

Pharmacological strategies for the treatment of congestive heart failure

Abstract

Congestive heart failure is a condition in which the heart muscle fails to supply adequate forward blood flow to vital organs. Systolic heart failure results when the heart muscle is weakened by processes such as heart attacks, alcohol abuse, infections, or rare disorders affecting the muscle itself. Diastolic heart failure results when the heart muscle fails to relax properly. Like a spring that stores energy as it is stretched, the heart muscle does the same. When it loses this elasticity, or “spring like” quality, diastolic heart failure results. CHF should be considered in the differential diagnosis of any adult patient who presents with dyspnea and/or respiratory failure. The diagnosis of heart failure is often determined by a careful history and physical examination and characteristic chest radiograph findings. The measurement of serum brain natriuretic peptide and echocardiography has substantially improved the accuracy of diagnosis. Therapy for CHF is directed at restoring normal cardiopulmonary physiology and reducing the hyperadrenergic state. The cornerstone of treatment is a combination of an angiotensin-converting-enzyme inhibitor and slow titration of a β blocker. Patients with CHF are prone to pulmonary complications, including obstructive sleep apnea, pulmonary edema, and pleural effusions. Continuous positive airway pressure and noninvasive positive-pressure ventilation benefit patients in CHF exacerbations. Despite its misleading name, “heart failure” does not mean that your heart suddenly stops working. Instead, heart failure develops slowly as your heart muscle gradually weakens. The term “failure” refers to your heart’s inability to pump enough blood to meet your body’s needs. In this review we focused on the drug for treatment of congestive heart failure.

Keywords: congestive heart failure, diastolic dysfunction, systolic dysfunction, obstructive sleep apnea, Cheyne-Stokes respiration, respiratory failure, noninvasive ventilation

Volume 6 Issue 4 - 2018

Amrish Kumar, Vrish Dhvaj Ashwlayan, Mansi Verma

Department of Pharmaceutical Technology, Dr. APJ. Abdul Kalam Technical University, India

Correspondence: Amrish Kumar, M. Pharm. (Pharmacology), Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology, NH-58, Baghat crossing Bypass Meerut-250005, Uttar Pradesh, India, Tel 09193273107, Email amrish.kumar:miet@gmail.com

Received: June 24, 2018 | Published: July 05, 2018

Introduction

Congestive heart failure (CHF) is a complex clinical syndrome that can result from any functional or structural cardiac disorder that impairs the ventricle’s ability to fill with or eject blood. Since there is no definitive diagnostic test for heart failure, it remains a clinical diagnosis that is largely based on a careful history and physical examination and supported by ancillary tests such as chest radiograph, electrocardiogram, and echocardiography. Heart failure is a common disease, affecting approximately 5 million people in the United States, and it occurs predominately in the elderly, with almost 80% of cases occurring in patients over the age of 65. The magnitude of the problem cannot be precisely assessed, because reliable population- based data on the prevalence, incidence, and prognosis are lacking. Nevertheless, several studies have found that CHF is associated with a 2-year mortality rate of approximately 45–50%, which approaches that of many malignancies. Moreover, from a societal perspective, caring for patients with CHF accounts for 2–3% of the federal health-care budget. The estimated direct and indirect cost of CHF in the United States in 2005 was \$27.9 billion. There are 2 mechanisms of reduced cardiac output and heart failure: systolic dysfunction and diastolic dysfunction. The most common causes of systolic dysfunction (defined by a left-ventricular ejection fraction of <50%) are ischemic heart disease, idiopathic dilated cardiomyopathy, hypertension, and valvular heart disease. Diastolic dysfunction (defined as dysfunction of left-ventricular filling with preserved systolic function) may occur in up to 40–50% of patients with heart failure, it is more prevalent in women, and it increases in frequency with each decade of life. Diastolic dysfunction can occur

in many of the same conditions that lead to systolic dysfunction. The most common causes are hypertension, ischemic heart disease, hypertrophic cardiomyopathy, and restrictive cardiomyopathy. Many patients who have symptoms suggestive of heart failure (shortness of breath, peripheral edema, and paroxysmal nocturnal dyspnea) but also have preserved left ventricular function may not have diastolic dysfunction instead; their symptoms are caused by other etiologies, such as lung disease, obesity, or occult coronary ischemia. This article will review the pathophysiology, diagnosis, and treatment of CHF, with specific discussion of the pulmonary manifestations and their treatment, including noninvasive positive-pressure ventilation (NPPV) strategies.¹

Drugs that decrease preload

Diuretics (Thiazides, Chlorthalidone, Furosemide, Ethacrynic acid)

Mechanism of action and pharmacologic effects: Diuretics relieve symptoms of chronic heart failure more rapidly than any other oral agent and are the only drugs that can control fluid retention. Diuretics alone, however, often cannot maintain the clinical stability of patients in heart failure for long periods of time. Thiazides diuretics such as hydrochlorothiazide act by blocking sodium and chloride reabsorption in the distal convoluted tubule.^{2–3} Sodium is avidly reabsorbed prior to reaching the distal convoluted tubule, with only 5% to 8% of the filtered sodium load being reabsorbed at this site.⁴ The thiazides are therefore relatively weak diuretics and are effective only in the early stages of CHF. More potent diuretics are eventually needed in most CHF patients. Partly because they tend to be “resistant” to

diuretic therapy. In addition, thiazides (with the possible exception of metolazone) are largely ineffective when glomerular filtration rate is below 30mL/min.⁵ Patients with moderate to severe CHF require a diuretic that is more potent than the thiazides, thus loop diuretics are widely utilized in this population. Loop diuretics such as furosemide and bumetanide act in the thick ascending limb of the loop Henle where they increase fractional excretion of sodium by 20% to 25%.⁶ Because loop diuretics are highly bound to plasma proteins, they are not highly filtered at the glomerulus. They reach the tubular lumen by active transport via the organic acid pathway (such as probenecid or organic products of uremia) can inhibit delivery of loop diuretics to their site of action and therefore decrease effectiveness. The loop diuretics induce a prostaglandin mediated increase renal blood flow, which contributes to their natriuretic effect. Co administration of non-steroidal anti-inflammatory drugs (e.g., indomethacin, ibuprofen) blocks this prostaglandin mediated effect and can also diminish response to loop diuretics maintain their effectiveness in the presence of impaired renal function although higher doses will often be necessary. The diuretic dosage used in a CHF patient is typically that which maintains the patients at a stable weight. For furosemide this will typically range from 40 to 240mg/d given on a once or twice daily basis.

Chlorthalidone inhibit sodium reabsorption in the cortical diluting segment and the first part of the distal tubule. Loop diuretics have the same effect on the entire ascending limb of the loop of Henle and reduce both the hypertonicity of renal medulla and the concentrating ability of the collecting ducts. As a result, loop diuretics are more potent than the thiazides or chlorthalidone. Loop or high-ceiling, diuretics inhibit the reabsorption of sodium and chloride in the ascending limb of the Henle as it passes of the renal medulla. The resulting reduction in the hypertonicity of the renal medulla impairs the concentrating ability of the collecting ducts. As a consequence, loop diuretics are the most potent of the diuretics, surpassing the effects produced by thiazides, chlorthalidone, and metolazone. Because loop diuretics increase the concentration of sodium presented to the distal convoluted tubules and collecting ducts, they also promote greater sodium-potassium exchange. As a consequence, potassium excretion is increased and patients may experience hypokalemia.

