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Primary Care Reports

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Volume 9, Number 2 **February 2003**

Heart Failure

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Editor's Note—*Heart failure is on the rise and reaching epidemic proportions.[1-2] Approximately 5 million Americans have heart failure (2% of the population), and the number is expected to increase during the next 30 years. Hospital admissions for heart failure have tripled over the last 3 decades and now approach 1 million per year. Most hospitals sustain financial loss with these admissions.*

The incidence of heart failure increases rapidly with age. It is the No. 1 diagonosis-related group in the elderly and the single largest expense for Medicare. Heart failure has the highest readmission rate of any hospital discharge diagnosis, largely due to patient noncompliance and failure to optimize patient management. Long-term prognosis with heart failure is poor, worse than most malignant tumors, with a 5-year survival of only 25-50%. Heart failure costs were estimated to be a staggering $38 billion in 1994 and probably are higher today. Two-thirds of these costs are hospital charges.

Because of the huge health and economic burden of heart failure, we now have several sets of guidelines, each focused on a different aspect of the heart failure syndrome: prevention, staging, workup, standard therapies, unresolved issues, and future therapies.[3-8] These guidelines are based on evidence from clinical trials. Despite this published information, slightly more than half of heart failure patients receive ACE inhibitors and less than half are treated with a beta-blocker.

This article reviews multiple aspects of heart failure, providing direction for workup and management of heart failure patients. All recommendations follow current published guidelines. Unresolved and controversial issues are reviewed, and future therapies are proposed.

Definition

Heart failure occurs when impaired cardiac function is inadequate to meet the metabolic needs of the body. It is a syndrome characterized by dyspnea, fatigue, fluid retention, and objective evidence of systolic or diastolic cardiac dysfunction. Heart failure is the end result of many diseases, including coronary artery disease, idiopathic dilated cardiomyopathy, hypertension, valvular heart disease, congenital heart disease, arrhythmias, and toxins. End-stage coronary artery disease is the most common cause, accounting for more than half of the cases.

Heart failure may be characterized in several ways: acute vs chronic, systolic vs diastolic, left vs right sided, and high vs low output. Acute heart failure refers to rapid cardiac decompensation leading to dyspnea, acute pulmonary edema, or fluid retention. Chronic heart failure refers to prolonged impairment in functional capacity due to dyspnea, fatigue, and fluid retention. The most common clinical presentation is chronic with acute exacerbations. Systolic heart failure refers to left ventricular contractile dysfunction. Diastolic heart failure occurs in the setting of normal left ventricular contractility and is associated with abnormal ventricular relaxation, left ventricular hypertrophy, diastolic dysfunction, and a small left ventricular cavity.[9-10] Diastolic heart failure, seen more commonly in the elderly and women, occurs with hypertension, coronary

Table 1. New York Heart Association Heart Failure Symptom Classification

NYHA Class	Level of Impairment
I	No symptoms with ordinary activities
II	Symptoms with moderate activities
III	Symptoms with mild activities
IV	Symptoms at rest or with minimal activities

artery disease, aortic stenosis, and myocardial fibrosis. Frequently, diastolic heart failure occurs in association with systolic failure, each contributing to cardiac dysfunction. Left-sided heart failure refers to symptoms of effort intolerance and dyspnea. Right-sided heart failure produces congestion in the systemic veins manifested by ascites and edema. Right-sided heart failure does not distinguish between which ventricle is more severely damaged, because right heart failure often is caused by left heart failure. Low-output heart failure is characterized by marked fatigue and effort intolerance, often in the absence of fluid retention. High-output failure is uncommon, occurring with thyrotoxicosis, anemia, arteriovenous fistula, and beri-beri. Heart failure symptoms may be described in terms of New York Heart Association Functional Class (NYHA FC) (*see Table 1*). Heart failure should always be designated as a syndrome secondary to a known cardiovascular disease and never as the final diagnosis.

Primary Care Reports , ISSN 1040-2497, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

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GST Registration Number: R128870672.
POSTMASTER: Send address changes to ***Primary Care Reports*** , P.O. Box 740059, Atlanta, GA 30374.

Periodicals postage paid at Atlanta, GA.
Back issues: $25. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $319
(Student/Resident rate: $160).

Multiple Copies
1-9 additional copies: $287 each; 10 or more copies: $255 each.

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This program has been approved by the American Academy of Family Physicians as having educational content acceptable for Prescribed credit hours. Term of approval covers issues published within one year from the beginning distribution date of Jan. 1, 2003. This volume has been approved for up to 50 Prescribed credit hours. Credit may be claimed for one year from the date of this issue.

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Statement of Financial Disclosure

In order to reveal any potential bias in this publication, we disclose that Dr. Wise (Editor-in-Chief) serves as a consultant to Aventis and Sanofi and does research for Astrazeneca. Dr. Hobbs, Dr. Mills (authors) and the peer reviewer report no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

Epidemiology

Some 550,000 new cases of heart failure are diagnosed annually. The prevalence, increasing with age, will become more common during the next 30 years. The mean age of patients with heart failure is 74 years with a male to female ratio of 1:1. The number of hospitalizations has increased steadily as a result of an aging population, improved therapeutics, and the inevitable progression of underlying cardiac diseases. Heart failure has the highest readmission rate of any discharge diagnosis. The prognosis of heart failure generally is poor. Half of the patients die suddenly, and most others die of progressive pump failure. Heart failure is responsible for approximately 280,000 deaths each year. Half of the heart failure population will die within 4-5 years of diagnosis; half of the patients with severe heart failure will die in 1-2 years. Prognosis is related to the severity of the syndrome in most cases. Markers of severe cardiac dysfunction include impaired exercise tolerance, reduced left ventricular ejection fraction, elevated B-type natriuretic peptide levels, wide QRS complex, hyponatremia, hypocholesterolemia, and cardiac cachexia.

Recent guidelines have concentrated on prevention of heart failure and management of end-stage patients.[6] In this classification, heart failure is divided into 4 stages (*see Table 2*). Stage A heart failure refers to patients who are at risk of developing heart failure but have no structural heart disease at present. These include patients with hypertension, coronary artery disease, diabetes mellitus, valvular heart disease, congenital heart disease, and use of cardiac toxins. Stage B heart failure refers to patients who have structural heart disease but are asymptomatic, corresponding to NYHA FC I. Stage C heart failure includes patients with symptoms and evidence of structural heart disease (NYHA FC II-III). This group of patients has received the most attention from clinicians. Stage D heart failure refers to patients with end-stage heart disease refractory to medical therapy. This stage corresponds to NYHA FC IV.

Pathophysiology

The pathophysiology of heart failure remains incompletely understood. There is a complex interrelationship between precipitating etiologies, compensatory pathophysiology, and progressive left ventricular dysfunction. Hemodynamic, neurohormonal, structural, and noncardiac abnormalities occur in heart failure. The classic hemodynamic abnormalities are low cardiac output and high intracardiac filling pressures. Low cardiac output leads to fatigue and effort intolerance, whereas high intracardiac filling pressures result in dyspnea and edema.

Neurohormonal abnormalities include activation of the sympathetic nervous system, stimulation of the renin-angiotensin-aldosterone system, release of vasopressin, and elevated levels of endothelin, natriuretic peptides, and cytokines.[11] Sympathetic activation is associated with increased plasma levels of norepinephrine, and patients with the highest levels have the worst prognosis.[12] Abnormalities caused by sympathetic activation include resting tachycardia, vasoconstriction, beta-receptor dysfunction (which also results from a change in phenotype of

Table 2. ACC/AHA Classification of Chronic Heart Failure

Stage	Description
A. High risk for developing heart failure	Hypertension, diabeties mellitus, CAD, family history of cardiomyopathy.
B. Asymptomatic heart failure	Previous MI, LV dysfunction, valvular heart disease.
C. Symptomatic heart failure	Structural heart disease, dyspnea and fatigue, impaired exercise tolerance.
D. Refractory end-stage heart failure	Marked symptoms at rest despite maximal medical therapy.

