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Congestive heart failure (CHF) is the most common DRG for Medicare patients in U.S. hospitals and is therefore the target of considerable regulatory attention due to its financial impact on the federal budget. The re-admission rate for CHF patients is also quite high, and Medicare has threatened not to pay hospitals for subsequent admissions within 30 days. Hospitals also are becoming highly compliant with core measures in CHF patients, as these are tracked in publicly reported web sites such as www.hospitalcompare.gov. Although these measures deal with hospitalized patients, the outpatient arena is where these patients spend the majority of their lives. With the increasing trend toward hospitalist management of Medicare patients, hospitalists argue, with some justification, that the re-admission rates are not their responsibility, but rather that of the primary care physicians to whom the patients are referred upon discharge. To reduce the re-admission rates, hospitals increasingly are utilizing home care services and CHF specialty clinics. This article highlights some of the recent advances in CHF evaluation and treatment to allow the primary care physician to become more familiar with current management to improve long-term outcomes and to better address the financial burden on the healthcare system.

—The Editor

Medical Advances in the Evaluation and Treatment of Heart Failure

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Introduction

Heart failure is a clinical syndrome that is characterized by the inability of the heart to meet the body's metabolic demands. (*See Table 1.*) This is attributed to either a functional or structural impairment of ventricular filling or ejection of blood. Patients manifest clinically with symptoms of low exercise tolerance and fluid retention.

Heart failure is a major public health problem in the western world. In the United States alone there are about 5 million Americans living with the diagnosis of heart

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failure. It is also estimated that another 550,000 Americans are diagnosed with this condition every year.[1] Heart failure accounts for about 15 million physician office visits every year.[2] It is the most common Medicare discharge diagnosis, accounting for more healthcare costs than any other condition in the United States.[3] The overall prevalence of heart failure is increasing. This increase has been attributed to the aging population and the advances in the treatment of coronary artery disease (CAD) that have led to more people surviving initial events of acute myocardial infarction.[4] Heart failure is primarily a disease of the elderly, as evidenced by the fact that 80% of the patients admitted with heart failure are older than 65 years.[5] The incidence of heart failure among people aged 65 years and older is about 10 per 1000 population.[1] The estimated direct and indirect cost of heart failure in the United States is $37.2 billion.[6]

Risk Factors

Hypertension is the most common risk factor for heart failure, followed by antecedent acute myocardial infarction (AMI).[7] Other risk factors include diabetes, metabolic syndrome, and dilated cardiomyopathy. (*See Table 2.*) Diabetes mellitus substantially increases the risk of developing heart failure, especially among post-menopausal women with established CAD. Heart failure incidence increases with each additional risk factor. For example, the annual incidence of heart failure among nondiabetic women with no risk factors is 0.4%. This risk increases to 3.4% in nondiabetic women with at least three risk factors. Among diabetic patients with no additional risk factors, the annual incidence of heart failure is 3.0%, compared with 8.2% among diabetics with at least three additional risk factors.[8] Dilated cardiomyopathy accounts for a substantial number of cases of heart failure. About one-third of patients with cardiomyopathy may have a genetic predisposition.[9] Thus, it may be important to screen family members of patients presenting with heart failure secondary to idiopathic cardiomyopathy.

Classification of Heart Failure

There are numerous ways of classifying heart failure and, in many cases, these categories overlap and may be ambiguous. The basis of these definitions has varied widely and has ranged from anatomical (right- vs left-sided heart failure), physiological (diastolic vs systolic), and, in some instances, clinical considerations (acute vs chronic). The World Health Organization (WHO) classification is based on myocardial disorder, i.e. ,dilated, hypertrophic, restrictive, arrhythmogenic right ventricular, and unspecified cardiomyopathies.[10] In recognition of the fact that heart failure is a progressive disorder, the American Heart Association (AHA) and American College of Cardiology (ACC) societies in collaboration have developed the staging criteria that take into account the development and progression of the disease. (*See Table 3.*) This classification has four stages: A through D. Stage A identifies patients who are at high risk for developing heart failure but have no structural abnormalities of the heart and have no symptoms of heart failure. These are patients who might have risk factors for developing heart failure, such as hypertension, diabetes, CAD, history of alcohol abuse, or exposure to cardiotoxins.

Executive Summary

- Common risk factors for congestive heart failure include hypertension, coronary artery disease, diabetes, obesity, and cardiomyopathy.
- Although brain natriuretic peptide correlates highly with symptoms of heart failure, other conditions such as advanced age, obesity, cirrhosis, and hypoxia also can increase values.
- ACE inhibitors are recommended in most patients with CHF but must be used in high doses to show reductions in mortality.
- Aldosterone antagonists have been shown to reduce mortality and hospital admissions in patients with NYHA class III or IV heart failure.
- Patients with advanced heart disease can have up to 50% one-year mortality, with half of these deaths being sudden.

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Table 1. Definition of Heart Failure

Heart failure is a clinical syndrome in which patients have the following features:
• **Symptoms of heart failure**
(Breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling) *and*
• **Signs typical of heart failure**
(Tachycardia, tachypnea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral edema, hepatomegaly) *and*
• **Objective evidence of a structural or functional abnormality of the heart at rest**
(Cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, raised natriuretic peptide concentration)

Reprinted with permission from: Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. *Eur Heart J* 2008;29:2388-2442: table 3.

Table 2. Risk Factors for Heart Failure

- Hypertension
- Coronary artery disease
- Diabetes
- Obesity
- Metabolic syndrome
- Use of cardiotoxins (illicit drug use)
- Family or personal history of cardiomyopathy
- Structural heart abnormalities (such as valvular abnormalities)

Table 3. Classification of Heart Failure (ACC/AHA)

STAGE A
At high risk for developing heart failure. No evidence of structural or functional abnormality. No signs or symptoms of heart failure.

STAGE B
Presence of structural heart disease without evidence of signs or symptoms.

STAGE C
Symptoms and signs of heart failure associated with underlying structural heart disease.

STAGE D
Advanced structural heart disease with marked symptoms of heart failure at rest despite maximal medical therapy.

Source: Hunt SA, et al. *Circulation* 2005;112:1825-1852.

Stage B includes patients with structural heart abnormalities but with no overt symptoms of heart failure. Patients in this stage might have left ventricular hypertrophy (LVH), reduced left ventricular ejection fraction (LVEF), valvular disease, and prior AMI but are asymptomatic.

Stage C includes patients who have all the factors in stages A and B, and in addition have symptoms of clinical heart failure. They not only have structural abnormality of the heart but also manifest clinical symptoms and signs of heart failure.

Stage D includes patients who are refractory to standard treatment of heart failure. These patients may require intravenous pressor agents, mechanical assist devices, heart transplant, or hospice care. In the ACC/AHA classification, patients can progress from one lower stage to a higher stage but never the reverse (i.e., from stage A to B, but never from B to A).

Another more clinically based classification is the New York Heart Association (NYHA) classification. This classification uses the presence or absence of symptoms of heart failure on functional capacity to classify severity of heart failure.[11] There are four classes in this classification: I through IV. (*See Table 4.*)

Causes of Heart Failure

The most common cause of heart failure in the western world is attributed CAD and often may be secondary to an AMI. CAD accounts for about 70% of the cases heart failure.[12] Heart failure also can result from nonischemic causes such as hypertension, cardiomyopathies, valvular disorders, pericardial disorders, or arrhythmias. See Table 5 for comprehensive list of etiologies of heart failure.