Therapeutic use: diuretics are appropriate first line agents for all grades of cardiac failure when sinus rhythm is present. When symptoms are mild, thiazides or chlorthalidone alone may suffice. In more severe cases, loop diuretics may be required, usually with other drugs, such as a vasodilator or digoxin. Potassium loss commonly encountered after administration of thiazides, chlorthalidone, and loop diuretics can be reduced by combining these drugs with a potassium-sparing diuretic, such as triamterene, amiloride, or spiro lactone. In all cases, careful monitoring of fluid and electrolyte levels is necessary. Alternative therapy involves supplementation with products such as potassium chloride.

Adverse effect: Thiazides, chlorthalidone can produce hypovolemia, hyponatremia, and hypokalemia. In addition, they can precipitate attacks of gout because they reduce the elimination of uric acid by the kidney. These drugs also produce hyperglycemia and aggravate preexisting diabetes mellitus. Other adverse reactions are anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice, and pancreatitis. Patients may experience the central nervous system effects of dizziness, vertigo, paresthesias, headache, and xanthopsia. Hypersensitivity reactions include

purpura, photosensitivity, rash, urticarial, necrotizing angitis, fever, respiratory distress including pneumonitis and anaphylactic reactions. Leukopenia, thrombocytopenia, agranulocytosis, aplastic anemia, and hemolytic anemia also have been reported. Despite this list, these drugs generally are considered to be quite safe when used in normal therapeutics doses.

Drug interaction

Angiotensin converting enzyme inhibitors: Enalapril, Captopril, Lisinopril used together with a diuretic in heart failure patients can produce a marked fall in blood pressure, possibly leading to postural hypotension. This can best be avoided by stopping the diuretic a few days before starting with low doses of the ACE inhibitor, thereafter, it may be possible to reintroduce the diuretic and increase the dose of the ACE inhibitor slowly.

Corticosteroids plus a diuretic can produce a greater potassium-lowering effect than either agent alone.

Digoxin toxicity is increased by hypokalemia. The reduction in plasma potassium level produced by diuretics increase the risk of digoxin toxicity. The increased sensitivity to digoxin appears to be related to the rate of fall in plasma potassium level and the extracellular-intracellular concentration ratio. Insulin And Oral Hypoglycemics may have their effects reduced by the hypoglycemic effects of diuretics. It may be necessary to use higher doses of insulin or oral hypoglycemic. Lithium excretion is reduced by diuretic induced hyponatremia. Diuretics can increase plasma lithium levels and increase lithium induced toxicities. Non Steroidal Anti-Inflammatory Drugs may inhibit the natriuretic response to diuretics, which offsets their therapeutic benefit in treating heart failure.

Doses

Thiazide and THIAZIDE-like drugs

Hydrochlorothiazide: Adults: Oral-initially 25 to 200mg/day; maintenance, 25 to 100mg/day. Children: Oral- 2mg/kg daily in two divided doses.

Chlorthalidone: Adults: Oral- 50 to 100mg/day, initially.

Metolazone: Adults: Oral- 5 to 10 mg/day, initially.

Loop Diuretic

Furosemide: Adults: Intravenous-40mg. Oral- initially 40-80mg; maximum, 200mg.

Ethacrynic Acid: Adults: Intravenous- 50 mg (0.5 to 1mg/kg). Oral- begin with 50 mg as a single daily dose after a meal and increase gradually by 50 mg daily, if necessary, to 150 to 200mg daily over 4 days. A few patients may require 200 mg increments until satisfactory response is obtained.

Potassium replacement

Potassium chloride: Adults: Oral- Prevention of hypokalemia-supplementary, approximately 20mEq/day. The treatment of depletion approximately 40mEq/day to a maximum of 100mEq/day.

Nitrates: The nitrates all activate guanylate cyclase to increase cyclic guanosine monophosphate (cyclic GMP) in vascular smooth muscle. The predominant hemodynamic effect of nitrates is to reduce preload, although a slight reduction in systemic vascular resistance may be

seen.^{7,8} Nitroglycerin has been used clinically for over a century and is available for intravenous, oral, sublingual, topical, transdermal, and buccal administration. For treatment of congestive heart failure, nitroglycerin is administered primarily by the intravenous route. The use of intravenous nitroglycerin is discussed under pharmacotherapy of Acute/ Severe Congestive Heart Failure. Relatively large doses of transdermal nitroglycerin (minimal dose of 60 mg/24hours) are needed to elicit a hemodynamic response in CHF patients.⁹

Mechanism of action and pharmacological effects: although nitrates dilate both venous capacitance vessels and precapillary (arteriolar) resistance vessels, they are used in the treatment of heavy failure primarily because of their ability to act as venodilators to reduce preload. Isosorbide dinitrate (Isordil; Sorbitrate) is effective orally for 4 to 6 hours after ingestion.

Therapeutic uses: On the basis of present data, isosorbide dinitrate may have a minor role in the treatment of congestive heart failure. The drug has been demonstrated to produce a significant but small improvement in exercise tolerance. When administered together with hydralazine, isosorbide dinitrate improved 2 year survival in one multicenter trial. Nitrates are contraindicated in the presence of severe anemia, glaucoma, increased intracranial pressure, myocardial infarction, or hypotension.

Adverse effects: headache and hypotension are the most common adverse effects if isosorbide dinitrate. The chronic use of any nitrate can lead to the development of tolerance. If the drug is then withdrawn, rebound vasoconstriction can occur.

Drug interactions: Ethanol plus a nitrate may produce hypotension.

Doses: Isosorbide Dinitrate: Oral-up to 40mg four times per day.

Drugs that decrease after load

Angiotensin converting enzyme inhibitors (Captopril, Enalapril, Lisinopril)

Mechanism of action and pharmacologic effect: Drugs that interfere with the renin-angiotensin axis can improve hemodynamics and have been effective for both acute and long-term treatment of CHF. A 12-week multicenter controlled trial showed that captopril (Capoten) improved ejection fraction, exercise tolerance, and cardiac function more than placebo. Enalapril (Vasotec), a newer, longer acting ACE inhibitor, has also been shown in controlled trials to benefit patients with CHF. A recent trial in 253 patients with severe CHF found that adding Enalapril to standard drugs improved functional status and decreased mortality by 40% at six months and by 31% at one year. Hyponatremic patients with CHF have a particularly poor prognosis that may be improved by treatment with an ACE inhibitor in addition to furosemide. Renin, released from the kidney, is converted to angiotensin I, which in turn is changed to angiotensin II by the angiotensin converting enzyme (ACE). ACE inhibitors block the conversion of angiotensin I to angiotensin II. Angiotensin II has two major effects. It constricts blood vessels and increase aldosterone secretion. By inhibiting the enzymatic conversion of angiotensin I to angiotensin II, ACE inhibitors dilate arterioles and veins, reducing respectively the afterload and the preload. In addition, by decreasing aldosterone secretion, ACE inhibitors reduce blood volume, further contributing to their ability to decrease preload. Captopril is effective without need for conversion to another form. Enalapril is a prodrug that is de-esterified in the liver to the active chemical enalaprilat. This

fact has little clinical significance, except for the fact that the initial effect of enalapril may take longer to appear as the body converts the drug to its active metabolite. In addition, it is not clear what effect hepatic damage may have on the ability of the liver to convert enalapril to enalaprilat. Lisinopril is the lysine derivative of enalaprilat. It is absorbed more slowly than enalapril after oral administration, but it does not require hydrolysis in the liver to form an active compound. Enalapril and lisinopril have longer half-lives (11 to 12 hours) than captopril (3 hours) and may be administered once a day, compared to the twice-daily regimen currently recommended for captopril. This convenience factor must be counterbalanced with the knowledge that the initial hypotensive effect seen in the approximately 50 per cent of patients taking an ACE inhibitor may be longer in duration if enalapril or lisinopril is used.

