Update on therapy for acute and chronic heart failure for family physicians
Applying advances in outpatient management

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Heart failure is a clinical syndrome characterised by an inability to provide sufficient cardiac output to meet tissue demands at normal ventricular filling pressures (1). The syndrome is a significant health issue in the United States, where almost 5 million people have received the diagnosis of heart failure and about a half million new cases are diagnosed annually. According to estimates, nearly a half billion dollars are spent on drugs for treatment of heart failure every year in the United States (2).

This review focuses on the latest advances in the management of acute and chronic heart failure in patients with left ventricular systolic dysfunction.

Acute versus chronic heart failure

Diminished left ventricular systolic function is distinguishable by an ejection fraction of less than 35% to 40% (1) and is usually accompanied by an increase in the left ventricular end systolic and diastolic diameters. In response, the body activates several compensatory mechanisms as it attempts to maintain adequate tissue perfusion. These mechanisms include stimulation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system, and local vasoregulation (3). Although beneficial in their initial stages, the mechanisms may have a net detrimental effect of left ventricular remodeling coupled with an excessive increase in myocardial oxygen consumption, which results in further deterioration of cardiac function.

Heart failure can be divided into acute and chronic forms on the basis of acuity of presentation and severity of signs and symptoms. In the past, both acute and chronic types were viewed primarily as haemodynamic disease and were treated with drugs that improve myocardial contractility (inotropic agents), optimise volume status (diuretics), and improve cardiac output through afterload reduction (vasodilator agents).
Although many of these drugs improved short-term symptoms in patients with chronic heart failure, they often failed to produce significant gains in long-term survival. In contrast, drugs that block neurohormonal factors, such as angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, have generally improved not only the symptoms of chronic heart failure but also long-term survival.

Treatment of chronic heart failure

To optimally tailor therapy for chronic heart failure to an individual patient in the outpatient setting, it is important to categorise the patient's disease into the appropriate New York Heart Association (NYHA) class (Table 1). Treatment goals for chronic heart failure include alleviation of symptoms and improvement of quality of life, prevention of progression of myocardial dysfunction, and prolongation of life. The various drugs used in the treatment of heart failure contribute differently to these therapeutic end points. Their differences are outlined in Table 2. A treatment algorithm that integrates the therapeutic options is shown in Figure 1.

ACE inhibitors

These agents prevent the conversion of angiotensin I to angiotensin II through inhibition of the angiotensin-converting enzyme, which results in diminution of the adverse effects of angiotensin II. Moreover, inhibition of this enzyme prevents the breakdown of bradykinin and enhances kinin-mediated prostaglandin synthesis. In the Studies of Left Ventricular Dysfunction (SOLVD) trial (4), treatment of mild to moderate heart failure (NYHA classes II and III) with enalapril (<20 mg/day) was associated with a 16% reduction in all-cause mortality compared with placebo (35.2% versus 39.7%; P=.0036). Enalapril use also resulted in a 26% decrease in risk of death or hospitalisation for worsening heart failure (P<.0001). Even patients with reduced cardiac function (ejection fraction, <35%) who are asymptomatic derive significant benefit from treatment with ACE inhibitors (i.e. reduction in risk of heart failure and rate of related hospitalisations) (5). Thus, it is recommended that all patients with heart failure and left ventricular systolic dysfunction receive an ACE inhibitor unless its use is contraindicated.

Beta-blockers

Once a patient's chronic heart failure is stabilised by an effective dose of ACE inhibitor, beta-blocker therapy should be initiated. Long-term treatment with carvedilol (6), bisoprolol fumarate (7), or long-acting metoprolol (8) has been shown in large randomised clinical trials to

improve the mortality rate in patients who have NYHA class II or III systolic dysfunction caused by ischaemic or nonischaemic cardiomyopathy and who already are taking ACE inhibitors and diuretics.