B receptor as well as receptor down-regulation), myocardial toxicity, adverse remodeling, cardiac arrhythmias, and activation of other neurohormones. Activation of the renin-angiotensin-aldosterone system leads to elevated levels of angiotensin-II and aldosterone. Angiotensin-II is a potent vasoconstrictor and growth factor, which causes sodium and water retention and release of aldosterone. Aldosterone, released from the adrenal cortex, induces sodium retention, potassium loss, sympathetic activation, baroreceptor dysfunction, and myocardial fibrosis. Vasopressin is released from the hypothalamus as a result of osmotic and baroreceptor stimuli. Vasopressin is a vasoconstrictor, which promotes sodium and water retention. Endothelin arises from multiple sources with the cardiovascular system. Elevated endothelin levels in heart failure are associated with growth and remodeling, vasoconstriction, and neurohormonal augmentation. Tumor necrosis factor, an inflammatory cytokine, arises from macrophages and causes cardiac cachexia, skeletal muscle dysfunction, and apoptosis in the failing heart. The altered loading conditions and myocardial changes mediated by this neurohormonal response to impaired cardiac function lead to short-term hemodynamic improvements but long-term deleterious effects through ventricular remodeling. In contrast, natriuretic peptides are volume regulatory hormones secreted by the atria and ventricles in response to elevated filling pressures. They are arterial and venous dilators, which promote sodium and water excretion, and modulate other neurohormones.

Cardiac remodeling, resulting from myocardial injury and neurohormonal activation, is characterized by left ventricular hypertrophy, dilatation, abnormal beta-receptor function, expression of fetal phenotype, interstitial fibrosis, and apoptosis. Remodeling causes the heart to assume a spherical rather than an elliptical shape. This altered geometry results in mitral and tricuspid regurgitation. Noncardiac organ dysfunction is common in heart failure. Low cardiac output decreases perfusion to the kidneys leading to sodium and water retention, as well as renal dysfunction. Skeletal muscle dysfunction impairs exercise capacity and causes further debilitation.

Symptoms

Patients with left ventricular dysfunction may be asymptomatic or may experience dyspnea, fatigue, and fluid retention. Common symptoms of heart failure include effort intolerance, lack of stamina, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, cough, weight gain, fluid retention, edema, abdominal bloating, nausea and vomiting, ascites, lightheadedness, anorexia, and muscle wasting. The clinician should seek evidence of underlying heart disease when interviewing the heart failure patient. Inquire about angina pectoris, previous myocardial infarctions, catheterizations, or cardiac surgery. Ask about hypertension, diabetes mellitus, heart murmurs, lung disease, thyroid problems, family history, tobacco abuse, hyperlipidemia, and anemia. Determine if there is a family history of cardiomyopathy, heart failure, or sudden death. It is also important to search for a precipitating cause of decompensated heart failure, although the most common cause is patient noncompliance with dietary restrictions or medications. Other causes of decompensation include inadequate medical treatment, arrhythmias (atrial fib/flutter), worsening renal function, other drugs (NSAIDS, diabetic TZD agents), infections, pulmonary embolism, myocardial ischemia, valvular regurgitation, anemia, hypothyroidism, or alcohol abuse. There is poor correlation between symptoms and left ventricular ejection fraction or prognosis. Mild symptoms do not necessarily equate with mild dysfunction. The initial severity of symptoms do not predict prognosis. Symptoms are best described in terms of NYHA functional class. Although this scheme is quite subjective, it correlates well with outcome.

Signs

Blood pressure, heart rate, and respiratory rate are variable in heart failure. Blood pressure may be normal, low, or high, although pulse pressure frequently is narrow. Heart rate may be normal or increased. Pulsus alternans, a beat-to-beat variation in the intensity of the pulse, indicates severe heart failure. Respirations may be normal or rapid with decompensation. Sleep disordered breathing is common. A patient with decompensated heart failure often is diaphoretic. Jugular venous distention and hepatojugular reflux (elicited by sustained elevation in JVP while pressing on the liver and noting further distention of the neck veins) indicate congestion and fluid overload. Pulmonary examination in chronic heart failure usually reveals clear lungs. Rales are heard with acute decompensation, and decreased breath sounds at the bases are noted with pleural effusions. Cardiac palpation frequently demonstrates a diffuse, displaced apical impulse. Rhythm may be regular or irregularly irregular with atrial fibrillation. Often the decompensated patient has resting tachycardia. The first heart sound usually is normal; the second heart sound may be paradoxically split from delayed mechanical or electrical activation of the left ventricle. A fourth heart sound reflects a noncompliant left ventricle, whereas a third heart sound often indicates elevated LV filling pressures. With heart rates over 90 beats/min in sinus rhythm, these sounds merge into a summation gallop. Murmurs of mitral and tricuspid regurgitation are common. Abdominal examination

may reveal hepatosplenomegaly and ascites. The legs often are edematous. Cool hands and feet signal low cardiac output. The presence of multiple physical signs increases the likelihood that heart failure is indeed the correct diagnosis.

Diagnostic Testing

The initial evaluation should define the etiology of the syndrome. The electrocardiogram may show Q waves or left bundle branch block, both good predictors of left ventricular dysfunction. Left ventricular hypertrophy may reflect either systolic or diastolic heart failure. Atrial fibrillation and atrial flutter are common. A normal electrocardiogram has a 90% negative predictive value in excluding heart failure. The chest radiograph often is abnormal, showing cardiomegaly and pulmonary congestion. Specific radiographic abnormalities include increased cardiothoracic ratio, prominent pulmonary arteries, increased pulmonary vascularity with redistribution of blood flow to upper lobes, pleural effusions, Kerley B lines, fluid in the fissures, interstitial edema, and alveolar edema. Recommended laboratory studies in heart failure include complete blood count, chemistry panel, thyroid function tests, lipid profile, and B-type natriuretic peptide (BNP) assay. Measurement of BNP level is an important screening test for heart failure.[13] BNP is released from the ventricles in response to pressure or volume overload, in an attempt to maintain sodium and fluid homeostasis. Normal levels are < 100 pg/mL. Decompensated heart failure is associated with levels of 700 to > 1300 pg/mL.[14] High normal values are seen in the elderly. Levels of BNP are elevated in chronic heart failure and correlate with severity and prognosis. Measurement of norepinephrine, renin, angiotensin II, aldosterone, vasopressin, endothelin, and cytokine levels are not recommended for routine patient management.

The echocardiogram is the single most useful test in assessing the heart failure patient. The study should document left ventricular size, hypertrophy, and ejection fraction in addition to visualizing valvular abnormalities. An echo study also provides an estimate of the right ventricular systolic pressure, size, and contractility. In experienced hands, Doppler echocardiography provides a fairly accurate assessment of diastolic dysfunction. Transesophageal echocardiography (TEE) is not recommended for routine assessment of the heart failure patient but may be useful in patients with an inadequate echo window, complicated valvular disease, prosthetic valves, or suspected intracardiac thrombi. Stress or dobutamine echocardiograms may be performed to screen for myocardial ischemia.

Cardiac catheterization is indicated in many patients. Right heart catheterization may clarify perplexing clinical situations by determining intracardiac pressures and cardiac output, thereby providing direction for tailored therapy. Left heart catheterization defines coronary anatomy and determines whether ischemic heart disease is the cause of heart failure. The clinician should have a low threshold for requesting catheterization studies to exclude coronary artery disease and provide hemodynamic information, because the findings may offer clues as to interventions that improve prognosis.

Metabolic stress testing (cardiopulmonary exercise testing), usually performed at larger centers, provides objective data on the level of functional impairment. Maximal oxygen consumption (peak VO_2) > 25 mL/kg/min is normal for middle-aged adults. Maximal oxygen consumption < 14 mL/kg/min indicates severe functional impairment and usually is the threshold for considering cardiac transplantation as a management option. The cardiopulmonary exercise test may also be used to differentiate cardiac from pulmonary impairment in patients with unexplained dyspnea.

Pulmonary function tests may be obtained to assess patients with dyspnea. Often, restrictive ventilatory impairment is seen in heart failure. Sleep apnea is common in heart failure, and polysomnography should be considered in patients with a history of nocturnal breathing difficulties and sleep disturbances.

Ambulatory Holter monitoring frequently detects ventricular arrhythmias in the heart failure population. These arrhythmias are nonspecific, but may be predictors of severe heart failure and subsequent mortality. In most cases, Holter monitoring will not identify candidates for antiarrhythmic or defibrillator (ICD) therapy. Sustained ventricular tachycardia, when detected, may indicate the need for an implantable defibrillator.