Therapeutic uses: ACE inhibitors represent a major advance in the development of antihypertensive therapy. As effective alone as beta blockers or diuretics, these drugs often produce fewer adverse effects than other antihypertensives. The alteration in blood chemistry, bradycardia, intermittent claudication, fatigue, cold extremities, and decrease in libido produced by either diuretics or beta blockers are not experienced by patients taking ACE inhibitors. As a result, many patients taking ACE inhibitors experience an increase in quality of life.

In addition to being effective alone, ACE inhibitors can be used to complement the antihypertensive effects of a diuretic or a beta blocker. ACE inhibitor also has an additive antihypertensive effect when combined with calcium channel blocker.

Adverse effects: Overall, the incidence of adverse effects is usually with ACE inhibitors than with other forms of antihypertensive therapy. Although initial clinical trials with relatively large doses of captopril found that 1 to 2 per cent of patients developed proteinuria and a smaller number demonstrated renal insufficiency, renal failure, polyuria oligouria, and urinary frequency, the cause and effect relationship with captopril is uncertain. Neutropenia or agranulocytosis that was probably drug related occurred in about 0.3 per cent of patients treated with captopril. Other adverse effects include a skin rash, angioedema, and dysgeusia. If the dose of captopril is restricted to a maximum of 150 mg/day, the incidence of adverse effects is reduced significantly. In addition to dose, the other factors that predispose and connective tissue disorders.

Severe symptomatic hypotension can occur after the first dose of captopril, particularly in diuretic treated patients who are salt depleted. This effect can be reduced or prevented if the diuretic is stopped or its dose reduced in the 3 to 4 days prior to captopril treatment. In addition, patients should be treated with low dose of captopril, in the range of 6.25 to 12.5mg/day, before increasing the dose of captopril gradually over the next few days and reinstating diuretic therapy slowly. Enalapril may cause headache, dizziness, nausea, diarrhea and hyperkalemia. Similarly to captopril, severe symptomatic hypotension can occur after the first dose of enalapril. Again, the effect is more prevalent in salt depleted patients. Because enalapril has a slower onset and longer duration of action than captopril, several hours may be required to produce the initial hypotensive effect, and the effect may last longer than that produced by captopril. Rash and taste disturbances may be less common with enalapril than with captopril. Lisinopril can also produce symptomatic hypotension, particularly in patients who are volume or sodium depleted as a result of diuretic therapy, salt restriction, and diarrhea or vomiting. Similarly

to enalapril this effect may be delayed until 4 to 6 hours after taking lisinopril.

Drug interactions

Diuretics and an ACE inhibitor used together can produce a powerful hypotensive effect, possibly leading to postural hypotension. This can best be avoided by stopping the diuretic a few days before starting with low doses of the ACE inhibitor. Thereafter, it may be possible to reintroduce the diuretic and increase the dose of the ACE inhibitor slowly. Non-steroidal, Anti-inflammatory Drugs can reduce the ability of ACE inhibitors to dilate blood vessels. Potassium Supplements and Potassium Sparing Diuretics should not be used with ACE inhibitors. Because ACE inhibitor decrease aldosterone secretion, they cause retention of Potassium. As a result, hyperkalemia can occur in patients receiving potassium supplement.

Doses

Captopril: Adults; Oral-initially, for mild to moderate hypotension, 12.5mg two or three times daily. For severe hypertension, over 1 to 2 weeks to 50mg two or three times daily. In volume depleted or hyponatremic patients, the initial dose should be 6.25 to 12.5mg three times daily.

Enalapril: Adults; Oral-initially 2.5 mg for patients on a diuretic, or 5mg for patients not on a diuretic. Maintenance dose, 10 to 40mg daily. Elderly; The initial dose should be 2.5mg.

Lisinopril: Adults; Oral- normal renal function- initially, 10 mg once daily; increase gradually to 20 to 40mg. Impaired renal function (serum creatinine \geq 3mg/dl or creatinine clearance $<$ 3ml/minute) -initial dose should be 5mg/day.²⁻⁶

Drugs that increase myocardial contractility (inotropic drugs)

Digoxin

Mechanism of action and pharmacological effects: Digoxin is the most frequently used of the digitalis glycosides. It increases intracellular Na^+ by inactivating Na^+/K^+ ATPase. The rise in intracellular Na^+ increases intracellular Ca^{++} concentrations by reducing Ca^{2+} transport out of the cell by the $\text{Na}^+-\text{Ca}^{++}$ exchange mechanism. Digoxin may also increase Ca^{++} entry into the heart cell through the calcium channel or stimulate the release of stored calcium from the sarcoplasmic reticulum. Digoxin's ability to increase cardiac contractility results from the increase in the intracellular concentration of Ca^{++} . In heart failure, the direct inotropic action of digoxin may increase cardiac output and thus decrease venous pressure, reduce heart size, and slow compensatory reflex tachycardia. Digoxin decreases ventricular volume and does not increase myocardial oxygen consumption in the failing heart. By increasing renal blood flow, digoxin promotes diuresis and reduces edema. Digoxin increases atrioventricular (AV) nodal conduction time and refractory period. This effect is due to increased vagal tone and decreased sympathetic drive to the heart. In addition, the improvement in cardiac output may slow the sinus rate in patients with cardiac failure. The delay in AV conduction benefits patients with atrial flutter or fibrillation. By reducing the speed at which impulse are transmitted to the ventricles, ventricular contraction rate is reduced. This allows more time for this chamber to fill and improves cardiac efficiency.

Therapeutic uses

Digoxin can be given intravenously or orally. Its action is relatively rapid, beginning within 5 to 30 minutes after intravenous injection and 1 to 2 hours after ingestion. Digoxin is excreted unchanged in the urine and has a half-life of about 1.5 days in patients with normal renal function. Digoxin's clearance varies directly with creatinine clearance, and the dosage must be reduced in proportion to a decrease in creatinine clearance. Elderly patients should also be given reduced maintenance dosage of digoxin. Premature and immature infants are particularly sensitivity to digoxin. Potassium depletion sensitizes the myocardium to digoxin and reduces its positive inotropic effects. Acute myocardial infarction, severe pulmonary disease, or advanced heart failure is often accompanied by an increased sensitivity to digoxin. Toxic levels of digoxin are only two to three times higher than therapeutically effective concentration. In view of this, methods have been developed to measure the concentrations of the cardiac glycosides in the serum of patients. Most hospital laboratories have a rapid radioimmunoassay method for the measurement of serum digoxin levels. The therapeutic window usually falls between 0.5 to 2.0ng/ml (1.0 to 2.6nmol/l). The development of the radioimmunoassay for digoxin has been a great help in managing patients. As the serum levels of digoxin approach 2.0ng/ml (2.6nmol/l) the physician is alerted to possible toxicities. Serum concentration of digoxin below 0.5ng/ml (1.0nmol/l) is usually ineffective. These values are, however, only an aid in the clinical management of the individual and must be taken in context with the condition of the patient. As explained earlier, several clinical conditions, such as hypokalemia, hypothyroidism, age, and myocardial infarction, can increase the action of digoxin on the heart. In the final analysis the physician's clinical judgement must serve as the basis for patient management. Congestive heart failure is the major indication for the use of digoxin. The increased myocardial contractility improves cardiac output and tissue perfusion and reduces venous congestion. Patients with congestive heart failure due to coronary heart disease, hypertensive heart disease with left to right shunts respond better to digoxin than those with congestive heart failure due to cardiomyopathy or Pulmonale.