In the US Carvedilol Heart Failure Study (6), carvedilol use (mean dose, 45 + 27 mg/day) decreased the mortality rate by 65% compared with placebo (3.2% versus 7.8%; P<.001), lowered the risk of hospitalisation for cardiovascular causes by 27% (14.1% versus 19.6%; P=.036), and decreased the combined risk of death and hospitalisation by 38% (15.8% versus 24.6%; P<.001).

Similarly, in the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) (7), 2,647 patients with NYHA class III or IV heart failure were randomly assigned to receive bisoprolol (<10 mg/day) or placebo. Their progress was followed for a mean of 16 months. Treatment with bisoprolol was associated with a 34% reduction in mortality rate compared with placebo (11.8% versus 17.3%; P<.0001) and a 32% reduction in risk of hospitalisation for heart failure (P<.0001).

Comparable findings were demonstrated in the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) (8), which randomly assigned 3,991 patients with chronic heart failure to receive either sustained-release metoprolol (<200 mg/day) or placebo. The investigators found that treatment with metoprolol was linked to a 35% reduction in mortality rate compared with placebo (7.2% versus 11.0%; P=.0062).

The efficacy of beta-blocker use in patients with severe heart failure was addressed in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial (9), which randomly assigned 2,289 patients with primarily NYHA class IV heart failure to receive either carvedilol or placebo. The trial's findings showed that treatment with carvedilol (mean dose, 37 mg/day) for a mean period of 10.4 months was associated with a 35% reduction in risk of death (95% confidence interval [CI], 19% versus 48%; P=.0014). However, it is important to note that this trial's criteria required that participants with severe heart failure be "clinically stable" and excluded those who had pulmonary rales, ascites, or significant peripheral oedema. Other exclusion criteria included acute cardiac or noncardiac illness that required intensive care or continued inpatient care, use of intravenous positive inotropic agents or intravenous vasodilators within 4 days, a systolic blood pressure of less than 85 mm Hg, a heart rate lower than 68 beats per minute, a serum creatinine level greater than 2.8 mg/dL (247.5 micromoles/L), an increase of more than 0.5 mg/dL (44.2 micromoles/L) in serum creatinine concentration, and a change in body weight of more than 1.5 kg during the 3- to 14-day screening period.
On the basis of these trial results, the latest guidelines recommend initiation of beta-blockers in all symptomatic patients with left ventricular systolic dysfunction, provided they are clinically stable and

have no contraindications to the therapy (2).

Diuretics

Thiazide diuretics target fluid overload by preventing absorption of sodium or chloride at specific sites in the renal tubules. These agents should not be used alone, even if symptoms are well controlled, because it has not been clearly shown that their use reduces mortality in patients with heart failure (2). Diuretics can provide rapid symptomatic relief and are crucial in optimising fluid balance. They should be used with an ACE inhibitor and a beta-blocker in the management of chronic heart failure in patients with a propensity for fluid retention.

Spironolactone (Aldactone) inhibits the neurohormonal axis by directly blocking the effects of aldosterone in the distal tubule of the kidney. The Randomized Aldactone Evaluation Study (10) assigned 1,663 patients with severe heart failure (recent or current symptoms of NYHA class IV heart failure) to receive either spironolactone (<50 mg/day) or placebo in addition to conventional therapy with ACE inhibitors and diuretics. After a mean follow-up period of 24 months, spironolactone use resulted in a 30% reduction in mortality rate compared with placebo (35% versus 46%; P<.001) and a 35% reduction in frequency of hospitalisation for worsening heart failure (relative risk of hospitalisation, 0.65; 95% CI, 0.54-0.77; P<.001). Important exclusion criteria of this trial included a serum creatinine level greater than 2.5 mg/dL (221 micromoles/L) and a serum potassium level greater than 5.0 mmol/L.