Management

The management of heart failure is challenging, because counseling, pharmacotherapy, procedures, devices, and rehabilitation are required. Specific aims of treatment are to prevent cardiac decompensation, slow progression of the disease, improve quality of life, prevent complications, and prolong survival. Patient education is important for successful heart failure management. Patients should be instructed to follow a low-sodium diet (2-3 g sodium daily) and restrict fluids (2 L daily). Overweight patients are encouraged to achieve ideal body weight. Heart failure patients should record their weights daily and keep a diary for review. Home blood pressure monitoring is useful in many patients. Cigarette smoking and excess alcohol consumption should be discouraged. An exercise program of mild to moderate intensity improves well being and functional status. Cardiac rehabilitation is helpful when available. Patients are instructed to recognize signs and symptoms of worsening heart failure and seek help if these develop. Close follow-up appointments with monitoring of compliance reduce hospitalizations. Patients should avoid taking nonsteroidal anti-inflammatory drugs (NSAIDs), insulin-sensitizing TZD agents, decongestants, and herbal remedies. Because heart failure is a complex syndrome, successful management involves several strategies in combination. A heart failure management program with its team approach provides multiple services, reduces costs, and prevents hospitalizations.[15]

The new ACC/AHA guidelines emphasize measures to prevent or delay the onset of heart failure and also discuss management of the end-stage patient. For patients with stage A heart failure (at risk but no structural abnormalities), treatment of hypertension, diabetes, coronary artery disease, and avoidance of cardiac toxins is important. For patients with stage D heart failure (end stage with refractory symptoms), a discussion about aggressive high-tech management options (transplant, LVAD, investigational therapies) vs end-of-life care should be conducted with the patient and family.

Drug Therapy For Long-term Management

Angiotensin-converting Enzyme (ACE) Inhibitors. ACE

inhibitors probably are the most important drugs used in the management of heart failure.[16] Multiple randomized, controlled trials have reported an overall 20% improvement in mortality for all stages of heart failure, as well as improvement in symptoms, exercise tolerance, quality of life, and left ventricular ejection fraction.[17-20] ACE inhibitors reduce the risk of hospitalizations and emergency department visits. These agents inhibit ACE, blocking the conversion of angiotensin I to angiotensin II, thereby reducing the detrimental effects of this hormone. ACE inhibitors also prevent the degradation of bradykinin, augmenting kinin-meditated prostaglandin synthesis and vasodilation. Other actions of ACE inhibitors include antihypertensive, anti-inflammatory, anti-fibrotic, reverse remodeling, and renal protective effects. ACE inhibitors should be initiated at low doses and titrated to achieve target doses or the maximally tolerated dose (*see Table 3*).[21] The benefits of ACE inhibitors appear to be a class effect, shared among many agents. Six ACE inhibitors currently are FDA approved for heart failure treatment: captopril, enalapril, lisinopril, quinapril, fosinopril, and benazepril. Ramipril and trandolapril are approved for heart failure following myocardial infarction. The main side effect of ACE inhibitors, intractable cough, occurs in 10-20% of patients and may necessitate substitution of an angiotensin receptor blocker or hydralazine/nitrate. ACE inhibitor cough is persistent, nonpositional and nonproductive. Before stopping an ACE inhibitor, the clinician should be certain that the ACE cough is the correct diagnosis. Other side effects of ACE inhibitors include hypotension, hyperkalemia, renal dysfunction, angioedema, and agranulocytosis. ACE inhibitors should not be prescribed to patients with acute renal failure, a history of angioedema, or during pregnancy. ACE inhibitors must be used *cautiously* in patients with relatively low blood pressure, creatinine > 3, renal artery stenosis, or high normal serum potassium levels. All patients with systolic or diastolic heart failure (or asymptomatic LV dysfunction) should be treated with an ACE inhibitor.

Angiotensin Receptor Blockers (ARBs). These agents block the effects of angiotensin II at the tissue level.[22] They are useful alternative drugs in heart failure therapeutics for patients who are ACE intolerant because of cough or angioedema (*see Table 4*).[23] These agents probably are not as effective as ACE inhibitors in heart failure but have fewer side effects.[24] ARBs are not associated with cough and may cause renal dysfunction or hyperkalemia. The benefits of "add-on" therapy are uncertain. When ARBs are added to either an ACE inhibitor or a beta blocker, patients may experience improvement in morbidity but not mortality.[25] When ARBs are added to an ACE inhibitor plus a beta-blocker, outcomes may worsen.

Hydralazine and Nitrates. These agents are arterial and venous dilators, respectively, and together they reduce afterload and preload. In addition, hydralazine has antioxidant properties, and nitrates inhibit growth and remodeling. Because multiple doses are required throughout the day, patient compliance with these drugs is difficult (*see Table 5*). This combination of vasodilators is inferior to ACE inhibitors in terms of survival, but they may actually improve ejection fraction and exercise tolerance more than ACE inhibitors.
Hydralazine/nitrates may be added to ACE inhibitors for additional hemodynamic benefit. Hydralazine/nitrates in combination are particularly useful in ACE-intolerant patients, especially those with renal dysfunction or hyperkalemia.

Beta-Blockers. Large, randomized control trials have shown that the beta-blockers carvedilol, long-acting metoprolol, and bisoprolol improve survival and symptoms in heart failure patients.[26-30] This is *not* a class effect; other beta-blockers do not have FDA approval for treating heart failure. Beta-blockers have antihypertensive, antiarrhythmic, anti-ischemic, and negative chronotropic properties. Beta-blockers modulate neurohormones, restore beta receptor function, and reverse remodeling.[31] Beta-blockers improve ejection fraction, quality of life, exercise capacity, and survival, in addition to reducing blood pressure, ischemia, and arrhythmias and hospitalizations.

Beta-blockers may be prescribed to euvolemic patients with left ventricular dysfunction and any class of heart failure.[32] Beta-blockers are initiated at low doses and slowly titrated to target levels over weeks to months (*see Table 6*). Initially, blocking sympathetic stimulation may worsen left ventricular ejection fraction and symptoms, but after several months, ejection fraction and symptoms improve. Side effects from beta-blockers include hypotension, lightheadedness, fluid retention, cardiac decompensation, and bradycardia. Caution must be used in prescribing beta-blockers to patients with reactive airway disease, heart block, sick sinus syndrome, hyponatremia, or hypotension.

Diuretics. Most patients with heart failure require diuretics to control symptoms of congestion. Diuretics have not been shown to improve survival but are important for success with other drugs, especially beta-blockers. Diuretics inhibit sodium resorption at various sites in the renal tubules.[33] Loop diuretics (furosemide, bumetanide, and torsemide) inhibit sodium resorption in the thick ascending segment in the loop of Henle. Thiazides, including metolazone, inhibit sodium resorption in the distal convoluted tubule. Spironolactone acts in the collect-

Table 3. ACE Inhibitor Dosing Table

Agent	Initial Dose (mg)	Target Dose (mg)	Frequency
Captopril* (Capoten)	6.25	50	TID
Enalapril* (Vasotec)	2.5	20	BID
Lisinopril* (Prinivil, Zestril)	2.5	40	QD
Ramipril** (Altace)	1.25	5	BID
Quinapril* (Accupril)	5	20	BID
Fosinopril* (Monopril)	2.5	20	BID
Benazepril* (Lotensin)	2.5	20	BID
Trandolapril** (Mavik)	1	4	QD

* FDA approved for heart failure
** FDA approved for post-myocardial infarction heart failure

Table 4. Angiotensin Receptor Blocker Dosing Table

Agent	Initial Dose (mg)	Maximal Dose (mg)
Valsartan (Diovan)*	80	320
Candesartan (Atacand)	16	32
Losartan (Cozaar)	25	100
Irbesartan (Avapro)	75	300
Telmisartan (Micardis)	40	80
Eprosartan (Tevetan)	400	800
Olmesartan (Benicar)	20	40

* FDA approved for heart failure in ACE intolerant patients

ing duct. Intravenous diuretics often are the first drugs given to patients with acute pulmonary edema, providing rapid symptomatic relief. Intravenous diuretics are used to treat hospitalized patients with fluid overload. Continuous infusion of loop diuretics may be needed for volume overloaded patients with diuretic resistance. Chronically, the dosing of diuretics requires careful attention to avoid intravascular volume contraction, while providing adequate drug effect to achieve euvolemia (*see Table 7*). Diuretics should not be prescribed as monotherapy, and diuretic doses should be reduced as patients achieve compensation. In severe heart failure, a loop diuretic may be given in combination with a thiazide such as metolazone to promote diuresis. A flexible, patient-guided diuretic regimen is recommended for chronic outpatient management of heart failure. Diuretics side effects include hyponatremia, hypokalemia, hypomagnesemia, hypotension, azotemia, and neurohormonal activation.

