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THE TREATMENT OF HEART FAILURE

Introduction

Heart failure is a progressive and complex clinical disease. When heart failure is left untreated or under treated, it may become fatal.[1] This disease is developed secondary to any cardiac abnormality that impedes the heart's ability to fill and/or empty. Diastolic and systolic dysfunctions are characterized by elevated end-diastolic pressure in a normal-size chamber and a reduced ejection fraction (EF) respectively. Symptoms of heart failure include shortness of breath (on exertion or at rest in advanced diseased state), orthopnea, paroxysmal nocturnal dyspnea, nocturia, mental status changes, anorexia and abdominal pain.[1]

Heart failure affects 4.8 million Americans, with approximately 400,000 to 700,000 new patients diagnosed each year.[1] This is approximately 1.5 to 2% of the population. There are as many as 20 million Americans with asymptomatic cardiac impairment. Americans greater than 65 years have a higher prevalence of developing heart failure and this trend is expected to rise as the population ages.[1]

Mortality from heart failure has increased six-fold over the last 40 years. The risk of death in patients with mild symptoms is 5% to 10% in twelve months but increases to 30% to 40% in patients with advanced disease. The annual direct cost of heart failure in terms of medications, hospitalizations, nursing home admissions, and medical follow-ups are estimated at $20 to $40 billion.[1]

The objective of this newsletter is to clarify which medications should be used, and in what sequence or combination, for the management of heart failure.

Pathophysiology

The pathophysiology of heart failure is complex, with 80-90% of cardiomyopathy patients exhibiting symptoms due to left ventricular dysfunction (LVD).[2] A depressed left ventricular EF, usually less than 40%, is the principal clinical marker of systolic dysfunction and is characterized by an increase in left ventricular end-diastolic and end-systolic

volumes.[2] Because of these volumetric changes, the heart initiates compensatory processes to maintain adequate cardiac output.[3] These processes include tachycardia, increased contractility, increased preload that results in an increased stroke volume, vasoconstriction, and ventricular hypertrophy with remodeling.[3]

One of the initial steps in the progression of heart failure is asymptomatic left ventricular dysfunction.[4] This step is initiated by an injury caused by any one or a combination of several disorders; coronary artery disease (CAD), hypertension, cardiomyopathy, or valvular disease.[1,4] Heart failure can be prevented by minimizing the risk of the initial cardiac injury. Measures should be taken to prevent any further cardiac injury after any cardiovascular diagnosis.[2]

Acute myocardial infarct (AMI) is another common etiology of heart failure. Patients with a recent or remote history of AMI have an increased risk of developing heart failure.[2]

New York Heart Association Classification

The New York Heart Association (NYHA) classes I through IV (table 1) is the most widely used system to classify heart failure patients. The system classifies patients according to the severity of their symptoms. Proper interventions can be provided to patients based on their staging in this classification system.

Table 1

New York Heart Association Functional Classification for Heart Failure[3]

Functional Class	
I	Patients with cardiac disease but without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Patients with cardiac disease that results in slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
III	Patients with cardiac disease that results in marked limitation physical activity without discomfort. Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.
IV	Patients with cardiac disease that results in an inability to carry on physical activity without discomfort. Symptoms of congestive heart failure are present even at rest. With any physical activity increased discomfort is experienced.

Treatment

The treatment of heart failure is dependent on the etiology and clinical course of the disease. The strategy for the management of stabilized heart failure patients in NYHA classes I to III is to prevent fluid retention, decrease symptoms and retard the progression of the disease.[2] Patients with heart failure due to primary valvular dysfunction should be candidates for surgery to repair or replace the diseased valve.[2]

Non-pharmacological treatment

The prevention of heart failure is similar to that of other cardiac diseases. Interventions such as losing weight, cessation of smoking, and discontinuation of alcohol intake are certainly recommended. In addition, proper management of diabetes mellitus and hyperlipidemia through diet and exercise are important.[1,2] Sodium restriction (2 to 3 g of sodium per day), supervised individualized aerobic exercise as tolerated by the patient, and up-to-date influenza and pneumococcal vaccines are also recommended.[2,5]

Pharmacological treatment

The three major facets of drug therapy in heart failure patients with or without symptoms are: 1) maintenance of fluid balance, 2) improvement of physical condition, and 3) the prevention of disease progression.[2]

Diuretics

Diuretics provide symptomatic relief and control of fluid retention in patients with NYHA class II, III and IV heart failure.[5] A daily dosing schedule of a loop diuretic based on the patient's fluid status is most appropriate. As a general rule, the diuretic should be started at a low dose and titrated to increase urine output and weight reduction at a rate of 0.5 to 1 kg per day until the patient is euvolemic.[3] Diuretic resistance is overcome with the use of intravenous diuretics, combination of two or more diuretics and by the short term use of dopamine or dobutamine for increased blood flow.[5] Diuretics should not be used as monotherapy because these agents have not proven to decrease the mortality rates in this patient population.[2]