Angiotensin II receptor blockers

Evidence suggests that ACE inhibitors are not completely effective in suppressing the formation of angiotensin II. Findings also indicate that alternative local and systemic pathways (e.g. the chymase pathway) may account for a significant amount of angiotensin II production.
Angiotensin II receptor blockers (ARBs) inhibit the neurohormonal system by blocking the action of angiotensin II at the receptor level, thereby inhibiting the actions of both ACE and non-ACE mechanisms. Unlike ACE inhibitors, ARBs do not inhibit the breakdown of bradykinin, and the lack of accumulation of kinins is thought to be the reason for the lower incidence of cough seen with use of these agents compared with ACE inhibitors. Results of long-term treatment have been similar with ARBs and with ACE inhibitors in terms of reduction of symptoms and mortality in patients with chronic heart failure (11).
Investigators in the Valsartan Heart Failure Trial (12) randomly assigned 5,010 patients with NYHA class II, III, or IV heart failure to receive either valsartan (<160 mg twice daily) or placebo in addition to standard therapy with ACE inhibitors, beta-blockers, digoxin, and diuretics. In this trial, the mortality rate was equivalent between the two groups and the combined end point of mortality and morbidity was 13.2% lower

with valsartan compared with placebo (P=.009), mainly due to a 24% reduction in the risk of hospitalisation for heart failure (13.8% versus 18.2%; P<.001). However, subgroup analysis showed an adverse effect on morbidity and mortality in the subgroup that received valsartan, an ACE inhibitor, and a beta-blocker (12). These findings raised concern about the safety potential of this triple-drug regimen.

Digitalis

Digitalis inhibits the sodium ion-potassium ion ratio in adenosine triphosphatase, resulting in increased cardiac contractility. Recent data suggest that digoxin (Digitek, Lanoxicaps, Lanoxin) also may attenuate the activation of the neurohormonal system by decreasing sympathetic outflow and renin suppression.
The Digitalis Investigation Group trial (13) randomly assigned 6,800 patients with mild to moderate heart failure to receive either digoxin or placebo. After a mean follow-up period of 37 months, treatment with digoxin did not affect survival (P=.80) but did decrease the risk of hospitalisation for heart failure by 28% compared with placebo (26.8% versus 34.7%; P<.001). Digoxin is recommended in patients with chronic heart failure who remain symptomatic despite treatment with ACE inhibitors and beta-blockers and in patients with both heart failure and atrial fibrillation who require control of the ventricular rate (2).

Hydralazine and nitrates

Long-term vasodilator therapy also has been shown to improve symptoms in patients with heart failure and, when given in addition to a standard regimen of digoxin and diuretics, to improve the mortality rate compared with placebo (14). However, vasodilators do not reduce mortality as much as ACE inhibitors.

The Vasodilator-Heart Failure Trial II (15) randomly assigned 804 men with chronic heart failure to receive either the combination of hydralazine hydrochloride (75 mg four times daily) and isosorbide dinitrate (40 mg four times daily) or enalapril (10 mg twice daily). The 2-year mortality rate was lower in the enalapril arm of the trial than in the hydralazine-nitrate arm (18% versus 25%; P=.016).

Thus, treatment with hydralazine (Apresoline) and oral nitrates is reserved mainly for patients with heart failure who are unable to tolerate ACE inhibitors or ARBs, primarily because of renal insufficiency, hyperkalaemia, hypotension, or cough (2).

Therapy for acute heart failure

Patients with decompensated heart failure should receive aggressive medical care, and their therapy needs to be aimed predominantly at improving haemodynamic and end-organ function (16). Acute exacerbation of heart failure should prompt a complete assessment of current haemodynamic and volume status and should initiate a search for any reversible exacerbating or inciting factors.

Clinically, it is useful to divide patients with acute exacerbations of heart failure into four broad groups: (1) patients with elevated volume and normal cardiac output, (2) those with elevated volume and low cardiac output, (3) those who have low volume and low cardiac output, and (4) those with normal volume and low cardiac output. Treatment options for the four subsets are outlined in Table 3.

A combination of these constellations of clinical findings is often present in patients who present with acute heart failure. In addition, patients may shift from one subset to another and thus require vigilant monitoring and adjustment of therapy. Insertion of a pulmonary artery catheter may help with the assessment of haemodynamic parameters.