Digoxin. Digoxin is indicated for the treatment of symptomatic heart failure (NYHA FC 2-4). It improves exercise capacity and ejection fraction and prevents decompensation and hospitalizations but has a neutral effect on mortality.[34] Digoxin has beneficial effects in heart failure regardless of the ejection fraction. Digoxin is classified as a neurohormonal modulating agent.[35] It inhibits the enzyme Na+/K+ ATPase. In the heart, this shifts calcium into the myocyte, enhancing contractility. In the central nervous system, this effect reduces sympathetic outflow. In the kidney, it decreases the release of renin. Digoxin also slows conduction through the AV node, controlling ventricular rate in atrial fibrillation. Digoxin has a low therapeutic-toxic range and a potential for drug toxicity. Use a low dose of digoxin (0.125 mg daily) in most patients, maintaining a serum digoxin level £ 1 mg/dL. Reduce the dose with renal dysfunction and with concomitant use of amiodarone (*see Table 5*).

Aldosterone Antagonists. Aldosterone is secreted by the adrenal cortex in response to angiotensin II.[36] It promotes sodium and water retention with potassium and magnesium loss. Aldosterone activates the sympathetic and inhibits the parasympathetic nervous system. It causes myocardial fibrosis and remodeling. Spironolactone, a weak diuretic and aldosterone antagonist, decreases mortality and hospitalizations in patients with severe heart failure.[37] This agent is indicated in NYHA Class III and IV patients with severe heart failure. Prescribe it at low doses (12.5-25 mg daily), and monitor serum potassium levels regularly. Its major side effects are hyperkalemia and gynecomastia. Spironolactone should be avoided in patients with serum creatinine > 2.0 mg/dL or potassium > 5.3 mmo/L.

Calcium Channel Antagonists. Short-acting calcium channel blockers are contraindicated in heart failure because they depress left ventricular function, worsen symptoms, activate neurohormones, and increase the risk of death. Amlodipine has a neutral effect on cardiac function and mortality.[38] It may be

Table 5. Other Heart Failure Drugs

Agent	Initial Dose	Maximal Dose	Guidelines
Digoxin	0.125 mg QD	0.25 mg QD	Reduce dose in renal dysfunction and in patients on amiodarone
Hydralazine	25 mg QID	100 mg QID	Use with nitrates
Isosorbide	20 mg TID	80 mg TID	Also useful for angina pectoris

Table 6. Beta Blocker Dosing Table

Beta Blocker	Initial Dose	Target Dose
Carvedilol* (Coreg)	3.125 mg BID	50 mg BID if > 75 kg 25 mg BID if < 75 kg
Metoprolol* succinate (Toprol XL)	12.5 mg QD	200 mg QD
Metoprolol tartrate (Lopressor)	12.5 mg BID	50 mg TID
Bisoprolol* (Zebeta)	2.5 mg QD	10 mg QD

* FDA approved for heart failure

prescribed adjunctively to treat angina pectoris or hypertension associated with heart failure. Long-acting calcium channel blockers may be useful for treating some patients with diastolic heart failure with normal left ventricular ejection fraction, but objective data are lacking.

Antiarrhythmic Drugs. Amiodarone is the preferred antiarrhythmic agent for patients with heart failure and low ejection fraction. It may be used to manage atrial fibrillation or high-grade ventricular arrhythmias. Class IA agents such as procainamide, quinidine, and disopyramide should be avoided. Beta-blockers, which have multiple beneficial effects in heart failure, also have antiarrhythmic properties. Implantable defibrillators are superior to drug therapy in preventing sudden cardiac death.

Anticoagulation. The risk of thromboembolic events in heart failure ranges from 1-3% annually. The prophylactic use of warfarin in these patients is controversial based on risk/benefit ratio. Specific indications for warfarin anticoagulation in heart failure include atrial fibrillation, left ventricular thrombus, left ventricular aneurysm, hypercoagulable state, history of prior thromboembolism, and patent foramen ovale. Aspirin has beneficial effects in patients with ischemic cardiomyopathy; no evidence supports its use in patients with normal coronary arteries. Clinical trials are now under way to determine whether anticoagulant agents should be given to all patients with heart failure.

Other Therapies. Statins are recommended for patients with ischemic cardiomyopathy because of multiple benefits. Dietary supplements such as coenzyme Q-10, carotene, antioxidants, thyroid hormone, and growth hormone are *not* recommended. Exercise training and cardiac rehabilitation improve the clinical status in heart failure patients. Diagnosis and treatment of sleep apnea is an important adjunctive measure and may help reduce elevated pulmonary artery pressures. Treatment of chronic anemia improves functional status. Heart failure management programs, guided by nurse specialists, improve quality of life, reduce hospital admissions, and decrease heart failure costs.

Intravenous Vasodilators for Decompensated Heart Failure (*see Table 8*)

Nitroprusside. Sodium nitroprusside is a potent short-term arterial and venous vasodilator metabolized by the liver to nitric oxide and cyanide. This afterload reducing agent is to treat acutely decompensated heart failure in patients with adequate systemic blood pressure. It is administered by continuous infusion in an ICU setting; invasive hemodynamic monitoring is required for safe use (*see Table 8*). It should be avoided in patients with active ischemia because it may cause coronary steal syndrome. It is associated with rebound worsening hemodynamic effects when the infusion is discontinued. During the infusion, patients should be optimized on oral vasodilator regimen (ACE inhibitors, nitrates/hydralazine) for long-term benefits. Prolonged infusions, especially in patients with renal dysfunction, may be associated with thiocyanate toxicity.

Nesiritide. Nesiritide, synthetic B-type natriuretic peptide, is a balanced venous and arterial vasodilator with modest natriuretic effects.[39] Nesiritide may be used to treat patients with decompensated heart failure who have dyspnea at rest or with minimal activities associated with fluid overload. It may be initiated in the emergency department or in the hospital. It normalizes hemodynamics, rapidly improves heart failure symptoms, and promotes diuresis. Nesiritide acts via specialized natriuretic peptide receptors on the cell surface of smooth and endothelial cells. Its primary action is smooth muscle cell relaxation and vasodilation. The onset of action occurs within 15 minutes and the half-life is 18 minutes. Nesiritide is administered by bolus followed by a

Table 7. Diuretic Dosing Table

Generic Name	Trade name	Class	Initial dose	Special Considerations
Furosemide	Lasix	Loop	20mg	Can be given intravenously. PO equivalent twice IV dose.
Bumetanide	Bumex	Loop	0.5 mg	Good oral bioavailability. Can be given intravenously. Oral and IV dose the same.
Torsemide	Demadex	Loop	5-10 mg	Best oral availability.
Ethacrynic acid	Edecrin	Loop	50 mg	Only diuretic with no sulfhydryl group. Used if allergic to furosemide.
Hydrochlorothiazide	Hydrodiuril	Thiazide	12.5 mg	Weak diuretic, used mainly for hypertension.
Metolazone	Zaroxolyn	Thiazide	2.5 mg	Give 1/2 hr before furosemide. Only available orally. High risk of hypokalemia.
Spironolactone	Aldactone	K^+ sparing	12.5 mg	Weak diuretic. Risk of hyperkalemia. Avoid in patients with renal failure. Gynecomastia in men. Only available orally.

