home page at www.pbm.va.gov or http://vaww.pbm.va.gov.

TREATMENT ALGORITHM



ACC/AHA Guidelines for the Evaluation and Management of HF

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

NYHA Functional Classification and Objective Assessment of HF

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

ANNOTATIONS

THE PHARMACOLOGIC MANAGEMENT OF CHRONIC HEART FAILURE

Annotations

A. Diagnose and Evaluate a Patient at Risk for or Suspected of Having Heart Failure (HF)

OBJECTIVES

- To identify patient factors associated with HF
- 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
- To distinguish systolic from diastolic dysfunction
- To evaluate the patient's functional status

BACKGROUND

As previously discussed in the Introduction, HF is a prevalent condition, especially in the older patient population, with a high rate of morbidity and mortality.[1] This treatment guideline focuses on the pharmacologic management of HF; the clinician is referred to other resources including comprehensive treatment guidelines or clinical expertise in the diagnosis and evaluation of patients with HF. The recommendations below are to be used as a general guide and are a summary of Class I Recommendations where there is evidence/consensus that the treatment/procedure is of benefit as per the ACC/AHA Practice Guidelines on initial and follow-up assessments of patients with HF.[1]

RECOMMENDATIONS

The following are Class I recommendations by the ACC/AHA (i.e., there is evidence and/or general agreement that a given procedure/therapy is useful and effective).[1]

Initial Assessment

- Obtain a thorough medical history and perform a comprehensive physical examination in patients suspected of having HF to identify risk factors or conditions that may lead to the development or progression of HF
- Obtain a comprehensive medication history (including past and current treatments for HF, alternative therapies, and antineoplastic agents) and past or current alcohol or illicit drug use
- Perform an assessment of the patient's ability to perform activities of daily living
- Document the patient's height, weight, and body mass index; assess the patient's volume status and evaluate for orthostatic blood pressure changes
- Obtain baseline laboratory parameters including a complete blood count, serum electrolytes with calcium and magnesium, blood urea nitrogen (BUN), serum creatinine (Cr), fasting blood glucose and glycosylated hemoglobin, lipid profile, liver function tests, and thyroid-stimulating hormone (TSH)
- Perform a twelve-lead electrocardiogram and chest radiograph
- Perform a two-dimensional echocardiography with Doppler to assess left ventricular ejection fraction (LVEF), left ventricular (LV) size, wall thickness, and valve function; radionuclide ventriculography to assess LVEF and volumes can also be performed
- Perform a coronary arteriography in patients with HF and angina or significant ischemia (unless not eligible candidate for revascularization)

Follow-Up Evaluations

- Perform an assessment of the patient's ability to perform activities of daily living at each clinic visit
- Assess the patient's volume status and weight at each clinic visit
- Inquire as to the patient's current use of alcohol, illicit drugs, alternative therapies, or antineoplastic agents; evaluate the patient's diet and intake of sodium

DISCUSSION

Heart failure is defined as a "complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood."[1] The leading causes of HF are coronary artery disease, hypertension (HTN), and dilated cardiomyopathy (i.e., a structural abnormality).[1] In addition, identification of other conditions or risk factors contributing to the development or progression of HF is important as some of these may be treated or avoided.[1]

Patients with heart failure typically present with symptoms including dyspnea and fatigue, as well as edema and rales on physical examination.[1] 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 LVEF of < 40%.[1] 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.

Medical history[1]

- Coronary artery disease
- Hypertension
- Valvular heart disease
- Diabetes
- Peripheral vascular disease
- Dyslipidemia
- Myopathy
- Rheumatic fever
- Mediastinal irradiation
- Sleep-disordered breathing
- Exposure to cardiotoxic agents (e.g., anthracyclines, trastuzumab, ephedra, high-dose cyclophosphamide)
- Alcohol or illicit drug use
- Smoking
- Exposure to sexually transmitted diseases
- Thyroid disorder
- Pheochromocytoma
- Obesity
- Family history of atherosclerotic disease, cardiomyopathy, sudden death, conduction system disease, skeletal myopathies, or tachyarrhythmias

Patient presentation: Patients with LV dysfunction generally present in one of the following manners:[1]

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

Patient symptoms of HF:[1,7,8] 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. Some patients with HF may have only signs of the condition without any active symptoms.

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- Shortness of breath (SOB)
- Fatigue

- Orthopnea
- Paroxysmal nocturnal dyspnea (PND)
- Dyspnea on exertion (DOE)
- Cough
- Edema
- Weight gain (anorexia may be seen in advanced HF)

Physical examination findings of HF:[7,8] 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. Some patients with HF may only have symptoms of the condition without any of the physical signs listed below.

- Tachycardia
- Increasing weight
- Jugular venous distention (JVD) or hepatojugular reflux
- Presence of S_3 (third heart sound)
- Laterally displaced apical impulse
- Pulmonary crackles or wheezes
- Hepatomegaly
- Peripheral (dependent) edema
- Abdominal distention or ascites

Laboratory Assessment:[1] Laboratory parameters are recommended to evaluate the patient for conditions that may contribute to the development or exacerbation of HF. The initial assessment should include:

- Complete blood count
- Serum electrolytes with calcium and magnesium
- Blood urea nitrogen, serum Cr
- Fasting blood glucose and glycosylated hemoglobin
- Lipid profile
- Liver function tests
- Thyroid-stimulating hormone
- B-type natriuretic peptide (BNP): elevated levels may be helpful in diagnosing a patient suspected of having HF or used to consider a diagnosis of HF when the diagnosis is unknown. The ACC/AHA recommends (i.e., weight of evidence/opinion is in favor of usefulness/efficacy) that the measurement of BNP may be useful in evaluating patients who present short of breath to the urgent care setting where the diagnosis of HF may be uncertain.[1,9] The ACC/AHA also states that the value of serial BNP measurements to guide therapy is not well established[1]

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 following recommendations of the ACC/AHA are for staging patients with HF based on the progression of disease.[1]

Table 8 ACC/AHA Guidelines for the Evaluation and Management of HF[1]

Stage	Disease Progression
A	Patients who are high risk for developing HF, but do not have structural heart disease
B	Patients who have structural damage to the heart, but have not developed symptoms
C	Patients with past or current HF symptoms and evidence of structural heart damage
D	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[10] that estimates the severity of disease based on patient

symptoms.[1] According to the above classification system, once a patient develops symptoms they should be treated according to the recommendations for patients with Stage C (even if NYHA Class I, see below), and do not return to Stage B.[1]

Table 9 NYHA Functional Classification and Objective Assessment of HF[10]

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

B. Management of Concomitant Cardiac Conditions and Risk Factors, Nonpharmacologic Interventions, and Treatment of Underlying Causes

OBJECTIVES

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

BACKGROUND

Identification and treatment of chronic medical conditions or risk factors that may impact the development or progression of HF is important in the overall management of patients at risk for HF or who have been diagnosed with the condition. Many of these diseases have clinical practice guidelines that have been reviewed and approved by the VA/DoD Evidence-Based Practice Work Group and can be found on the VA Office of Quality and Performance Web site at http://www.oqp.med.va.gov/cpg/cpg/htm.

RECOMMENDATIONS

Control risk factors

The following are Class I recommendations by the ACC/AHA (i.e., there is evidence and/or general agreement that a given procedure/therapy is useful and effective)[1]

- Control HTN (http://www.oqp.med.va.gov/cpg/cpg/htm)
- Treat hyperlipidemia (http://www.oqp.med.va.gov/cpg/cpg/htm)
- Treat DM (http://www.oqp.med.va.gov/cpg/cpg/htm)
- Encourage smoking cessation (http://www.oqp.med.va.gov/cpg/cpg/htm) and discourage alcohol consumption and illicit drug use
- Control ventricular rate or restore sinus rhythm in patients with supraventricular tachyarrhythmias
- Treat thyroid disorders
- Conduct periodic evaluations for signs and symptoms of HF
- Manage atherosclerotic vascular disease
- For those with a family history of cardiomyopathy or who are receiving cardiotoxic medications, perform a noninvasive evaluation of LV

DISCUSSION

Treatment of conditions that may lead to HF

Patients with hypertension, diabetes mellitus, or atherosclerotic vascular disease, or those who smoke tobacco are at an increased risk for the development of HF.[1,11,12] Treatment of these conditions and other

risk factors can contribute to an improvement in patient outcomes,[1,13-19] and it is recommended that patients be treated according to the corresponding VA/DoD clinical practice guidelines (available at http://www.oqp.med.va.gov/cpg/cpg/htm).

Recommendations in selected patients

Atrial fibrillation: In patients with HF due to systolic dysfunction and atrial fibrillation requiring rate control, a beta-adrenergic blocker is preferred due to its favorable effect on patients with HF (in patients that are hemodynamically and otherwise stable).[1] Digoxin is also commonly used. Some patients may require combination therapy with digoxin and a beta-adrenergic blocker.[20] Although the long-term use of diltiazem and verapamil [calcium channel blockers (CCBs) with atrioventricular (AV) nodal blocking activity] have been associated with worsening LV dysfunction in patients with HF, patients with atrial fibrillation and rapid ventricular response resistant to combinations of digoxin and a beta-adrenergic blocker have responded with better rate control by adding diltiazem or verapamil. The decision to add diltiazem or verapamil in such patients should be based on weighing the benefit of better rate control against the deleterious long-term effects of these drugs. If additional rate control is needed, referral should be made to a cardiologist with expertise in electrophysiology.

Anticoagulation: Warfarin anticoagulation [with a target international normalization ratio (INR) of 2.5; range 2.0 to 3.0] is recommended in patients with HF and atrial fibrillation, previous systemic or pulmonary thromboembolism, or mobile LV thrombus.[21,22] The routine use of warfarin anticoagulation for HF has not been confirmed by controlled clinical trials.[1,23] The Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial, was unable to demonstrate a significant difference between warfarin, aspirin, and clopidogrel in patients with HF. Another trial comparing warfarin to aspirin in patients with HF is currently underway.[24] Arterial thromboembolism may occur in patients with HF due to systolic dysfunction as a result of the low cardiac output and poor contractility. 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.[25] However, a post-hoc analysis of a single study is not evidence enough to recommend anticoagulation in patients with systolic dysfunction. Patients with atrial fibrillation and HF with contraindications to warfarin (e.g., increased risk of bleeding, difficulty adhering to the medication regimen or regular INR monitoring, current alcohol abuse or frequent falls) should receive aspirin unless contraindicated.[26,27] For patients with HF who do not have coronary disease, additional information is needed as to the risk vs. benefit of recommending aspirin therapy.[28,29]

Concomitant HTN and/or angina: Patients with systolic HF and concomitant HTN should be maximized on therapy with agents such as diuretics, ACEIs, and beta-adrenergic blockers, or beta-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 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: 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 once daily 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 (combined risk of death and major cardiovascular hospitalizations) between groups. There was a trend toward a decrease in all-cause mortality with amlodipine (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.[30] This result was not considered *a priori* endpoint. The

survival benefit of amlodipine in patients with nonischemic dilated cardiomyopathy found in the original PRAISE trial was not confirmed in PRAISE-2.[31]

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 twice daily 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.[32]

Clinical practice guidelines have stated that only trials with amlodipine and felodipine have provided long-term safety data in patients with HF.[22] The evidence with amlodipine suggests that this agent does not adversely affect survival in patients with systolic HF. Felodipine or amlodipine may be considered in patients with HF due to systolic dysfunction for the treatment of hypertension for those who have been maximized on pharmacotherapy including diuretics, ACEIs, and beta-adrenergic blockers, and an angiotensin II receptor antagonist, hydralazine/nitrate, or aldosterone antagonist, as indicated; or beta-adrenergic blockers and long-acting nitrates in patients with concomitant angina.

Cardiac amyloidosis: 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.

Conventional wisdom has been that digoxin and CCBs should be avoided in patients with amyloid cardiomyopathy.[33,34] However, this point is controversial[35] and supported by only weak published evidence. Several case reports suggest a sensitivity to digoxin,[36-41] however one prospective autopsy study found no association.[42] 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.[35] The data supporting a CCB sensitivity is based on case reports for nifedipine[43,44] and verapamil.[45] Both these drugs can exacerbate chronic systolic dysfunction independent of etiology. No case reports of other CCBs have been found to suggest sensitivity to them. The following recommendations are based on review of available evidence:

- Avoid verapamil and diltiazem (except in patients with atrial fibrillation and rapid ventricular rate that do not achieve rate control on a beta-adrenergic blocker and digoxin), and nifedipine in systolic dysfunction of all etiologies
- 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
- 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
- Use felodipine or amlodipine only according to prescribing guidelines; monitor patients with known or suspected amyloid cardiomyopathy very closely when using any CCB
- Consider using other agents for diastolic dysfunction before resorting to a CCB in patients with known or suspected amyloid cardiomyopathy

Medications to avoid or to be used with caution

- **Anti-arrhythmic agents:** Anti-arrhythmic agents, other than beta-adrenergic blockers, are not recommended to suppress asymptomatic ventricular arrhythmia or ectopy. Class I antiarrhythmic 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.[46-49] Patients with ventricular arrhythmias should be referred to a cardiologist for individualized treatment

