

Chronic heart Failure management

This article provides readers with essential pharmacologic background information for treating chronic heart failure. Use of digoxin, spironolactone, ACE inhibitors and ARBs is discussed, as well as treatment with combinations of drugs.

By Amish Raval, MD; and
J. Malcolm O. Arnold, MD



An Overview

Chronic heart failure (CHF) is a clinical syndrome of typical symptoms, such as shortness of breath, or fatigue associated with evidence of cardiac dysfunction. Objective evidence from a chest X-ray and/or an echocardiogram should be obtained, other causes of the symptoms should be excluded and an appropriate response to treatment can confirm the diagnosis. Despite these steps, CHF is often overlooked or misdiagnosed in

the early stages and, therefore, undertreated (see case study on the following page).

This syndrome affects more than 350,000 Canadians and its incidence continues to rise rapidly, particularly among the elderly.¹ A total of 20% of hospitalized patients have either a primary or secondary diagnosis of CHF, and the rates of hospitalization are increasing.² Approximately 50% of patients diagnosed with CHF will die within five years and the one-year mortality ranges between 25% and 40% after diagnosis.³

About the author...



Dr. Raval is a cardiology subspecialty resident at the University of Western Ontario London Health Sciences Centre.

About the author...



Dr. Arnold is a staff cardiologist and heart failure specialist at the London Health Sciences Centre, director of research affairs for the division of cardiology, director of the cardiology research program in the Lawson Research Institute, and chair of the University of Western Ontario Department of Medicine Research Committee.

Causes and Precipitating Factors

The most common underlying cause of CHF in North America is ischemic cardiomyopathy, defined as ventricular dysfunction as a direct result of coronary artery disease. Ischemic cardiomyopathy is the principal attributable cause of CHF in over two-thirds of hospitalized patients.⁴ Other important causes of CHF include the following:

- Idiopathic dilated cardiomyopathy;
- Valvular heart disease;
- Hypertension; and
- Alcoholic cardiomyopathy (Table 1).

High-output CHF is uncommon, but can be due to severe anemia, thyrotoxicosis, beriberi and Paget's disease. Several important precipitating factors can exacerbate CHF in a patient with underlying left ventricular (LV) dysfunction, including the following:

- Medication non-compliance;
- Excessive sodium intake;
- Atrial fibrillation;
- Further ischemia; and
- Uncontrolled hypertension.

Pathophysiology

The most common type of CHF is systolic dysfunction associated with reduced LV contractility and reduced cardiac output. Typically, LV dilatation progressively occurs and the reduced forward flow results in decreased renal perfusion. Subsequently, this activates the sympathetic nervous system and the renin-angiotensin-aldosterone system, which results in increased angiotensin II mediat-

Table 1

Principally Attributable Causes of Heart Failure

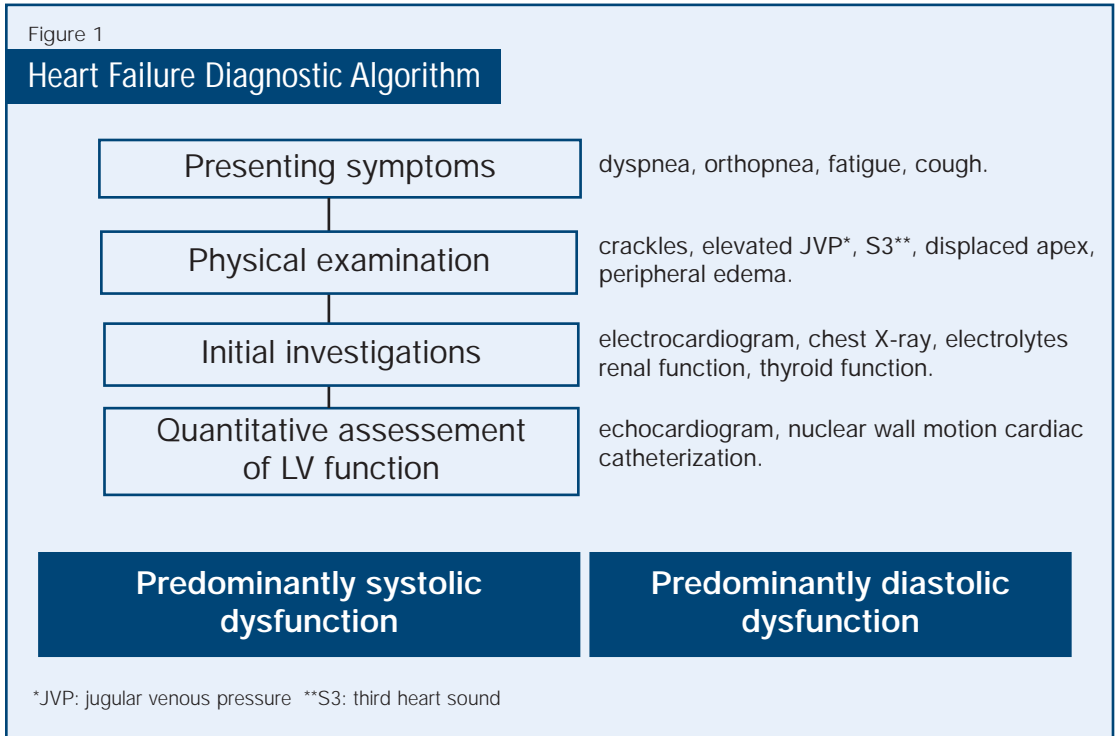
- Ischemic cardiomyopathy
- Valvular heart disease
- Idiopathic dilated cardiomyopathy
- Alcoholic cardiomyopathy
- Drug-induced cardiomyopathy (*i.e.*, anthracyclines)
- Hemochromatosis
- Thyroid abnormalities (hypothyroidism or hyperthyroidism)
- Beriberi and other nutritional deficiencies
- Tachycardia-induced cardiomyopathy
- Restrictive cardiomyopathy
- Hypertrophic cardiomyopathy
- Amyloidosis