Pathophysiology

Numerous conceptual models have been proposed to explain heart failure; however, no single model effectively explains the complexity of the heart failure syndrome. Earlier models conceived heart failure as a result of excessive salt and water retention leading to poor renal flow (cardiorenal model).[13] Following this was the hemodynamic model that conceived heart failure as a problem of "pump failure" with resultant excessive peripheral vasoconstriction.[14] These models could not, however, explain the progression of heart failure once the original insult causing heart failure was removed. More recently, the neuro-hormonal model has attempted to explain the progression of heart failure as resulting from the effects of biochemical molecules released in response to injury of the heart.[15] These biomedical chemicals include catecholamines, through the activation of the adrenergic nervous system (ANS); and angiotensin II and aldosterone

Table 4. NYHA Functional Classification of Heart Failure

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

Source: New York Heart Association

Table 5. Causes of Heart Failure

CAUSE	COMMENTS
Ischemic heart disease	CAD is the most common cause
Valvular heart disease	Primary disorder is valve abnormality
Hypertension	Commonly due to LVH leading to diastolic dysfunction and not uncommonly systolic dysfunction.
Diabetes	Associated with diastolic/systolic failure
Infections	Viral myocarditis, bacterial endocarditis, and rheumatic fever are examples
Arrhythmias	Tachycardias such as atrial fibrillation
Metabolic causes	Hypo/hyperthyroidism, Paget's disease, hypophosphatemia
Systemic diseases	Connective tissue diseases such as systemic lupus erythematosus (SLE)
Toxin	Cocaine, alcohol, certain chemotherapeutic agents
Genetic disorder	Cardiomyopathies
Pregnancy	Post-partum cardiomyopathy

CAD = Coronary artery disease; LVH = Left ventricular hypertrophy

through the activation of the rennin-angiotensin-aldosterone system (RAAS). The mechanism by which injury to the heart progresses into overt heart failure is shown in Figure 1. With a reduction in cardiac output resulting from an insult on the heart (index event), compensatory mechanisms are set in motion with the goal of maintaining adequate cardiac output for tissue perfusion. An activated ANS and RAAS results in the over-expression of catecholamines, angiotensin II and aldosterone, respectively. These biochemical molecules have profound maladaptive effects on myocardial cells. Some of these effects include loss of myocytes, hypertrophy, and fibrosis of the myocardium (also known as remodeling). The overall result is that the heart configuration changes from the elliptical shape to a more spherical shape, which is hemodynamically less efficient for pumping out blood. Patients may be asymptomatic after the index event, but with persistence of these maladaptive changes, patients develop overt symptoms of heart failure. Therapeutic agents such as beta-blockers and angiotensin-converting enzyme inhibitors (ACEI) have been shown to improve survival in heart failure by ameliorating the effects of these maladaptive changes through directly acting on the ANS and RAAS, respectively.[16-18] This conceptual framework helps to explain the changes in the development of systolic dysfunction (heart failure with depressed ejection faction, less than 45%). However, the maladaptive changes in diastolic dysfunction (heart failure with preserved ejection fraction) are not very well understood.

Evaluation

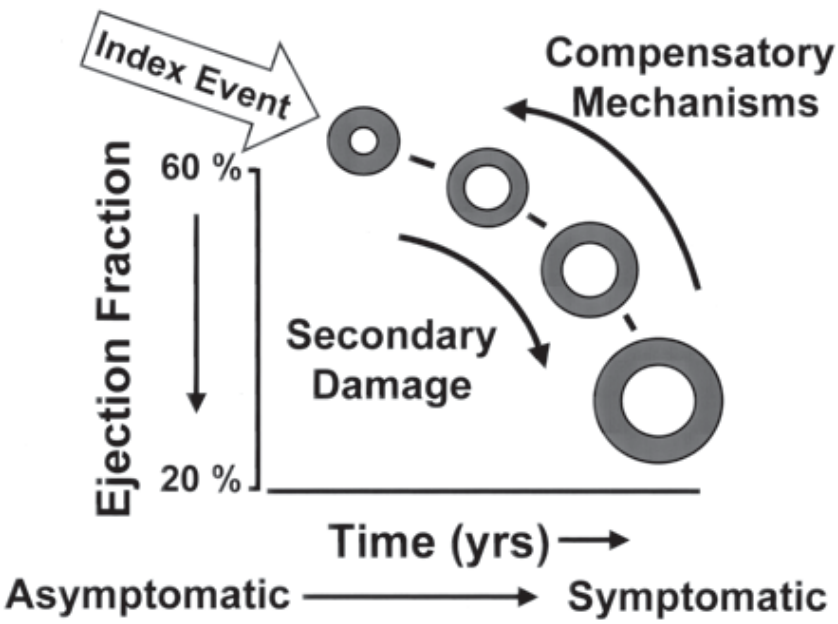
Evaluation of patients with heart failure begins with a thorough history and physical examination. A detailed history should elicit patients' risk factors or behaviors associated with the development and progression of heart failure. Direct inquiry about past or current history of CAD, congenital heart disease, valvular diseases, and illicit drug use may help point to etiology of heart failure. It is also important to establish the baseline functional status using the NYHA classification for future monitoring of therapy and progression of the disease.

Many tests routinely are used to evaluate patients with heart failure. Diagnostic tests usually are better at detecting heart failure with systolic dysfunction than heart failure with preserved systolic function. Laboratory evaluation should include tests that reveal disorders that will lead to or cause progression of heart failure. Initial studies should include urinalysis, complete blood count, basic metabolic profile, thyroid function tests, and lipid profile. (*See Table 6.*)

Other tests should include electrocardiogram (ECG). ECG may reveal rhythm abnormalities or signs of ischemia pointing to possible etiologies that may have precipitated or exacerbated heart failure.

Chest X-ray (CXR) allows the physician to assess pulmonary congestion as well as rule out other respiratory causes of shortness of breath. In chronic heart failure,

Figure 1. Pathogenesis of Heart Failure



Heart failure begins after an index event produces an initial decline in pumping capacity of the heart. After this initial decline in pumping capacity of the heart, a variety of compensatory mechanisms are activated, including the adrenergic nervous system, the renin-angiotensin system, and the cytokine system. In the short term, these systems are able to restore cardiovascular function to a normal homeostatic range, with the result that the patient remains asymptomatic. However, with time, the sustained activation of these systems can lead to secondary end-organ damage within the ventricle, with worsening LV remodeling and subsequent cardiac decompensation. As a result of resultant worsening LV remodeling and cardiac decompensation, patients undergo the transition from asymptomatic to symptomatic heart failure.