- **Calcium channel blockers:** Most CCBs (except felodipine and amlodipine; refer to above discussion) should not be used in patients with systolic dysfunction
- **Non-steroidal anti-inflammatory drugs (NSAIDs):** NSAIDs may cause fluid retention and should be avoided;[1,50,51] alternative anti-inflammatory agents may be used (e.g., non-acetylated salicylates)
- **Antineoplastic agents:** Antineoplastic agents such as anthracyclines or trastuzumab may lead to the development of HF and should be avoided, if possible
- **Thiazolidinediones (TZDs):** TZDs**,** including rosiglitazone and pioglitazone, are used in the management of patients with DM and have been found to cause edema, an adverse effect that is more common when a TZD is used in combination with other oral hypoglycemic agents or insulin. In addition, clinical trials with the TZDs generally did not include patients with NYHA class III or IV HF and an increased risk of HF in patients prescribed the TZDs has been reported, although the risk appears to be low. Current recommendations include evaluation of the patient's cardiac and fluid status prior to prescribing a TZD and upon follow-up. If a TZD is prescribed in patients without HF but who have one or more risk factors for HF,[52] or in patients who have NYHA class I or II HF, a low dose should be started and the patient should be closely monitored for signs and symptoms of HF including shortness of breath, edema, or excessive or rapid weight gain, as treatment with a TZD has been associated with worsening of HF, and a higher rate of hospitalization and cardiovascular related events. Treatment with a TZD should be reconsidered in patients who develop HF after initiation of the drug. Clinician discretion may be used in patients receiving a TZD who are stabilized and without evidence of volume overload. The use of a TZD is contraindicated in patients with NYHA Class III or IV HF.
- **Cilostazol:** Cilostazol, a phosphodiesterase (PDE) inhibitor used in the management of intermittent claudication and as antiplatelet therapy, is contraindicated in patients with HF due to the decreased survival seen in patients with NYHA class III or IV HF receiving other PDE type 3 inhibitors
- **Metformin:** Metformin should not be used in patients with unstable or acute congestive HF due to the propensity for hypoperfusion or hypoxemia and resultant increased risk of developing lactic acidosis

Additional recommendations[22,53,54]

- Patients and their families or caregivers should receive education on HF, dietary restrictions including reducing salt intake and fluid control (especially in advanced HF), weight monitoring to assess fluid status, moderation of alcohol intake, weight loss if obese, regular physical activity or exercise training if appropriate, smoking cessation, drug therapy and importance of adherence to the medication regimen, symptoms associated with worsening HF and what to do if they occur, and prognosis
- Unless contraindicated, influenza vaccination should be offered every fall
- 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
- An implantable cardioverter-defibrillator or cardiac resynchronication therapy should be considered in appropriate patients but are beyond the scope of this document.
- 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 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

C. Pharmacologic Management of HF with Preserved Left Ventricular Ejection Fraction

OBJECTIVE

- To review the pharmacologic recommendations for patients with HF and preserved LVEF

BACKGROUND

In patients with HF and normal LVEF 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. As patients with HF and normal LVEF are often symptomatic, these patients may also be categorized as Stage C HF according to the ACC/AHA.[1] In addition, there is a high rate of morbidity and mortality seen in these patients.[1,55]

Compared to HF due to systolic dysfunction, there is a paucity of data from randomized trials about the pharmacologic management of patients with preserved LVEF,[1,56-71] despite the estimate that 20-60% of patients with HF can be considered to have normal LVEF (depending on the definition for reduced LVEF).[1] Since questions remain regarding the optimal treatment of patients with HF and normal LVEF, it is recommended that these patients be treated in conjunction with a cardiologist if the patient does not adequately respond to initial interventions.

RECOMMENDATIONS

Drug Therapy

The following are Class I recommendations by the ACC/AHA (i.e., there is evidence and/or general agreement that a given procedure/therapy is useful and effective)[1]

- Control HTN
- Control ventricular rate in patients with atrial fibrillation
- Use diuretics in patients with symptoms of volume overload (e.g., pulmonary congestion or peripheral edema)

The following are Class IIb recommendations by the ACC/AHA (i.e., the usefulness/efficacy is less well established by evidence/opinion)[1]

- Consider use of beta-adrenergic blockers, ACEIs, non-dihydropyridine calcium channel blockers, or angiotensin II receptor antagonists in patients with controlled HTN who continue to have symptoms
- Use of digoxin to improve symptoms is not well established
- Restoring and maintaining sinus rhythm in patients with atrial fibrillation may be useful to improve symptoms

DISCUSSION

General principles of lowering systolic and diastolic blood pressure, treating myocardial ischemia, controlling heart rate and blood volume, and providing anticoagulation for patients with atrial fibrillation apply to these patients as well as to patients with systolic dysfunction. Conditions that can lead to HF with a normal LVEF (e.g., HTN, coronary artery disease, aortic stenosis) should also be treated.[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.

The majority of clinical trials in patients with HF and preserved LVEF have been in a limited number of patients. The CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity) Preserved trial[71] enrolled 3023 patients with HF and LVEF > 40% and compared the addition of an angiotensin II receptor antagonist (candesartan) or placebo to current therapy. Median follow-up was 36.6 months. The primary endpoint of cardiovascular mortality or HF hospitalizations occurred in 22% of

patients receiving candesartan compared to 24% of patients in the placebo group; a difference that was not statistically significant.

D. Interventions in Patients With Asymptomatic Left Ventricular Systolic Dysfunction

OBJECTIVE

- To provide recommendations for patients with asymptomatic LV systolic dysfunction (Stage B)

BACKGROUND

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

RECOMMENDATIONS

Drug Therapy

- Use an ACEI and beta-adrenergic blocker in patients with a recent or remote history of MI, regardless of LVEF
- Use an ACEI in patients with a reduced LVEF who do not have symptoms of HF
- A beta-adrenergic blocker is indicated in patients without a history of MI who have reduced LVEF and do not have symptoms of HF
- An angiotensin II receptor antagonist may be given to patients with a history of MI who have a reduced LVEF and do not have symptoms of HF if they are intolerant of ACEIs

DISCUSSION

Patients with a Recent or Remote History of Myocardial Infarction

Prescribing an ACEI in patients with an acute or recent MI[72,73] and evidence of left ventricular systolic dysfunction (generally defined as LVEF < 40%) may reduce mortality and slow the progression to symptomatic heart failure.[74-77] In the Survival and Ventricular Enlargement (SAVE),[74] Acute Infarction Ramipril Efficacy (AIRE),[75,76] and Trandolapril Cardiac Evaluation (TRACE)[77,78] trials, patients with a recent MI and evidence of HF experienced a significant decrease in all-cause mortality and risk of developing severe HF 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.[75] Patients with a history of MI without reduced LVEF may also benefit from treatment with an ACEI.[16,79]

The use of a beta-adrenergic blocker in patients with asymptomatic left ventricular systolic dysfunction post-MI reduces the risk of cardiovascular morbidity and mortality.[80-83] In the Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) trial that randomized 1959 patients with a LVEF $\leq$ 40% post-MI to carvedilol or placebo, there was not a statistically significant difference in the primary endpoint of all-cause mortality or cardiovascular hospitalizations (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 in patients on carvedilol compared to placebo.[84] Although the results of this study did not achieve statistical significance, the endpoints were numerically 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 beta-adrenergic blocker in patients with asymptomatic left ventricular systolic dysfunction post-MI.

Combination therapy with a beta-adrenergic blocker and an ACEI may also be beneficial in patients with left ventricular systolic dysfunction post-MI.[85-87]

In the Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL), losartan (target dose 50mg once daily) was compared to captopril (target dose 50mg three times daily) in 5477 high-risk (i.e., signs and symptoms of HF or Q-wave MI) patients with acute MI. After a mean follow-up of 2.7 years, the primary endpoint of all-cause mortality occurred in 18% of patients on losartan and 16% of patients on captopril, a difference that was not statistically significant.[88] In another trial comparing an angiotensin II receptor antagonist with an ACEI in patients with MI complicated by HF, LV dysfunction, or both, the Valsartan in Acute Myocardial Infarction Trial (VALIANT) randomized 14,703 patients to treatment with valsartan (target dose 160mg twice daily), captopril (target dose 50mg three times daily), or the combination of valsartan (target dose 80mg twice daily) and captopril (target dose 50mg three times daily). During a median follow-up of 24.7 months, the primary endpoint of all-cause mortality was similar in the treatment groups and occurred in 19.9% of patients randomized to valsartan, 19.5% treated with captopril, and 19.3% receiving the combination. Treatment with valsartan was found to be noninferior to captopril for the endpoint of all-cause mortality.[89] Based on these results, an angiotensin II receptor antagonist can be considered in patients who are intolerant to an ACEI (refer to Annotation G) in high risk patients following MI.[1]

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.[90] In the Prevention trial component of the 12 year follow-up of SOLVD (median duration of follow-up for the Prevention trial 11.2 months), there was a significant reduction in all-cause mortality in patients treated with enalapril (median duration during trial 3.2 years) compared to those receiving placebo (50.9% vs. 56.4%).[91]

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.[92] 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 beta-adrenergic blockers in patients with asymptomatic HF (not in the post-MI setting) has not been critically evaluated, current recommendations include use of a beta-adrenergic blocker in this patient population.[1,83-85]

Digoxin is currently recommended in patients with symptomatic HF to improve clinical status and decrease the risk of hospitalization due to HF,[93] after optimization of standard therapy. Since there is not a significant reduction in disease progression or mortality, digoxin is not recommended in patients with asymptomatic left ventricular dysfunction.[1]

EVIDENCE

Grading System		**USPSTF[6]**			**ACC/AHA[1]**	
Intervention	**References**	**QE**	**OQ**	**SR**	**CR**	**LE**

Use an ACEI in patients with a recent or remote history of MI, regardless of LVEF	SAVE (1992) AIRE (1993) GISSI-3 (1994) ISIS-4 (1995) TRACE (1995) AIREX (1997) HOPE (2000) TRACE 12yr (2005) PREAMI (2006) ACC/AHA (2005) HFSA (2006)	I I I I I II-1 I II-1 I III III	I	A	I	A
Use a beta-adrenergic blocker in patients with a recent or remote history of MI, regardless of LVEF	Norwegian trial (1981) BHAT (1982) Chadda (1986) Gottlieb (1998) CAPRICORN (2001) ACC/AHA (2005) HFSA (2006)	I I II-2 II-2 I III III	I	A	I	A
Use an ACEI in patients with a reduced LVEF who do not have symptoms of HF	SOLVD (1992) SOLVD 12yr (2003) ACC/AHA (2005) HFSA (2006)	I II-1 III III	I	A	I	A
A beta-adrenergic blocker is indicated in patients without a history of MI who have reduced LVEF and do not have symptoms of HF	Chadda (1986) CAPRICORN (2001) SAVE (1997) ACC/AHA (2005) HFSA (2006)	II-2 I II-2 III III	II	B	I	C
An angiotensin II receptor antagonist may be given to patients with a history of MI who have a reduced LVEF and do not have symptoms of HF if they are intolerant of ACEIs	OPTIMAAL (2002) VALIANT (2003) ACC/AHA (2005)	I I III	I	A	I	B

E. Systolic Dysfunction and Assessment for Symptoms of Volume Overload

OBJECTIVE

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

BACKGROUND

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.

RECOMMENDATION

Initial Assessment of Volume Status

The following is a Class I recommendation by the ACC/AHA (i.e., there is evidence and/or general agreement that a given procedure/therapy is useful and effective)[1]

- Patients presenting with HF should receive an assessment of volume status

DISCUSSION

Symptoms of volume overload include ankle swelling, weight gain, fatigue, orthopnea, PND, DOE, SOB at rest and nocturnal cough. The physical 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 (refer to Annotation F).[1]

F. 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 L)

BACKGROUND

Many patients with HF will present with symptoms of fluid retention and require treatment with a diuretic. It is recommended that the diuretic should be continued (particularly in patients with NYHA III or IV failure) even if symptoms resolve to prevent recurrence of volume overload. Patients should notice symptomatic improvement early on with diuretic therapy; however, a diuretic should not be prescribed alone in patients with Stage C HF but combined with drug classes that have been shown to reduce morbidity and mortality.[1]

RECOMMENDATION

Diuretic Therapy in Stage C HF

- A diuretic is indicated in patients with current or previous symptoms of HF with evidence of fluid retention

DISCUSSION

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 6-8 hours, hydrochlorothiazide 6-12 hours, metolazone 12-24 hours) and in their ability to cause sodium excretion ('low ceiling' diuretics like hydrochlorothiazide or 'high ceiling' diuretics like furosemide). As HF progresses, a delay in absorption and failure to filter the drug in the tubular fluid may be contributing factors to the need for increasing diuretic doses in some patients.[1,94-96]

There have been no long-term properly blinded, randomized controlled clinical outcome 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.[1,97-100] The majority of patients enrolled in long-term trials demonstrating a decreased morbidity or mortality with ACEI or beta-adrenergic blocker therapy, were also receiving a diuretic.

Some patients with HF may experience a recurrence of symptoms if diuretic therapy is withdrawn.[101] In one trial the risk of requiring reinstitution of diuretic therapy was 36% in patients in the withdrawal group compared with controls.[102] 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.[103]

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).[1,100] Patients with

symptoms of fluid overload benefit from treatment with a diuretic in conjunction with an ACEI and beta-adrenergic blocker,[1] and possibly digoxin.[104]

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 < 40 mL/min.[1] 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), consideration of change to another loop diuretic, or intravenous diuretics.[1, 94-96,104-111] 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]

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) within 1 to 2 weeks after initiating therapy; consider checking serum levels of magnesium (especially if high doses diuretic used), sodium, calcium, bicarbonate, uric acid, glucose as indicated. Use of an ACEI (or angiotensin II receptor antagonist) 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

EVIDENCE

Grading System		**USPSTF[6]**			**ACC/AHA[1]**	
Intervention	**References**	**QE**	**OQ**	**SR**	**CR**	**LE**
Use a diuretic in patients with evidence of fluid retention	Wilson (1981)	I	II	B	I	C
	Richardson (1987)	I				
	Parker (1993)	I				
	Patterson (1994)	I				
	ACC/AHA (2005)	III				
	HFSA (2006)	III				

G. Angiotensin-Converting Enzyme Inhibitors

OBJECTIVE

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

BACKGROUND

Due to their beneficial effects on morbidity and mortality, an ACEI should be prescribed in patients with Stage C HF, unless contraindicated. Therapy should be initiated at low doses and titrated to target doses or patient tolerability.

RECOMMENDATION

ACEI Therapy in Stage C HF

- An ACEI is recommended in all patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated

DISCUSSION

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]

In addition to improving HF symptoms and functional status,[1,112-118] treatment with an ACEI has been shown to decrease the frequency of hospitalization and the mortality rate[91,119-123] (Appendix C).