ed peripheral vasoconstriction, aldosterone release, sodium retention and volume overload.

The second important mechanism of CHF is diastolic dysfunction, defined as impaired filling of the LV with normal or only minimally reduced contractility (preserved systolic function). This form of cardiac dysfunction is common, affecting up to 40% of CHF cases in community practice.^{5,6} Examples of predominant diastolic dysfunction causing CHF include the following:

- LV hypertrophy due to hypertension or aortic stenosis;
- Hypertrophic cardiomyopathy; and
- Restrictive cardiomyopathy.

While diastolic dysfunction can certainly occur in isolation, many cases of diastolic dysfunction have co-existing systolic dysfunction. Although observational evidence suggests the prognosis of patients with predominant diastolic dysfunction is equally as



poor as those with systolic dysfunction, large CHF clinical trials have failed to address this important group.

Diagnostic Algorithm

The typical complaint of a patient with CHF is shortness of breath on exertion (Figure 1). The New York Heart Association (NYHA) classification system is commonly used to characterize functional limitation and has been shown to correlate with adverse prognosis (Table 2).⁷ Other symptoms related to pulmonary and system congestion and poor cardiac output include the following:

- Orthopnea;
- Paroxysmal nocturnal dyspnea;
- Cough;
- Peripheral edema;
- Weight gain;
- Lethargy;

- Fatigue; and
- Altered mental status.

Sensitive signs indicative of LV dysfunction include the following:

- An elevated jugular venous pressure;
- Rales;
- Hepatomegaly;
- Cool distal extremities; and
- Peripheral edema.

A laterally displaced apical beat and a third heart sound are highly specific findings of a dilated and poorly contractile LV. A careful history and physical examination are crucial to increase clinical suspicion and lead to an accurate diagnosis, especially in patients presenting early with mild symptoms.

The 12-lead electrocardiogram is often non-specific, but can be helpful in the diagnosis of ischemic cardiomyopathy, arrhythmias and chamber enlargement. A prolonged QRS duration in a patient with non-ischemic cardiomyopathy has been associated with a worse prognosis.⁸

Laboratory tests are not diagnostic of CHF, but some are helpful in assessing risk factors and complications. In the initial work-up of a patient suspected of having CHF, it is recommended that the following be measured:

- Serum electrolytes;
- Urea;
- Creatinine;
- Fasting glucose;
- Lipid profile; and
- A complete blood cell count.

Hyponatremia may occur in severe CHF, which reflects marked activation of the neurohumoral system with fluid retention, and is associated with a worse prognosis.⁹ A test for thyroid-stimulating hormone should be considered, particularly in the elderly, as hypothyroidism or hyperthyroidism causing CHF is treatable. In younger male patients, serum ferritin should be considered if hemochromatosis is suspected. Cardiac-specific enzymes should also be measured to rule out myocardial infarction in acute CHF (co-existent with severe and prolonged angina). Markers of neurohormonal activation, such as brain natriuretic peptide, are powerful predictors of prognosis and may be used clinically in the future.

A chest X-ray can identify cardiac silhouette enlargement, pulmonary alveolar edema, vascular redistribution, Kerley B lines, or pleural effusions.

It is also useful in ruling out other confounding primary lung diseases as a cause of dyspnea.

All patients suspected of having CHF should have a quantitative assessment of LV function performed, as is strongly recom-

Table 2

NYHA Classification

Class I- Patients with heart disease who are completely symptom-free.

Class II- Slight limitation of physical activity because of symptoms (*i.e.*, shortness of breath, chest pain) occur only with more than ordinary physical activity.

Class III- Marked limitation of physical activity because symptoms occur even with ordinary physical activity (*i.e.*, eating meals).

Class IV- Severe limitation of physical activity because symptoms occur even at rest (*i.e.*, in a sitting or lying position).