Diuretics complement digoxin because they reduce blood volume and venous congestion. However, care must be taken to prevent hypokalemia. It is usually necessary to use a potassium sparing diuretic with the thiazides, chlorthalidone, metolazone, or furosemide or to supplement the patient's diet with potassium. The role, and success, of digoxin in the treatment of cardiac disorders can be divided into those conditions involving arrhythmias and those in which the patients have a normal sinus rhythm. In the former, digoxin is still considered often to be a useful drug. In the latter, its place is challenged. The role of digoxin in the treatment of patients with cardiac failure and atrial fibrillation is still accepted. By slowing the ventricular rate, digoxin allows more time for filling. This action, combined with its inotropic effects, improves cardiac output and provides patients with significant clinical benefit. Because of its ability to increase AV conduction time, digoxin is widely used in the treatment of supraventricular tachyarrhythmia. The most common use for the drug is the treatment of atrial fibrillation with rapid ventricular response. By the same token, atrial flutter can also be managed by digoxin to produce a ventricular rate of 70 to 100beats/minutes. Paroxysmal supraventricular tachycardia can also be treated with digoxin, provided that it can be established that digoxin is not the cause of the arrhythmia. Digoxin can often be successful in interrupting the reentrant circuit in the

Wolf-Parkinson-White syndrome. It is contraindicated, however, in patients in whom the syndrome is associated with atrial fibrillation.

As suggested earlier, however, digoxin's role in patients with sinus rhythm is controversial. Most studies suggest that digoxin's inotropic effect persist during chronic therapy, but it has been difficult to demonstrate the clinical usefulness of the drug. Whether or not digoxin provides significant additional benefit to the patients in sinus rhythm over that produced by diuretic therapy is uncertain. There is no evidence that digoxin improves long term survival in patients with cardiac failure. Because of its toxicities and the recent introduction of ACE inhibitors in the treatment of heart failure, the use of digoxin in patients with heart failure and normal sinus rhythm may well fall to third line therapy, behind diuretics and ACE inhibitors.

Adverse effects

Digoxin can produce a variety of arrhythmias. The withdrawal of sympathetic stimulation and the addition of a high degree of vagal activity can produce marked sinus bradycardia. On the other hand, digoxin's ability to increase automaticity can lead to paroxysmal or non-paroxysmal atrial tachycardia or can convert atrial flutter into fibrillation. Digoxin's ability to impair AV conduction can produce a complete heart block. This effect, combined with the increased automaticity in AV tissue, may lead to AV junctional rhythms, including tachycardia. The most common ventricular rhythm is premature ventricular depolarization. These appear as coupled beats (bigeminy) with an ectopic beat immediately following the normal beat. This can progress to ventricular tachycardia and ventricular fibrillation. Tolerance to digoxin is reduced in old age, renal insufficiency, and hypothyroidism, and acute myocardial infarction. Hyperkalemia can increase the AV block produced by digoxin, and hypokalemia can enhance ectopic pacemaker automaticity. Hypercalcemia and hypomagnesemia increase tissue sensitivity to digoxin. Cardioversion increases tissue sensitivity to digoxin, and this can lead to serious arrhythmias.

Treatment of digoxin intoxication

Discontinue digoxin until all sign of toxicity are abolished. Depending on the degree of intoxication, this may be all the treatment required. If potassium levels are low, potassium chloride may be given in divided doses totaling 50 to 80mEq for adults (5 to 8mEq/hour), provided renal function is adequate. When correction of the arrhythmia is urgent, and the serum potassium concentration is low or normal, potassium is administered intravenously in 5 per cent dextrose in water. A total of 40 to 100mEq (30 mEq/500 ml) at a rate of 20 mEq/hour may be given if the arrhythmia is uncontrolled and the potassium well tolerated. Electrocardiographic monitoring is indicated to avoid potassium toxicity (e.g., peaking of T waves). In children, potassium preparation may be given orally in divided doses totaling 1 to 1.5mEq/kg (1g potassium chloride contains 13.4mEq). When correction of the arrhythmias is urgent, give potassium at a rate of approximately 0.5mEq/hour while monitoring the electrocardiogram. Potassium should be administered as a solution containing 20mEq or less/500 ml in 5 per cent dextrose in water. The total dose of potassium should generally not exceed 2mEq/kg.

Potassium should not be used and may be dangerous for severe or complete heart block due to digoxin, not related to any tachycardia. The ECG should be observed continuously so that the infusion may be promptly stopped when the desired effect is achieved. Other agents

that have been used in the treatment of digoxin intoxication include lidocaine, phenytoin, quinidine, procainamide, and beta blockers. The three last-mentioned agents should be used with caution when AV block is a component of digoxin intoxication because they may exaggerate this arrhythmic property. Purified digoxin specific antibody fragments bind with digoxin and the resulting complex is excreted by the kidney. This approach to treating digoxin toxicity appears to be highly effective.

Drug interactions

Amiodarone increases digoxin serum concentration. Amiloride increases digoxin has similar effects on the myocardium. Calcium and digoxin have similar effects on the myocardium. Parenteral calcium has been reported to precipitate cardiac arrhythmias in patients receiving digoxin. Diuretics with the exception of potassium-sparing diuretics, can cause hypokalemia and increase digoxin toxicity. Metoclopramide may decrease digoxin absorption from the gastrointestinal tract. Propafenone increases serum digoxin concentration.

Quinidine can increase serum digoxin levels by reducing renal and nonrenal clearance of the drug. Gastrointestinal disturbances and ventricular arrhythmias have occurred as result of this interaction. The dose of digoxin should be reduced by 50 per cent before starting therapy with quinidine. Patients receiving both drugs should be monitored carefully, particularly during the initial 5 days of combined therapy. If quinidine is discontinued, patients should be monitored for under digitalization. Rifampin can decrease serum digoxin concentration.

Doses

Digoxin

Intravenous Digitalization: 10 years and over; 0.25 to 0.5mg, then 0.25mg at 4 to 6 hour intervals as required to a maximum 1.0mg. Total pediatric intravenous digitalization doses- Give in divided amounts at 6 hour intervals. Premature infants: 0.015 to 0.025mg/kg. Full term newborn infants: 0.02 to 0.03mg/kg. 1 month to 2 years: 0.03 to 0.05mg/kg. 2 to 5years: 0.025 to 0.035mg/kg. 5 to 10years: 0.015 to 0.03mg/kg.

Intravenous maintenance: Premature Infants; 20 to 30 per cent of the oral loading dose. Full term infants and children: 24 to 30 per cent of oral loading dose.

Oral digitalization: Adults: 0.5 to 0.75mg, then 0.25 to 0.5mg every 6 to 8 hours as required.