Volume status of patients with acute heart failure should be optimised with diuretics, if needed, and stable haemodynamics must be demonstrated satisfactorily before initiation of therapy with neurohormonal blocking agents. Nitroprusside sodium (Nitropress), given intravenously, may be preferred in critically ill patients who require afterload reduction with an agent that allows rapid adjustment of response. An intra-aortic balloon pump can provide rapid afterload reduction in patients with severe heart failure and may serve as a temporising measure before more definitive therapy.

Use of a short-acting oral ACE inhibitor is a reasonable approach in patients whose condition is more stable and, compared with long-acting agents, allows more precise titration of dose. Initiation of beta-blocker therapy in a patient with acute decompensated heart failure is contraindicated because it initially may result in transient worsening of left ventricular function. If the patient already takes beta-blockers as an outpatient, therapeutic options include continuing beta-blockers and adding aggressive intravenous diuretic therapy, cutting the outpatient beta-blocker dose to half, and temporarily discontinuing beta-blocker therapy. Choice among these options depends on the severity of clinical presentation.

Current recommendations discourage use of beta-blockers in acutely ill patients in the intensive care unit who have one or both of the following: marked fluid retention or refractory heart failure requiring intravenous inotropic support. Once the patient's condition is stable from the perspectives of haemo-dynamics and volume, beta-blocker therapy may be started gradually.

Severe heart failure refractory to maximal medical management

Despite the improvement in both cardiac contractility and peripheral vasodilatation seen with use of positive inotropic agents, long-term oral therapy (17) and

intermittent intravenous infusions (18) have been associated with potentially deleterious effects on survival. Nevertheless, in a highly select patient with severe symptoms who cannot be weaned from continuous inotropic support and who is not a candidate for other devices or transplantation, inotropic agents given by continuous infusion may provide measurable improvement in quality of life. After proper discussion with the patient about the benefits and risks of such treatment, therapy with these agents may be considered. B-type natriuretic peptide (BNP) is a hormone synthesised by the ventricle in response to volume expansion and wall stress. Elevated levels of plasma BNP have been associated with worse morbidity and mortality rates in patients with chronic heart failure (19). Nesiritide (Natrecor), a vasodilator that is a human recombinant form of BNP, is administered as a continuous infusion in patients with acute heart failure. It has been shown to lower pulmonary capillary wedge pressure more effectively than intravenous nitroglycerin or placebo during acute exacerbations of heart failure (20). Guidelines for its use continue to evolve.

Biventricular pacing resynchronises ventricular contraction in a failing heart and is gaining acceptance as a therapeutic option for patients with symptomatic heart failure and a widened QRS interval on electrocardiography. The Multicenter InSync Randomized Clinical Evaluation trial (21) included 453 patients with moderate to severe heart failure, an ejection fraction of 35% or less, and an intraventricular conduction delay (>130 milliseconds) who were receiving optimal medical management. In this study, atrial synchronised biventricular pacing (i.e. leads in one atrium and both ventricles) significantly improved exercise tolerance, functional class, and quality of life.
Left ventricular assist devices are currently used as mechanical "bridge" devices to cardiac transplantation in patients with severe heart failure that is refractory to maximal supportive therapy. These devices divert blood out of the left ventricle through a large inflow conduit inserted in the left ventricular apex, into a pump-driven system, back into a large outflow conduit, and into the ascending aorta. Investigators in the Randomized

Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure trial (22) randomly assigned 129 patients with end-stage heart failure who were ineligible for cardiac transplantation to receive a left ventricular assist device or optimal medical management. Use of the device resulted in significant benefit to survival compared with optimal medical management at 1 year (52% versus 25%; P=.002) and at 2 years (23% versus 8%; P=.09). However, effectiveness was limited by a 28% to 42% incidence of infection, bleeding, and device failure.