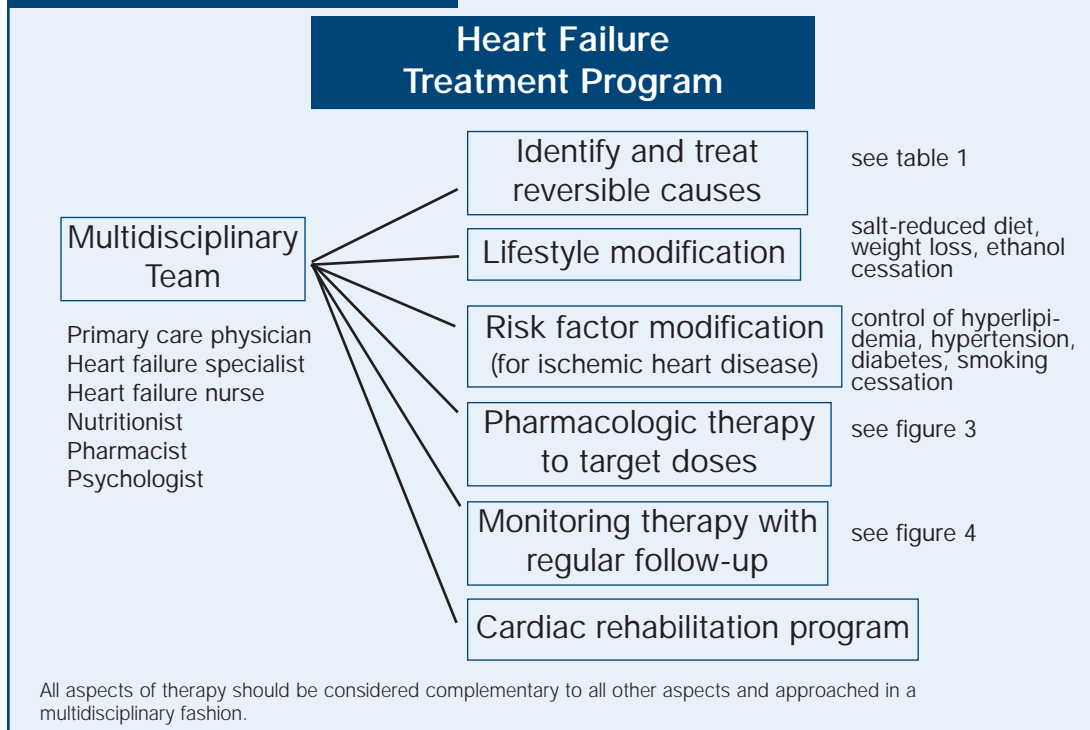
mended in national guidelines.¹⁰ The importance of this assessment cannot be understated, due to the following:

- Clinical examination alone is poor at identifying a reduced ejection fraction;
- Large, randomized trials of therapy with angiotensin converting enzyme (ACE) inhibitors and beta blockers have proven mortality benefit in those with a reduced ejection fraction;¹¹⁻²¹ and
 - Simply performing an echocardiogram can have a favorable effect on overall survival, perhaps by alerting physicians to the seriousness of the disease process and by promoting active evidence-based therapy.²²

An echocardiogram is most useful in this regard as it can estimate ejection fraction, measure chamber sizes, assess for any potentially treatable valvular abnormalities, look for regional wall motion abnormalities and is, in general,

Figure 2

Goals of CHF Management



easily accessible. Evidence of diastolic dysfunction is shown by LV hypertrophy, normal contractility but abnormal relaxation, and an abnormal doppler flow pattern during ventricular filling. Radionuclide angiography or cardiac catheterization are other ways of assessing LV function. Nuclear myocardial perfusion imaging and/or coronary angiography should be performed in high-risk patients suspected of having CAD, as improved LV function and survival have been shown in suitable candidates receiving revascularization.

Goals of CHF Management

The first step in managing the population burden of CHF lies in prevention (Figure 2). This applies particularly to managing well-known

risk factors that predispose a patient to CAD, including hypertension, hyperlipidemia, smoking and diabetes. Identification of potentially reversible causes and precipitating factors leading to CHF (*i.e.*, excessive salt or alcohol intake, medication non-compliance, thyroid disorders, ischemia) should also be identified and treated.

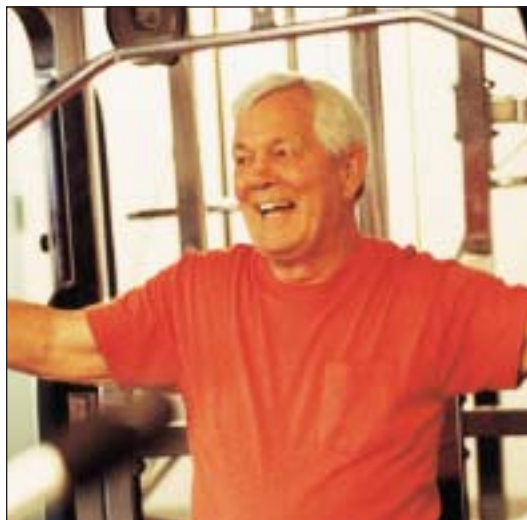
It is essential that CHF patients be well-educated about their condition and that important lifestyle modifications are emphasized. Education should be patient-specific, involve family and caregivers, and should include oral, written and visual aids. The management of CHF, therefore, requires a multi-disciplinary approach which includes not just primary-care physicians, but also cardiovascular specialists, dietitians, CHF nurses, pharmacists, psychologists, and home-care providers. A common

treatment plan and approach should be established and reinforced. These multi-disciplinary interventions have been shown to improve patient compliance, reduce costs and prevent re-hospitalizations in patients admitted to hospital with CHF.^{1,10,12-14}

Sodium restriction advice should be individualized in the CHF patient, depending on the severity of his/her condition. For those with asymptomatic LV dysfunction, it may be appropriate to advise them not to add salt to meals. For those with mild to moderately severe CHF, sodium intake should be limited to 2 g to 2.5 g (5 g to 6 g of salt). For those with severe CHF, sodium intake should be limited to 1.2 g to 1.8 g (3 g to 4.5 g of salt). This will assist in reducing symptoms of congestion. Large fluctuations in daily sodium intake should be avoided. Measuring morning weight daily on the same scale (after emptying the bladder and before getting dressed and having breakfast) is a crucial part of the CHF management plan. A day-to-day weight increase of > 1 kg should prompt a careful assessment of dietary sodium and fluid intake and may require a diuretic dose up-titration.