In the Captopril-Digoxin Multicenter Trial, patients with mild to moderate HF were randomized to placebo, captopril, or digoxin in addition to treatment with diuretics for 6 months. Compared with placebo, patients on captopril experienced significant improvement in exercise tolerance and decreased frequency of hospital or emergency care for worsening HF. Similar results were not seen with digoxin.[119] 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 and a 26% decreased risk of death or hospitalizations for HF compared to patients on placebo.[120] 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% in the risk of death at 2 years compared to patients on the combination of isosorbide dinitrate (ISDN) and hydralazine.[121] 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. Treatment with enalapril significantly decreased all-cause mortality at 6 months by 40%.[122]

The possibility of racial differences in response to therapy has been seen in a subanalysis of V-HeFT and V-HeFT II. In V-HeFT I, white patients did not experience the same mortality benefit as black patients on ISDN and hydralazine (compared to placebo). In V-HeFT II, white patients on an ACEI experienced a decrease in mortality compared to treatment with ISDN and hydralazine. There was not a statistically significant difference in mortality between treatments in black patients.[124] 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.[125] 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.[92] Results of a trial comparing treatment with the combination of ISDN and hydralazine vs. placebo in self-identified black patients (the majority being treated with an ACEI or angiotensin II receptor antagonist and a beta-adrenergic blocker) are discussed in Annotation J. Further trials will need to be conducted to determine if therapy with an ACEI for HF should to be modified based on patient demographics.

It is recommended that an ACEI be offered to all patients with reduced left ventricular systolic dysfunction unless the patient has specific contraindications:[1,126]

1. A history of angioedema, anuric renal failure, or other documented hypersensitivity to an ACEI
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. Hypotension in patients at risk of cardiogenic shock

Prior to initiating ACEIs, obtain baseline serum potassium, Cr, and BUN; ACEIs should be used cautiously in patients with serum Cr > 3mg/dL. Before initiating therapy, patients should first be assessed for adequate volume status. In patients taking diuretics, symptomatic hypotension may occur following

initiation of an ACEI; if the diuretic cannot be reduced or discontinued, consider a lower starting dose of an ACEI. If the patient is on a potassium-sparing diuretic when an ACEI is begun, close monitoring of potassium is recommended. Alternatively, if the patient is hypokalemic or normokalemic, the potassium-sparing diuretic may be stopped while titrating the ACEI and re-started later, with subsequent close monitoring of potassium. An ACEI should also be used with caution with an aldosterone antagonist (refer to Annotation L). Concomitant use with an NSAID should be avoided whenever possible as NSAIDs used in conjunction with an ACEI may worsen renal function and contribute to hyperkalemia (refer to Appendix B for common drug interactions). 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 Appendices A and C).[1] 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, these agents are often underutilized, and frequently at low doses,[127-129] although this may depend on the clinical setting.[130]

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.[131,132] This is important since other factors may preclude a patient from achieving target doses. 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.[133] 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.[134]

Every effort should be made to titrate patients to the doses used in clinical trials, although if this is not feasible, patients should be maintained on the maximum tolerated dose.[1] Patients prescribed an ACEI prior to discharge from the hospital are more likely to be on an ACEI long-term compared to those not discharged on an ACEI.[135] In addition, initiation of a beta-adrenergic blocker should not be delayed due to an inability to achieve target doses of an ACEI,[1] as patients treated with a beta-adrenergic blocker derived benefit regardless if the patient were receiving low or high doses of an ACEI.[136]

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.[137] Dosage should be modified if the patient develops any of the following:[128]

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.[138-140] 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

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.[141,142] 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.[24,143] 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.[24] 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.[143] In a retrospective analysis of over 22,000 patients from six long-term randomized controlled trials, treatment with an ACEI decreased the risk of major clinical outcomes (composite death, MI, stroke, HF hospitalization, or revascularization) by 20% in patients also receiving aspirin, and by 29% in patients not on concomitant aspirin therapy (interaction test not statistically significant).[144] Two additional evaluations of patients prescribed an ACEI in conjunction with aspirin compared to an ACEI without aspirin, did not find an association between outcome and concomitant aspirin use.[145,146] A dose-related adverse effect of aspirin was reported in one retrospective evaluation where there was an increase in mortality in the patients receiving high dose aspirin ($\geq$ 325mg) compared to those on low dose or no aspirin.[147] 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.[24,141-147] A prospective evaluation of patients with systolic HF receiving warfarin, aspirin, or clopidogrel reported no significant difference in the primary outcome of death, MI, or stroke; although there was a significant reduction in HF hospitalizations with warfarin compared to aspirin.[148,149] This trial was terminated early due to poor enrollment.[148] Therefore, 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.

EVIDENCE

Grading System		**USPSTF[6]**			**ACC/AHA[1]**	
Intervention	**References**	**QE**	**OQ**	**SR**	**CR**	**LE**
An ACEI is recommended in all patients with Stage C HF, unless contraindicated	CONSENSUS (1987) SOLVD (1991) V-HeFT II (1991) SOLVD 12yr (2003) ACC/AHA (2005) HFSA (2006)	I I I II-1 III III	I	A	I	C

H. Beta-Adrenergic Blockers

OBJECTIVE

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

BACKGROUND

Due to their beneficial effects on morbidity and mortality, a beta-adrenergic blocker should be used in patients with Stage C HF, unless contraindicated. Therapy should be initiated at low doses and titrated to target doses or based on patient tolerability. The majority of clinical trials evaluating efficacy of a beta-adrenergic blocker in patients with HF were conducted in patients receiving an ACEI and a diuretic. Patient factors may be taken into consideration when determining whether to initiate therapy first with an ACEI or beta-adrenergic blocker; with subsequent addition of the alternate drug class.

RECOMMENDATION

Beta-Adrenergic Blocker Therapy in Stage C HF

- Stable patients with current or prior symptoms of HF due to systolic dysfunction should receive therapy with a beta-adrenergic blocker that has proven to reduce mortality (i.e., bisoprolol, carvedilol, sustained release metoprolol succinate) unless contraindicated

DISCUSSION

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 beta-receptor down-regulation, LVH, cardiotoxic effects, and arrhythmia. It is thought that one or more of these effects may contribute to HF progression.[1,150] Therefore, using a beta-adrenergic blocker in a patient with HF due to systolic dysfunction could potentially negate some of these adverse effects on the heart.

Numerous trials have been conducted that demonstrate the beneficial effects of beta-adrenergic blockers in reducing symptoms, hospitalization, and progression of disease in patients with HF due to systolic dysfunction.[1,151-165] However, more recent evidence has demonstrated a mortality benefit with the use of beta-adrenergic blockers in this patient population[159-167] (Appendix C). The beta-adrenergic blockers that have been studied for chronic HF and have demonstrated a reduction in mortality include bisoprolol, carvedilol, and sustained release metoprolol succinate. Bisoprolol, titrated to 10 mg once daily, was compared to placebo in patients with primarily NYHA class III HF receiving standard therapy in the second Cardiac Insufficiency Bisoprolol Study (CIBIS II). The primary endpoint of all-cause mortality was reduced with bisoprolol, occurring in 11.8% of patients, compared to 17.3% of patients on placebo.[160] Carvedilol was studied in patients with NYHA class II and III HF (U.S. Carvedilol Heart Failure Study),[161] as well as in patients with more severe HF as in the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS).[162] After a median of 6.5 months, the primary endpoint of death was reported in 3.2% of patients in the U.S. Carvedilol Study receiving carvedilol (target dose 25 mg twice daily) compared to 7.8% of patients on placebo.[161] In COPERNICUS, the primary endpoint of all-cause mortality occurred in 11.3% of patients randomized to carvedilol compared to 16.8% of patients receiving placebo.[162] In the Carvedilol Or Metoprolol European Trial (COMET), carvedilol at a target dose of 25 mg twice daily was compared to the immediate-release formulation of metoprolol tartrate, at target doses of 50 mg twice daily. All-cause mortality was reported to be lower in patients on carvedilol (33.9%) compared to patients receiving metoprolol (39.5%) in this study (additional discussion below).[167] All-cause mortality was also a primary endpoint in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), and was reported in 7.3% of patients randomized to the extended-release formulation of metoprolol succinate (metoprolol XL at a target dose 200mg once daily) compared to 10.9% of patients receiving placebo.[159]

It is unknown if other beta-adrenergic blockers have a similar benefit, as not all beta-adrenergic blockers studied have shown a clear reduction in mortality.[151,167,168]

These agents have also demonstrated efficacy in patients with advanced HF.[160,162,169] 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 with carvedilol,[162] 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 significant decrease in risk of total mortality (39%), death due to worsening HF (55%), hospitalization due to worsening HF (45%), and combined all-cause mortality or all-cause hospitalization (29%) compared to placebo.[169]

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.[170]

The difference in response to treatment with a beta-adrenergic blocker based on race has also been evaluated. After subgroup analysis in the Beta-Blocker Evaluation of Survival Trial (BEST), there was a significant survival benefit in nonblack patients but not in black patients.[168] These results are contrary to findings from a retrospective comparison of patients enrolled in the U.S. Carvedilol Study where the benefit of carvedilol was not statistically significantly different between black and nonblack patients.[171] A 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 beta-adrenergic blockers depending on race concluded that black patients should derive the same benefits as white patients when treated with bisoprolol, carvedilol, or metoprolol succinate (the results of BEST were not included in the pooled analysis).[92]

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.[167,172-174] Although COMET demonstrated a statistically significant improvement in survival with carvedilol compared to immediate-release metoprolol (tartrate), it is unknown whether there is a difference between carvedilol and immediate-release metoprolol tartrate or metoprolol succinate (metoprolol XL) when prescribed at the recommended target doses. Since metoprolol succinate was not available at the time of enrollment in COMET, immediate-release metoprolol tartrate was selected as the comparator to carvedilol, at doses that were expected to result in comparable beta-blockade. Much of the discussion about the results of COMET includes the difference in target dose and effect on resting heart rate.[175] 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).[161,167] The mean dose of metoprolol tartrate 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).[151,167] The mean dose in MERIT-HF was 159mg/d and achieved a reduction in heart rate of 14 beats per minute.[159] Whether these factors had an influence on the results is unknown. Very few trials with beta-adrenergic blockers that are available in the U.S. other than bisoprolol, carvedilol, or metoprolol succinate have been published. It is therefore unknown if treatment with other beta-adrenergic blockers would provide the same benefits as seen with the agents that have demonstrated a reduction in mortality in patients with heart failure.[176,177]

The majority of patients included in the beta-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 beta-adrenergic blocker trials show a reduction in mortality of approximately 30 to 35%.[85,177-179] It is felt that the use of an ACEI and beta-adrenergic blocker in patients with HF is synergistic[180] and should be used in combination whenever possible.[1] Whether to begin treatment naïve patients with a beta-adrenergic blocker or an ACEI has yet to be resolved; according to the results from CIBIS III, it appears that initial therapy with bisoprolol may be as safe and efficacious as starting treatment with enalapril (refer to Appendix C for detailed results).[166] In patients with HF, utilization of the beta-adrenergic blockers is typically not as high as that seen with the ACEIs,[4] even though patient tolerability appears to be similar.[181] As the majority of clinical trials evaluating efficacy of a beta-adrenergic blocker in patients with HF were conducted in patients receiving an ACEI and a diuretic,

clinicians may choose to initiate therapy with a beta-adrenergic blocker once the patient has been stabilized on treatment with an ACEI.[54] Initiation of therapy with a beta-adrenergic blocker may be considered prior to achieving a target dose of the ACEI, with concomitant titration;[53] as benefit with combination therapy, even at lower doses of an ACEI, has been demonstrated.[1,131,133] Every effort should be made to achieve target doses of both an ACEI and beta-adrenergic blocker as tolerated by the patient. Implementation of treatment guideline recommendations should be emphasized in order to provide patients with the opportunity for optimal drug therapy benefit.[4]
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Caution should be exercised when initiating a beta-adrenergic blocker 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. Selection of a different beta-adrenergic blocker may also be considered.[182] Another factor that may contribute to a need for a delay in titration is a low heart rate;[79] although, the absolute increase in risk for hypotension, dizziness, and bradycardia is small and should be weighed against the overall benefit of beta-adrenergic blockers seen in clinical trials.[182] Clinicians who do not have experience with beta-adrenergic blockers in patients with HF should consult with a cardiologist or healthcare provider specializing in the management of HF. Another opportunity to initiate therapy may be predischarge, provided the patient is stable and their condition does not necessitate use of intravenous therapy for HF.[1,183] It is important that patients with HF on a beta-adrenergic blocker are titrated carefully to a target dose as used in clinical trials or as tolerated (refer to Appendices A and C).[184-191] Common drug interactions are listed in Appendix B.

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; with optimal doses achieved in 8 to 12 weeks[53]), and an adequate duration of treatment (3-12 months before effects are seen).

Beta-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 beats per minute.[1] If the patient is on digoxin with a HR of less than 60 bpm, reconsider digoxin in favor of the benefits of a beta-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.[1,159-161,192]

EVIDENCE

Grading System		**USPSTF[6]**			**ACC/AHA[1]**	
Intervention	**References**	**QE**	**OQ**	**SR**	**CR**	**LE**
Use a beta-adrenergic blocker with proven mortality benefit in patients with stable Stage C HF	US Carvedilol (1996)	I	I	A	I	A
	MERIT-HF (1999)	I				
	CIBIS-II (1999)	I				
	COPERNICUS (2001)	I				
	Shibata (2001)	I				
	CIBIS I & II (2002)	I				
	COMET (2003)	I				
	ACC/AHA (2005)	III				
	HFSA (2006)	III				

I. Angiotensin II Receptor Antagonists

OBJECTIVE

- To provide recommendations for the appropriate use of the angiotensin II receptor antagonists in patients with a diagnosis of systolic HF

BACKGROUND

Due to the established beneficial effects of the ACEIs and beta-adrenergic blockers in treating patients with HF, long-term outcome trials with the angiotensin II antagonists have been conducted in patients already receiving standard therapy for HF or in patients who are unable to tolerate an ACEI. Treatment with an angiotensin II receptor antagonist has shown a beneficial effect in reducing cardiovascular death and HF hospitalizations in patients unable to tolerate an ACEI, as well as in addition to standard therapy; although data are conflicting as to the benefit of adding an angiotensin II receptor antagonist to patients receiving an ACEI and a beta-adrenergic blocker. The effect of treatment with an angiotensin II receptor antagonist on all-cause mortality has not yet been established.