Table 8. Intravenous Agents Used in Heart Failure

Drug	Dose	Special Considerations
Nitroprusside	10-500 mcg/min	Thiocyanate accumulation in renal failure; may provoke ischemia by coronary steal; vasodilator; ICU only.
Nesiritide	2 mcg/kg/bolus then 0.01 mcg/kg/min	Fixed weight-based dose; Vasodilator; occasional hypotension.
Nitroglycerin	10-500 mcg/min	Anti-ischemic, vasodilator; limited by vascular headache; hypotension; tolerance develops rapidly.
Dobutamine	2-20 mcg/kg/min	Beta receptor agonist; pro-arrhythmic; ↑HR; ↑Ischemia.
Milrinone	0.25-0.75 mcg/kg/min	Phosphodiesterase inhibitor; vasodilator; may improve pulmonary hypertension; used in patients taking beta blockers; pro-arrhythmic.

continuous infusion (*see Table 8*). In most cases, invasive hemodynamic monitoring is not required. However, telemetry monitoring, blood pressure recordings, and electrolyte determinations are mandatory. The usual length of infustion is 1-2 days. During the infusion, intravenous diuretics are administered, and vasodilators are up-titrated.

Nitroglycerin. Intravenous nitroglycerin is a venous vasodilator at low doses and an arterial vasodilator at high doses. It reduces ventricular preload and improves myocardial ischemia. Nitroglycerin is started at low doses and titrated upward to achieve hemodynamic and clinical benefits (*see Table 8*). Its effectiveness is limited by tachyphylaxis, which develops within hours after initiation of therapy. Headache occurs in 20% and hypotension in 5% of patients treated with this agent.

Intravenous Inotropic Agents for Hypotension and Low Cardiac Output

Dobutamine. Dobutamine is an intravenous inotropic agent that acts directly on cardiac beta receptors.[40] It increases adenylate cyclase activity, converting ATP to cyclic AMP, which releases calcium from the sarcoplasmic reticulum and leads to enhanced contractility. Dobutamine increases cardiac output, heart rate, and myocardial oxygen consumption. It has the potential of provoking arrhythmias and aggravating ischemia. Dobutamine may be administered by continuous infusion in a hospital setting for hypotensive or low output heart failure (*see Table 8*). The onset of action is 1-2 minutes and the half-life is 2 minutes. Continuous outpatient dobutamine infusions sometimes are administered as palliative therapy to improve symptoms and decrease hospitalizations in patients with end-stage heart failure, but survival may be shortened with this therapy. Intermittent outpatient infusions are not recommended.

Milrinone. Milrinone, a phosphodiesterase III inhibitor, is a positive inotropic and vasodilating agent. Milrinone prevents the degradation of cyclic AMP, the second messenger for improving contractility. Milrinone may be more potent as a pulmonary artery vasodilator than dobutamine. It has minimal chronotropic properties but may increase the risk for cardiac arrhythmias. Milrinone is infused for hypotensive or low-output heart failure (*see Table 8*). A recent study showed that routine inpatient milrinone infusions for decompensated heart failure were associated with arrhythmias and hypotension but did not reduce length of stay.[41] Milrinone (or dobutamine) may stabilize patients waiting in the hospital for cardiac transplantation. Milrinone occasionally is given as an outpatient continuous infusion for palliation of end-stage heart failure. Intermittent outpatient milrinone infusions are not recommended.

Dopamine. Dopamine is a sympathomimetic amine and the immediate precursor of norepinephrine. It exerts dose-dependent physiologic effects when administered intravenously to heart failure patients.[42] At low doses, dopamine activates dopaminergic receptors in the mesenteric arteries and kidneys, producing renal vasodilation. At medium doses, it increases the release of norepinephrine from sympathetic neurons, stimulating cardiac beta-receptors and producing a positive inotropic effect. At high doses, it activates alpha-receptors in the peripheral vasculature causing vasoconstriction (*see Table 8*). In most centers, dopamine has been replaced by dobutamine and milrinone. It is controversial whether "renal dose dopamine" has any benefit; clinical trial data failed to show a renal protective effect with this agent.

Electronic Devices for Heart Failure

Biventricular Pacing. Conduction disturbances occur in a third of patients with advanced heart failure, usually left bundle branch block. The QRS widens as heart failure progresses, and patients with the widest QRS have the poorest prognosis. A wide QRS usually reflects left ventricular dyssynchrony, which causes inefficient contractility, low cardiac output, decreased ejection fraction, prolonged mitral regurgitation, and cardiac remodeling. Biventricular pacing, also known as resynchronization therapy, uses a 3-lead pacing system consisting of a right atrial lead, a right ventricular lead, and a left ventricular lead placed via the coronary sinus into a left lateral cardiac vein.[43] Left ventricular lead placement, technically difficult and tedious, has a 10% failure rate. Indications for biventricular pacing are symptomatic heart failure (NYHA FC III-IV), despite a good medical regimen and a wide QRS (> 130 ms). The pacemaker is synchronized by echocardiography to improve contractility. Benefits of resynchronization therapy include improvement in left ventricular ejection fraction, cardiac output, mitral regurgitation, quality of life, exercise tolerance, NYHA FC, and survival. Approximately 67% of patients treated with biventricular pacing experience improvement in

heart failure symptoms. However, it is difficult if not impossible to identify patients prospectively who will benefit from this therapy.

Implantable Defibrillators. Approximately half of all heart failure patients die suddenly. Placement of a defibrillator is indicated for survivors of a cardiac arrest, sustained ventricular tachycardia, inducible sustained ventricular tachycardia in the electrophysiology laboratory in patients with an ischemic CM and an EF < 35%, and post-myocardial infarction patients with low ejection fraction.[44-45] It is not known whether ICD placement should be recommended for all patients with heart failure and low ejection fraction. Devices are superior to antiarrhythmic drugs in preventing sudden death.

Surgical Therapies

Bypass surgery, valve repair, and ventricular reconstruction. Screening for underlying coronary artery disease is an important aspect of heart failure management. Physicians should have a low threshold for performing cardiac catheterization in this population. If coronary artery disease is detected and myocardial ischemia or hibernation is present, coronary artery bypass surgery or percutaneous coronary intervention (stent/angioplasty) should be performed if suitable target vessels are present. Although surgery is associated with higher risk in patients with low ejection fraction, improvement in left ventricular function and heart failure symptoms may occur. Following revascularization, these patients should continue with a comprehensive heart failure medical management program, including ICD implantation if LVEF is < 35%.

In some patients, coronary arteries are normal but severe mitral or tricuspid valvular regurgitation is present. In experienced centers, these patients can successfully undergo valve repair or replacement and have improvement in heart failure symptoms. In patients with chronic atrial fibrillation, this approach may include a maze procedure to restore sinus rhythm. Medical therapy should be continued postoperatively in all instances.

Left ventricular reconstruction is performed in selected centers for patients with ischemic cardiomyopathy.[46] Surgical repair consists of resection of left ventricular aneurysm or scar, followed by reconstruction of the left ventricle to change its shape from spherical to elliptical. The mitral and tricuspid valves are repaired and coronary arteries bypassed. Often a left ventricular pacing lead is attached at the time of surgery and used for resynchronization pacing if the patient remains symptomatic postoperatively. These patients also require continuation of medical therapy after surgical reconstruction.

Left Ventricular Assist Devices (LVADs). Left ventricular assist devices are mechanical pumps used to support the failing heart in patients with cardiogenic shock.[47] These pumps are electrically powered and are implanted surgically. Several LVADs are FDA approved for clinical use: HeartMate, Novacor, Thoratec, and Abiomed. The HeartMate and the Novacor are implanted in the abdomen and connected via an external cable to an electrical power source. The inflow cannula is attached to the apex of the left ventricle and separated from the pumping chamber by a bioprosthetic valve. An outflow cannula connects the pumping chamber with the aorta. These devices provide pulsatile blood flow at a rate of 4-10 L/min. The Thoratec and the Abiomed are external devices connected via large cannulae to the circulatory system. The Abiomed often is used as a means of stabilizing patients with cardiogenic shock following cardiac surgery or acute MI. The Thoratec device provides left ventricular and right ventricular support via external pumping chambers. In general, an LVAD is used as a "bridge to cardiac transplantation" in suitable individuals. Very few patients with dilated cardiomyopathy recover sufficient cardiac function to allow explantation of an LVAD. These devices are limited by a