Oral maintenance: Adult: 0.125 to 0.500mg daily. Elderly: 0.125 to 0.250mg.

Pediatric oral digitalization: Total pediatric doses-give in divided amounts at 6hour intervals. Premature Infants: 0.025 to 0.035mg/kg. Full term newborn infants: 0.025 to 0.035mg/kg. 1 month to 2 years: 0.035 to 0.06mg/kg, 2 to 5 years: 0.03 to 0.04mg/kg, 5 to 10 years: 0.02 to 0.035 mg/kg, Over 10 years: 0.01 to 0.015 mg/kg.

Pediatric oral maintenance: Premature infants; 20 to 30 per cent of loading dose given per day. Full term infants and children; 25 to 35 per cent of oral loading dose given per day.⁷

Amrinone

Amrinone is a potent inotropic vasodilator. It increases myocardial

contractility, even after full doses of digoxin, and reduce left and right ventricular filling pressures and pulmonary capillary wedge pressure. The drug improves resting and exercise hemodynamics, increases left ventricular ejection fraction, and improves exercise capacity. Amrinone has been used in patients with severe chronic congestive heart failure not adequately controlled by digoxin, antiarrhythmic drugs, and vasodilators. In patients with atrial fibrillation or flutter, digoxin should be administered concomitantly to control the possible enhanced AV conduction induced by amrinone. In such case, and in patients with multifocal or runs of premature ventricular contractions, careful dose titration and close ECG monitoring is advisable during intravenous therapy. The potential for arrhythmia, present in congestive heart failure, may be increased by amrinone. Administration of amrinone has reduced platelet counts to 100,000 platelets/mm³ in 2.4 percent of patients. Blood platelets counts should be determined before and during amrinone therapy. Clinically significant lowering of platelets counts ($\leq 50,000$ platelets/mm³) warrants discontinuation of amrinone therapy. Amrinone should not be used in severe obstructive aortic or pulmonic valvular disease in lieu of surgical relief of the obstruction. Fluid and electrolyte change should be monitored carefully during amrinone therapy. Amrinone has been reported to produce fever and nephrogenic diabetes insipidus. Hepatotoxicity has occurred rarely.

Drug interactions: Disopyramide and amrinone should be administered concomitantly with caution until additional clinical experience is available.

Doses: Adults; Intravenous-initially, 0.75mg/kg bolus over 2 to 3 minutes. Maintenance-infuse at rate of 5 to 10 μ g/kg/minute. Based on clinical response, an additional bolus injection of 0.75mg/kg may be given 30 minutes after initiation of therapy. Maintain infusion at approximately 5 to 10 μ g/kg/minute such that the total daily dose (including boluses) does not exceed 10mg/kg. Amrinone administration is not recommended for a period over 24 hours unless the potential benefit clearly surpasses the risk of longer therapy.

Dobutamine

Dobutamine stimulate beta₁ receptor in the heart. In contrast to other sympathomimetic, dobutamine, in moderate doses, increases cardiac output with minimal effects on heart rate. As a result, myocardial oxygen requirements are not as great with dobutamine as with drugs that increase both cardiac output and heart rate. Dobutamine does not dilate renal vessels, increase glomerular filtration, or improve sodium excretion. Intravenous dobutamine is used for short term therapy to increase cardiac output in patients with severe chronic cardiac failure. In patients who have atrial fibrillation with rapid ventricular response, digoxin should be used prior to starting dobutamine therapy. Because dobutamine facilitate AV conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. During dobutamine administration, monitor ECG, heart rate, and blood pressure continuously. In addition, monitor pulmonary wedge pressure and cardiac output whenever possible. Hypovolemia should be corrected with suitable volume expanders before starting dobutamine infusion. Clinical experience with dobutamine administration after myocardial infarction has been insufficient to establish the safety of this use. Large dose of dobutamine can increase both heart rate and blood pressure. Dobutamine's adverse effects include tachycardia, angina pain, arrhythmias, headache, and hypertension. Nausea and vomiting may also be seen. Caution should exercised in giving dobutamine to patients with hyperthyroidism.

Drug interactions: Antidepressants may potentiate the pressor response to dopamine. Monoamine Oxidase Inhibitors increase

the activity of dobutamine because dobutamine is metabolized by monoamine oxidase. Sympathomimetic and dopamine may produce additive effects and should be used concomitantly with caution.

Doses: Adults; Intravenous-infusion usually between 2.5 and 10 μ g/kg/minute. On occasion, it may be necessary to raise the dose to as high as 40 μ g/kg/minute.⁸

Non pharmacologic therapy

Recent studies demonstrate that cardiac resynchronization therapy (CRT) offers a promising approach to selected patients with chronic heart failure. Delayed electrical activation of the left ventricle, characterized on the ECG by a QRS duration that exceeds 120ms, occurs in approximately one-third of patients with moderate to severe systolic heart failure. Since the left and right ventricles normally activate simultaneously, this delay results in asynchronous contraction of the left and right ventricles, which contributes to the hemodynamic abnormalities of this disorder. Implantation of a specialized biventricular pacemaker to restore synchronous activation of the ventricles can improve ventricular contraction and hemodynamics. Recent trials show improvements in exercise capacity, NYHA classification, quality of life, hemodynamic function, and hospitalizations.^{9,10} A device that combined CRT with an implantable cardioverter-defibrillator (ICD) improved survival in addition to functional status. CRT is currently indicated only in NYHA class III–IV patients receiving optimal medical therapy (ACE inhibitors, diuretics, β -blockers, and digoxin) and with a QRS duration of 120ms or greater and an ejection fraction of 35% or less. Sudden cardiac death, primarily due to ventricular tachycardia and fibrillation, is responsible for 40% to 50% of the mortality in heart failure patients. In general, patients in the earlier stages of heart failure with milder symptoms are more likely to die from sudden death, whereas death from pump failure is more frequent in those with advanced heart failure. Most of these patients have complex and frequent ventricular ectopy, although it remains unknown whether these ectopic beats contribute to the risk of malignant arrhythmias or merely serve as markers for individuals at higher risk for sudden death. What is clear is that empirical treatment with class I antiarrhythmic agents, although they can suppress ventricular ectopy, adversely affects survival.¹¹ Unlike the class I drugs, the class III antiarrhythmic agent amiodarone has a low proarrhythmic potential, but it has not been shown consistently to prevent sudden death in patients with heart failure. Because of its lack of benefit, in addition to its multiple adverse effects and drug interactions, amiodarone is not recommended for the prevention of sudden death. In cardiac arrest survivors with a reduced ejection fraction, the ICD is superior to antiarrhythmic drug therapy for improving survival.¹² The role of the ICD in primary prevention of sudden death is less certain. Compared with antiarrhythmic drugs, an ICD improves survival in patients with coronary artery disease and an ejection fraction of 30% or less. However, the role of the ICD in patients with nonischemic cardiomyopathy and those with ejection fractions of 30% or greater remains an unsettled issue and hopefully will be clarified by the results on ongoing clinical trials.