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about 20% of patients may not have pulmonary markings of congestion on CXR because of compensatory increase in lymphatic drainage of fluid.[19] One of the most useful diagnostic tests in evaluating heart failure is the 2-dimension echocardiogram (2-D Echo). This test noninvasively assesses the functional capacity of the cardiac chambers and the presence of structural abnormalities. It also establishes a baseline reference point for future comparison of heart failure progression. In special situations in which myocardial disease is suspected, such as myocarditis, cardiac magnetic resonance imaging (MRI) can be done to evaluate for this disorder.[20] Myocardial biopsy is now rarely performed in the diagnosis of heart failure except in patients with acute fulminant heart failure of unknown etiology with ventricular arrhythmias and/or atrioventricular conduction delays, or in patients suspected of having infiltrative processes such as amyloid, hemochromatosis, and restrictive cardiomyopathy of unknown etiology.

Patients presenting for the initial workup for heart failure should have CAD ruled out, as underlying ischemia is the most common etiology of heart failure.

More recently, serum assays of brain natriuretic peptide (BNP) and N-terminal pro BNP (NT-proBNP) have been shown to correlate highly with symptoms of heart failure, particularly in systolic dysfunction.[21] BNP is released from distended heart muscle as occurs in volume overload states. A number of patient factors besides heart failure can cause elevated levels. Factors that can elevate these serum assays include advanced age, obesity, liver cirrhosis, tachycardia, hypoxemia, and renal function.[22] A normal level of BNP in a patient not receiving treatment has a high negative predictive value for heart failure.

Therapy

Treatment of HF is linked to the ACC/AHA staging guidelines. One of the important aspects of treatment of heart failure is the recognition and treatment of risk factors that predispose to the development and progression of heart failure. These risk factors should be addressed adequately so as to mitigate the effects of the remodeling process in all the heart failure stages. Another therapeutic goal for stages C and D is to treat the disabling symptoms of heart failure.

Stage A. The goal of management of stage A heart failure is the prevention of progression of disease by treating risk factors. Adequately treated hypertension can lead to profound reduction in the incidence of heart failure. In some studies, optimally treating hypertension translated to as much as a 30-50% reduction in the development of left ventricular hypertrophy and heart failure.[23] Patients with diabetes and hypertension can be treated with ACEIs or ARBs to prevent the remodeling of the ventricles and subsequent progression of heart failure. Patients who smoke, drink alcohol, or use drugs are counseled to abstain from these risky behaviors.

Stages B, C, D. The goal of therapy for patients with these stages of heart failure is to decrease the progression of disease, improve symptoms, and minimize the risk factors for the development and progression of the disease. Some of the interventions include salt restrictions and avoidance of nonsteroidal anti-inflammatory drugs (which can cause fluid retention and worsening of heart

Table 6. Common Laboratory Tests in the Initial Evaluation of Heart Failure

LAB TEST	CLINICAL COMMENTS
Urinalysis	Rule out infections, proteinuria, glycosuria for diabetes
Complete blood count	Anemia can precipitate heart failure or can be a complication of infective endocarditis and other systemic diseases. High white blood cell count may indicate presence of infection.
Basic metabolic panel	Evaluate for hyperglycemia. Creatinine may indicate presence of renal failure and may necessitate heart failure therapy adjustment, i.e., ACEI/ARB or aldosterone blocker. Hypokalemia may be complication of diuretics.
Thyroid functioning test	Hyperthyroidism and hypothyroidism can both precipitate heart failure. Amiodarone therapy can complicate thyroid function.
Iron (Fe) studies	Anemia from iron deficiency can precipitate heart failure. Hemochromatosis is one cause of heart failure.
B-type natriuretic peptide	Elevated levels may make diagnosis of heart failure likely.
Elevated cardiac markers	May suggest the AMI in the setting of CAD as etiology of heart failure
Lipid profile	To guide the treatment of cardiovascular risk reduction
Liver function test	Elevated levels maybe seen hepatic congestion as a complication of heart failure.

failure).[24] There are also specific therapeutic agents that have been shown to have improved outcomes in patients with heart failure that should be considered. (*See Table 7.*)

ACE Inhibitors

The use of ACEIs is recommended for most patients with stages B, C, and D. These classes of medications have been shown to confer survival benefit to patients with heart failure, after myocardial infarction, and improve heart failure symptoms and reverse remodeling by blunting the activity of the RAAS.[25-27] The effects of these medications are not dose-dependent. The effects of low-dose ACEI on mortality have not been any different than in those patients taking high-dose regimens in most randomized clinical trials.[28-31]

Beta Blockers

Beta blockers have been shown to confer clinical benefits in patients with all stages of heart failure. The benefits that beta blockers confer include improved survival, reduced morbidity, improved quality of life, reduced rate of hospitalizations, improvement in remodeling, and reduced incidence of sudden cardiac death.[32-33] Studies have shown improvements in the systolic function and reversal of remodeling with just 3-4 months of treatment with beta blockers.[34-36] In some cases the improvement in mortality and hospitalization was seen as early as 14-21 days after initiation of therapy.[37] Beta blockers should be initiated when the patient is hemodynamically stable at low doses and titrated slowly over 2-4 weeks. Caution should be exercised in patients with hyperactive airways disease, bradyarrhythmias, and in patients known to be diabetics with frequent hypoglycemic episodes.

Angiotensin Receptor Blockers (ARBS)

ARBs block the effects of angiotensin II at the angiotensin II type 1 receptor site. ARBs are comparable but not superior to ACE inhibitors.[38-40] There are reports of increased adverse events in patients who were receiving a combination of ACEIs and ARBs.[41-42] ARBs, therefore, generally are recommended in patients who are not able to tolerate ACEIs due to cough and angioedema.

Aldosterone Antagonists

Aldosterone antagonists are another class of medications that have a beneficial role in heart failure.[43] Patients with heart failure have elevated levels of aldosterone, leading to salt and water retention. Aldosterone also works locally on the heart muscle to induce myocardial fibrosis and hypertrophy. Aldosterone antagonists counteract these effects, thereby inhibiting the remodeling process.[44] The addition of these agents in patients with advanced heart failure (NYHA class III or IV) has been shown in randomized controlled studies to improve mortality outcomes and hospital admissions for heart failure.[45] Patients on aldosterone antagonists must be monitored closely for serum potassium and creatinine. These medications generally are not started if the serum potassium is more than 5.0 mmol/L or the serum creatinine is more than 2.5 mg/dL.

Table 7. Commonly Used Drugs in Heart Failure

DRUG	DOSAGE RANGE	DRUG CLASS COMMENTS
ACEI		
Captopril	6.25 mg tid to 50 mg tid	Needs close monitoring of electrolytes and renal function.
Enalapril	2.5 mg bid to 10-20 mg bid	
Lisinopril	2.5-5 mg bid to 20-40 mg bid	Cough as side effect common.
Ramipril	1.25-2.5 mg qd to 10 mg qd	
Beta Blockers		
Carvedilol	3.125 mg bid to 25-50 mg bid	Can cause worsening of HF, bradycardia, hypotension, and bronchial spasms.
Bisoprolol	1.25 mg qd to 10 mg qd	
Metoprolol succinate	12.5-25 mg qd to 200 mg qd	
Digitalis Gycosides		
Digoxin	0.125 mg qd to 0.25 mg qd	Narrow therapeutic window, monitor levels in patients with renal disease, elderly and with hypokalemia. No benefit on survival but shown to have effect on morbidity.
Aldosterone Inhibitors		
Spironolactone	25 mg qd to 50 mg qd	Electrolytes and renal function should be monitored carefully, especially in patients taking concomitant ACEI.
Eplerenone	25 mg qd to 50 mg qd	
Angiotensin Receptor Blockers		
Candesartan	8 mg qd to 32 mg qd	As effective as ACEI. Use these agents if patient is not able tolerate ACEI due to cough or angioedema.
Irbesartan	75 mg qd to 300 mg qd	
Losartan	25 mg to 100 mg qd	
Valsartan	80 mg to 320 mg qd	