Figure 1. Heart Failure Diagnostic Algorithm

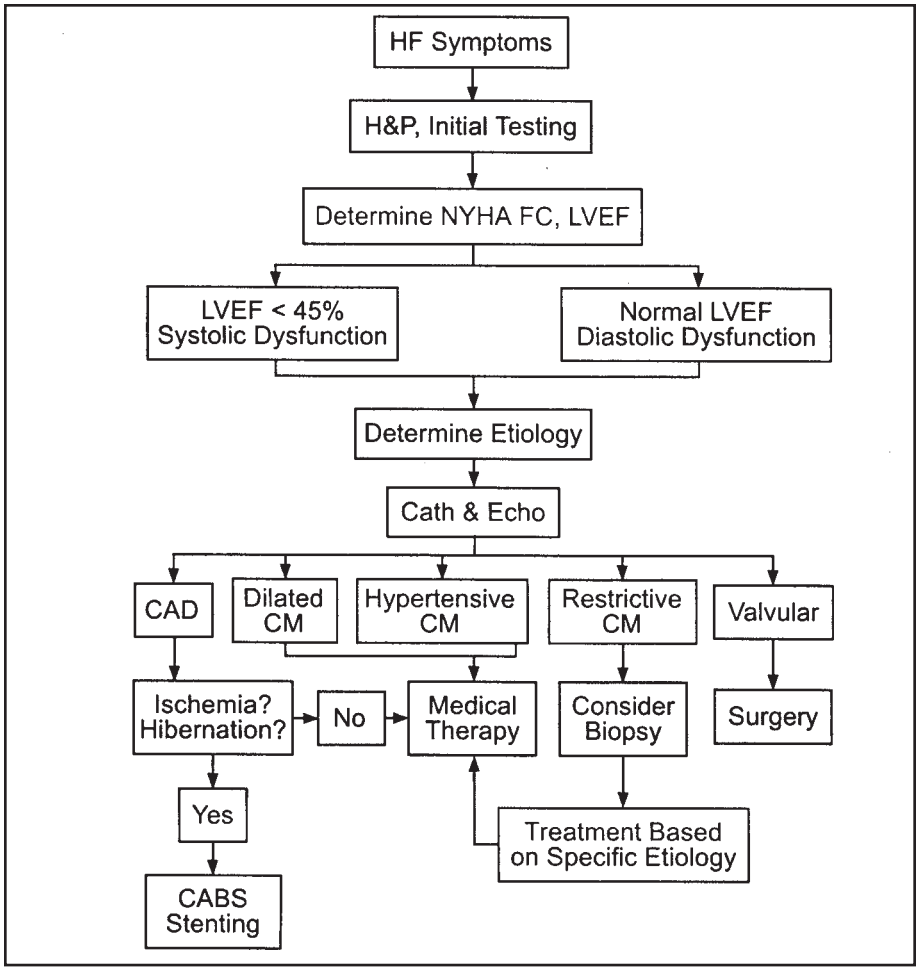
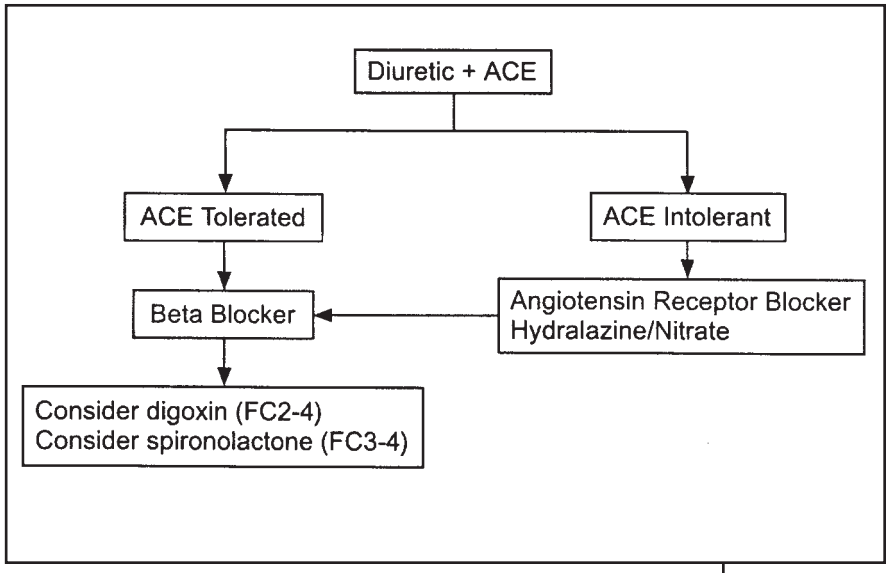


Figure 2. Heart Failure Management Algorithm



high infection rate, thromboembolic complications, and mechanical failures. Smaller LVADs with continuous nonpulsatile flow are undergoing clinical trials.

Cardiac Transplantation. Cardiac transplantation is a management option for a very small subset of heart failure patients.[48] In general, these patients are younger and have disabling heart failure symptoms despite maximal medical therapy. Patients are otherwise healthy except for heart failure but have poor estimated survival. The number of donor hearts in the United States is steadily decreasing despite altruistic efforts to increase organ donation. Approximately 2000 heart transplants are performed nationwide annually.[49] Contraindications to cardiac transplantation include recent malignancy, morbid obesity, systemic disease limiting survival or rehabilitation, active smoking, medical noncompliance, renal or hepatic failure, active infection, or recent pulmonary infarction. Patients referred to a heart transplant center undergo extensive medical and psychosocial evaluation. If selected for listing, the patients are prioritized according to severity of illness based on United Network for Organ Sharing (UNOS) criteria. Status I patients require inotropic or mechanical support for the failing heart. Status II patients remain at home on oral medical therapy. Mortality associated with cardiac transplantation is approximately 10% during the first year and 50% by year 10. Complications include infection, rejection, allograft coronary artery disease, renal dysfunction, and malignancy. All patients are maintained on multiple immunosuppressive medications. Complications frequently are related to over- or under-immunosuppression.

Clinical Decision Making

Figure 1 provides a diagnostic algorithm for evaluating patients with heart failure. The echocardiogram and cardiac catheterization are the most important diagnostic techniques for determining etiology and structural abnormalities. Figure 2 is a management algorithm in which a diuretic and an ACE inhibitor are given as initial therapy. The clinician is provided with guidelines for additional pharmacological agents. Indications for hospitalization include severe dyspnea at rest or with minimal activities, marked fluid retention and weight gain, worsening renal or hepatic function, hypotension, cardiac arrhythmias or syncope, unstable angina pectoris, or need for IV diuretics or vasodilators. Indications for referral to a tertiary heart failure center include NYHA FC 3-4 symptoms despite maximally tolerated medications, complex cases with frequent decompensations, possible candidates for biventricular pacing, surgical therapies, cardiac transplantation, investigational therapies, or palliative home inotropic therapy.

Future Directions

The outcomes of several recent clinical trials in heart failure have favored device and surgical therapies over conventional pharmacological approaches. However, several new classes of investigational drugs are undergoing clinical trial evaluation: oral inotropics, newer diuretics, vasopressin antagonists, and aldosterone antagonists.[50] Clinical trials of newer LVADs and surgical devices (cardiac support and shape devices) currently are under way.

Summary

Heart failure has become a common clinical problem associated with high cost, morbidity, and mortality. In describing heart failure, it is important to determine the etiology, NYHA functional class, systolic vs diastolic dysfunction, and acute vs chronic decompensation. All patients with left ventricular dysfunction should be treated with an ACE inhibitor initially and then a beta-blocker. Although diuretics do not improve mortality, they are necessary for symptom relief in most patients. Digoxin may be added to the regimen for symptomatic heart failure, and an aldosterone antagonist is used for patients with severe heart failure. Biventricular pacing and cardiac defibrillators should be considered in selected cases. Surgical therapies may help to reverse heart failure symptoms, and surgical management should be considered as an important adjunctive measure.

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7. The most common etiology of heart failure is:
   a. alcohol abuse.
   b. atrial fibrillation.
   c. hypertension.
   d. coronary artery disease.

8. The pathophysiologic response to heart failure:
   a. restores many patients to good health.
   b. improves cardiac hemodynamics and heart size.
   c. worsens cardiac function and prognosis.
   d. is a temporary response to acute decompensation.

9. Most of the expense associated with heart failure:
   a. is associated with diagnostic testing.
   b. is related to prescription drugs.
   c. is due to hospitalizations.
   d. is used to finance heart transplants.