Conclusion

The management of acute and chronic heart failure continues to evolve rapidly. In patients with chronic heart failure, inhibition of the neurohormonal axis with agents such as ACE inhibitors and beta-blockers has improved morbidity and mortality rates significantly. In contrast, patients with acute exacerbation of decompensated heart failure require an aggressive approach targeted at improving haemodynamics and end-organ function.

The cornerstones of the management of acute heart failure are identification of potentially reversible causes and immediate initiation of supportive therapy to optimise volume status and cardiac output. Administration of positive inotropic agents and placement of an intra-aortic balloon pump when clinically indicated may provide significant haemodynamic benefits while awaiting definitive therapy. Patients whose heart failure is refractory to conventional measures should be considered for referral to a heart transplantation center, where they can be evaluated for possible transplantation and, if necessary, initiation of mechanical circulatory support with a ventricular assist device.

Care of patients with severe heart failure will continue to be a challenge that requires proper selection from the pharmacologic, interventional, and mechanical options available.

Table 1: New York Heart Association functional classification of heart failure

New York Heart Association functional classification of heart failure	
Class	**Functional assessment**
I	Able to perform ordinary activities without symptoms; no limitation of physical activity
II	Ordinary physical activity produces symptoms*; slight limitation of physical activity
III	Less-than-ordinary physical activity produces symptoms; moderate limitation of physical activity
IV	Symptoms present even at rest; severe limitation of physical activity
*Symptoms may include dyspnoea, chest pain, fatigue, and palpitations. Activity level should be assessed with consideration for patient's age-group.	

Figure 1: Approach to outpatient management of Heart failure patient

Treat Exacerbating Conditions
Control blood pressure
Ensure dietary and medication compliance
Obtain smoking cessation
Limit alcohol consumption
Treat thyroid disease, anaemia
Avoid class 1 antiarrhythmic drugs,
Non-steroidal anti-inflammatory,
Non-dihydropyridine calcium channel blockers

Unable to tolerate ACE
Inhibitor due to cough or
angioedema

Treat with ACE Inhibitor
With or without diuretic to
Ensure clinical euvolemia

Treat with ARB

Unable to tolerate
ARB or ACE
Inhibitor due to
renal insufficiency,
hyperkalaemia or
hypotension