Patients who are well-educated about their CHF treatment may be able to self-adjust diuretic doses within certain physician-advised limits. Patients should not increase their diuretic dose for more than two or three days without a physician assessment and without repeat blood work for electrolytes and renal function.

Fluid restriction is not generally a necessary component of the treatment plan in most patients, unless a situation of severe refractory volume overload exists or significant hyponatremia develops. For the latter problem, free water restriction to between one litre and 1.5 litres per day is the usual treatment. Alcohol consumption should be discouraged as it is not



Supervised regular, aerobic and resistive exercise can improve a patient's sense of psychological well-being, exercise tolerance and may reduce symptoms.

only an important cause of cardiomyopathy in high doses, but it may also depress LV function further if another underlying cause of CHF exists.

Supervised regular, aerobic and resistive exercise can improve a patient's sense of psychological well-being, exercise tolerance and may reduce symptoms.¹ Cardiac rehabilitation programs are ideally suited to progressively train patients with mild or moderate CHF following an initial stress test to establish an individualized exercise prescription. Severe decompensated CHF patients, who are at risk for life-threatening arrhythmias, should be advised to temporarily avoid strenuous exercise.

A Drug Review

Pharmacologic Management

As with cancer chemotherapy, CHF therapy includes combination drug therapy using several important, evidence-based agents that target different aspects of the neurohumoral milieu and the failing LV. Agents which are proven to improve long-term survival should be titrated up to the target doses used in major clinical trials (Figures 3 and 4). Important side effects need to be monitored and, if discovered, dose adjustments or logical substitutions may be required. Recently, the Canadian Cardiovascular Society has updated its guidelines based on new advances and clinical trial evidence.¹

Diuretics

Loop diuretics are powerful agents effective in improving the symptoms of CHF by not only reducing extracellular volume, but also by reducing preload acutely by venodilatation. Furosemide, ethacrynic acid and bumetanide are the most common agents used in clinical practice. While the typical initiating dose in those with preserved renal function is 20 mg to 40 mg of furosemide daily, careful dose adjustments are necessary as other agents, such as ACE inhibitors or beta blockers, are being introduced or titrated up to their target doses. Loop diuretic doses may need downward titration over days to weeks as ACE inhibitors or angiotensin II receptor blockers (ARBs) are introduced, or possibly increased. Beta blocker therapy should be slowly initiated if congestive symptoms



develop. Occasionally, daily doses up to 240 mg of furosemide are required in refractory patients and in those with renal impairment. The use of metolazone, 2.5 mg to 5 mg 30 minutes prior to the furosemide dose, can be used for severely volume overloaded hospitalized individuals. Patients should be monitored carefully for hypokalemia or hypomagnesemia, which can precipitate life-threatening arrhythmias. In the majority of patients, chronic metolazone use is not required as other drugs are optimized.

Spirolactone blocks the effect of aldosterone-mediated sodium retention and potassium excretion in CHF patients. At a daily dose of 25 mg, it has been found to have significant survival benefit in the Randomized Aldactone Evaluation Study (RALES), when used in patients with the following:²⁶

Figure 3

Drug Therapy for Heart Failure

Type of Drug	Initial Starting Dose	Monitoring	Target
Loop Diuretics	Furosemide 20 mg/day to 40mg/day	Daily weights Electrolytes* Renal function*	Symptom relief Weight loss of 0.5 kg/day to 1.0 kg/day until ideal weight achieved, then maintenance daily dose
Nitrates	Nitroglycerin patch 0.4 mg/12h apply at bedtime	Blood pressure*	Symptom relief Maintenance nitrate usually not required
ACE inhibitor	Isordil 30 mg po tid up to 90 mg po tid Captopril 12.5 mg po tid Enalapril 2.5 mg po bid Lisinopril 2.5 mg po daily Ramipril 2.5 mg po daily	Blood pressure* Electrolytes* Renal Function* Rash/Angioedema	Captopril 50 mg po tid Enalapril 10 mg po bid Lisinopril 20 mg po daily Ramipril 10 mg po daily
BB	Metoprolol 6.25 mg bid Carvedilol 3.125 mg po daily Bisoprolol 1.25 mg po daily	Blood pressure Heart rate* Worsening congestion Bronchospasm	Metoprolol 100 mg po bid Carvedilol 50 po bid Bisoprolol 25 mg po bid
ARB	Losartan 12.5 mg po daily Valsartan 40 mg po bid	Blood pressure* Electrolytes* Renal function*	Losartan 50 mg po daily Valsartan 160 mg po bid
Spirolactone	Spirolactone 12.5 mg po daily	Blood pressure* Electrolytes* Renal function* Painful gynecomastia	Spirolactone 25 mg po daily
Digoxin	Digoxin 1 mg loading dose over 24 hours 0.125 mg po daily- weight < 60kg, abnormal renal function 0.25 mg po daily otherwise	None, unless signs of toxicity (<i>i.e.</i> , nausea, vomiting, visual complaints). Look for multiple drug-drug interactions	Symptom relief maintenance daily dose 0.125 mg to 0.25 mg daily

*Suggest check on dose initiation, one week later, one week after each dose titration and monthly when target dose achieved and patient is stable. Recheck blood pressure and heart rate if symptoms or orthostatic presyncope develop and titrate medication dose down as necessary.