Diuretics

Diuretics are usually the initial medications administered to patients who are symptomatic (stage C and D heart failure). These medications are effective at reducing the pulmonary congestion and cardiac afterload.[46] The combination of loop diuretics with thiazide can be effective in optimizing diuresis in advanced cases.[47-48]

Digoxin

Digoxin can be used in symptomatic patients with low ejection fraction. It has been shown in randomized controlled studies to reduce hospitalization and improve heart failure symptoms. It does not affect survival outcomes, however.[49] It is important to monitor electrolytes and renal function in patients receiving digoxin to prevent toxicity. Low serum digoxin concentration (lower than 0.09 ng per milliliter) can be as effective as higher therapeutic ranges previously recommended in maintaining therapeutic response.[50] Digoxin also is beneficial in patients with concomitant atrial fibrillation and systolic dysfunction, as it can be used to control ventricular rate in patients with atrial fibrillation. Contraindications for digoxin include second- or third-degree heart block (without a permanent pacemaker), pre-excitation syndromes, and previous evidence of digoxin intolerance.

Hydralazine and Isosorbide Dinitrate

In patients with heart failure and systolic dysfunction who are unable to tolerate ACEIs or ARBs, a combination of hydralazine and isosorbide dinitrate could be considered. This combination therapy has been shown to reduce mortality and hospitalization and to improve quality of life.[51-53] Evidence of benefit is strongest in African-Americans. The medications must be titrated over a period of 2-4 weeks. This combination is contraindicated in patients with symptomatic hypotension, lupus syndrome, and severe renal failure.

Diastolic Heart Failure

Diastolic heart failure deserves special mention because of the high prevalence of this disorder; yet, there is still a paucity of outcome data from long-term randomized placebo-controlled trials. Most of the available data on the therapeutic interventions have been in heart failure with systolic dysfunction. Diastolic heart failure is defined by the presence of heart failure symptoms in a patient with

normal left ventricular ejection fraction and no valvular abnormalities on echocardiography.[54] Approximately 50% of patients with a diagnosis of heart failure have normal or preserved left ventricular function.[55] The prevalence of diastolic heart failure is highest in patients older than 75 years, and most often in women.[56] The preeminent problem in diastolic heart failure is the impaired ability of the ventricles to relax, leading to increased end-diastolic ventricular pressures in relation to a given ventricular blood volume. Thus with just a slight increase in blood volume, blood pressure, or even the presence of tachycardia in a patient with impaired ventricular relaxation could lead to substantial elevation of left atrial pressures and pulmonary edema manifesting with exercise intolerance. Treatment in the acute setting involves gentle diuresis as well as aggressively treating hypertension and controlling heart rate. However, long-term treatment strategies remain to be fully studied. Current treatment recommendations have been generally extrapolated from the interventions used in the treatment of heart failure with systolic dysfunction. The use of beta blockers, ACEIs, and calcium channel blockers generally is recommended in diastolic heart failure.[57-60] In the CHARM-preserved study, an angiotensin receptor blocker was associated with lower hospitalization and a non-statistically significant trend toward lower mortality.[61]

Non Pharmacological Therapies

There are nonpharmacological approaches to treatment of some patients with heart failure. All patients with heart failure must be evaluated and treated for CAD. Angioplasty and surgical revascularization can lead to improvement of ischemic symptoms and ejection fraction, and can reduce the incidence of sudden death.[62] Some patients with stage C and D heart failure may benefit from bypass surgery. Some studies are looking at the role of surgical procedures designed for the treatment of heart failure. Some of these procedures include mitral valve repair, mechanical devices to reduce wall stress, and surgical excision of infarcted tissue.[63-65] Mechanical devices for stage D patients may provide a bridging gap modality in patients awaiting heart transplantation or even those patients who are not candidates for transplant surgery.[65] Cardiac resynchronization therapy with biventricular pacers has been shown to be effective in the treatment of patients with heart failure and left bundle branch blocks on a 12-lead electrocardiogram. These devices have been shown to improve exercise tolerance and quality of life and to reduce the rate of hospitalizations. Resynchronization therapy also been to shown to reverse the remodeling effects and improve the ejection fraction of the heart.[66-69]

Sudden Cardiac Death

Patients with heart failure are at an increased risk of sudden cardiac death.[70] Sudden death usually results from ventricular tachyarrhythmias. Sudden death resulting from cardiac causes accounts for about 50% of all cardiovascular deaths.[71] Patients with advanced heart disease such as those with systolic dysfunction and NYHA class III or IV may have up to 50% one-year mortality, with half of these deaths being sudden.[72] Patients with severe systolic dysfunction presenting with syncope, for instance, may need to be referred for electrophysiological testing for inducible arrhythmias and possible insertion of mechanical devices.

Summary

Heart failure is a debilitating progressive disease that has severe morbidity and mortality. The prevalence of heart failure is increasing because of the aging population. Physicians must work toward incorporating evidence-based therapies that have been known to decrease morbidity and mortality in heart failure. A promising report from the Framingham study showed that there was increased survival with the diagnosis of heart failure.[73] Despite this, evidence shows that treatment of heart failure is less than optimal.[74] In keeping with the recent classification of heart failure by the ACC/AHA, physicians must focus on identifying and treating those patients with risk factors to prevent heart failure from developing.

References

1. American Heart Association. Heart Disease and Stroke Statistics: 2005 Update. Dallas, TX: American Heart Association; 2005.
2. O'Connell JB, Bristow MR. Economic impact of heart failure in the United States: Time for a different approach. *J Heart Lung Transplant* 1994;13:S107-S112.
3. Massie BM, Shah NB. Evolving trends in the epidemiologic factors of heart failure: Rationale for preventive strategies and comprehensive disease management. *Am Heart J* 1997;133:703-712.
4. Senni M, Tribouilloy CM, Rodeheffer RJ, et al. Congestive heart failure in the community: Trends in incidence and survival in a 10-year period. *Arch Intern Med* 1999;159:29-34.
5. Masoudi FA, Havranek EP, Krumholz HM. The burden of chronic congestive heart failure in older persons: Magnitude and implications for policy and research. *Heart Fail Rev* 2002;7:9-16.
6. Centers for Medicare & Medicaid Services. Health Care Financing Review: Medicare & Medicaid Statistical Supplement. Table 5.5: Discharges, Total Days of Care, and Program Payments for Medicare Beneficiaries Discharged from Short-Stay Hospitals, by Principal Diagnoses Within Major Diagnostic Classifications (MDCs): Calendar Year 2006. Baltimore, MD: Centers for Medicare and Medicaid Services; 2005. Available at: http://www.cms.hhs.gov/MedicareMedicaid StatSupp.