The most common adverse effects of diuretics are electrolyte depletion (potassium and magnesium), the activation of renin-angiotensin-aldosterone system, hypotension and azotemia. Rash and hearing dysfunction may be precipitated with the use of very large doses.[2] Electrolyte depletion may cause the patient to become pro-arrhythmic. The activation of the renin-angiotensin-aldosterone system may enhance the frequency and severity of electrolyte depletion.[2]

Angiotensin-converting enzyme (ACE) inhibitors

All patients with systolic dysfunction, with or without symptoms, should be on ACE inhibitors for long term therapy, unless there is a clinical contraindication or intolerance to these agents.[2] Hypotension (BP < 80 mmHg), angioedema, bilateral renal artery stenosis, anuric renal failure, significant hyperkalemia (serum K > 5.5mmol), markedly increased serum creatinine (> 3 mg/dl), severe cough, and pregnancy are contraindications to the use of ACE inhibitors.[2,5,6] Serum creatinine and potassium should be checked within 1-2 weeks of starting therapy and regularly thereafter. Attaining euvolemic status in the patient is very important because excess fluid can blunt the effect of ACE inhibitors.[2] Clinical response to ACE inhibitors may be delayed for up to 1-2 months, therefore ACE inhibitor therapy should not be withdrawn. Long term treatment with ACE inhibitors has shown a decreased risk of mortality and hospitalization.[2]

The adverse effects of ACE inhibitors include hypotension, worsening renal function, hyperkalemia (5-15% for NYHA classes II and III; 15-30% for class IV patients), cough (5-15%), angioedema (<1%), rash and taste disturbances.[2]

Beta-andrenergic receptor blockers (beta blockers)

In addition to diuretics and ACE inhibitors, beta-blockers should be used in all stable NYHA class II and III patients with left ventricular dysfunction with an ejection fraction of <35 to 45% unless they have a contraindication or are intolerant to beta blockers.[2,6] Bisoprolol, metoprolol CR/XL , and carvedilol have been shown in clinical studies to improve clinical symptoms, and decrease the risk of mortality and hospitalization in patients with NYHA class II or III heart failure.[5,8] Carvedilol is the only drug that has been shown in clinical studies to decrease the risk of death and hospitalization in patients with NYHA class IV.[7] Also, carvedilol and extended release metoprolol are the only FDA approved drugs for heart failure, but other beta blockers are pending approval for this indication.[4] Beta-blockers should not be used in patients with bronchospastic disease, symptomatic bradycardia, and advanced heart block.[2,7] Patients with asymptomatic bradycardia (heart rate 60 beats/min) should be monitored carefully when on beta-blockers. Heart failure patients must first be stable and euvolemic before beta-blocker initiation.

Starting doses of beta-blockers should be very low and titrated slowly if the lower doses have been well tolerated. Patients and clinicians are advised that clinical response to beta-blockers may be delayed for up to 2 to 3 months but this delay should not be a reason to discontinue their use. Long term therapy is associated with improvement of symptoms and decrease in the risk of worsening heart failure, death and hospitalization.[2]

The major adverse effects of beta-blockers that should be monitored are hypotension, fluid retention, worsening heart failure and decreased heart rate/heart block. Others include nausea, diarrhea, fatigue, depression and sexual dysfunction.[2]

Cardiac glycosides

Digoxin is the only glycoside that has FDA approval for the treatment of heart failure.[2] Digoxin has its primary effect on the improvement of clinical status by relieving symptoms of heart failure.[2] It should be used concomitantly with loop diuretics, ACE inhibitors and beta-blockers in patients with normal sinus rhythm to improve clinical symptoms and to reduce the frequency of hospitalization in NYHA classes II to IV patients.[2,6] Digoxin has no therapeutic benefit in NYHA class I patients.[2] Digoxin may be initiated early in patients who have been started on ACE inhibitors and/or beta blockers (during the lag period of these agents) or may be added on to relieve symptoms in patients already on ACE inhibitors and/or beta blockers who continue to experience symptoms of heart failure.[2,6]

The dosage range of 0.125 to 0.25 mg daily or every other day is effective for symptomatic control in heart failure patients.[2] The benefit of the long term use of digoxin in heart failure patients is still being studied.[2]

Aldosterone antagonist

Spironolactone 25 - 50 mg can reduce mortality in classes III and IV heart failure patients.[2] Patients with current or recent NYHA class IV heart failure, EF < 35%, serum creatinine level < 2.5 mg/dl and serum potassium level 5.0 mmol/L can benefit from low dose spironolactone use according to the RALES study that showed 30% and 36% reduction in mortality and hospitalization respectively. Spironolactone can be combined with ACE inhibitors, loop diuretics and digoxin.[2,6] The primary major adverse effect associated with spironolactone is gynecomastia.[2,4,6]