ACE: Angiotensin converting enzyme BB: Beta blocker ARB: Angiotensin II receptor blocker po: by mouth tid: three times per day bid: twice per day

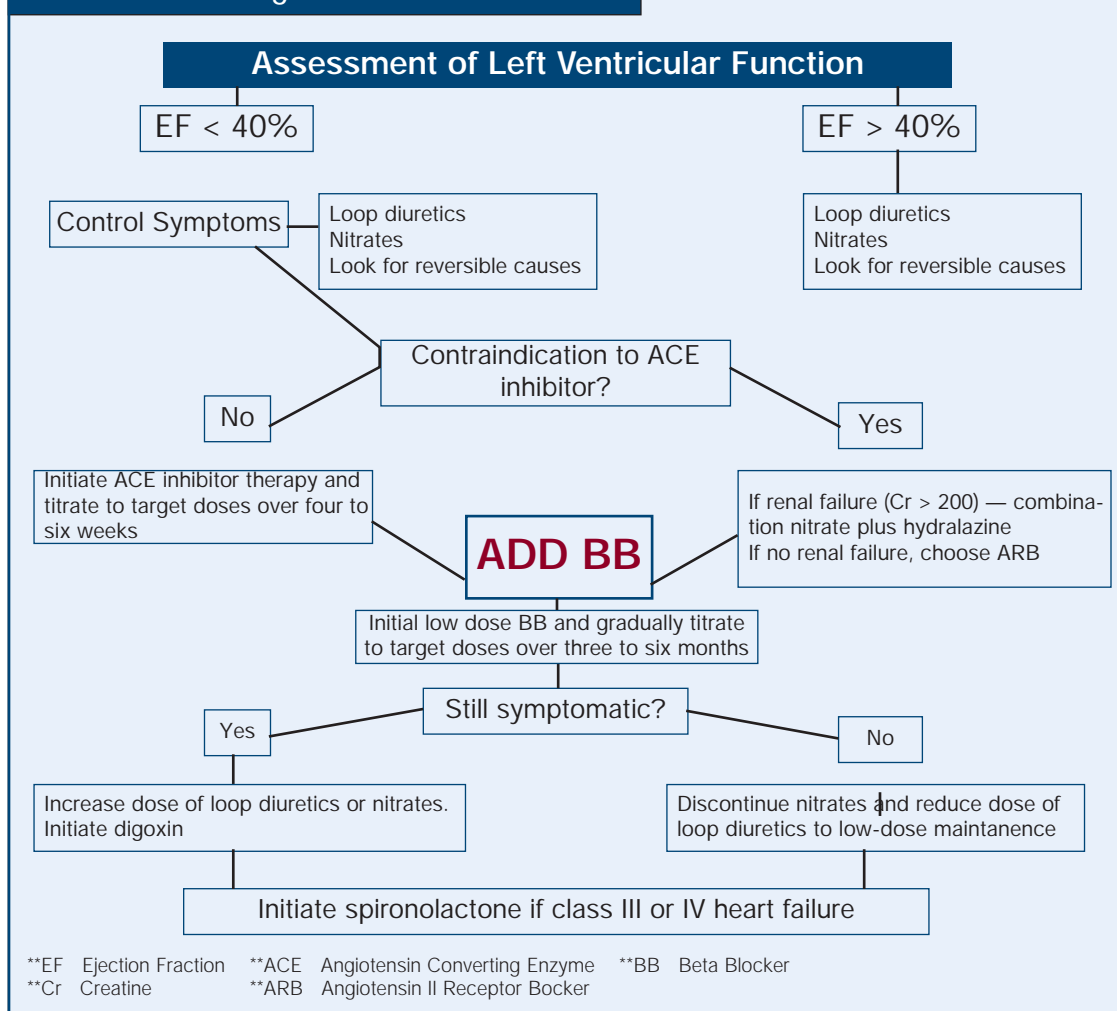
- Stable class III or IV heart failure;
- A LV ejection fraction $\leq 35\%$;
- Normal potassium (< 5.0 mmol/L);
- Creatinine < 221 $\mu\text{mol/L}$ (25mg/dL); and
- Those taking other proven agents, such as ACE inhibitors.²⁷

While there was no increase in the poten-

tially life-threatening risk of hyperkalemia, the patients in the trial were carefully monitored and all potassium supplements were discontinued. Serum potassium should be measured at week one, then every four weeks for the first 12 weeks, then every three months for up to

Figure 4

Heart Failure Drug Treatment Algorithm



one year, and every six months thereafter. If serum potassium is elevated at any time (> 5.0 mmol/L), the dose may be reduced to 25 mg every other day. Painful gynecomastia occurs in some men. Caution is required in patients with moderate renal impairment, especially in association with diabetes, where very careful monitoring is required as hyperkalemia is more frequent. To date, there is no evidence showing benefit of spironolactone in mild CHF.