7. Levy D, Larson MG, Vasan RS, et al. The progression from hypertension to congestive heart failure. *JAMA* 1996;275: 1557-1562.
8. Bibbins-Domingo K, Lin F, Vittinghoff E, et al. Predictors of heart failure among women with coronary disease. *Circulation* 2004;110:1424-1430.
9. Francis GS, Pierpont GL. Pathophysiology of congestive heart failure secondary to congestive and ischemic cardiomyopathy. *Cardiovasc Clin* 1988;19:57-74.
10. Richardson P, McKenna W, Bristow M, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies. *Circulation* 1996;93: 841-842.
11. Gibelin P. An evaluation of symptom classification of systems used for the assessment of patients with heart failure in France. *Eur J Heart Fail* 2001;3:739.
12. Fox KF, Cowie MR, Wood DA, et al. Coronary artery disease as the cause of incident heart disease in the population. *Eur Heart J* 2001;22;228-236.
13. Packer M. The neurohormonal hypothesis: A theory to explain the mechanism of disease progression in heart failure. *J Am Coll Cardiol* 1992;20:248-254.
14. Mann D, Bristow MR. Mechanisms and models in heart failure: The biomechanical model and beyond. *Circulation* 2005;111:2837-2849.
15. Bristow MR. The adrenergic nervous system in heart failure. *N Engl J Med* 1984; 311:850-851.
16. Currie PJ, Kelly MJ, McKenzie A, et al. Oral beta-adrenergic blockade with metoprolol in chronic severe dilated cardiomyopathy. *J Am Coll Cardiol* 1984;3:203-209.
17. Ikram H, Fitzpatrick D. Double-blind trial of chronic oral beta blockade in congestive cardiomyopathy. *Lancet* 1981;2: 490-493.
18. Foult JM, Tavolaro O, Antony I, et al. Coronary vasodilation induced by intracoronary enalaprilat: An argument for the role of a local renin-angiotensin system in patients with dilated cardiomyopathy. *Eur Heart J* 1989;10(suppl F):97-100.
19. Stevenson LW, Perloff JK. The limited reliability of physical signs for estimating hemodynamics in chronic heart failure. *JAMA* 1989;261:884-888.
20. De Cobelli F, Pieroni,M, Esposito A. Delayed gadolinium-enhanced cardiac magnetic resonance in patients with chronic myocarditis presenting with heart failure or recurrent arrhythmias. *J Am Coll Cardiol* 2006;47:1649-1654.
21. Maisel A. B-type natriuretic peptide levels.a potential novel "white count" for congestive heart failure. *J Card Failure* 2001;7:183-193.
22. Weinfeld MS,Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. *Am Heart J* 1999;138:285-290.
23. Mosterd A, D'Agostino RB, Silbershatz H, et al. Trends in the prevalence of hypertension, antihypertensive therapy, and left ventricular hypertrophy from 1950 to 1989. *N Engl J Med* 1999;340:1221-1227.
24. Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: An underrecognized public health problem. *Arch Intern Med* 2000;160: 777-784.
25. Munzel T, Keaney JF Jr. Are ACE inhibitors a "magic bullet" against oxidative stress? *Circulation* 2001;104:1571-1574.
26. Khalil ME, Basher AW, Brown EJ Jr, et al. A remarkable medical story: Benefits of angiotensin-converting enzyme inhibitors in cardiac patients. *J Am Coll Cardiol* 2001;37:1757-1764.
27. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA* 1995;273:1450-1456. [Erratum, *JAMA* 1995;274:462.]
28. Gullestad L, Aukrust P, Ueland T, et al.Effect of high- versus low-dose angiotensin converting enzyme inhibition on cytokine levels in chronic heart failure. *J Am Coll Cardiol* 1999;34:2061-2067.
29. Nanas JN, Alexopoulos G, Anastasiou-Nana MI, et al. Outcome of patients with congestive heart failure treated with standard versus high doses of enalapril: A multicenter study. *J Am Coll Cardiol* 2000;36:2090-2095.
30. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation* 1999;100:2312-2318.
31. Tang WH, Vagelos RH, Yee YG, et al. Neurohormonal and clinical responses to high- versus low-dose enalapril therapy in chronic heart failure. *J Am Coll Cardiol* 2002;39:70-78. [Erratum, *J Am Coll Cardiol* 2002;39:746.]
32. Foody JM, Farrell MH, Krumholz HM. Beta-blocker therapy in heart failure: Scientific review. *JAMA* 2002;287:883-889.
33. Farrell MH, Foody JM, Krumholz HM. Beta-blockers in heart failure: Clinical applications. *JAMA* 2002;287:890-897.
34. Bristow M. Beta-adrenergic receptor blockade in chronic heart failure. *Circulation* 2000;101;558-569.
35. Groenning B, Nilsson J, Sondergaard L, et al. Antiremodeling effects on the left ventricle during beta-blockade with metoprolol in the treatment of chronic heart failure. *J Am Coll Cardiol* 2000,36:2072-2080.
36. Hall S, Cigarroa C, Marcoux L, et al. Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade. *J Am Coll Cardiol* 1995;25;1154-1161.
37. Krum H, Roecker EB, Mohacsi P, et al. Effects of initiating carvedilol in patients with severe chronic heart failure:results from the COPERNICUS study. *JAMA* 2003;289:712-718.
38. Cohn J N, Tognoni G; Valsartan heart failure trial investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345: 1667-1675.
39. McMurray JJ, Pfeffer MA, Swedberg K, et al. Which inhibitor of the rennin angiotensin system should be used in chronic