10. Current guidelines emphasize the importance of ACE inhibitors and beta-blockers in heart failure management:
    a. because diuretics work so well already.
    b. because these drugs may help when digoxin fails.
    c. because these agents have minimal side effects.
    d. because these drugs have proven survival benefits.

11. Which statement about intravenous drugs for heart failure is true?
    a. Vasodilators improve hemodynamics quickly.
    b. Milrinone and dobutamine are not proarrhythmic.
    c. Nitroglycerin has sustained vasodilator effect.
    d. Nesiritide improves cardiac output by positive inotropic actions.

12. Approximately half of all heart failure patients die suddenly. The most effective intervention for preventing this complication is:
    a. amiodarone therapy.
    b. quinidine and digoxin in combination.
    c. implantable defibrillators.
    d. class 1-C antiarrhythmic agents.

13. Patients with heart failure should be:
    a. reassured because transplant is always an option.
    b. referred for surgical evaluation if severe mitral regurgitation and atrial fibrillation are present.
    c. always managed medically because surgical risk in heart failure patients is prohibitive.
    d. treated initially with dietary supplements and herbal remedies.

Answers: 7(d); 8(c); 9(c); 10(d); 11(a); 12(c); 13(b)

CME Instructions

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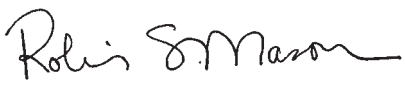

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PHARMACOLOGY WATCH

FDA Issues 'Black Box' Warning Based on WHI Study

The FDA has mandated a "Black Box" warning for all estrogen and estrogen/progestin products for use by postmenopausal women. The new warnings are based on analysis of data from the Women's Health Initiative (WHI) study that was published July 2002. The box warning emphasizes that these drugs have been associated with increased risks for heart disease, heart attacks, strokes, and breast cancer and that they are not approved for heart disease prevention. Wyeth Pharmaceuticals, the manufacturer of Premarin, Prempro, and Premphase, products that were used in the WHI study, are also required to change their indications to: treatment of severe vasomotor symptoms, vulvar and vaginal atrophy associated with menopause, prevention of postmenopausal osteoporosis, and should only be used when the benefit clearly outweighs the risk. The labeling will also be required to include consideration of other therapies for the atrophy and osteoporosis indications, and to recommend use of the lowest dose for the shortest duration possible. While Wyeth's products are the focus of this initial press release and FDA action, all estrogen products will be subject to new labeling. The FDA is also recommending future research to answer questions regarding the risks of lower-dose estrogen products and if other types of estrogens and progestins are associated with lower risk of CVD and breast cancer. The complete press release can be viewed at www.fda.gov.

ALLHAT: Thiazide for Hypertension Treatment

Thiazide diuretics should be considered first-line therapy for hypertension, according to the authors of the ALLHAT study published in December. In a finding that surprised nearly everyone (especially the sponsors of the study) in patients with hypertension and at least one other cardiovascular risk factor, the diuretic chlorthalidone was associated with better cardiovascular outcomes at less cost and with equal tolerability compared to a calcium channel blocker or an ACE inhibitor. ALLHAT enrolled more than 33,000 patients from 623 centers in the United States, Canada, and the US Virgin Islands. Patients were randomized to the calcium channel blocker amlodipine, the angiotensin-converting enzyme inhibitor lisinopril, or chlorthalidone. Mean follow-up was 4.9 years with the primary outcome being combined fatal CHD or nonfatal MI. Secondary outcomes included all-cause mortality, stroke, combined CHD, and combined cardiovascular disease (CVD). The 6-year rate of the primary outcome and all-cause mortality was virtually identical for all 3 drugs. Chlorthalidone was superior to amlodipine in preventing heart failure (10.2% vs 7.7%, RR, 1.38, 95% CI, 1.25-1.52) and was superior to lisinopril for lowering blood pressure and in 6-year rates of combined cardiovascular disease including stroke (6.3% vs 5.6%) and heart failure (8.7% vs 7.7%). With improved cardiovas-

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cular outcomes, lower cost, and equal tolerability, the study concludes that thiazide-type diuretics are superior in preventing one or more forms of CVD and that they should be the preferred agent in antihypertensive therapy, and should be included in all multidrug regimens (*JAMA*. 2002;288:2981-2997). An accompanying editorial calls ALLHAT "one of the most important trials of antihypertensive therapy" and suggests that national guidelines should be changed to emphasize use of thiazide diuretics as initial therapy (*JAMA*. 2002;288:3039-3042).

Candesartan Effective Against Migraines

The angiotensin II receptor blocker candesartan is effective in preventing migraine headaches, according to a new study. Norwegian researchers looked at 60 patients age 18-65 with 2-6 migraines per month. Patients were randomized in a double-blind placebo-controlled crossover study with the main outcome being number of days with headache. Secondary outcomes included use of pain medications and triptans, hours with headache, headache severity, and days lost from work. During the 12-week study, the mean number of days with headache was 18.5 with placebo vs 13.6 with candesartan (P = .001) in the intention to treat analysis (n = 57). Patients were considered a candesartan responder if they noted a reduction of 50% or more of days with headache (18 of 57 patients, 31.6%) or days with migraine (23 of 57 patients, 40.4%). Although this represented a minority of patients, those who did respond benefited from effective migraine prophylaxis. Candesartan's tolerability profile was comparable with placebo (*JAMA*. 2003;289:65-69).

Cough! No Cold Relief from Echinacea

Echinacea offers no benefit in treating the common cold according to a study from the University of Wisconsin. A total of 148 college students with recent onset colds were randomized to an encapsulated mixture of unrefined Echinacea (*E purpurea* herb and root and *E angustifolia* root) 6 times a day on the first day of illness and 3 times a day on the subsequent days up to a total of 10 days. The main outcome was the severity and duration of self-reported symptoms of URI. No statistically significant differences were detected between Echinacea and placebo groups for any of the measured outcomes, which included trajectories of severity over time or mean cold duration. No significant side effects were noted with Echinacea. The study concludes that no detectable benefit or harm could be found with Echinacea treatment for the common cold (*Ann Intern Med*. 2002;137:939-946).

COX-2 Inhibitors and GI Benefits Could Be Overrated

Could the GI benefits of COX-2 inhibitors be overrated? A new study suggests that the COX-2 inhibitor celecoxib is no safer than a combination of diclofenac plus omeprazole with regard to ulcer risk in patients with a history of peptic ulcer disease and arthritis. Researchers from Hong Kong recruited patients with arthritis and NSAID-related bleeding ulcers. After their ulcers had healed, 287 patients who were negative for *Helicobacter pylori*, were randomly assigned to receive celecoxib 200 mg twice a day plus placebo, or diclofenac 75 mg twice a day plus 20 mg of omeprazole for 6 months. Recurrent bleeding ulcer occurred in 7 patients receiving celecoxib and 9 receiving diclofenac/omeprazole (4.9% vs 6.4%). Renal adverse events including hypertension, peripheral edema, and renal failure occurred in 24.3% of patients receiving celecoxib and 30.8% of those receiving diclofenac/omeprazole. The authors suggest that neither regimen offered effective protection against recurrent ulcer complications or renal adverse effects (*N Engl J Med*. 2002;347:2104- 2110).

FDA Actions

Pfizer's new anti-migraine drug, eletriptan (Relpax) has been approved by the FDA for marketing. The drug that is available in 20-mg and 40-mg tablets has been shown to be effective in aborting migraine headaches within 2 hours. The company is marketing a 80-mg tablet in Europe, but the FDA refused to approve the higher dose due to an increase in adverse events.

Montelukast (Singulair), Merck's leukotriene inhibitor, has been approved by the FDA for the treatment of seasonal allergic rhinitis. The drug has been on the market since 1998 for the treatment of asthma in adults and children. This new indication is the first for a leukotriene inhibitor, and creates a new, nonantihistamine treatment modality for this indication. Montelukast was approved for symptoms of seasonal allergic rhinitis in adults and children aged 2 years and older. It is available in 10 mg strength for adults, and a chewable 4 mg or 5 mg strength for children. ■

AMERICAN HEALTH CONSULTANTS®

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports,* and *Sports Medicine Reports.*

VOLUME 8, NUMBER 2 PAGES 3-4 FEBRUARY 2003

Stroke Reduction in Older Hypertensives with Abnormal Nocturnal Blood Pressure Dipping

Source: Hishide Y, et al. *Am J Hypertens*. 2002;15:844-850.