ACE Inhibitors

All patients with symptomatic or asymptomatic CHF and an LVEF $\leq 40\%$, should be taking an ACE inhibitor at the target doses used in the major clinical trials.^{28-31,26} These doses have also been strongly advocated by several published national guidelines.^{1,10-11} In clinical trials, these agents have been shown to stabilize LV function, improve functional class, reduce hospital readmissions, and improve long-

term survival. They remain the backbone of pharmacologic management in CHF. They work mainly by blocking the conversion of angiotensin I to angiotensin II, resulting in a reduction in angiotensin II-mediated vasoconstriction and aldosterone-mediated sodium retention.

Bilateral renal artery stenosis, severe aortic stenosis, severe renal insufficiency (*i.e.*, creatinine > 200 IU/L), and refractory hyperkalemia (potassium > 5.5 mmol/L) are considered absolute contraindications for the use of ACE inhibitors. A troublesome chronic cough, which is bradykinin-mediated, can occur as a specific side effect to ACE inhibitors, and occurs in 5% of patients.¹ Patients may be willing to live with a mild cough as a nuisance side effect when they understand the benefits of ACE inhibitor therapy. Not infrequently, the cough is secondary to worsening CHF, rather than an adverse effect of the ACE inhibitor, and is helped by temporary increases in diuretic therapy. Angioedema occurs in 0.1% of patients, can be life threatening, and patients should be instructed to stop the drug if such symptoms or signs occur.

No large differences appear to exist between the variety of available ACE inhibitors in terms of either benefit or side effect profile. Clinical trials have identified the target effective doses for enalapril (10 mg twice daily), lisinopril (20 mg to 30 mg once daily), captopril (50 mg three times daily) and ramipril (10 mg once daily). Typically, the dose is initiated low and titrated up over several weeks for an outpatient, or over several days for an inpatient. Patients should be instructed to report any orthostatic lightheadedness, hives or rash. Blood pressure (BP) checks are necessary after dose initiation and after any dose increase. BP should be taken monthly thereafter, as hypotension may ensue if high

doses of diuretics have been used. Symptomatic hypotension can often be avoided by lowering the dose of diuretic or other vasodilator drugs. Similarly, electrolytes and creatinine should be checked one week after dose initiation or with any dose increase, and every second month thereafter to monitor for hyperkalemia or renal dysfunction.

ARBs

So far, two angiotensin receptors have been identified that bind to angiotensin II, however, it is the angiotensin II type 1 receptor that potentiates the deleterious effect of angiotensin II. ARBs were developed with the knowledge that ACE inhibitors do not completely prevent angiotensin II formation as alternative pathways exist, circumventing the ACE. An ARB, therefore, might more completely inhibit angiotensin II mediated actions than do ACE inhibitors alone, assuming comparable tissue penetration and activity.

In the Evaluation of Losartan In The Elderly (ELITE II) trial comparing captopril *versus* losartan for NYHA class II to IV patients with an ejection fraction of about 40%, no significant difference in mortality was seen between these two agents.¹²

Similarly, the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study revealed no significant difference between candesartan and enalapril in patients with mild to moderate CHF on beta blocker therapy, although the combination of all three therapies demonstrated a somewhat improved ejection fraction and decreased ventricular volumes, as compared to monotherapies.¹³

Finally, the Valsartan Heart Failure (Val-HeFT) trial of > 5,000 patients added val-

Case Discussion

Following a complete history and physical, bloodwork was obtained, including electrolytes, urea, creatinine and thyroid-stimulating hormone. An ECG and chest X-ray were obtained and the patient was initiated on furosemide 20 mg once daily and educated about dietary salt and fluid restriction. An echocardiogram revealed reduced left ventricular contractility and an estimated ejection fraction of 35%. An angiotensin converting enzyme inhibitor was prescribed, initially at low doses and gradually titrated as blood pressure, lytes and renal function remained stable. Three months later, the patient continued to have dyspnea and a beta blocker was introduced at a low dose and slowly titrated up to the target level.

sartan (target 160 mg twice daily) or placebo on top of optimal medical therapy, including an ACE inhibitor, in patients with chronic stable NYHA class II to IV heart failure and an ejection fraction of $\leq 40\%$. Valsartan did not reduce mortality, but significantly reduced CHF hospitalizations and improved NYHA functional class. The greatest relative benefit was seen if patients randomized to valsartan were not using a beta blocker. Therefore, an ACE inhibitor plus beta blocker remains first-line therapy, though an ARB (*i.e.*, valsartan) may be used if the patient cannot tolerate either the ACE inhibitor or the beta blocker.¹⁴

Of some importance, fewer side effects have been reported with the ARB, as compared to the ACE inhibitor, though both agents may cause renal dysfunction in susceptible patients. Not all of the broad-based benefits of ACE inhibitors, however, have yet been shown for ARBs. ACE inhibitors, therefore, remain the first-line choice.¹

Vasopeptidase Inhibitors

Omapatrilat, a novel vasopeptidase inhibitor, is a highly potent and selective inhibitor of neutral endopeptidase and ACE. This drug is being tested in a large-

scale clinical trial and preliminary evidence suggests it results in functional improvement, few side effects, and a trend toward mortality benefit.¹⁵