Pharmacologic therapy

Standard first-line therapies

ACE inhibitors

ACE inhibitors are the cornerstone of pharmacotherapy of patients with heart failure. By blocking the conversion of angiotensin I to angiotensin II by ACE, the production of angiotensin II and, in turn, aldosterone is decreased but not completely eliminated. This

decrease in angiotensin II and aldosterone attenuates many of the deleterious effects of these neurohormones, including reducing ventricular remodeling, myocardial fibrosis, myocyte apoptosis, cardiac hypertrophy, NE release, vasoconstriction, and sodium and water retention. Thus ACE inhibitor therapy appears to play an important role in preventing angiotensin II-mediated progressive worsening of myocardial function. The endogenous vasodilator bradykinin, which is inactivated by ACE, is also increased by ACE inhibitors, along with the release of vasodilatory prostaglandins and histamine.^{13,14} The precise contribution of the effects of ACE inhibitors on bradykinin and vasodilatory prostaglandins is unclear. However, the persistence of clinical benefits with ACE inhibitors despite the fact that angiotensin II and aldosterone levels return to pretreatment levels suggests that this is a potentially important effect.^{15,16} Numerous placebo-controlled trials have documented the favorable effects of ACE inhibitor therapy on hemodynamic variables, clinical status, and symptoms in heart failure.¹⁷ Hemodynamic effects observed with long-term therapy include significant increases in cardiac index, stroke work index, and stroke volume index, as well as significant reductions in left ventricular filling pressure, SVR, MAP, and heart rate. Significant improvements in clinical status, functional class, exercise tolerance, and left ventricular size also are well documented. When compared with placebo, patients treated with ACE inhibitors have fewer treatment failures, fewer hospitalizations, and fewer increases in diuretic dosages. The acute response to ACE inhibitor therapy is greater in patients with high levels of plasma renin activity. However, long-term hemodynamic and clinical responses to ACE inhibition cannot be predicted from the plasma renin activity or from response to the initial dose of ACE inhibitor.

The beneficial effect of ACE inhibitors on mortality has been documented conclusively, with numerous trials showing a 20% to 30% relative reduction in mortality with ACE inhibitor therapy compared with placebo. A long-term (12-year) follow-up of the Studies of Left Ventricular Dysfunction (SOLVD) prevention and treatment trials demonstrated sustained survival benefits in patients treated with enalapril. In addition to improving survival, ACE inhibitors also reduce the combined risk of death or hospitalization, slow the progression of heart failure, and reduce the rates of reinfarction. The benefits of ACE inhibitor therapy are independent of the etiology of heart failure (ischemic versus nonischemic) and are observed in patients with mild, moderate, or severe symptoms. ACE inhibitors clearly are superior to vasodilator therapy with hydralazine-isosorbide dinitrate. The most common cause of heart failure is ischemic heart disease, where MI results in loss of myocytes, followed by ventricular dilatation and remodeling. Captopril, ramipril, and trandolapril all have been shown to benefit post-MI patients whether they are initiated early (within 36 hours) and continued for 4 to 6 weeks or started later and administered for several years. Collectively, these studies indicate that ACE inhibitors after MI improve overall survival, decrease the development of severe heart failure, and reduce reinfarction and heart failure hospitalization rates. The benefit occurs within the first few days of therapy and persists during long-term treatment. The effects are most pronounced in higher-risk patients, such as those with symptomatic heart failure or reduced EFs, with 20% to 30% reductions in mortality reported in these patients.

Post-MI patients without heart failure symptoms or decreases in EF also benefit from ACE inhibitors, but the magnitude of this effect is less pronounced, with all-cause mortality reduced by 7% to 11%. In addition to their benefits in patients with established heart failure,

ACE inhibitors also are effective for prevention of heart failure. The SOLVD prevention trial showed that enalapril decreased the risk of hospitalization for worsening heart failure and reduced the composite end point of death and heart failure hospitalization in patients with asymptomatic left ventricular dysfunction. The development of diabetes mellitus, an important risk factor for cardiovascular disease that also increases morbidity and mortality in heart failure patients, is reduced by enalapril in patients with chronic heart failure. In a posthoc analysis of the Heart Outcomes Prevention Evaluation (HOPE) trial, ramipril reduced the development of new-onset heart failure by nearly 25% in patients with normal EFs and no symptoms of heart failure. Despite the overwhelming benefit demonstrated with ACE inhibitors, there is substantial evidence that these agents are underused and underdosed in patients with heart failure. These data indicate that significant numbers of heart failure patients do not receive ACE inhibitors, and of those who are receiving these agents, many may be taking lower than recommended doses. The most common reasons cited for underuse or underdosing are concerns about safety and adverse reactions to ACE inhibitors, especially in patients with underlying renal dysfunction or hypotension. The use of ACE inhibitors in patients with renal insufficiency is particularly relevant because it occurs in 25% to 50% of heart failure patients and is associated with an increased risk of mortality. Recent evidence indicates that ACE inhibitors in post-MI patients with decreased left ventricular function may be more effective in patients with renal insufficiency. In this retrospective cohort study, nearly 21,000 Medicare patients with confirmed MIs and EFs of less than 40% on hospital discharge were studied. In patients receiving an ACE inhibitor at hospital discharge, those with a serum creatinine level of greater than 3mg/dL had a 37% increase in 1-year survival compared with only a 16% increase in patients with a serum creatinine level of less than 3mg/dL.

Since many heart failure patients have concomitant disorders (e.g., diabetes, hypertension, or previous MI) that also may be affected favorably by ACE inhibitors, renal dysfunction should not be a contraindication to ACE inhibitor use in patients with left ventricular dysfunction. However, these patients should be monitored carefully for the development of acute renal failure and/or hyperkalemia, with special attention to risk factors associated with this complication of ACE inhibitor therapy.^{18,19} No dose-dependent differences in mortality have been reported for ACE inhibitors. In the ATLAS trial, over 3000 patients with NYHA class II–IV heart failure and an EF of 30% or less were randomized to receive either low-dose (2.5–5mg/day) or high-dose (32.5–35mg/day) lisinopril for a median of 45 months.²⁰ No differences in mortality were found between the high and low-dose groups. However, the composite end point of death or hospitalization for any cause was reduced significantly by 12% and heart failure hospitalizations decreased by 24% in the high-dose group. In many positive trials of other heart failure therapies (e.g., β -blockers, aldosterone antagonists), intermediate ACE inhibitor doses generally were used as background therapy. These results emphasize that clinicians should attempt to use ACE inhibitor doses proven to be beneficial in clinical trials, but if these doses are not tolerated, lower doses can be used with the knowledge that there are likely only small differences in efficacy between the high and low doses. In summary, the evidence that ACE inhibitors improve symptoms, slow disease progression, and decrease mortality in heart failure is unequivocal. As such, all patients with documented left ventricular dysfunction, irrespective of symptomatology, should receive ACE inhibitors unless there are contraindications or intolerance is present.

β-blockers

It may seem paradoxical that within this chapter β-blockers are listed as drugs that may exacerbate or worsen heart failure and as standard therapy for the management of chronic heart failure, but both are true. Initiation of β-blocker therapy at normal doses in patients with heart failure has the potential to lead to symptomatic worsening or decompensation owing to the drug's negative inotropic effect. However, there is also overwhelming evidence that if stable patients are initiated on low doses of a β-blocker, with slow upward dose titration over several weeks, they can expect to derive significant benefits. As such, the ACC/AHA guidelines on the management of heart failure recommend that β-blockers should be used in all patients with stable systolic heart failure unless they have a contraindication or have been shown clearly to be unable to tolerate β-blockers. Patients should receive a β-blocker even if their symptoms are well controlled with diuretic and ACE inhibitor therapy because they remain at risk for progression of disease. Additionally, it is not essential that ACE inhibitor doses are optimized prior to initiation of β-blocker therapy because patients are more likely to accrue benefit from addition of a β-blocker than from an increase in their ACE inhibitor dose. β-Blockers have been studied extensively, with data on more than 10,000 participants of placebo-controlled trials. Carvedilol, metoprolol controlled release/extended release (CR/XL), and bisoprolol are the best studied of the β-blockers in heart failure.