Treat with B-Blocker

**Consider Hydralazine
and Nitrate**

Patient remains
symptomatic

Consider Digoxin

NYHA class III or IV
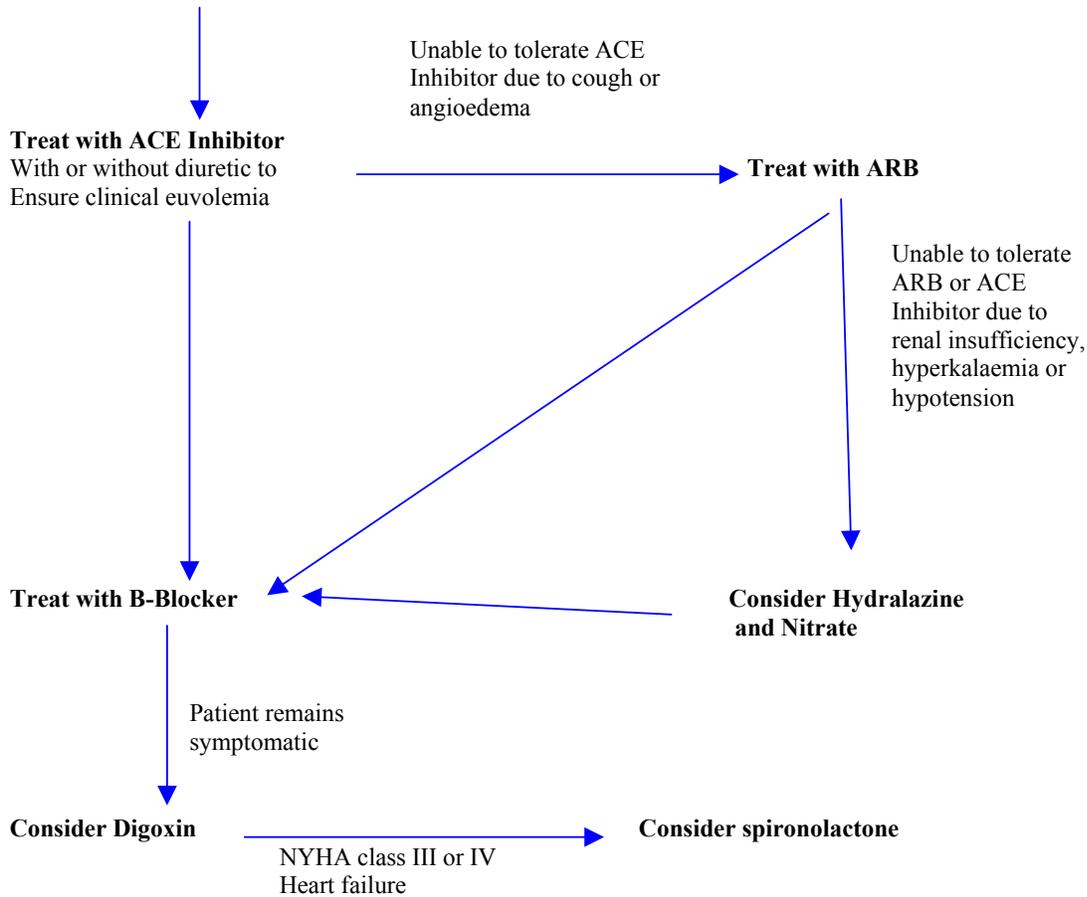Heart failure

Consider spironolactone

Table 2: Drugs used in management of chronic heart failure according to NYHA class

Drug	NYHA class I	NYHA class II	NYHA class III	NYHA class IV	Comments
Diuretics	-	+	+	+	Mainstay for optimising volume status; no proven mortality benefit
Digoxin (Digitek, Lanoxicaps, Lanoxin)	-	+	+	+	Neutral on mortality; symptomatic benefit; withdrawal associated with heart failure exacerbation
ACE inhibitors	+	+	+	+	Beneficial effects on morbidity and mortality in all patients with heart failure; first-line agent in heart failure
Spironolactone (Aldactone)	-	-	+	+	Mortality benefits in patients with NYHA class III or IV who are already taking ACE inhibitors; watch for hyperkalaemia; incremental benefit of spironolactone in addition to combination of ACE inhibitors and beta-blockers is unknown
Beta-blockers	-	+	+	+	Mortality benefits in patients with NYHA class II to IV; first-line agent in chronic heart failure; use in patients with NYHA class IV only if condition is clinically stable
Angiotensin II receptor blockers	-	+	+	+	Improvement in composite end point in patients with NYHA class II to IV heart failure; use with caution in patients already taking both ACE inhibitors and beta-blockers; second-line agent in patients who cannot tolerate ACE inhibitors because of cough or angioedema
Hydralazine HCl (Apresoline) and nitrates in combination	-	+	+	+	Improvement in symptoms and haemodynamics; second-line agent in patients who cannot tolerate ACE inhibitors or angiotensin II receptor blockers because of renal insufficiency, hyperkalaemia, or hypotension
Calcium channel blockers	-	-	-	-	Use of nondihydropyridines contraindicated in patients with systolic dysfunction; use of amlodipine (Norvasc) or felodipine (Plendil) may be considered only in patients with severe refractory hypertension who are unresponsive to agents listed above
ACE, angiotensin-converting enzyme; NYHA, New York Heart Association; +, agent used; -, agent not used.					

Table 3: Therapeutic approach to severe acute heart failure

Clinical assessment*	Treatment options
Elevated volume, normal cardiac output	Diuretics
Elevated volume, low cardiac output	Afterload-reducing agentsDiureticsInotropic therapyIntra-aortic balloon pump**
Low volume, low cardiac output	Judicious volume resuscitation
Normal volume, low cardiac output	Afterload-reducing agentsInotropic therapyIntra-aortic balloon pump**

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