Nitrates and Hydralazine

The combination of high-dose isosorbide dinitrate (90 mg three times daily) and hydralazine (50 mg four times daily) for both preload and afterload reduction in symptomatic CHF patients, has been shown to modestly improve functional class and survival in the Vasodilator-Heart Failure (V-HeFT I) trial, compared to placebo, but was inferior to the benefits of ACE inhibitors shown in V-HeFT II.^{30,32} These agents are typically reserved for use in CHF patients with concomitant renal impairment, where the use of an ACE inhibitor or ARB has worsened renal function significantly. Long-acting nitrate preparations in the patch form (doses 0.4 mg to 0.8 mg for 12 hours on and 12 hours off) are useful in reducing symptoms of pulmonary congestion in acute or severe CHF, particularly when applied at bedtime when a patient is most likely to develop orthopnea from being supine.

Beta Blockers

In CHF management, beta blockers have demonstrated improved patient survival, improved ejection fraction and reduced sudden cardiac death in those with all severities of CHF, except those in severe cardiogenic shock. Beta blockers, if tolerated, should be used in every patient with systolic heart failure. By blocking a chronically maladaptive sympathetic nervous system, these agents may initially reduce LV contractility and worsen CHF symptoms as the dose is being upwardly titrated.

While there is a commonly held notion that beta blocker therapy should be avoided in patients with severe class III or IV heart failure, it seems the greatest benefit is seen precisely in these patients. The transient and initial worsening of CHF can be managed by more aggressive diuretic therapy. The dose should be started very low and very gradually titrated upward over several weeks to the target doses used in major trials. There is abundant evidence to recommend that all patients with systolic heart failure should be placed on a beta blocker with the caveat that they be monitored frequently for hypotension, bradycardia and evidence of worsening CHF.¹⁶⁻²¹ CHF patients with asthma, symptomatic bradycardia, and severe peripheral vascular disease, generally should not receive a beta blocker.

Digoxin

Digitalis has withstood the test of time and, although a relatively weak inotropic agent, it has been shown to improve symptoms and reduce hospitalization rates.³³ While no mortality benefit has been demonstrated, it is used for symptomatic relief in more severe CHF and for additional rate control in patients with



Currently, the only established surgical approach to CHF therapy is cardiac orthotopic transplantation.

atrial fibrillation and a rapid ventricular response. The dose must be adjusted according to renal function, weight and sex. The dose should be reduced by half if amiodarone is started and caution is also required with some other drugs, such as warfarin.

Warfarin

Patients with CHF are at an increased risk of atrial fibrillation, venous thromboembolic disease and stroke. Due to the inherent bleeding risk associated with warfarin, it is reserved for those patients with atrial fibrillation, mechanical valve prosthesis, previous thromboembolic, LV mural thrombus, or those with very severe LV systolic dysfunction, although the latter remains controversial.

Cardiac Transplantation

Currently, the only established surgical approach to CHF therapy is cardiac orthotopic transplantation. Due to the small donor pool and the multiple potential side effects, cardiac transplantation is reserved for patients with refractory and severe cases of CHF due to poor LV function, but who are otherwise in good health. Although powerful pharmacologic approaches to CHF therapy have developed over the past two decades, the overall prevalence of the problem and waiting lists for transplantation also have become longer. LV assist devices have emerged in some specialized centres as a tool bridging the gap between time from enlistment to transplantation. Similarly, exciting work is being done on creating an artificial heart.

Endothelin Antagonists


Serum levels of endothelin, a naturally occurring endogenous vasoconstrictor, are elevated in patients with CHF. While the endothelin-1 receptor antagonist, bosentan, seems promising in pilot studies, enrasentan resulted in a worsening of CHF in a recently completed trial.

Synchronized Biventricular Pacing

Patients with underlying cardiomyopathy frequently have associated intraventricular conduction delays, resulting in asynchronous contraction of the ventricles. This results in a mechanical disadvantage for efficient pumping of blood. A biventricular pacing device has one lead in the coronary sinus causing initial electrical activation of the lateral wall of the LV, and

a lead in the typical right ventricular apex location. By synchronizing electrical activation, ventricular contraction may be enhanced and any secondary mitral regurgitation that may result from delayed septal activation, may be reduced. The Multicenter InSync Randomized Clinical Evaluation trial, the Multisite Stimulation in Cardiomyopathies trial and the Pacing Therapy for Congestive Heart Failure multicenter trial have all demonstrated greater improvement in symptoms and exercise tolerance at six months in patients treated with cardiac resynchronization therapy.³⁴ The long-term effects of this therapy are still unknown.

Conclusion

Several other issues surrounding CHF therapy exist (*i.e.*, anticoagulation, implantable cardioverter-defibrillators, LV assist devices) but are beyond the scope of this discussion. Currently, the mainstay of therapy for CHF due to LV function is an ACE inhibitor (or ARB), a beta blocker, and diuretics to reduce symptoms and prolong life for this deadly condition. As our understanding of the complex neuro-humoral milieu and its interaction with cardiac myocyte phenotypic and genotypic expression becomes clearer, novel CHF therapies with very specific targets will emerge in the future. 