Each has been studied in large populations, with a primary study end point of mortality, and each has been shown to reduce mortality significantly compared with placebo. The CIBIS-II trial studied bisoprolol in over 2600 patients, most of whom had class III heart failure. The study was stopped prematurely because of the 34% reduction in mortality associated with bisoprolol.⁶⁰ Post-hoc analyses showed a 44% reduction in sudden death and a 26% reduction in death due to worsening heart failure. The data from the largest β-blocker mortality trial to date, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF), were very similar to those with bisoprolol. In this study, nearly 4000 patients were randomized to metoprolol CR/XL (Toprol XL) or placebo.²¹ Most of the patients had class II or III heart failure. Again, the study was halted prematurely because of a 34% reduction in total mortality, with a 41% reduction in sudden death and a 49% reduction in death from worsening heart failure. Multiple post-hoc subgroup analyses suggested that all analyzed subgroups benefited from the therapy. Following publication of these trials, the value of β-blockers in class II and III heart failure patients was clear, and they became standard therapy in these patients. However, there remained questions about their value or safety in patients with class IV heart failure.

The Carvedilol, Prospective, Randomized, Cumulative Survival (COPERNICUS) trial was designed to test carvedilol in the severe heart failure population and, like the other studies, was stopped prematurely because of the drug's significant survival benefit. Specifically, carvedilol produced a 35% relative reduction in mortality and an impressive 7.1% absolute reduction in mortality (from 18.5% to 11.4%). Thus there is now clear evidence of benefit with β-blockers in all patients with symptomatic systolic heart failure. In addition to data on the effects of β-blockers on survival, there are data showing improvements in numerous other end points. All the large clinical trials have shown β-blockers to produce 15% to 20% reductions in all-cause hospitalization and 25% to 35% reductions in hospitalizations for worsening heart failure. The positive effects of β-blockers on the left ventricle systolic function also have been very consistent across

studies. Following several weeks to months of therapy, β-blockers have been documented consistently to increase EFs by 5 to 10 units (e.g., from an EF of 20% to 25% or 30%), to decrease ventricular mass, to improve the sphericity of the ventricle, and to reduce systolic and diastolic volumes (LVESV and LVEDV). These effects are often collectively called reverse remodeling, referring to the fact that they return the heart toward more normal size, shape, and function.

While the effects of β-blockers on survival prolongation and left ventricular reverse remodeling could be argued to be greater than those of any other drugs used in heart failure, this is not the case for their symptomatic benefits. Many, but not all studies, have shown improvements in the NYHA functional class, patient symptom scores or quality-of-life assessments (such as the Minnesota Living with Heart Failure Questionnaire), and exercise performance, as assessed by the 6-minute walk test. Thus it is important to educate patients that they will not necessarily notice dramatic symptomatic improvements with β-blocker therapy. However, even in the absence of symptomatic improvement, positive effects on disease progression and survival are still anticipated. A number of potential mechanisms have been suggested to explain the beneficial effects of β-blockers in heart failure patients. Although not clearly elucidated, it seems likely that the mechanisms of benefit include antiarrhythmic effects, slowing or reversing the detrimental ventricular remodeling caused by sympathetic stimulation, decreased myocyte death from catecholamine-induced necrosis or apoptosis, and prevention of fetal gene expression and the other detrimental effects of SNS activation described earlier.²²

Diuretics^{23,24,25}

The compensatory mechanisms in heart failure stimulate excessive sodium and water retention, often leading to signs and symptoms of systemic and pulmonary congestion. Consequently, diuretic therapy is recommended for all patients with clinical evidence of fluid retention. Among the drugs used for management of heart failure, the diuretics are most rapid in producing symptomatic benefits. The majority of patients with heart failure will require chronic diuretic therapy to control their fluid status, and as such, diuretics represent a cornerstone of heart failure therapy. However, because they do not alter disease progression (or prolong survival), they are not considered mandatory therapy. Thus patients who do not have fluid retention would not require diuretic therapy. The primary goal of diuretic therapy is to reduce symptoms associated with fluid retention and pulmonary congestion, improve quality of life, and reduce hospitalizations from heart failure. They accomplish this by decreasing edema and pulmonary congestion through reduction of preload. Although preload is a determinant of cardiac output, the Frank-Starling curve shows that patients with congestive symptoms have reached the flat portion of the curve. A reduction in preload improves symptoms but has little effect on the patient's stroke volume or cardiac output until the steep portion of the curve is reached. However, diuretic therapy must be used judiciously because over diuresis can lead to a reduction in cardiac output and symptoms of dehydration. Once diuretic therapy is initiated, dosage adjustments are based on symptomatic improvement and daily body weight. Change in body weight is a sensitive marker of fluid retention or loss, and it is recommended that patients monitor their status by taking daily morning body weights. Patients who gain a pound per day for several consecutive days or 3 to 5 lb in a week should contact their health care provider for instructions (which often will be to increase the diuretic dose temporarily). Such action often will allow patients to prevent a decompensation that requires hospitalization.

Nitrates and hydralazine

Nitrates and hydralazine were combined originally in the treatment of heart failure because of their complementary hemodynamic actions. Nitrates, by activating guanylate cyclase to increase cyclic guanosine monophosphate (cGMP) in vascular smooth muscle, are primarily venodilators, thus producing reductions in preload. Hydralazine is a direct-acting vasodilator that acts predominantly on arterial smooth muscle to reduce SVR and increase stroke volume and cardiac output its effects on preload are minimal. Recent evidence suggests that these agents also may have beneficial effects in heart failure beyond their hemodynamic actions by inhibiting the ventricular remodeling process, preventing nitrate tolerance, and attenuating cellular mechanisms associated with heart failure progression. Compared with placebo, the combination of hydralazine and isosorbide dinitrate (ISDN) reduced mortality in patients receiving diuretics and digoxin (but not ACE inhibitors or β -blockers).²⁶ However, another trial comparing the combination with an ACE inhibitor found that mortality was lower in the ACE inhibitor group. Adverse effects (primarily headache and gastrointestinal complaints) with combined hydralazine-ISDN were common, limiting their use in many patients. Patient compliance also was an important issue because hydralazine-ISDN therapy was given four times daily in these trials. Whether less frequent administration provides equivalent benefit is unknown. Current guidelines recommend that hydralazine-ISDN should not be used instead of ACE inhibitors as standard therapy in heart failure or substituted for ACE inhibitors in patients who are tolerating an ACE inhibitor. The combined use of hydralazine-ISDN may be considered a therapeutic option in patients unable to take an ACE inhibitor or an ARB because of renal insufficiency, hyperkalemia, or possibly hypotension. However, it should be anticipated that compliance with this regimen will be poor and the risk of adverse effects high. Therefore, given the proven benefits and low risk of adverse effects, many clinicians now prefer ARBs in patients who cannot tolerate an ACE inhibitor. There are no controlled trials evaluating the benefits of adding hydralazine-ISDN therapy to patients who remain symptomatic despite ACE inhibitor and/or β -blocker treatment.