heart failure and left ventricular systolic dysfunction:results of the CHARM low left ventricular ejection fraction trials. *Circulation* 2004;110:2618-2626.
40. Pitt B, Poole-Wilson PA, Segal R, et al. Effects of losartan compared with captopril on mortality in patients with symptomatic heart failure: Randomised trial — the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000;355: 1582-1587.
41. Baruch L, Anand I, Cohen IS, et al. Augmented short- and long-term hemodynamic and hormonal effects of an angiotensin receptor blocker added to angiotensin converting enzyme inhibitor therapy in patients with heart failure. Vasodilator Heart Failure Trial (V-HeFT) Study Group. *Circulation* 1999;99:2658-2664.
42. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: The CHARM-Added trial. *Lancet* 2003;362:767-771.
43. McMurray JJ, O'Meara E. Treatment of heart failure with spironalactone-trial and tribulations. *N Eng J Med* 2004;351: 526-528.
44. Weber KT. Aldosterone in congestive heart failure.*N Eng J Med* 2001;345:1689-1697.
45. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341:709-717.
46. Faris R, Flather M, Purcell H, et al. Current evidence supporting the role of diuretics in heart failure: A meta analysis of randomized control trials. *Int j Cardiol* 2002;82:149-158.
47. Ellison D. Diuretic drugs and the treatment of edema: From clinic to bench and back again. *Am J Kidney Dis* 1994;23: 623-43.
48. Brater DC. Diuretic therapy. *N Engl J Med* 1998;339:387-395.
49. [No authors listed.] The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;336:525-533.
50. Adams KF, Gheorghiade M, Uretsky BF, et al. Clinical benefits of low serum digoxin concentrations in heart failure. *J Am Coll Cardiol* 2002;39:946-953.
51. Cohn JN, Johnson G, Ziesche, et al. A comparison of enalpril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325: 303-310.
52. Taylor AL, Ziewsche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004;351:2049-2057.
53. Loeb HS, Johnson G, Henrick A, et al. Effect of enalapril, hydralazine plus isosorbide dinitrate and prazosin on hospitalization in patients with chronic congestive heart failure. The V-Heft VA cooperative studies group. *Circulation* 1993; 87(6suppl):V178-V187.
54. Hunt SA, Baker DW, Chin MH, et al. Guidelines for the evaluation and management of chronic heart failure in the adult: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 2001;38:2101-2113. Accessed August 16, 2004, at www.acc.org/clinical/guidelines/failure/VI_diastolic.htm.
55. Vasan R, Benjamin E, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: An epidemiologic perspective. *J Am Coll Cardiol* 1995;26:1565-1574.
56. Gaasch WH, Zile MR. Left ventricular diastolic dysfunction and diastolic heart failure. *Ann Rev Med* 2004;55:373-394.
57. Aronow WS, Kronzon I. Effect of enalapril on congestive heart failure treated with diuretics in elderly patients with prior myocardial infarction and normal left ventricular ejection fraction. *Am J Cardiol* 1993;71:602-604.
58. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction > or = 40% treated with diuretics plus angiotensin-converting enzyme inhibitors. *Am J Cardiol* 1997;80:207-209.
59. Setaro JF, Zaret BL, Schulman DS, et al. Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. *Am J Cardiol* 1990;66:981-986.
60. Warner JG, Metzger DC, Kitzman DW, et al. Losartan improves exercise tolerance in patients with diastolic dysfunction and a hypertensive response to exercise. *J Am Coll Cardiol* 1999;33:1567-1572.
61. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: The CHARM-Preserved Trial. *Lancet* 2003;362:777-781.
62. Baumgartner WA. What's new in cardiac surgery. *J Am Coll Surg* 2001;192:345-355.
63. Raman JS, Hata M, Storer M, et al. The mid-term results of ventricular containment (ACORN WRAP) for end-stage ischemic cardiomyopathy. *Ann Thorac Cardiovasc Surg* 2001;7:278-281.
64. Bishay ES, McCarthy PM, Cosgrove DM, et al. Mitral valve surgery in patients with severe left ventricular dysfunction. *Eur J Cardiothorac Surg* 2000;17:213-221.
65. Starling RC, McCarthy PM, Buda T, et al. Results of partial left ventriculectomy for dilated cardiomyopathy: Hemodynamic, clinical, and echocardiographic observations. *J Am Coll Cardiol* 2000;36:2098-2103.
66. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;344:873-880.
67. Auricchio A, Stellbrink C, Block M, et al. Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. *Circulation* 1999;99:2993-3001.

68. Kerwin WF, Botvinick EH, O'Connell JW, et al. Ventricular contraction abnormalities in dilated cardiomyopathy: Effect of biventricular pacing to correct interventricular dyssynchrony. *J Am Coll Cardiol* 2000;35:1221-1227.
69. Stellbrink C, Breithardt O-A, Franke A, et al. Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. *J Am Coll Cardiol* 2001;38:1957-1965.
70. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: Epidemiology, transient risk, and intervention assessment. *Ann Intern Med* 1993;119:1187-1197.
71. Myerburg RJ, Interian A Jr, Mitrani RM, et al. Frequency of sudden cardiac death and profiles of risk. *Am J Cardiol* 1997;80:10F-19F.
72. Pye MP, Cobbs SM. Mechanisms of ventricular arrhythmias in cardiac failure and hypertrophy. *Cardiovas Res* 1992; 26:740-750.
73. Levy D, Kenchaiah S, Lasron M, et al. Long-term trends in the incidence of and survival with heart failure. *N Eng J Med* 2002;347:1397-1402.
74. Cleland JG, Cohen-Solal A, Aguilar JC, et al; IMPROVEMENT of Heart Failure Programme Committees and Investigators. Improvement programme in evaluation and management; Study Group on Diagnosis of the Working Group on Heart Failure of The European Society of Cardiology. Management of heart failure in primary care (the IMPROVEMENT of heart failure programme): An international survey. *Lancet* 2002;360:1631-1639.

Physician CME Questions

5. A patient presents with no symptoms of heart failure but has a long-standing history of hypertension and is noted to have left ventricular hypertrophy on echocardiography. Which ACC/AHA classification stage of heart failure does he have?
   A. stage A
   B. stage B
   C. stage C

Primary Care Reports

CME Objectives

Upon completion of this educational activity, participants should be able to:

• summarize recent, significant studies related to the practice of primary care medicine;

• evaluate the credibility of published data and recommendations related to primary care medicine;

• discuss the advantages and disadvantages of new diagnostic and therapeutic procedures in the primary care setting.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge.

To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a credit letter. When your evaluation is received, a credit letter will be mailed to you.

D. stage D

6. All of the following combinations of medication have been shown to reduce mortality in patients with heart failure *except*:
   A. ACEIs and beta blockers
   B. hydralazine-isorsobide dinitrate
   C. digoxin and a diuretic
   D. ARBs and beta blockers

7. A 70-year-old man with a prior history of hypertension was recently diagnosed with stage B heart failure. His echocardiogram showed an ejection fraction of 40%. He was started on an ACEI in addition to a beta blocker for optimal management of his heart failure. Two weeks after discharge from the hospital, he developed a dry irritating cough. He has no signs of fluid overload. What should be the next step?
   A. Start diuretic therapy.
   B. Stop ACEI and start an ARB.
   C. Add an aldosterone antagonist.
   D. Start digoxin.

8. A 65-year-old active white male with a history of heart failure with ejection fraction of 30% presents with a history of passing out while at home. The episode was witnessed by his wife, who reports that he suddenly collapsed while sitting in the chair watching TV. He was admitted and worked up for the passing out episode. His cardiac and neurology workup were normal except for a left bundle branch block that he has on ECG, which has been present for 2 years. His medication includes an ACEI, a beta blocker, and aspirin. What would be the best option of management for this patient?
   A. Reassure him and discharge home.
   B. Refer him for electrophysiologist for evaluation.
   C. Restrict his physical activity.
   D. Stop his beta-blocker therapy.

9. All of the following conditions may cause an elevated brain natriuretic peptide level *except*:
   A. cirrhosis of the liver
   B. renal failure
   C. stroke
   D. obesity

CME Answer Key

5. B
6. C
7. B
8. B
9. C

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Prevention of diabetes: The long-term outlook

Source: Diabetes Prevention Program Research Group; et al. *Lancet* 2009;374:1677-1686.

NUMEROUS RANDOMIZED CLINICAL trials show that a variety of interventions can prevent the development of type 2 diabetes (DM2) in subjects with prediabetes (i.e., impaired glucose tolerance, defined as a 2-hour post-load glucose of 140-199 mg/dL). Lifestyle interventions (i.e., intensive diet and exercise programs) are generally at least as effective as pharmacotherapy (e.g., metformin, rosiglitazone, orlistat). Some experts quibble with the term "prevent," preferring instead to indicate that our prediabetes interventions simply "delay" diabetes. Since persons at high risk for DM2 are likely to remain in a high-risk group indefinitely, the long-term picture of interventions to prevent DM2 is important.