RECOMMENDATIONS

Angiotensin II Receptor Antagonist in Stage C HF

- An angiotensin II receptor antagonist with demonstrated efficacy (i.e., candesartan and valsartan) in the treatment of HF is recommended in patients with Stage C HF who are unable to tolerate therapy with an ACEI

- Addition of an angiotensin II receptor antagonist to standard therapy (i.e., an ACEI and beta-adrenergic blocker) may be considered to decrease cardiovascular death or HF hospitalizations in patients with persistent symptoms (see discussion below); although it should also be noted that routine use of an ACEI, angiotensin II receptor antagonist, and aldosterone antagonist is not recommended

DISCUSSION

Angiotensin-converting enzyme inhibitors 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 angiotensin II receptor antagonists selectively block the angiotensin II type1 receptor so that the effects of angiotensin II are blocked regardless of how it is produced. 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.[1]

Trials have been conducted evaluating the majority of the angiotensin II receptor antagonists, demonstrating a favorable effect on patient symptoms or NYHA functional class compared to placebo,[191-195] with comparable benefits to an ACEI.[196-201] Results of long-term effects on morbidity and mortality have been published in patients treated with the angiotensin II receptor antagonists, candesartan, losartan, and valsartan. The results of these trials are briefly discussed with details found in Appendix C.

One of the first trials to evaluate long-term morbidity and mortality outcomes with an angiotensin II receptor antagonist in patients with HF was ELITE II (Evaluation of Losartan in the Elderly); which evaluated 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).[202] This trial was a follow-up to the original ELITE Study, that although not hypothesized *a priori*, reported a favorable mortality rate with losartan.[203] In ELITE II, there was no significant difference in all-cause mortality between the treatment groups (17.7% on losartan vs. 15.9% on captopril). 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.[202]

The Val-HeFT (Valsartan Heart Failure Treatment) study was a placebo-controlled trial that evaluated the addition of valsartan 160 mg twice daily to patients with HF on standard therapy (93% ACEI, 35% beta-adrenergic blockers). Overall mortality (a primary endpoint) was similar, occurring in 19.7% of patients in the valsartan group and 19.4% of patients on placebo. The combined primary endpoint of mortality and morbidity (i.e., cardiac arrest with resuscitation, HF hospitalization, or intravenous inotropic agents or

vasodilators for over 4 hours) occurred in 28.8% and 32.1% of patients on valsartan and placebo, respectively. This included a reduction in hospitalizations for HF (13.8% valsartan vs. 18.2% placebo). 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 in patients receiving valsartan in conjunction with an ACEI and beta-adrenergic blocker. Patients who were not on an ACEI or beta-adrenergic blocker experienced a significant reduction in mortality (p=0.012). Patients on valsartan but not on an ACEI (with or without a beta-adrenergic blocker) had a lower risk of death and a lower risk of the combined endpoint.[204] A subanalysis of the 366 patients in Val-HeFT who were not on an ACEI reported a 33% decrease in all-cause mortality (p=0.017) and a 53% decrease in combined morbidity and mortality (p<0.001).[205]

The CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity) Overall program combined the results of three placebo-controlled trials evaluating therapy with candesartan titrated to a target dose of 32mg once daily:[206] CHARM-Added evaluated patients with systolic HF on standard therapy (100% ACEI; 55% beta-adrenergic blockers);[207] CHARM-Alternative studied patients with systolic HF and previous ACEI intolerance;[208] and CHARM-Preserved included patients with HF and LVEF > 40%.[70] In CHARM-Overall, the primary outcome of all-cause mortality was numerically reduced with candesartan, although the result did not achieve statistical significance. The secondary endpoint of combined CV death or HF hospitalization was significantly reduced by 16% compared to placebo.[206] In a pooled analysis of patients with LVEF $\leq$ 40%, there was a significant 12% reduction in mortality.[209]

In the CHARM-Added trial, the combined primary endpoint of CV mortality or HF hospitalization was significantly reduced by 15% compared to placebo in patients on candesartan in addition to standard therapy including an ACEI. The difference in all-cause mortality was not statistically significant. In the subgroup of patients on therapy with candesartan in combination with an ACEI and beta-adrenergic blocker, there was also a significant reduction in the risk of CV death or HF hospitalization compared to patients on placebo; the difference in all-cause mortality in this subgroup was not statistically significant.[207] This is in conflict with the increase in mortality seen in the subgroup analysis of Val-HeFT in patients on combination ACEI, beta-adrenergic blockers, and angiotensin II antagonist.[204] Regarding the addition of an angiotensin II receptor antagonist to standard therapy for HF, the ACC/AHA HF clinical practice guidelines recommend (Class IIb: i.e., usefulness/efficacy is less well established by evidence/opinion) that this may be considered in patients with persistent symptoms despite standard therapy for HF (Level of Evidence B).[1] It is also important to note that the routine use of an ACEI, angiotensin II receptor antagonist, and aldosterone antagonist is not recommended.[1]

The combined primary endpoint of CV mortality or HF hospitalization was reduced by 23% in patients with a history of ACEI intolerance randomized to candesartan compared to those on placebo in the CHARM-Alternative trial. There was not a statistically significant reduction in all-cause mortality.[208]

The angiotensin II receptor antagonists have yet to be shown to be equivalent or superior to the ACEIs in reducing long-term outcomes of morbidity and mortality in randomized controlled trials of patients with HF. A meta-analysis of 38,080 patients reported that use of an angiotensin II receptor antagonist in patients with HF reduced all-cause mortality [OR (odds ratio) 0.83; 95% CI 0.69-1.00] compared to placebo, although this was influenced largely by data from CHARM-Alternative. There was also a statistically significant reduction in HF hospitalizations (OR 0.64; 95% CI 0.53-0.78) with an angiotensin II receptor antagonist compared to placebo. There was not a significant difference in all-cause mortality or HF hospitalizations when data with an angiotensin II receptor antagonist were compared to results with an ACEI. The analysis also compared an angiotensin II receptor antagonist in combination with an ACEI vs. an ACEI alone, without a significant difference in all-cause mortality; although there was a statistically significant reduction in HF hospitalizations (OR 0.77; 95% CI 0.69-0.87) favoring combination therapy.[210] These results are similar to a previous meta-analysis of 12,469 patients that reported a trend toward improved mortality and hospitalizations with an angiotensin II receptor antagonist compared to placebo in patients not on an ACEI, and the combination of an angiotensin II receptor antagonist and ACEI significantly reduced the risk of hospitalizations compared to patients on an ACEI alone.[211] Another meta-

analysis reported a reduction in morbidity and mortality, but not mortality alone, in patients receiving an angiotensin II receptor antagonist in combination with an ACEI, regardless of a beta-adrenergic blocker, or when a beta-adrenergic blocker was not part of therapy. Combined morbidity and mortality, or the endpoint of mortality alone, was not reduced in patients receiving all three classes of medications.[212]

Use of an angiotensin II receptor antagonist 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 angiotensin II receptor antagonist.[213]

An angiotensin II receptor antagonist should be used with extreme caution in a patient who has previously experienced angioedema on an ACEI.[1] The incidence of angioedema in patients taking ACEIs is approximately 0.1-1.2 %.[214] 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.[215] Angioedema has been reported with the angiotensin II receptor antagonists but to a much lesser degree than ACEIs. The exact mechanism is unknown; in ACEIs, it is thought to be related to bradykinin accumulation. In the CHARM-Alternative trial with candesartan in patients with HF and a history of ACEI intolerance, 3 of 1013 patients randomized to candesartan experienced angioedema. One of these patients required discontinuation of the drug (0.1%). All 3 cases occurred out of the 39 patients who previously experienced angioedema or anaphylaxis on an ACEI (7.7%). None of the 1015 patients who received placebo experienced angioedema.[208] There have been a number of published case reports of angioedema in patients treated with an angiotensin II receptor antagonist.[214,216-230] In approximately one-third of these cases, the patients previously experienced angioedema with an ACEI. Therefore, extreme caution is warranted in patients who have previously experienced angioedema.[216,224,226,227,231]

The angiotensin II receptor antagonists, like the ACEIs, decrease release of aldosterone from the adrenal cortex, which can lead to decreased potassium excretion. It is unclear at this time if treatment with an angiotensin II receptor antagonist would be an appropriate alternative in patients who develop hyperkalemia on an ACEI.[120,201,203,232] In the CHARM-Overall programme, hyperkalemia resulted in discontinuation of study drug in 2.2% of patients on candesartan compared to 0.6% patients on placebo ($p<0.0001$). In the overall analysis, 41% of patients received concomitant treatment with an ACEI and approximately 17% were on spironolactone.[206] As with the ACEIs, it is recommended that patients on an angiotensin II receptor antagonist have their blood pressure, renal function, and potassium reevaluated within one to two weeks after initiating therapy, and monitored after dose adjustments.[1] Patients receiving an angiotensin II receptor antagonist in conjunction with and ACEI, potassium supplements, or potassium-sparing diuretics (including spironolactone) should be monitored closely as combination therapy may result in an increased potassium level. Other clinically significant drug interactions with the angiotensin II receptor antagonists are listed in Appendix B.

EVIDENCE

Grading System		**USPSTF[6]**			**ACC/AHA[1]**	
Intervention	**References**	**QE**	**OQ**	**SR**	**CR**	**LE**
Use an angiotensin II receptor antagonist in patients on standard therapy for HF who cannot tolerate an ACEI	Val-HeFT (2001) Maggioni (2002) Jong (2002) CHARM-Alternative (2003) CHARM Overall (2003) Lee (2004) ACC/AHA (2005) HFSA (2006)	I II-2 I I I I III III	I	A	I	A
Consider an angiotensin II receptor antagonist in addition to standard therapy (i.e., an ACEI and beta-blocker) in patients with persistent symptoms	Val-HeFT (2001) Jong (2002) CHARM-Added (2003) CHARM Overall (2003) Lee (2004) Dimopoulos (2004) ACC/AHA (2005) HFSA (2006)	I I I I I I III III	II	B	IIb	B

J. Hydralazine in Combination with a Nitrate

OBJECTIVE

- To provide recommendations for the appropriate use of hydralazine and a nitrate in patients with a diagnosis of systolic HF

BACKGROUND

An earlier trial compared the combination of hydralazine and isosorbide dinitrate (ISDN) to therapy with an ACEI and based on these results, the combination of hydralazine and ISDN was considered a therapeutic option in patients unable to tolerate an ACEI. The combination of hydralazine and ISDN had not been previously studied in addition to standard therapy (i.e., an ACEI and beta-adrenergic blocker); however, results of a recent trial in self-identified black patients reported a significant reduction in mortality and HF hospitalization with the combination of hydralazine and ISDN. It is not clear whether these results can be extrapolated to the general patient population.

RECOMMENDATION

Therapy with Hydralazine and a Nitrate in Stage C HF

- The combination of hydralazine and a nitrate should be considered, especially in African American patients with NYHA Class III or IV HF, who continue to have symptoms despite therapy with an ACEI (or an angiotensin II receptor antagonist if an ACEI is not tolerated) and beta-adrenergic blocker

- The combination of hydralazine and a nitrate may be considered as an alternative to an ACEI in patients who are unable to tolerate an ACEI (or angiotensin II receptor antagonist) due to hypotension, renal insufficiency, hyperkalemia, or possibly, angioedema

DISCUSSION

Peripheral vasodilators such as ISDN (venodilator) and hydralazine (arterial vasodilator) can produce favorable hemodynamic effects in patients with HF.[1] Earlier trials evaluated the combination of hydralazine and ISDN in patients receiving standard therapy for HF (at the time, digoxin and a diuretic). In the first of these two VA trials, the Vasodilator-Heart Failure Trial I (V-HeFT I), treatment with ISDN and hydralazine was reported to significantly reduce mortality by two years compared to placebo (25.6% vs. 34.3%, respectively).[233] The second trial, V-HeFT II, compared treatment with ISDN and hydralazine to that of an ACEI in HF patients (majority with NYHA class II or III HF). Mortality with ISDN and hydralazine was similar to that seen in V-HeFT I (25%), although mortality after two years was lower in patients treated with an ACEI (18%) compared to patients on hydralazine and ISDN.[121] The authors concluded that the similar reduction in mortality seen with the combination of hydralazine and ISDN in V-HeFT I and V-HeFT II, compared with the mortality in the placebo group, along with the reduction in mortality seen with an ACEI, suggested that there is benefit in using a vasodilator as part of the treatment regimen in patients with HF, and that there may be an additional benefit of using the two treatments together.[121]

As discussed previously, 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.[125] Different results have been found with hydralazine and ISDN, where there has been a greater benefit in black patients compared to white patients.[124] Racial differences in response to therapy have been reported in subanalyses of the V-HeFT I and V-HeFT II trials. The annual mortality rate was significantly lower in black patients receiving ISDN and hydralazine in V-HeFT I compared to black patients receiving placebo (9.7% vs. 17.3%, respectively); a similar effect was not seen in white patients on hydralazine and ISDN vs. placebo (annual mortality rate 16.9% vs. 18.8%, respectively).[124] In V-HeFT II, white patients on enalapril experienced a significant decrease in mortality compared to treatment with hydralazine and ISDN (annual mortality rate 11.0% vs.

14.9%, respectively), whereas black patients did not have a similar benefit (annual mortality rate with enalapril 12.8% vs. 12.9% with hydralazine and ISDN).[124]

More recently, the African-American Heart Failure Trial (A-HeFT), a long-term morbidity and mortality trial in self-identified black patients with NYHA class III to IV HF, evaluated the fixed-dose combination of hydralazine and ISDN compared to placebo. The majority of patients enrolled in the trial were also receiving treatment with an ACEI (or angiotensin II receptor antagonist), a beta-adrenergic blocker, diuretic, and digoxin; over one-third of patients were also receiving an aldosterone antagonist. The trial was planned for 18 months of follow-up but was terminated early (mean follow-up 10 months) due to a significant reduction in mortality in patients receiving treatment (6.2%) compared to those on placebo (10.2%). Treatment was associated with a 43% improvement in survival. There was also a significant 33% reduction in first hospitalization for HF (another pre-specified component of the primary endpoint) with treatment compared to placebo (16.4% vs. 24.4%, respectively). The primary endpoint was a composite score (possible range -6 to +2, with a higher score representing a better outcome) with weighted values based on mortality, survival to the end of the trial, first hospitalization for HF, no hospitalizations, and change in quality of life. It was reported that patients receiving the combination hydralazine and ISDN had a primary composite score of -0.1±1.9 compared to -0.5±2.0 in the placebo group (p=0.01), indicating a benefit with hydralazine and ISDN in addition to standard drug therapy.[234]

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.