The relationship between adverse cardiovascular events and blood pressure (BP) is direct and linear. Numerous prospective randomized trials indicate that reduction of BP produces a substantial reduction in stroke, with less impressive benefits demonstrated for coronary heart disease (CHD) end points. Since most clinical trials have been based upon clinic or 'casual' BP measurements, rather than 24-hour monitoring (ABPM), we have much less information about whether specific attributes of BP during the circadian pattern variations are important indicators of cardiovascular risk. Some data have indicated that not only is ABPM a much more potent prognosticator for cardiovascular risk, but that specifically, persons whose blood pressure does not evidence the normal 10% or greater decline in the evening (so-called "non-dippers") are at substantially greater risk for target organ damage.

In this prospective study of elderly hypertensives (n = 811) who underwent ABPM, the cardiovascular end point effect of treatment upon nondipper hypertensives was much more dramatic than on dippers (ie, 'normal pattern'). Additionally, individuals who were determined to be 'white-coat' hypertensives by ABPM did not show the beneficial reduction of CV end points as seen in nondippers. Increasing application of ABPM may help discern high-risk HTN groups most likely to benefit from intervention. ■

Primary Prevention of Hypertension

Source: Whelton PK, et al. *JAMA*. 2002;288:1882-1888.

According to JNC VI reporting, as many as 43 million adults in America have hypertension (HTN), defined as blood pressure > 140/90. Although treatment with a variety of agents has been shown to reduce cardiovascular morbidity and mortality, effective primary prevention would be a more desirable goal. The National High Blood Pressure Education Program Coordinating Committee has provided evidence-based recommendations for primary prevention of hypertension in this communication.

The interventions documented to be efficacious in prevention of HTN include weight loss, reduction in dietary sodium, moderation in alcohol, increased physical activity, increased dietary potassium, and adherence to a DASH type diet.

Specifically, the interventions recommended include maintaining BMI < 25, keeping dietary sodium to < 2.4 g daily, engaging in at least 30 minutes of vigorous activity (such as brisk walking) most days of the week, limiting daily alcohol to 30 mL of ethanol (or the equivalent) including at least 3500 mg/d of dietary potassium, and following a diet that is rich in fruits, vegetables, and low-fat diary products, but modest in saturated and total fat.

Blood pressure reductions from these interventions may be as large as those seen with pharmacotherapy for HTN, and have been demonstrated to be sustainable. ■

Effect of Aggressive Screening and Treatment on Prostate Cancer Mortality

Source: Lu-Yao G, et al. *BMJ*. 2002;325:740-743.

There remains a great deal of heated debate about the appropriate use of PSA screening amongst asymptomatic men. Although mortality for prostate cancer has declined since the mid-1990s, it remains uncertain whether this favorable outcome is indeed attributable to enhanced screening. Insight about the relationship between prostate cancer mortality and screening may be gained by comparing two different populations of men who underwent different patterns of PSA screening. During the 1987-1990 time period, men in the Seattle-Puget Sound region (n = 94,000) were more than 5 times more likely to undergo PSA testing than men in Connecticut (n = 120,000). Correspondingly, biopsy rates in the West Coast population were more than twice that of the East Coast population.

Over an 11-year follow-up, there was no discernible difference in prostate cancer mortality between the 2 populations. In ensuing years, the prostate cancer screening rates became much more similar. The men in these analyses were all 65 years or older, hence applicability for younger men is uncertain. Nonetheless, the mortality of prostate cancer effects mostly men older than age 70, so the

age of this group matches the demographic consequences of the disease. This study suggests that more avid PSA screening may not reduce prostate cancer mortality. ■

Diuretics, Mortality, and Nonrecovery of Renal Function in Acute Renal Failure

Source: Mehta RL, et al. *JAMA*. 2002;288:2547-2553.

Diuretics are commonly used in the setting of acute renal failure (ARF), based upon premises that they will reduce volume in extracellular volume overload and may convert oliguric ARF to nonoliguric ARF. To date, no randomized clinical trials have confirmed anticipated benefits in survival or restoration of renal function as a result of diuretic treatment. Mehta and associates postulated that diuretics in ARF would actually increase mortality and forestall recovery of renal function, and they studied critically ill ARF patients (n = 820) at 4 teaching hospitals. ARF was defined as BUN > 40 mg/dL, creatinine > 2.0 mg/dL, or an increase of creatinine > 1 mg/dL over baseline.

Using a covariate-adjusted model, diuretic use was associated with a 68% increase in in-hospital mortality, and a similar (77%) increase in likelihood of death or nonrecovery of renal function. Diuretics used included furosemide, bumetanide, metolazone, and HCTZ, with no demonstrable differences in outcomes dependent on any particular agent, whether used as monotherapy or combination therapy. Patients who were least responsive to diuretics (in terms of urinary output) were disproportionately at risk for adverse outcomes. Mehta et al posit that delay in using dialysis, while medical (diuretic) therapy is used, may indeed by injurious; they further suggest that diuretics, though not yet conclusively proven to be harmful by this single trial, are unlikely to provide benefit in the setting of ARF among critically ill patients. ■

Nut and Peanut Butter Consumption and Risk of DM-2 in Women

Source: Jiang R, et al. *JAMA*. 2002;288:2554-2560.

Recent trials have confirmed that both pharmacologic treatment (acarbose or metformin) and lifestyle intervention (weight loss and exercise) may prevent onset of type 2 diabetes (DM-2) in high-risk individuals. Recent data suggest that it is the type (saturated vs unsaturated) rather than the total fat percentage of diet that better predicts risk of DM-2. Higher intake of saturated fat and transfat negatively affect both glucose metabolism and insulin resistance. Since nuts contain primarily unsaturated fats, as well as fiber, magnesium, vitamins, minerals, and antioxidants, they theoretically provide a dietary substance that could favorably affect likelihood of developing DM-2.

To study the relationship between nuts and DM-2, Jiang and associates evaluated the participants in the Nurses Health Study (n = 121,700 women). Information collected on these women includes family history of diabetes, body weight, smoking, and physical activity; additionally, dietary questionnaires quantitated intake of nuts, dividing inquiry into peanuts, nuts, and peanut butter.

Women in the highest quartile of nut ingestion (at least 5 times weekly) when compared with those who almost never consumed nuts (lowest quartile) demonstrated an age-adjusted 0.55 relative risk (RR) for DM-2. A similar comparison specific to peanut butter showed an RR of 0.79 comparing quartile 1 to quartile 4. Because there has been some concern that increasing nuts in the diet might worsen weight management issues, the fact that this study found that ingestion of nuts in the highest quartile was not associated with significantly greater weight gain than those eating nuts less frequently is reassuring. When coupled with the epidemiologic studies suggesting favorable effects of nuts upon lipids and coronary heart disease, this study provides increasing impetus for clinician endorsement of nut consumption. ■

Optimal Diets for Prevention of CHD

Source: Hu FB, Willett WC. *JAMA*. 2002;288:2569-2578.

The classic diet-heart hypothesis postulates that dietary saturated fat and cholesterol are causally associated with coronary heart disease (CHD). Though the evidence for this hypothesis is sufficiently compelling that few clinicians debate its veracity, other components of diet, or their effects in concert, may be equally pertinent to the development of CHD.

A MEDLINE search produced 147 trials assessing diverse dietary factors, which indicated that omega-3-fatty acids, trans-fatty acids, carbohydrates, glycemic index, fiber, folate, individual foods (eg, nuts), and specific dietary patterns demonstrate a relationship with cardiovascular disease. From these data, several strategies, in addition to cholesterol reduction, are well substantiated to be associated with lesser risk of CHD: substitution of unsaturated fat (especially polyunsaturated) for saturated fat, reduction of transfatty acids, increases of omega-3 fatty acids (ie, from fish oil or plant sources), and a diversified diet which includes high intake of fruits, vegetables, nuts, and whole grains (low in refined grains). Despite the fact that common practice for management of obesity, an important contributor to CHD, suggests restriction of dietary fat to < 30% of total energy intake, the data to support such intervention are lacking. Rather, it may be more prudent to focus upon the favorable dietary characteristics detailed above, contained within a moderately hypocaloric diet. ■

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