The Diabetes Prevention Program (DPP) was one of the largest diabetes prevention trials ever performed. At 2.8 years, incidence of DM2 was reduced 58% with lifestyle, and 31% with metformin (compared to placebo). A recent report by the Diabetes Prevention Program Research Group provides a window of insight into data 10 years from the date of randomization.

Compared to placebo, subjects in the lifestyle intervention group had a 34% reduction in new onset DM2; the metformin group had an 18% risk reduction.

Follow-up of subjects enrolled in the DPP indicates a long-term risk reduction in development of DM2 attained with lifestyle or metformin intervention. Whether you call it prevention or delay, less DM2 at 10 years is a good thing. ■

Does it matter how we lower LDL?

Source: Taylor AJ, et al. *N Engl J Med* 2009;361:2113-2122.

BASED UPON A PRESUMED DIRECT relationship between LDL lowering and reduction in CV events for persons with vasculopathy, many clinicians enthusiastically embraced the combination of ezetimibe (EZT) and statins, especially when therapeutic LDL goals were difficult to attain with a statin alone. After the ENHANCE trial, which questioned the ability of EZT to effectively regress carotid atherosclerosis, clinicians began to rethink the issue, fueled additionally by disappointing data from trials of torceptrapib, an HDL-raising drug, which not only did not reduce CV events, but actually worsened CV risk, and was subsequently withdrawn from consideration for FDA approval.

A single clinical trial, the Coronary Drug Project, showed CV risk reduction with niacin in long-term follow-up. Because of adverse effects that limit more universal use of niacin, agents that were much better tolerated (like EZT) appeared to be a more suitable choice.

A clinical trial was performed to evaluate the comparative efficacy of extended-release niacin with EZT in persons with known coronary disease or with a CHD risk equivalent (e.g., DM). All subjects were already on a statin and had achieved an LDL < 100 mg/dL. Over 14 months, the performance of niacin to regress carotid intima-media thickness was significantly greater than EZT. Indeed, the incidence of CV events was significantly lower in the niacin group also (1% vs 5%).

Although EZT is effective in reducing LDL, it has not been shown to have a favorable effect upon CV or vascular surrogate endpoints; hence, its use must be reconsidered. ■

Identifying risk factors for falls in seniors

Source: Leveille SG, et al. *JAMA* 2009;302:2214-2221.

AMONG OLDER ADULTS, FALLS REMAIN in the top 10 causes of death. Risk factors for falls include vitamin D status, cognitive status, physical decline, and mobility impairment. The epidemiologic magnitude of fall risk has motivated the search for other risk factors.

Leveille et al studied a population of community-dwelling senior citizens (age > 70 years) in the greater Boston area. Each participant (n = 749) was assessed for chronic pain, and reassessed on a monthly basis for 18 months. During this interval, subjects reported 1029 falls.

Subjects were stratified into pain scores by tertile. Most pain syndromes were associated with disorders like osteoarthritis, and included individuals with a single painful area as well as multiple symptomatic sites.

There was a linear relationship between pain scores and risk for falls. Subjects with two or more painful sites had approximately 20% greater risk of falls when compared to persons without pain. Although one might think that analgesic use prompted by joint pain might explain a greater incidence of

falls, such a relationship was not demonstrable in this population.

Why pain is associated with falls is uncertain. Perhaps pain leads to deconditioning, leading to falls. There is also some support for cognitive effects of chronic pain that might lead to lesser executive alacrity, impairing the ability to respond to precipitants of a fall. It remains to be shown whether superior pain control will reduce fall risk. ■

Resistance vs aerobic exercise and COPD

Source: O'Shea S, et al. *Chest* 2009; 136:1269-1283.

COPD IS CURRENTLY THE 4TH MOST common cause of death in the United States. Other than smoking cessation, only oxygen therapy in late-stage disease has been shown to modify disease. Pharmacotherapy provides improvements in symptoms and pulmonary function tests, but has not been shown to alter disease progression.

Physical deconditioning is commonplace in COPD. Indeed, the pathologic phenomenon seen in COPD of dynamic hyperinflation — an even greater diminution in ability to utilize expiratory reserve during exercise than at rest — helps explain why COPD patients may lack enthusiasm for aerobic exercise. Resistance exercise trials indicate that COPD patients can improve muscle strength, but whether such improvements translate into incremental symptomatic benefit or ability to participate in activities of daily living is uncertain.

O'Shea et al performed a meta-analysis of 18 controlled trials employing progressive resistance exercises for COPD patients. The data show some benefits of resistance exercise in ability to rise from a sitting position and climb stairs; however, trials comparing aerobic training vs resistance training indicated more favorable outcomes for activities like cycling, and that resistance training added to aerobic training provides little if any additional benefit. Finally, studies that indicated resistance training benefits for activities of daily living were ranked as having higher risk of bias. More studies specifically addressing the effects of resistance training upon functionality in COPD are needed. ■

Breast cancer outcomes and soy intake

Source: Shu XO, et al. *JAMA* 2009;302: 2437-2443.

ESTROGEN (EST) IS FELT TO PLAY A role in the development of breast cancer (BCA), and modulation of estrogen is utilized as a treatment for BCA. Soy foods contain a large amount of phytoestrogens, which impact natural estrogen receptors. Soy components have also been shown to possess anticancer effects. Ultimately, whether dietary soy affects important outcomes like survival or progression of disease among subjects with cancers that may be estrogen-sensitive — like BCA — is critical to ascertain.

Shu et al studied data from the Shanghai Breast Cancer Survival Study, which provides a population of Chinese breast cancer survivors (n = 5042). After approximately 4 years of follow-up, the relationship between soy intake and BCA recurrence, overall mortality, and BCA-related deaths was evaluated. There was a consistent, linear, and inverse relationship between soy intake and mortality and BCA recurrence. When compared with persons in the lowest quartile of soy intake, those in the highest quartile enjoyed a 29% lower relative risk of mortality, and a 32% lower risk of BCA recurrence.

The relationship between soy intake and favorable outcomes was not altered by estrogen receptor-positive or -negative status or tamoxifen use.

Average soy intake in U.S. women (1-6 mg/day) is markedly less than Chinese women (47 mg/d). Whether incremental dietary soy increases in the U.S. population will translate into risk reduction has not been determined. ■

Oxygen therapy for cluster headache

Source: Cohen A, et al. *JAMA* 2009; 302:2451-2457.

THE PAIN OF CLUSTER HEADACHE (CLUS) is among the most severe of any clinical syndrome. The advent of triptans, especially sumatriptan injection, has restructured the landscape of CLUS management, since SQ sumatriptan has been shown to provide effective CLUS pain relief within 15 minutes. Unfortunately, since some patients with CLUS have multiple attacks per day, for multiple days, triptan dosing limitations preclude use in these high-frequency sufferers. Additionally, CLUS patients with CAD are unable to use triptans.

Another first-line CLUS treatment is high-flow oxygen (OXY). Advantageous aspects of oxygen treatment include its low adverse-effect profile, ability to be combined with other treatments, and applicability for multiple attacks within a short time frame. Despite commonplace clinical use, trial data on OXY are quite limited.