EVIDENCE

Grading System		USPSTF[6]			ACC/AHA[1]	
Intervention	**References**	**QE**	**OQ**	**SR**	**CR**	**LE**
Consider combination of hydralazine and a nitrate, especially in African American patients in NYHA Class III or IV, who continue to have symptoms despite therapy with an ACEI (or angiotensin II receptor antagonist if an ACEI is not tolerated) and beta-adrenergic blocker	A-HeFT (2004) V-HeFT I (1986) V-HeFT II (1991) ACC/AHA (2005) HFSA (2006)	I I I III III	I	B	IIa	A
Consider combination of hydralazine and a nitrate in patients unable to take an ACEI or angiotensin II receptor antagonist due to hypotension, renal insufficiency, or drug intolerance	V-HeFT I (1986) V-HeFT II (1991) ACC/AHA (2005) HFSA (2006)	I I III III	II	C	IIb	C

K. Digitalis

OBJECTIVE

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

BACKGROUND

Trials with digoxin have shown it to be beneficial in reducing HF associated symptoms and hospitalizations in patients on standard therapy at trial enrollment (i.e., diuretic and an ACEI), but not in improving survival.

RECOMMENDATION

Digoxin Therapy in Stage C HF

- Digoxin may be useful in decreasing hospitalizations in patients with current or previous HF symptoms

DISCUSSION

Digoxin is thought to be beneficial in patients with systolic HF through inhibition of sodium-potassium adenosine triphosphatase resulting in reduced activation of the neurohormonal system and increased contractility of the heart.[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 appears to continue to have a role in the treatment of patients with HF by improving patient symptoms and decreasing hospitalizations, without adversely affecting survival.[56,119,132,235]

According to a meta-analysis, treatment with digoxin in patients with HF due to systolic dysfunction can reduce the incidence of clinical deterioration[235,236] by 12% compared to patients on placebo.[235] 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 and a decreased exercise tolerance, worsening NYHA class, decreased quality of life and LVEF.[237] 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.[238]

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.[56] In a 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, but not in the women who were treated with digoxin. 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). The median serum digoxin concentration was significantly higher in women compared to men (0.9ng/ml based on 475 randomly selected women vs. 0.8ng/ml in 1653 randomly selected men at one month after randomization; p=0.007); although, there was not a statistically significant difference at 12 months (0.6ng/ml in randomly selected men and women, respectively). Due to these findings, the authors suggest that the role of digoxin in women be reevaluated.[239] Others suggest that a lower dose with a resultant serum concentration < 1ng/ml be used.[239,240]

More recently, the relationship between serum digoxin concentrations and morbidity and mortality in women in the DIG trial were evaluated. This retrospective analysis demonstrated a reduction in death or HF hospitalization and no increase in mortality in women with a digoxin concentration 0.5-0.9ng/ml. A serum digoxin concentration of 1.2-2.0ng/ml was associated with an increase in risk for death in women.[241] Another retrospective analysis of the DIG trial did not find a relationship on outcomes based on race.[242]

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 beta-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 particularly useful 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 once daily or every other day) 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.[243-246] In both the RADIANCE and PROVED trials, the mean digoxin serum concentration was 1.2ng/ml and in the DIG trial, the mean serum digoxin level was 0.8 ng/ml at 12 months.[237,238,244,246] 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.[247] A post hoc analysis of the DIG trial showed a linear relationship for mortality and increasing serum digoxin concentrations with a lower mortality seen in patients with a digoxin serum concentration of 0.5-0.8ng/ml, no reduction in mortality at 0.9-1.1ng/ml, and an increase in mortality at levels $\geq$1.2ng/ml. The analysis was limited to men.[248] The authors concluded that lower levels may provide optimal benefit without the risk of detrimental effects seen with higher levels,[246,247] 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:

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. Medications are added that affect the serum digoxin concentration (e.g., quinidine, verapamil, amiodarone, antibiotics, anticholinergics) (refer to Appendix B), or the sensitivity to digoxin by altering potassium levels

EVIDENCE

Grading System		USPSTF[6]			ACC/AHA[1]	
Intervention	**References**	**QE**	**OQ**	**SR**	**CR**	**LE**
Consider digoxin to improve functional status and reduce frequency of hospitalizations if continued symptoms	Captopril-Digoxin (1988) Jaeschke (1990) RADIANCE (1993) PROVED (1993) DIG (1999) Hood (2004) ACC/AHA (2005)	I I I I I I III	II	B	IIa	B

L. Aldosterone Antagonists

OBJECTIVE

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

BACKGROUND

Aldosterone antagonists (e.g., spironolactone, eplerenone) 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, with concern for 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.[1,249] 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.

RECOMMENDATION

Aldosterone Antagonist Therapy in Stage C HF

- An aldosterone antagonist is beneficial in selected patients (e.g., moderately severe to severe HF symptoms with reduced LVEF, or patients with LVEF $\leq$ 40% early post-MI, and with adequate kidney function and no hyperkalemia) who can be monitored for hyperkalemia or renal dysfunction

DISCUSSION

The above recommendations are based on the Randomized Aldactone Evaluation Study (RALES), 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 beta-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 (45.9% on placebo vs. 34.6% on spironolactone). There was also a significant 35% decrease in hospitalizations due to worsening HF in patients on spironolactone; these patients also experienced significant improvement in symptoms.[249]

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy Survival Study (EPHESUS) compared an aldosterone antagonist, eplerenone (mean dose 42.6mg per day), to placebo in 6642 patients with acute MI complicated by LV dysfunction, and symptoms of HF (patients with DM could be enrolled without having HF symptoms), with the majority on standard therapy for this indication. Ninety percent of patients had symptomatic HF. Treatment with eplerenone significantly reduced the primary endpoints of death from any cause (14.4% of patients on eplerenone vs. 16.7% of patients in the placebo group) and death from cardiovascular causes or first hospitalization for a cardiovascular event, including HF, recurrent acute MI, stroke, or ventricular arrhythmia (eplerenone 26.7% vs. placebo 30.0%).[250] Based on these data, an aldosterone antagonist may also be considered early after an acute MI in patients with LV dysfunction and HF.[1,53]

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.[251] The risk vs. benefit of using an aldosterone antagonist in these patients needs to be determined. An aldosterone antagonist may contribute to serious hyperkalemia if not used properly in patients with HF.[251,252]

In addition to hyperkalemia, aldosterone antagonists can cause gynecomastia, gastrointestinal side effects, and menstrual irregularities. In RALES, 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 in both the RALES and EPHESUS trials, patients with serum creatinine > 2.5 mg/dL and serum potassium > 5.0 mmol/L were excluded and patients were not taking other potassium-sparing diuretics. In EPHESUS, the mean serum Cr concentration was 1.1 mg/dl at baseline.[250] In clinical practice, reports of discontinuations due to hyperkalemia appear to be higher than seen in the clinical trial.[253-255] Hyperkalemia occurs more frequently in patients receiving potassium supplements and in patients with renal insufficiency. Use of potassium supplements with an aldosterone antagonist should be avoided unless hypokalemia develops. The aldosterone antagonists 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.[256] An aldosterone antagonist should also be used with caution in patients receiving ACEIs or angiotensin II receptor antagonists due to the potential for hyperkalemia; potassium should be monitored closely in these patients.[257,258] In general, potassium supplements should be discontinued when therapy with an aldosterone antagonist is initiated.[1] Serum potassium should be monitored within 3 days

and at 1 week, and every 4 weeks for the first 3 months, then every 3 months thereafter.[249,252] 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.[257-260] If the potassium increases to > 5.5 mEq/L, the aldosterone antagonist should be discontinued or the dose reduced. If serious hyperkalemia develops, therapy with the aldosterone antagonist should be discontinued.[1]

The initial dose of spironolactone used in RALES 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.[252] Refer to Appendix B for common drug interactions.

EVIDENCE

Grading System		USPSTF[6]			ACC/AHA[1]	
Intervention	**References**	**QE**	**OQ**	**SR**	**CR**	**LE**
Consider low dose of an aldosterone antagonist (e.g., 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 mEq/L) and kidney function is adequate (serum Cr ≤ 2.5 mg/dL in men; ≤ 2.0 mg/dL in women) and in whom potassium and renal function can be carefully monitored	RALES (1999) ACC/AHA (2005) HFSA (2006)	I III III	I	A	I	B
Consider addition of an aldosterone antagonist in patients on standard therapy for HF with LVEF ≤ 40% early post-MI, who have a normal potassium and adequate kidney function; patients should be monitored for changes in potassium and kidney function	EPHESUS (2003) ACC/AHA (2005) HFSA (2006)	I III III	I	A	NA	NA

M. Continue Present Management and Schedule Regular Follow-up

OBJECTIVE

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

BACKGROUND

Patients should receive 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, nonpharmacologic measures, and adverse effects to therapy. Patients should be scheduled for routine laboratory monitoring. The patient should also be assessed for any change in functional status or frequency of hospitalizations, and medication therapy should be optimized. A multidisciplinary approach to care and follow-up should be utilized if appropriate to potentially improve care and outcomes.[1,22,53]

RECOMMENDATIONS

General Recommendation

- Patients should receive regular follow-up

Multidisciplinary Disease Management Programs

The following is a Class I recommendation by the ACC/AHA (i.e., there is evidence and/or general agreement that a given procedure/therapy is useful and effective)[1]

- Recommended for patients at high risk for hospital admission or clinical deterioration to facilitate implementation of clinical practice guidelines, address barriers to behavioral change, and to decrease the risk of HF hospitalization

The following is a Class IIb recommendation by the ACC/AHA (i.e., the usefulness/efficacy is less well established by evidence/opinion)[1]

- Consider for patients at low risk for hospital admission or clinical deterioration to facilitate implementation of clinical practice guidelines

Performance Measures (refer to discussion in Introduction)

The following is a Class IIa recommendation by the ACC/AHA (i.e., the weight of evidence/opinion is in favor of usefulness/efficacy)[1]

- Performance measures based on clinical practice guidelines may improve quality of patient care

DISCUSSION

Routine follow-up is an essential component of the overall management of patients with HF.[1,261] At this time the patient's functional status can be evaluated and any adjustments made to the medication regimen. The presence of any adverse events should also be determined. 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, angiotensin II receptor antagonists, and aldosterone antagonists may all increase potassium, leading to potential toxicity.[1]

Adherence to the medication regimen is often not optimal[262,263] and may lead to clinical deterioration in patients with HF.[5] 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.

Some facilities may have interdisciplinary HF disease management clinics or specialized programs to provide continuity of care and improve treatment outcomes for patients with HF.[1,186,265-282] Heart failure disease management clinics have improved patient outcomes including improved function status,[186,272,274] fewer hospitalizations,[272-275,282] a reduction in mortality,[186,266,275-278] increased utilization of ACEI and/or beta-adrenergic blockers or their doses.[186,266,267,278] In addition, reports suggest the use of these disease management programs may be cost-effective.[186,273]

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.[1,279] 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. 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]

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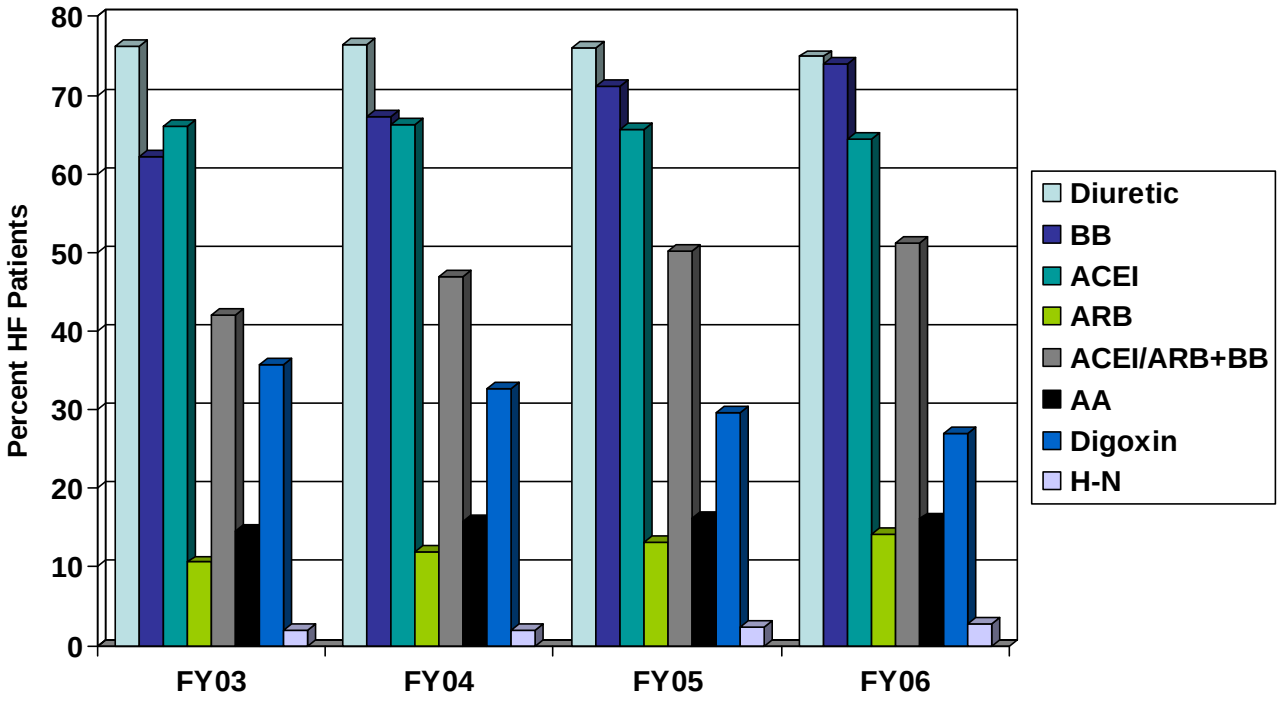
Figure: VA Utilization of Medications for HF by Drug Class