Angiotensin II receptors blockers, nitrates and calcium channel blockers

Angiotensin II receptors blockers (ARBs) are only recommended for the treatment of heart failure if a patient is intolerant to ACE inhibitors. Although currently being studied, there is no strong evidence at the present time to support the combination therapy of ACE inhibitors and ARBs. Further studies are needed before ARBs can find a well-defined place in the drug therapy of heart failure.[1,5]

Traditionally, the combination of hydralazine and nitrates were the drug of choice for patients intolerant to ACE inhibitors, but the frequency of dosing (three to four times daily) and side effect profiles caused clinicians to switch to ARBs. The V-HeFT II study with NYHA classes II and III heart failure patients showed that an ACE inhibitor (enalapril up 20 mg/day) reduced the risk for death by 28% when compared to the combination of hydralazine (300 mg/day) and nitrates (isosorbide dinitrate 160 mg/day).[1]

Calcium channel blockers do not add any benefit to the therapy of heart failure patients. Three clinical trials (PRAISE, PRAISE-2 and V-HeFT) involving amlodipine and felodipine demonstrated a neutral effect on the risk of mortality in heart failure patients. First generation calcium channel blockers are contraindicated in heart failure patients because the failing heart demonstrates a defect in the delivery of calcium to the contractile proteins. First generation calcium channel blockers may have a deleterious effect on survival and should not be used.[1,5]

Conclusion

Heart failure is a chronic, debilitating disease affecting many Americans and costing the health care system billions of dollars.[2] The proper treatment strategy for heart failure patients requires an ongoing follow-up and continual adjustment of therapy.[9] The goals of therapy for heart failure with NYHA classes I to IV are: 1) to improve symptoms, 2) to decrease the risk of hospitalization thus containing health care costs, and 3) to decrease the risk of death.[2,9]

Clinicians now have drugs that can achieve all three goals of treatment. These drugs include loop diuretics, spironolactone and digoxin for symptom improvement and beta-blockers and ACE inhibitors for the retardation of disease progression and reduction in the risks of mortality and hospitalization.[1,2,5]

The appropriate classification of heart failure patients into the NYHA functional classification system I to IV will help to allow the clinician to develop a proper treatment plan. The combination of the loop diuretics, aldosterone antagonists, beta-blockers, and ACE inhibitors have shown beneficial effects in the prevention of hospitalization and reduction in the risk of death.[1,2,3,4,5] The role of clinicians charged with care of heart failure patients is to optimize doses of heart failure drug therapy,

screen for drugs that exacerbate heart failure, monitor for adverse drug effects and educate patients.[9] In so doing, patients with heart failure can both experience an improved quality and length of life, and contain the cost of drug therapy.[3,9]

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MISSOURI MEDICAID STATISTICS (October 2000 through September 2001)

Total # Patients with CHF*	# Patients with CHF using Calcium Channel Blockers*	Medical costs for all patients with CHF*	Pharmacy costs for all patients with CHF*
16,920	3,968	$201,329,341.97	$60,047,734.10

* Diagnoses inferred from Medicaid claims

Top 25 Products Ranked by Amount Paid

Summary for Period: 10/2000 to 09/2001

Drug	Paid	Rx	Paid/Rx
OLANZAPINE	$39,951,114.00	140,313	$284.73
RISPERIDONE	$23,933,737.00	169,579	$141.14
CELECOXIB	$14,096,093.00	153,666	$91.73
OMEPRAZOLE	$12,893,814.00	97,063	$132.84
FLUOXETINE	$12,565,852.00	117,493	$106.95
DIVALPROATE	$12,164,966.00	137,437	$88.51
SERTRALINE	$11,340,119.00	159,530	$71.08
PAROXETINE	$10,886,173.00	147,006	$74.05
ATORVASTATIN	$10,856,025.00	140,144	$77.46
LANSOPRAZOLE	$10,835,021.00	94,856	$114.23
GABAPENTIN	$10,762,443.00	105,215	$102.29
OXYCODONE	$10,724,291.00	60,888	$176.13
QUETIAPINE	$10,175,203.00	62,402	$163.06
ROFECOXIB	$9,955,071.00	125,534	$79.30
AMLODIPINE	$7,145,571.00	136,764	$52.25
BUSPIRONE	$6,748,985.00	63,031	$107.07
METFORMIN	$6,651,041.00	108,739	$61.17
LORATADINE	$6,563,524.00	124,985	$52.51
VENLAFAXINE	$6,350,235.00	75,929	$83.63
CITALOPRAM	$5,817,886.00	93,043	$62.53
SIMVASTATIN	$5,810,894.00	54,631	$106.37
MIRTAZAPINE	$5,699,996.00	81,632	$69.83
ANTIHEMOPHILIC FACTOR	$5,670,944.00	709	$7,998.51
EPOETIN ALFA	$5,669,975.00	21,443	$264.42
CLOPIDOGREL	$5,503,252.00	58,695	$93.76
Totals:	$268,772,225.00	2,530,727	$106.20