Cohen et al performed a randomized placebo-controlled study to compare 100% oxygen vs room air (both delivered at 12 L/min for 15 minutes). Study participants (n = 109) were followed for 5 years, with instructions to treat at least 4 attacks of CLUS with either OXY or placebo (room air). All subjects received indistinguishable separate tanks of 100% oxygen and room air, and were instructed to alternate tanks for sequential CLUS episodes in their home.

The primary endpoint of the study was percent of individuals pain-free at 15 minutes. OXY was much superior to air (78% vs 20% pain free). Randomized, placebo-controlled confirmation of our clinical practice supports continued appropriateness of OXY for CLUS. ■

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Dabigatran: An Oral Direct Thrombin Inhibitor

In this issue: Results from a Phase 3 study of dabigatran, intensive lipid-lowering in CVD, H1N1 vaccine dosing and efficacy, and FDA Actions.

Anticoagulation without monitoring?

Dabigatran is an oral direct thrombin inhibitor, currently being used in many countries as an alternative to warfarin. It is anxiously awaited in this country primarily because, unlike warfarin, it does not require monitoring with blood tests. The drug has been shown to be as effective as warfarin in preventing stroke in patients with atrial fibrillation (*N Engl J Med* 2009;361:1139-1151).

A new study published in December 2009 compares the two drugs in the treatment of acute venous thromboembolism. In a randomized, double-blind, non-inferiority trial, patients with acute venous thrombus embolism were given a median of 9 days of parenteral anticoagulation therapy, then were randomized to oral dabigatran (150 mg twice a day) or warfarin that was dose-adjusted to achieve an INR of 2.0-3.0. The primary outcome was 6-month incidence of recurrent symptomatic, objectively confirmed venous thromboembolism and related deaths. Of the patients randomized to receive dabigatran, 2.4% had recurrent venous thromboembolism compared to 2.1% of patients on warfarin (difference in risk of 0.4%; 95% confidence interval [CI], -0.8 to 1.5; $P < 0.001$ for the prespecified non-inferiority margin). Major bleeding episodes occurred in 1.6% of patients on dabigatran vs 1.9% of patients on warfarin. Episodes of any bleeding were 16.1% with dabigatran and 21.9% with warfarin. There was no difference in the number of deaths, acute coronary syndromes, or abnormal liver function tests between the two groups. Treatment was discontinued due to adverse events in 9% of patients on dabigatran and 6.8% of patients on warfarin. The authors concluded that for treatment of acute venous thromboembolism, a fixed dose of dabigatran is as effective as warfarin, has similar safety, but does not require laboratory monitoring (*N Engl J Med* 2009;361:2342-2352).

Physicians and patients alike in the United States have been awaiting an orally effective anticoagulant that doesn't require monitoring. Dabigatran, a direct thrombin inhibitor, may soon fill that role. The drug, which has the additional advantage of having minimal drug and food interactions, has been available in Canada and Europe for almost 2 years, and with the completion of Phase 3 trials such as this one, there is speculation the FDA may take action this year. ■

Intensive lipid-lowering and CVD

Follow-up analysis of two of the most famous lipid-lowering trials confirms that intensive lipid-lowering therapy continues to be beneficial in the longer term. The PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) trial, first published in 2004,

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compared moderate lipid-lowering using standard-dose pravastatin to intensive lipid-lowering with high-dose atorvastatin after acute coronary syndrome. The study showed high-dose therapy significantly reduced the occurrence of death, myocardial infarction, stroke, and unstable angina requiring hospitalization or revascularization occurring more than 30 days after the event. The new post-hoc analysis (*J Am Coll Cardiol* 2009; 54:2358-2362) followed patients for up to 2 years and showed continued benefit in reduction of the primary endpoint (16%; P = 0 .005) with high-dose therapy, as well as reduction of additional events (19%; P = 0.009).

The IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) study compared high-dose atorvastatin with usual dose simvastatin for the prevention of events subsequent to a first event. The study was published in 2005, and while not showing reduction in mortality in the 4.8 years of study, it did show a reduction in secondary cardiovascular outcomes with high-dose therapy. The new analysis looked at not only time to first event, but also second, third, fourth, and fifth events. High-dose therapy significantly reduced subsequent events by 17%-28%. The authors concluded that continued intensive statin therapy continues to be more effective than standard statin therapy, even beyond the first vascular event (*J Am Coll Cardiol* 2009;54:2353-2357).

Both these studies suggest that staying the course with intensive lipid-lowering in patients with cardiovascular disease is an effective long-term strategy. ■

H1N1 dosing and efficacy

Three recent studies in the Dec. 17, 2009, *New England Journal of Medicine* confirm that a single dose of the H1N1 vaccine is effective for most healthy adults and children age 3 and older. In the first study, 240 patients were equally divided to receive 15 µg or 30 µg of hemagglutinin antigen by IM injection. By day 21, antibody titers of 1:40 were observed in 95.0% of patients who received the 15 µg dose and 89.1% of patients who received the 30 µg dose (*N Engl J Med* 2009;361:2405-2413).

In the second study from China, antibody titers were done at 21 days after a first injection of 15 µg with or without adjuvant. A titer of 1:40 was achieved in 75% of subjects between age 3 and 11, 97.1% of subjects between age 12 and 17, 97.1% of subjects between age 18 and 60, and 79.1% of subjects age 61 and older. Alum adjuvant did not significantly raise antibody titers. Although a second injection at 21 days raised antibody titers, the authors conclude that a single dose of 15 µg induced a typically protective antibody response in the majority of subjects between age 12 and 60 (*N Engl J Med* 2009;361:2414-2423).

In the third study, standard H1N1 vaccine was compared to a MF59-adjuvanted vaccine (derived from cell culture rather than egg-based). A number of injection schedules were tested. Local reactions and muscle aches were more frequent in the MF59-adjuvanted vaccine. Although higher antibody titers were seen with the adjuvanted vaccine, significant titers were also seen within non-adjuvanted vaccine within 2-3 weeks (*N Engl J Med* 2009;361:2424-2435).

These findings confirm data previously published in the *Lancet* in the fall of 2009 confirming that one dose of the H1N1 vaccine seems adequate, although two doses may be required for younger children. Currently, the Centers for Disease Control and Prevention (CDC) recommends two doses for children younger than age 10, but the recommendations may change based on these findings.

In related news, the CDC is reporting that safety data regarding the H1N1 vaccine is "reassuring," with a rate of serious complications such as Guillain-Barré syndrome no higher than "background rates." The rate of adverse event reporting has been higher with the H1N1 vaccine compared to seasonal flu; however, most of these reports have been for mild reactions and may be attributed to the higher rate of awareness associated with the new vaccine. ■

FDA Actions

The FDA has approved the first generic version of donepezil (Aricept®) for the treatment of Alzheimer's disease. The new generic will be marketed as 5 mg and 10 mg orally disintegrating tablets, which dissolve on the tongue and do not need to be swallowed. Generic donepezil is expected to be available later this year. ■

An FDA advisory panel is recommending expansion of the indication for rosuvastatin (Crestor®) to include patients with normal cholesterol levels and no history of cardiovascular disease. The recommendation is based on the JUPITER trial, which showed a reduction in cardiovascular risk in patients with normal LDL cholesterol but high C-reactive protein who were treated with rosuvastatin. ■