Denominator=patients with at least one diagnosis of heart failure (i.e., at least one inpatient primary diagnosis or any outpatient diagnosis within 24 months prior to the end date of the fiscal year) and at least one active prescription during the fiscal year
Active prescription=at least 90 days of therapy during the given year
Combination therapy=prescriptions for both medications overlapping ≥ 50%
AA=aldosterone antagonist; ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor antagonist; BB=beta-adrenergic blocker; ACEI/ARB+BB=ACEI or ARB in combination with BB; H-N=hydralazine in combination with a nitrate

Appendix A: Medications Commonly Used for the Management of HF[a-c]

In general, patients should be titrated to target doses as used in randomized controlled trials (refer to Appendix C), or highest tolerated dose

DRUG	INITIAL DOSE	MAXIMUM DOSE[d]	COMMENTS/CAUTIONS
Diuretics			
Furosemide	20 to 40 mg given once or twice daily	600 mg in divided doses	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
Bumetanide	0.5 to 1.0 mg given once or twice daily	10mg in divided doses	Add potassium supplement or low dose potassium-sparing diuretic[e] if the patient becomes hypokalemic (serum K^+ < 4.0 mEq/L)
Ethacrynic acid	50 mg once or twice daily	400mg in divided doses	Use cautiously in poorly controlled DM, symptomatic BPH, or in patients with increased risk of volume depletion
Torsemide	10 to 20 mg once daily	200 mg once daily	Furosemide usually administered once daily unless higher doses (e.g., > 160mg/d) are needed, then more frequent daily dosing should be considered
Hydrochlorothiazide	25 mg given once or twice daily	200 mg in divided doses	Ethacrynic acid may be used in patients with sulfonamide sensitivity
Chlorthalidone	12.5 to 25 mg once daily	100 mg once daily	Thiazides lose effectiveness in patients with CrCl < 40 mL/min
Indapamide	2.5 mg once daily	5 mg once daily	Reserve indapamide for patients with CrCl < 25 mL/min
Metolazone[f,g]			Reserve metolazone for intermittent use as an
Zaroxolyn®	2.5 to 5 mg once daily	20 mg once daily	adjunct to loop diuretics for diuresis in patients with HF or in patients with CrCl < 25 mL/min;
Mykrox®	0.5 mg once daily	1 mg once daily	thiazide/loop combinations are also effective and are less expensive
Angiotensin Converting Enzyme Inhibitor			
Captopril[h]	6.25 to 12.5 mg three times daily	50 mg three times daily[d]	Start with lower or less frequent doses in patients with renal insufficiency; use with caution in patients with renal artery stenosis
Enalapril	2.5 mg twice daily	10 to 20mg twice daily[d]	Should not be used if K+ > 5.5 mEq/L that cannot be reduced
Fosinopril	5 to10 mg once daily	20 to 40 mg once daily[d]	Due to the potential risk for fetal abnormalities in patients taking ACEIs during pregnancy, it is recommended that therapy be discontinued as soon as a woman becomes pregnant. Alternate therapy should be considered. ACEIs should only be prescribed in pregnant women when the benefit clearly outweighs the potential risk for fetal abnormalities
Lisinopril	2.5 to 5 mg once daily	20 to 40 mg once daily[d]	
Beta-adrenergic blockers			
Metoprolol succinate (XL)	12.5 to 25 mg once daily; double dose every 2 weeks to target dose	200 mg once daily[d] (or highest dose tolerated)	Low initial doses should be implemented; use slow gradual increases in the dosage
Bisoprolol	1.25 mg once daily; increase by 1.25 mg every week until 5 mg once daily, then increase by 2.5 mg every 4 weeks to target dose	10 mg once daily[d]	Effects are generally seen in 3-12 months Carvedilol should be given with food to reduce the incidence of orthostatic hypotension Consider separating the ACEI, adjusting dose of diuretic, or temporary ACEI dose reduction if dizziness occurs
Carvedilol (alpha & beta antagonist)	3.125 mg twice daily; titrate at minimum of every 2 weeks to target dose	25 mg twice daily[d] (should be titrated as tolerated to 50mg twice daily if ≥ 85kg)	Should not be abruptly discontinued
Angiotensin II Receptor Antagonists			
Candesartan	4 to 8 mg once daily	32 mg once daily[d]	Contraindicated in 2nd and 3rd trimesters pregnancy due to potential neonatal/fetal

Valsartan	40 to 80 mg divided twice daily	320 mg divided twice daily[d]	morbidity and death Use with caution in patients with renal artery stenosis Should not be used if K+ > 5.5 mEq/L that cannot be reduced Consider lower doses in patients with intravascular volume depletion
Hydralazine in Combination with a Nitrate			
Hydralazine	112.5 to 150 mg divided three times daily	225 to 300 mg divided three times daily[d]	Hydralazine: Adverse effects include dizziness, headache, lupus-like syndrome, nausea, tachycardia**,** postural hypotension Advise patient to take with food
Isosorbide dinitrate	30 to 60 mg divided three times daily	120 to 160 mg divided three times daily[d]	ISDN: Adverse effects include flushing, headache, postural hypotension, rash May cause an increase in ocular pressure; caution with presence of glaucoma
Digoxin			
Digoxin	0.125 to 0.25 micrograms once daily	Usually 0.25 micrograms once daily (0.375 to 0.5 micrograms once daily may be used rarely)	Initiate therapy with 0.125 micrograms once daily (or every other day) in patients > 70, with impaired kidney function, or with a low lean body mass Lower trough serum digoxin concentrations may be preferable (i.e., 0.5-0.9ng/ml), and should not exceed 1.1ng/ml Signs of toxicity include confusion, nausea, vomiting, abdominal pain, diarrhea, anorexia, fatigue, arrhythmias, visual disturbances
Aldosterone Antagonists			
Spironolactone	12.5 to 25 mg once daily	25 mg once daily[d]	If CrCl < 50 ml/min, initial dose should be 12.5 mg once daily or 25 mg every other day for spironolactone and 25 mg once daily of eplerenone; not recommended if CrCl < 30 ml/min Monitor closely for hyperkalemia (should not be used if baseline K+ > 5.0 mEq/L) or renal dysfunction; patients may also experience gynecomastia, especially with spironolactone
Eplerenone	25 mg once daily	50 mg once daily[d]	

[a] Adapted from McEvoy GK, ed. American Hospital Formulary Service Drug Information, Bethesda, MD:American Society of Health-System Pharmacists, Inc., 2006.
[b] Adapted from Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc., May 2006.
[c] Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis 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 (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). American College of Cardiology Web site. Available at: http://www.acc.org/clinical/guidelines/failure/index.pdf.
[d] Target doses (also refer to Appendix C for target doses in randomized controlled trials)
[e] 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)
[f] The brand names of metolazone are not bioequivalent, therefore doses vary
[g] Intermittent use recommended once the response of the patient is stabilized
[h] One hour before meals, on an empty stomach
[i] Also available as a fixed-dose combination product ISDN 20mg/hydralazine 37.5 mg, one to two tablets three times daily; ISMN once daily has also been used in place of ISDN; hydralazine dosing variable, total daily dose may also be divided two to four times daily

Appendix B. Drug Interactions with Agents Used in HF[a,b]

DRUG CLASS	INTERACTING DRUG	DESCRIPTION
DIURETICS		
	ACEI	↑ hypotensive effect in the presence of intensive diuretic therapy due to sodium depletion and hypovolemia; effects of loop diuretics may be ↓ by inhibition of antiotensin II production [significance=3]
	Bile Acid Resins	↓ absorption of all diuretics; bile acid resin should be taken at least 2 hours after diuretic [significance=2]
	Digoxin	Loop and thiazide diuretics may induce hypokalemia which may ↑ risk of digitalis toxicity [significance=2]
	Dofetilide	Risk of torsade de pointes increased with hypokalemia [significance=1]
	Lithium	With thiazides, a compensatory ↑ in proximal tubule reabsorption of sodium occurs, which results in ↑ lithium reabsorption (reduce lithium dose by 50%); ↑ plasma lithium concentrations may also occur with loop diuretics [significance=2]
	Oral hypoglycemics	Thiazides may ↓ hypoglycemic effects of sulfonylureas possibly due to ↓ insulin sensitivity, ↓ insulin secretion or ↓ in K^+ [significance=2]
	K^+preparations, ACEI, ARBs	K^+sparing diuretics used concomitantly may ↑ K^+ serum levels [significance=3]
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) [significance=4]
	Lithium	Potential for ↑ serum lithium levels and resultant toxicity [significance=2]
	NSAIDs	NSAIDs ↓ antihypertensive effects due to inhibition of PG synthesis resulting in ↓ GFR, ↓ sodium and water excretion, and vasoconstriction [significance=2]
	K^+ preparations K^+-sparing diuretics	Concomitant therapy may ↑ K^+ serum levels [significance=1]
ANGIOTENSIN II RECEPTOR ANTAGONISTS		
	Digoxin	See digoxin for description of drug interaction [significance=4]
	Lithium	Angiotensin II receptor antagonists may ↓ lithium renal secretion and ↑ serum lithium levels [significance=2]
	K^+ preparations K^+-sparing diuretics	Concomitant therapy may ↑ K^+ serum levels [significance=1]

BETA-ADRENERGIC BLOCKERS		
	Cimetidine	Hypotension and bradycardia have been reported with propranolol and metoprolol when used with cimetidine due to ↑ serum levels of beta-blockers that undergo hepatic metabolism [significance=2]
	Diltiazem **Verapamil**	Combination may potentiate the pharmacologic effects of beta-blockers; additive effects on cardiac conduction [significance=2]
	Epinephrine	Noncardioselective agents may ↑ the pressor response resulting in ↑ in HTN/ bradycardia [significance=1]
	Lidocaine	↑ toxicity due to reduced hepatic metabolism of lidocaine [significance=2]
	NSAIDs	NSAIDs ↓ antihypertensive effect due to inhibition of PG synthesis resulting in ↓ GFR, ↓ sodium and water excretion, and vasoconstriction [significance=2]
	Neuroleptics	Some beta-blockers and neuroleptics (chlorpromazine/ thioridazine) may ↑ the plasma concentrations of one another; monitor for enhanced effects of both drugs; concomitant use of thioridazine and propranolol or pindolol is contraindicated [significance=1]
	Oral hypoglycemics	↓ hypoglycemic action may occur, may also mask symptoms of hypoglycemia (more likely with nonselective beta-blocker); clinical significance is unclear [significance=5]
	Prazosin	Potential for ↑ postural hypotension [significance=2]
	Propafenone	↑ hypotensive effect has been seen with propranolol and metoprolol due to inhibition of metabolic clearance; HF and nightmares have been reported [significance=2]
	Rifampin	May enhance the hepatic metabolism of propranolol and metoprolol; enzyme induction effect may resolve after a 3-4 week washout period [significance=2]
	Theophylline	↑ serum concentration in a dose-dependent manner has been seen with propranolol [significance=2]
CALCIUM CHANNEL BLOCKERS		
	Beta-blockers	See beta-blockers for description of drug interaction [significance=2]
	Carbamazepine	↑ toxicity has been noted with verapamil and diltiazem due to ↓ metabolism of carbamazepine; felodipine bioavailability may be ↓, making it difficult to achieve therapeutic felodipine concentrations [significance=2]
	Cyclosporine	Blood concentrations have ↑ with verapamil, diltiazem and nicardipine; renal toxicity has been reported [significance=2]
	Digoxin	Verapamil, diltiazem, bepridil, and nisoldipine have ↑ digoxin levels by 20-70% [significance=1]
	Lithium	Combination with verapamil or diltiazem may result in neurotoxicity that may occur without attendant ↑ in serum level [significance=4]
	HMG-CoA reductase inhibitors	Diltiazem produces marked ↑ lovastatin and simvastatin concentrations through inhibition of CYP3A4, therefore potential for ↑ toxicity (rhabdomyolysis reported with atorvastatin and simvastatin in combination with diltiazem); ↑ concentration of simvastatin seen with concomitant verapamil [significance=2]
	Quinidine	Verapamil inhibits metabolism of quinidine leading to ↑ toxicity [significance=1]; nifedipine appears to ↓ blood concentrations [significance=4]
	Theophylline	Inhibition of hepatic metabolism with verapamil and diltiazem may lead to ↑ serum levels [significance=4]

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) [significance=1]
	Beta-blockers	Carvedilol may ↑ serum digoxin concentrations; potential for synergistic bradycardia with propranolol [significance=2]
	Cyclosporine	↑ serum digoxin concentrations; may need to discontinue digoxin or ↓ dose when treatment resumed; monitor for toxicity (i.e. anorexia, nausea, vomiting, diarrhea, fatigue, visual disturbances, confusion, and ventricular tachycardia) [significance=1]
	Diuretics	↑ risk of digitalis toxicity due to diuretic induced hypokalemia [significance=1]
	Quinidine	↑ serum digoxin concentrations; may need dose ↓ ~ 50%; monitor for toxicity (i.e. anorexia, nausea, vomiting, diarrhea, fatigue, visual disturbances, confusion, and ventricular tachycardia) [significance=1]
	Spironolactone	Renal excretion of digoxin may be reduced; false increases in plasma digoxin concentrations may occur depending on the assay method used [significance=2]
	Telmisartan	May increase digoxin peak plasma concentrations (49%) and in trough concentrations (20%); monitor digoxin levels when starting, adjusting, or discontinuing therapy with telmisartan [significance=4]
	Verapamil (see also Calcium Channel Blockers)	↑ 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) [significance=1]
SPIRONOLACTONE		
	Digoxin	See digoxin for description of drug interaction [significance=2]
	Mitotane	Spironolactone may antagonize the activity of mitotane; avoid concomitant use [significance=4]
	Potassium, other potassium-sparing diuretics, ACEIs, ARBs	Coadministration may result in hyperkalemia [significance=1]
VASODILATORS		
Hydralazine	Beta-blockers	Serum levels of propranolol or metoprolol may be ↑ with hydralazine use; clinical effects may be enhanced [significance=2]
Nitrates	**PDE 5 inhibitors**	Sildenafil, tadalafil, and vardenafil potentiate the hypotensive effects of nitrates, severe hypotension may occur; concomitant use is contraindicated [significance=1]