References

1. Liu P, Arnold M, Belenkie I, et al: The 2001 Canadian Cardiovascular Society consensus guideline update for the management and prevention of heart failure. *Can J Cardiol* 2001; 17 (Suppl E):5E-25E.
2. Massie BM, Shah NB. Evolving trends in the epidemiology of heart failure: Rationale for preventative strategies and comprehensive disease management. *Am Heart J* 1997; 133:703-12.

3. Ho KK, Pinsky JL, Kannel WB, et al: The epidemiology of heart failure: The Framingham study. *J Am Coll Cardiol* 1993; 325:293-302.
4. Raval A, Marchiori G, Arnold JMO: Improving the continuity of care following discharge of patients hospitalized with heart failure: Is the discharge summary adequate? *J Card Failure* 1998; 4(3):1-56.
5. Bonow RO, Udelson JE: Left ventricular diastolic dysfunction as a cause of congestive heart failure: Mechanisms and management. *Ann Intern Med* 1992; 117:502-10.
6. Banerjee P, Banerjee T, Khand A, et al: Diastolic Heart Failure: Neglected or Misdiagnosed. *J Am Coll Cardiol* 2002; 39:138-41.
7. Cohn JN, Rector TS: Prognosis of congestive heart failure and predictors of mortality. *Am J Cardiol* 1988; 62:25A-30A.
8. Silverman ME, Pressel MD, Brackett JC, et al: Prognostic value of the signal averaged electrocardiogram and a prolonged QRS in ischemic and nonischemic cardiomyopathy. *Am J Cardiol* 1995; 75:460-4.
9. Chin MH, Goldman L: Correlates of major complications or death in patients admitted to the hospital with congestive heart failure. *Arch Intern Med* 1996; 156(16):1814-20.
10. Hunt SA, Baker DW, Chin MH, et al: ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary. *J Am Coll Cardiol* 2001; 38(7):2101-13.
11. The Task Force on Heart Failure of the European Society of Cardiology: The Guidelines for the diagnosis of heart failure. *Br Heart J* 1995; 16(6):741-51.
12. Pitt B, Poole-Wilson PA, Segal R, et al: Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: Randomized trial — the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000; 355:1568-9.
13. McKelvie RS, Yusuf S, Pericak D, et al: Comparison of candesartan, enalapril, and their combination in congestive heart failure: Randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study: The RESOLVD Pilot Study. *Circulation* 1999; 100:1056-64.
14. Cohn JN, 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(23):1667-75.
15. Rouleau JL, Pfeffer MA, Stewart DJ, et al: Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial. *Lancet* 2000; 356(9230):615-20.
16. Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group: Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. *Lancet* 1993; 342:1441-6.
17. U.S. Carvedilol Heart Failure Study Group: The effect of carvedilol on morbidity and mortality in patients with chronic Heart Failure. *N Engl J Med* 1996; 334:1349-55.
18. Merit HF Group: Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL randomized interventions trial in congestive heart failure. *Lancet* 1999; 353(9169):2001-7.
19. CIBIS-II Investigators and Committees: The cardiac insufficiency study II: A randomized trial. *Lancet* 1999; 353:9-13.
20. Dargie HJ: Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: The CAPRICORN randomised trial. *Lancet* 2001 5; 357(9266):1385-90.
21. The beta-blocker evaluation of survival trial investigators: A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med* 2001; 31:344(22):1659-67.
22. Clarke K, Gray D, Hampton JR: Evidence of inadequate investigation and treatment of patients with heart failure. *Br Heart J* 1994; 71:584-7.
23. Stewart S, Marley JE, Horowitz JD: Effects of a multidisciplinary, home-based intervention on unplanned readmissions and survival among patients with chronic congestive heart failure: A randomised controlled study. *Lancet* 1999; 354:1077-83.
24. Rich MW, Gray DB, Wittenberg C, et al: Effect of a multidisciplinary intervention on medication compliance in elderly patients with congestive heart failure. *Am J Med* 1996; 101:270-6.
25. Rich MW, Beckham V, Wittenberg C, et al: A multidisciplinary intervention to prevent readmission of elderly patients with congestive heart failure. *N Engl J Med* 1995; 333:1190-5.
26. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993; 342:821-8.
27. Randomized Aldactone Evaluation Study Investigators: The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; 341:709-17.
28. CONSENSUS Trial Study Group: The effects of enalapril on mortality in severe congestive heart failure — Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987; 316:1429-35.
29. SOLVD Investigators: The effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992; 327:685-92.
30. Cohn JN, Johnson G, Ziesche S, et al: A comparison of enalapril with hydralazine — Isosorbide dinitrate in the treatment of chronic congestive heart failure (V-HeFT II). *N Engl J Med* 1991; 325:303-10.
31. Pfeffer M, Braunwald E, Moye S, et al: Effect of captopril on morbidity and mortality in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival and Ventricular Enlargement (SAVE) Trial. *N Engl J Med* 1992; 327:669-77.
32. Cohn JN, Archibald D, Phil M: Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a veterans administration cooperative study (V-HeFT 1). *N Engl J Med* 1986; 314:1547-52.
33. The Digitalis Investigation Group: The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997; 336:525-34.
34. Cazeau S, Leclercq C, Lavergne T, et al: Effects of multiseite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001; 344(12):873-80.