[a] Wickersham RM, et al. eds. Drug Facts and Comparisons, St. Louis: Wolters Kluwer Health, Inc., 2006.
[b] Online Facts and Comparisons 4.0 http://online.factsandcomparisons.com/ Accessed August 2006.
Significance: 1=potentially severe or life-threatening; interaction suspected, established or probable in well controlled studies; 2=may cause deterioration in patient's clinical status; interaction suspected, established or probable in well controlled studies; 3=causes minor effects; interaction suspected, established or probable in well controlled studies; 4=may cause moderate to major effects, very limited data; 5=minor to major effects, interaction is unlikely or not good evidence of an altered clinical effect; **Bold=**major drug interaction
AUC=area under the curve; CV=cardiovascular; CYP=cytochrome P-450 enzyme system; GFR=glomerular filtration rate; PDE=phosphodiesterase; PG=prostaglandin

Appendix C: Long-term, Randomized, Controlled, Outcome Trials in Systolic HF by Drug Class

Angiotensin Converting Enzyme Inhibitors

Trial	Patient Population	N	Treatment	Duration	Results	Study Conclusions	Quality Rating
SOLVD[120] **1991** MC, R, DB (vs. placebo) U.S., Canada, Belgium Supported by NHLBI; Merck Sharpe and Dohme provided drug/placebo	NYHA I (11%), II (57%), III (30%), IV (2%) Mean EF 24.8%	2569	Enalapril 10 mg twice daily (target dose) vs. Placebo <u>HF therapy</u> BB: 8% Digitalis: 67% Diuretics: 86% Vasodilators (any): 51%	Average 41.4 months	**Primary Endpoint:** Total mortality (16% ↓ with enalapril 95% CI 0.05-0.26; ARR 4.6%, NNT 22) **Endpoint** / **Enalapril (N=1285)** / **Placebo (N=1284)** / **p value** Primary: 452 (35.2%) / 510 (39.7%) / <0.0036 Death or HF hosp: 613 (47.7%) / 736 (57.3%) / <0.0001 **Target dose on monotherapy:** Bisoprolol (65%) vs. enalapril (84%) **Mean dose:** 16.6 mg per day (patients taking study drug); 11.2 mg per day (all randomized patients)	Enalapril significantly reduced mortality and HF hospitalizations in patients with HF	Good
CONSENSUS[122] **1987** MC, R, DB, PG (vs. placebo) Scandinavia Supported by Merck Sharpe and Dohme	All patients with NYHA IV at randomization	253	Enalapril 20 mg twice daily (maximum dose) vs. Placebo <u>HF therapy</u> BB: 3% Digitalis: 93% Furosemide: 98% Hydralazine: 2% ISDN: 46% Spironolactone: 53%	Average 188 days	**Primary Endpoint:** All-cause mortality at 6 months (40% ↓ with enalapril; ARR 17.7%, NNT 6) **Endpoint** / **Enalapril (N=127)** / **Placebo (N=126)** / **p value** Primary: 33 (26%) / 55 (44%) / 0.002 Total mortality: 50 (39%) / 68 (54%) / 0.003 **Maximum dose:** Enalapril (28 patients) vs. placebo (57 patients) **Mean dose:** 18.4 mg per day	Enalapril reduced mortality in patients with severe HF on conventional therapy (i.e., diuretics and digitalis)	Good

ARR=absolute risk reduction; CI=confidence interval; DB=double-blind; EF=ejection fraction; HF=heart failure; hosp=hospitalizations; ISDN: isosorbide dinitrate; N=number of patients; NNT=number needed to treat; NYHA=New York Heart Association; PG=parallel group; R=randomized

Beta-Adrenergic Blockers

Trial	Patient Population	N	Treatment	Duration	Results	Study Conclusions	Quality Rating
CIBIS III[166] **2005** MC, PROBE (BB 1st vs. ACEI 1st) Europe, Australia, Tunisia Supported by Merck KGaA	NYHA II (49%), III (51%) Mean EF 28.8%	1010	(Initial monotherapy X 6 months) Bisoprolol 10 mg once daily (target dose) vs. (Initial monotherapy X 6 months) Enalapril 10 mg twice daily (target dose) Followed by combination therapy X 6 to 24 months HF therapy Cardiac glycoside: 32% Diuretics: 84% Aldosterone antagonist: 13%	Mean 1.22 yrs	**Primary Endpoints:** Combined all-cause mortality or all-cause hosp (per protocol analysis bisoprolol 1st vs. enalapril 1st HR 0.97 95% CI 0.78-1.21; ITT 178 (35.2%) vs. 186 (36.8%) HR 0.94 95% CI 0.77-1.16; p=0.019[a]) **Endpoint** / **Bisoprolol 1st (N=505[b])** / **Enalapril 1st (N=505[b])** / **p value** Primary: 163 (32.4%) / 165 (33.1%) / 0.046[a] CV death[c]: 55 (NR) / 56 (NR) / 0.86 HF hosp[d]: 63 (NR) / 51 (NR) / 0.23 [a]test for noninferiority; [b]N for ITT; [c] IHR 0.97; [d]HR 1.25 **Target dose on monotherapy:** Bisoprolol (65%) vs. enalapril (84%)	Bisoprolol 1st noninferior to enalapril 1st in ITT analysis, but not by per-protocol analysis; initial therapy with bisoprolol may be as safe and efficacious as starting with enalapril	Fair
COMET[167] **2003** MC, R, DB, PG (BB vs. BB) Europe Supported by F Hoffmann La Roche and GlaxoSmithKline	NYHA II (48%), III (48%), IV (4%) Mean EF 26%	3029	Carvedilol 25 mg twice daily (target dose) vs. Metoprolol IR 50 mg twice daily (target dose) HF therapy ACEI: 91% ARB: 7% Digoxin: 59% Diuretics: 99% Aldosterone antagonist: 11%	Mean 58 months	**Primary Endpoints:** 1) All-cause mortality (↓ with carvedilol vs. metoprolol; HR 0.83 95% CI 0.74-0.93; ARR 5.6%, NNT 18); and 2) Composite all-cause mortality or all-cause admission (HR 0.94 95% CI 0.86-1.02) **Endpoint** / **Carvedilol (N=1511)** / **Metoprolol (N=1518)** / **p value** Primary1: 512 (33.9%) / 600 (39.5%) / 0.017 Primary2: 1116 (73.9%) / 1160 (76.4%) / 0.122 **Target dose:** Carvedilol (75%) vs. metoprolol IR (78%) **Mean dose:** Carvedilol (41.8 ± 14.6 mg per day); metoprolol IR (85 ± 28.9 mg per day)	Carvedilol had a greater benefit on survival compared to metoprolol IR in patients with chronic HF on standard therapy (i.e., diuretics plus ACEI)	Fair
COPERNICUS[163] **2001** MC, R, DB (vs. placebo) U.S., Canada, Mexico, Europe, S. America, Israel, S. Africa, Australia Supported by SmithKline Beecham and Boehringer-Mannheim	Severe HF (≥ 2 months dyspnea or fatigue at rest or minimal exertion, EF < 25%) Mean EF 19.9%	2289	Carvedilol 25 mg twice daily (target dose) vs. Placebo HF therapy ACEI or ARB: 97% Digoxin: 66% Diuretics: 99% Spironolactone: 20%	Mean 10.4 months (stopped early due to improved survival)	**Primary Endpoint:** All-cause mortality (35% ↓ with carvedilol; 95% CI 0.19-0.48; ARR 5.5%, NNT 18) **Endpoint** / **Carvedilol (N=1156)** / **Placebo (N=1133)** / **p value** Primary: 130 (11.3%) / 190 (16.8%) / 0.0014 Death or hosp: 425 (36.8%) / 507 (44.8%) / <0.001 **Target dose:** Carvedilol (65.1%) vs. placebo (78.2%) at 4 months **Mean dose:** 37 mg per day	Carvedilol reduced the rate of death in patients with severe HF on conventional therapy (i.e., diuretics plus ACEI or ARB)	Good

Beta-Adrenergic Blockers (continued)

Trial	Patient Population	N	Treatment	Duration	Results	Study Conclusions	Quality Rating
MERIT-HF[159] **1999** MC, R, DB (vs. placebo) U.S., Europe Supported by Astra Hässle AB	NYHA II (41%), III (56%), IV (3.4%) HF Mean EF 28%	3991	Metoprolol XL 200 mg once daily (target dose) vs. Placebo HF therapy ACEI: 90% ARB: 7% Digoxin: 64% Diuretics: 90%	Mean 1 yr (terminated early due to survival benefit)	**Primary Endpoints:** 1) All-cause mortality (↓ with metoprolol XL; RR 0.66 95% CI 0.53-0.81; ARR 3.6%, NNT 28); and 2) Combined all-cause mortality and all-cause hosp admissions (NR) **Endpoint** / **Metoprolol XL (N=1990)** / **Placebo (N=2001)** / **p value** Primary1: 145 (7.3%) / 217 (10.9%) / 0.00009 CV death: 128 (6.4%) / 203 (10.2%) / 0.00003 **Target dose:** Metoprolol XL (64%) vs. placebo (82%) **Mean dose:** 159 mg	Metoprolol XL significantly improved survival in patients with symptomatic HF on standard therapy for HF (i.e., diuretics plus ACEI)	Good
CIBIS II[160] **1999** MC, R, DB (vs. placebo) Europe Supported by E Merck	NYHA III (83%), IV (17%) Mean EF 27.5%	2647	Bisoprolol 10 mg once daily (target dose) vs. Placebo HF therapy ACEI: 96% Digoxin: 52% Diuretics: 99%	Mean 1.3 yrs (stopped early due to improved survival)	**Primary Endpoint:** All-cause mortality (↓ with bisoprolol; HR 0.66 95% CI 0.54-0.81; ARR 5.5%, NNT 18) **Endpoint** / **Bisoprolol (N=1327)** / **Placebo (N=1320)** / **p value** Primary: 156 (11.8%) / 228 (17.3%) / <0.0001 CV death: 119 (9%) / 161 (12.2%) / 0.0049 **Target dose:** Bisoprolol 10 mg (564 patients); 7.5 mg (152 patients); 5 mg (176 patients) **Most common dose:** 10 mg	Bisoprolol significantly improved survival in patients with stable symptomatic HF (NYHA class III to IV) on standard therapy (i.e., diuretics plus ACEI)	Good
US Carvedilol[161] **1996** MC, R, DB (vs. placebo) U.S. Supported by Roche and GlaxoSmithKline	NYHA II (53%), III (44%), IV (3%) Mean EF 23%	1094	Carvedilol 25 to 50 mg twice daily (target dose) or 6.25, 12.5, or 25 mg twice daily (dose-ranging protocol) vs. Placebo HF therapy ACEI: 95% Digoxin: 91% Diuretics: 95%	Median 6.5 months (stopped early due to improved survival)	**Primary Endpoint:** Death (65% ↓ with carvedilol; 95% CI 0.39-0.80; ARR 4.6%, NNT 22) **Endpoint** / **Carvedilol (N=696)** / **Placebo (N=398)** / **p value** Primary: 22 (3.2%) / 31 (7.8%) / <0.001 CV hosp: 98 (14.1%) / 78 (19.6%) / 0.036 **Target dose:** Achieved in 80% of patients **Mean dose:** 45 ± 27 mg per day	Carvedilol reduced the risk of death in patients with symptomatic HF on standard therapy (i.e., diuretics plus ACEI); individual protocols designed to assess nonfatal endpoints, with mortality prespecified to evaluate safety and benefit in overall trial	Fair

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker; ARR=absolute risk reduction; CI=confidence interval; CV=cardiovascular; DB=double-blind; EF=ejection fraction; HF=heart failure; hosp=hospitalizations; HR=hazard ratio; IR=immediate-release; ITT=intention-to-treat analysis; N=number of patients; NNT=number needed to treat; NR=not reported; NYHA=New York Heart Association; PROBE=prospective, randomized, open-label, blinded endpoint evaluation; R=randomized; RR=relative risk; XL=extended-release; yrs=years

Angiotensin II Receptor Antagonists

Trial	Patient Population	N	Treatment	Duration	Results	Study Conclusions	Quality Rating
CHARM-Overall[206] **2003** MC, R, DB, PG (vs. placebo) U.S., Canada, Europe, S. Africa, Australia, Malaysia Supported by AstraZeneca R&D	NYHA II (45%), III (52%), IV (3%) HF EF < 40% (57%); EF ≥ 40% (43%)	7601	Candesartan 32 mg once daily (target dose) vs. Placebo HF therapy ACEI: 41% BB: 55% Digoxin: 43% Diuretics: 83% Spironolactone: 17%	Median 37.7 months	**Primary Endpoint:** All-cause mortality; no statistically significant difference vs. placebo (unadjusted HR 0.91 95% CI 0.83-1.00) **Endpoint** / Candesartan (N=3803) / **Placebo (N=3796)** / **p value** Primary: 886 (23%) / 945 (25%) / 0.055 CV death/HF hosp: 1150 (30.2%) / 1310 (34.5%) / <0.0001 **Target dose:** Candesartan (63%) vs. placebo (75%) at 6 months **Mean dose:** 24 mg at 6 months	Candesartan significantly reduced CV deaths and HF hospitalizations	Good
CHARM-Alternative[208] **2003** MC, R, DB (vs. placebo) U.S., Canada, Europe, S. Africa, Australia, Malaysia Supported by AstraZeneca R&D	NYHA II (48%), III (49%), IV (4%) HF Mean EF 30% ACEI intolerant	2028	Candesartan 32 mg once daily (target dose) vs. Placebo HF therapy BB: 55% Digoxin: 45% Diuretics: 85% Spironolactone: 25%	Median 33.7 months	**Primary Endpoint:** Composite CV death or HF hospitalizations; ↓ with candesartan (unadjusted HR 0.77 95% CI 0.67-0.89; ARR 7.0%, NNT 14) **Endpoint** / **Candesartan (N=1013)** / **Placebo (N=1015)** / **p value** Primary: 334 (33%) / 406 (40%) / 0.0004 CV death: 219 (21.6%) / 252 (24.8%) / 0.072 HF hosp: 207 (20.4%) / 286 (28.2%) / <0.0001 No significant difference (p=0.11) in all-cause death (not a pre-specified endpoint) **Target dose:** Candesartan (59%) vs. placebo (73%) at 6 months **Mean dose:** 23 mg at 6 months	Candesartan significantly reduced CV deaths and HF hospitalizations in patients with symptomatic HF who are ACEI intolerant	Good
CHARM-Added[207] **2003** MC, R, DB (vs. placebo) U.S., Canada, Europe, S. Africa, Australia, Malaysia Supported by AstraZeneca R&D	NYHA II (24%), III (73%), IV (3%) Mean EF 28%	2548	Candesartan 32 mg once daily (target dose) vs. Placebo HF therapy ACEI: 100% BB: 55% Digoxin: 58% Diuretics: 90% Spironolactone: 17%	Median 41 months	**Primary Endpoint:** Composite CV death or HF hospitalizations; ↓ with candesartan (unadjusted HR 0.85 95% CI 0.75-0.96; ARR 4.4%, NNT 23) **Endpoint** / **Candesartan (N=1276)** / **Placebo (N=1272)** / **p value** Primary: 483 (37.9%) / 538 (42.3%) / 0.011 CV death: 302 (23.7%) / 347 (27.3%) / 0.029 HF hosp: 309 (24.2%) / 356 (28.0%) / 0.014 No significant difference (p=0.086) in all-cause death (not a pre-specified endpoint) **Target dose:** Candesartan (61%) vs. placebo (73%) at 6 months **Mean dose:** 24 mg at 6 months	The addition of candesartan to treatment with an ACEI and other standard therapy for HF significantly reduced CV deaths and HF hospitalizations in patients with symptomatic HF	Good

Angiotensin II Receptor Antagonists (continued)

Trial	Patient Population	N	Treatment	Duration	Results	Study Conclusions	Quality Rating
Val-HeFT[204] 2001 MC, R, DB (vs. placebo) U.S., Europe, S. Africa, Australia Supported by Novartis Pharma	NYHA II (62%), III (36%), IV (2%) Mean EF 27%	5010	Valsartan 160 mg twice daily (target dose) vs. Placebo <u>HF therapy</u> ACEI: 93% BB: 35% Digoxin: 67% Diuretics: 85% Spironolactone: 5%	Mean 23 months	**Primary Endpoint:** 1) Overall mortality (no statistically significant difference vs. placebo); and 2) Combined morbidity and mortality (↓ with valsartan; RR 0.87 97.5% CI 0.77-0.97; ARR 3.3%, NNT 30) **Endpoint** / **Valsartan (N=2511)** / **Placebo (N=2499)** / **p value** Primary1: 495 (19.7%) / 484 (19.4%) / 0.80 Primary2: 723 (28.8%) / 801 (32.1%) / 0.009 HF hosp*: 346 (13.8%) / 455 (18.2%) / <0.001 *adjudicated hosp for worsening HF as 1st event **Target dose:** Valsartan (84%) vs. placebo (93%) **Mean dose:** 254 mg	Valsartan significantly reduced the combined morbidity and mortality endpoint when given to patients with HF currently on therapy; a post hoc analysis noted an increase in mortality in patients receiving combination of valsartan with an ACEI and BB	Good
ELITE II[202] 2000 MC, R, DB (vs. ACEI) U.S., Canada, Europe, S. Africa, S. America Supported by Merck Research Laboratories	NYHA II (52%), III (43%), IV (5%) Mean EF 31%	3152	Losartan 50 mg once daily (target dose) vs. Captopril 50 mg three times daily (target dose) <u>HF therapy</u> BB: 22% Digoxin: 50% Diuretics: 78%	Median 1.5 yrs	**Primary Endpoint:** All-cause mortality; no statistically significant difference vs. captopril (HR 1.13 95.7% CI 0.95-1.35) **Endpoint** / **Losartan (N=1578)** / **Captopril (N=1574)** / **p value** Primary: 280 (17.7%) / 250 (15.9%) / 0.16 Secondary*: 142 (9.0%) / 115 (7.3%) / 0.08 HF hosp*: 270 (17.1%) / 293 (18.6%) / 0.32 *composite sudden cardiac death or resuscitated cardiac arrest **Mean dose:** NA **Target dose:** NA	Losartan was not found to be superior to captopril in reducing all-cause mortality in patients with HF currently on therapy; designed as a superiority trial, unable to determine equivalence between losartan and captopril	Good

ACEI=angiotensin-converting enzyme inhibitor; ARR=absolute risk reduction; BB=beta-blockers; CI=confidence interval; CV=cardiovascular; DB=double-blind; EF=ejection fraction; HF=heart failure; hosp=hospitalizations; HR=hazard ratio; N=number of patients; NA=not available; NNT=number needed to treat; PG=parallel-group; R=randomized; RR=relative risk; Sx=symptoms; yrs=years

Hydralazine/Isosorbide Dinitrate

Trial	Patient Population	N	Treatment	Duration	Results	Study Conclusions	Quality Rating
A-HeFT[234] 2004 MC, DB, RCT (vs. placebo) U.S. Supported by NitroMed	Self-identified black with (African descent) NYHA III or IV HF ≥ 3 months Mean EF ~24%	1050	ISDN/HYD 40 mg/75 mg three times daily (120 mg/225 mg total daily target dose) vs. Placebo HF therapy ACEI: 69% ARB: 17% BB: 74% Carvedilol: 55% Digoxin: 60% Diuretics: 90% Spironolactone: 39%	10 months (terminated early due to difference in mortality)	**Primary endpoint:** Composite score (weighted values for all-cause mortality, 1st HF hosp during 18 months, change in QOL by MLHF at 6 months); possible score -6 to +2 **Endpoint** / **ISDN/HYD (N=518)** / **Placebo (N=532)** / **p value** Primary (score): -0.1±1.9 / -0.5±2.0 / 0.01 All-cause death: 32 (6.2%) / 54 (10.2%) / 0.02 1st HF hosp: 85 (16.4%) / 130 (24.4%) / 0.001 Change QOL*: -5.6±20.6 / -2.7±21.2 / 0.02 *lower score reflects better QOL **Survival:** 43% improvement with ISDN/HYD (HR 0.57; p=0.01) **Target dose:** ISDN/HYD (68%) vs. placebo (88.9%); p<0.001 **Mean # tabs/d:** ISDN/HYD (3.8±2.5) vs. placebo (4.7±2.2); p<0.001	Combination ISDN/HYD, in addition to standard therapy for HF, improved survival and decreased rate of first hospitalizations for HF, in self-identified black patients with NYHA class III to IV HF	Fair
V-HeFT II[121] 1991 MC (VA), DB, RCT (vs. ACEI) U.S. Supported by VA Cooperative Studies	Males with primarily NYHA II (51%) or III (43%) HF Mean EF ~29%	804	ISDN/HYD 40 mg/75 mg four times daily (160 mg/300 mg total daily target dose) vs. Enalapril 10 mg twice daily (20 mg total daily target dose) HF therapy Digoxin Diuretics	Ave 2.5 yrs	**Primary Endpoint:** Overall and 2-yr mortality; 2-yr mortality ↓ with ACEI vs. ISDN/HYD (risk reduction 28.2%; ARR 7.0%, NNT 14) **Mortality** / **ISDN/HYD (N=401)** / **ACEI (N=403)** / **p value** Overall: 153 (38.2%) / 132 (32.8%) / 0.08 2-yr: NR (25%) / NR (18%) / 0.016 HF hosp: 78 (18.4%) / 76 (18.9%) / NR **Ave daily dose:** ISDN/HYD (100/199 mg); enalapril (15 mg)	Mortality was lower with enalapril compared to ISDN/HYD, a difference that was statistically significant at 2 yrs	Fair
V-HeFT I[233] 1986 MC (VA), DB, RCT (vs. prazosin or placebo) U.S. Supported by VA Cooperative Studies	Males with chronic congestive HF Mean EF ~30%	642	ISDN/HYD 40 mg/75 mg four times daily (160 mg/300 mg total daily target dose) vs. Prazosin 5 mg four times daily (20 mg total daily target dose) vs. Placebo HF therapy Digoxin Diuretics	Ave 2.3 yrs	**Primary Endpoint:** Overall and 2-yr mortality; ↓ in 2-yr mortality with ISDN/HYD (risk reduction 34%, CI 0.04 to 0.54; ARR 8.7%, NNT=12) **Mortality** / **ISDN/HYD (N=186)** / **Placebo (N=273)** / **p value** Overall*: NR (36.2%) / NR (46.9%) / NR 2-yr: NR (25.6%) / NR (34.3%) / <0.028 *by 3 yrs, mortality risk reduction 36% with ISDN/HYD vs. placebo; small sample size > 3yrs **Ave daily dose:** ISDN/HYD (136/270 mg); prazosin (18.6 mg)	Mortality reduced with ISDN/HYD compared to placebo up to 3 yrs; unable to determine benefit beyond this point	Fair

ACEI=angiotensin-converting enzyme inhibitor; AE=adverse event; ARB=angiotensin II receptor blocker; ARR=absolute risk reduction; Ave=average; BB=beta-adrenergic blocker; DB=double-blind; EF=ejection fraction; HF=heart failure; hosp=hospitalizations; ISDN/HYD=isosorbide dinitrate and hydralazine; MC=multicenter; n=number of patients; MLHF=-Minnesota Living with Heart Failure questionnaire; NNT=number needed to treat; NR=not reported; NYHA=New York Heart Association; QOL=quality of life; RCT=randomized controlled trial; VA=Veterans Affairs Medical Center; yrs=years

Digitalis

Trial	Patient Population	N	Treatment	Duration	Results	Study Conclusions	Quality Rating
DIG[93] **1997** MC, R, DB (vs. placebo) U.S., Canada NHLBI and VA Cooperative study; drug and placebo provided by Glaxo Wellcome	NYHA I (13%); II (54%); III (31%), IV (2%) HF Mean EF 29%	6800	Digoxin dosed per algorithm (based on age, gender, weight, and kidney function) vs. Placebo HF therapy ACEI: 95% Diuretics: 82%	Mean 37 months	**Primary Endpoint:** All-cause mortality; no statistically significant difference vs. placebo (RR 0.99 95% CI 0.91-1.07) **Endpoint** / **Digoxin (N=3397)** / **Placebo (N=3403)** / **p value** Primary: 1181 (34.8%) / 1194 (35.1%) / 0.8 CV death: 1016 (29.9%) / 1004 (29.5%) / 0.78 HF hosp: 910 (26.8%) / 1180 (34.7%) / <0.001 **Median dose (at randomization):** 0.25 mg once daily **Mean serum digoxin concentration (steady state at 12 months):** 0.80 ng/ml	All-cause mortality was not significantly reduced with digoxin; there was a significant decrease in HF hospitalization in patients with HF receiving treatment with digoxin	Good

ACEI=angiotensin-converting enzyme inhibitor; CI=confidence interval; CV=cardiovascular; DB=double-blind; EF=ejection fraction; HF=heart failure; hosp=hospitalizations; N=number of patients; NYHA=New York Heart Association; R=randomized; RR=relative risk

Aldosterone Antagonists

Trial	Patient Population	N	Treatment	Duration	Results	Study Conclusions	Quality Rating
EPHESUS[250] **2003** MC, R, DB (vs. placebo) U.S., Canada, Europe, Latin America Supported by Pharmacia	Days from MI to R (7.3) HF symptoms (90%) Mean EF 33%	6632	Eplerenone 25 mg once daily (50 mg once daily target dose) vs. Placebo Drug therapy ACEI or ARB: 87% BB: 75% Diuretics: 61%	Mean 16 months	**Primary Endpoints:** 1) Time to death (any cause); ↓ with eplerenone (RR 0.85 95% CI 0.75-0.96; ARR 2.3%; NNT 43); 2) Time to death from CV causes or 1st CV hosp; ↓ with eplerenone (RR 0.87 95% CI 0.79-0.95; ARR 3.3%; NNT 30) **Endpoint** / **Eplerenone (N=3319)** / **Placebo (N=3313)** / **p value** Primary1: 478 (14.4%) / 554 (16.7%) / 0.008 CV death or hosp: 885 (26.7%) / 993 (30.0%) / 0.002 **Mean dose:** 42.6 mg once daily	Eplerenone significantly reduced combined death from CV cause or CV hospitalization in patients with acute MI complicated by LVD and HF	Good
RALES[249] **1999** MC, R, DB (vs. placebo) U.S., Canada, Mexico, Europe, S. America, S. Africa, New Zealand, Japan Supported by Searle	NYHA III (71%), IV (29%) HF Mean EF 25%	1663	Spironolactone 25 mg once daily (increased to 50 mg once daily if signs or symptoms of HF progression without hyperkalemia) vs. Placebo HF therapy ACEI: 95% BB: 11% Digoxin: 74% Diuretics: 100%	Mean 24 months (terminated early due to survival benefit)	**Primary Endpoint:** All-cause mortality; ↓ with spironolactone (RR 0.70 95% CI 0.60-0.82; ARR 11.4%; NNT=9) **Endpoint** / **Spironolactone (N=841)** / **Placebo (N=822)** / **p value** Primary: 284 (34.6%) / 386 (45.9%) / <0.001 CV death: 226 (27.5%) / 314 (37.3%) / <0.001 HF hosp: 215 (26.2%) / 300 (35.7%) / <0.001 **Mean dose:** 26 mg once daily	Spironolactone significantly reduced all-cause mortality in patients with severe HF	Good

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker; ARR=absolute risk reduction; BB=beta-blockers; CI=confidence interval; CV=cardiovascular; DB=double-blind; EF=ejection fraction; HF=heart failure; hosp=hospitalizations; LVD=left ventricular dysfunction; MI=myocardial infarction; N=number of patients; NYHA=New York Heart Association; NNT=number needed to treat; R=randomized; RR=relative risk