Conclusion

Heart failure imposes a tremendous economic burden on the health care system. In patients over age 65, it is the most common reason for hospitalization, with hospital admission rates for this disorder continuing to increase. Heart failure is also associated with 30% to 50% readmission rates during the 3 to 6 months after initial discharge. Current estimates of costs of heart failure treatment in the United States exceed \$40 billion, with most of the costs associated with hospitalization. The prevalence of heart failure and the costs associated with patient care are expected to increase as the population ages and as survival from ischemic heart disease are improved. Thus approaches to improve the quality and cost-effectiveness of care for these patients may have a significant impact on health care costs. Studies to assess the cost-effectiveness of drug therapy for heart failure have been reviewed recently. Carvedilol reduced the number of heart failure-related hospital admissions compared with placebo, resulting in a significant savings in hospital costs. The cost per life year saved with carvedilol was \$12,799, which is similar to that of other medical therapies. β -blockers reduced Medicare costs by approximately \$6000 per patient, primarily owing to a reduction in the rates of hospitalization, and resulted in reduced hospital and physician revenue.

In the DIG trial, patients treated with digoxin had fewer hospitalizations for heart failure, but digoxin produced an absolute decrease of only 2.8% in hospitalizations for any cause. Although no prospective economic analyses have been performed, studies using decision-analysis techniques indicate that ACE inhibitors are cost-effective. While not providing direct cost estimates, number needed to treat (NNT) is often a useful index that provides a sense of the cost effectiveness of a given therapy. In the case of the ACE inhibitors and β -blockers, the NNT to prevent one death has ranged from 7 to 20 patients for the ACE inhibitor studies (including most of the postMI studies) and from 14 to 26 patients for the β -blocker studies. These numbers compare favorably with and in fact are superior to most other cardiovascular therapies. In the case of both drug classes, the benefits are greater (NNT lower) for the patients with more severe heart failure. As the management of heart failure has become increasingly complex, the development of disease-management program approaches that use multidisciplinary teams has attracted significant interest. These programs use several broad approaches, including heart failure specialty clinics and/or home-based interventions. Most are multidisciplinary and may include physicians, advanced practice nurses, dieticians, and pharmacists.

In general, the programs focus on optimization of drug and nondrug therapy, patient and family education and counseling, exercise and dietary advice, intense follow up by telephone or home visits, and monitoring and management of signs and symptoms of decompensation. Collectively, studies evaluating this disease-management approach have reported fewer hospitalizations, improved functional capacity and symptoms, reduced health care costs, and improved patient satisfaction and quality of life compared with usual care. The improvement in outcome in these studies may be related to better adherence to heart failure treatment guidelines by cardiologists compared with other physicians. Pharmacists can play an important role in the multidisciplinary team management of heart failure. Compared with conventional treatment, pharmacist intervention that included medication evaluation and therapeutic recommendations, patient education, and follow-up telephone monitoring reduced hospitalizations for heart failure. Adherence to guideline-recommended therapy was improved by pharmacist intervention. Thus the role and cost benefits of pharmacist involvement in the multidisciplinary care of heart failure patients are now apparent and should include optimizing doses of heart failure drug therapy, screening for drugs that exacerbate heart failure, monitoring for adverse drug effects and drug interactions, educating patients, and patient follow-up.

Acknowledgements

None.

Conflict of interest

The author declares that there is no conflict of interest.

References

1. Todd PA, Heel RC. Enalapril. A review of its pharmacodynamics and pharmacokinetic properties and therapeutic use in congestive heart failure. *Drugs*. 1986;31(3):198–248.
2. Riegger AJ. ACE Inhibitors in congestive heart failure. *Cardiology*. 1989;76(Suppl 2):42–49.
3. Brogden RN, Todd PA, Sorkin EM. Captopril. An update of its

- pharmacodynamics and pharmacokinetic properties, and therapeutic use in hypertension and congestive heart failure. *Drugs*. 1988;36(5):540–600.
4. Jessup M. Angiotensin converting enzyme inhibitors: Are there significant clinical differences. *J Am Coll Cardiol*. 1989;36(6):1248–1250.
 5. Lees KR. Angiotensin converting enzyme inhibitors. *Rational drug therapy*. 1988;22:1–6.
 6. Mc Murray J, Lang CC, MacLean DD et al. A survey of current use of angiotensin converting enzyme inhibitors by Scottish physician in the treatment of chronic failure. *Scot Med J*. 1989;34(2):425–426.
 7. Ogilvie RI, Klassen GA. Metabolic Effect and Uptake of [H]Digoxin in the Forearm of Man. *Clinical Science*. 1972;42(5):567–577.
 8. Elkayam U, Janmohamed M, Habib M, et al. Vasodilators in the management of acute Heart failure. *Crit Care Med*. 2008;36(1 Suppl):S95–105.
 9. Abraham WT, Hayes DL. Cardiac resynchronization therapy for heart failure. *Circulation*. 2003;108(21):2596–2603.
 10. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004;350(21):2140–2150.
 11. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med*. 1991;324(12):781–788.
 12. Di Marco JP. Implantable cardioverter-defibrillators. *N Engl J Med*. 2003;349(19):1836–1847.
 13. Ooi H, Colucci W. Pharmacological treatment of heart failure. In: Hardman JG, Limbird LE, eds. Goodman and Gilman's *The Pharmacological Basis of Therapeutics*. New York: McGraw Hill; 2001. 901–932 p.
 14. Bristow M, Port J, Kelly R. Treatment of heart failure: Pharmacological methods. In: Braunwald E, Zipes DP, Libby P, eds. *Heart Disease. A Textbook of Cardiovascular Medicine*, 6th ed. Philadelphia: Saunders; 2001. 562–599 p.
 15. Jorde UP, Ennezat PV, Lisker J, et al. Maximally recommended doses of angiotensin-converting enzyme (ACE) inhibitors do not completely prevent ACE-mediated formation of angiotensin II in chronic heart failure. *Circulation*. 2000;101(8):844–846.
 16. Jorde UP, Vittorio T, Katz SD, et al. Elevated plasma aldosterone levels despite complete inhibition of the vascular angiotensin-converting enzyme in chronic heart failure. *Circulation*. 2002;106(9):1055–1057.
 17. Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: A systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet*. 2000;355(9215):1575–1581.
 18. Shlipak MG. Pharmacotherapy for heart failure in patients with renal insufficiency. *Ann Intern Med*. 2003;138(11):917–924.
 19. Schoolwerth AC, Sica DA, Ballermann BJ, et al. Renal considerations in angiotensin converting enzyme inhibitor therapy: A statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. *Circulation*. 2001;104(16):1985–1991.
 20. 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. ATLAS Study Group. *Circulation*. 1999;100(23):2312–2318.
 21. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353(9169):2001–2007.
 22. Bristow MR. Mechanistic and clinical rationales for using beta-blockers in heart failure. *J Card Fail*. 2000;6(2 Suppl 1):8–14.
 23. Shankar SS, Brater DC. Loop diuretics: From the Na-K-2Cl transporter to clinical use. *Am J Physiol Renal Physiol*. 2003;284(1):F11–21.
 24. Kramer BK, Schweda F, Riegger GA. Diuretic treatment and diuretic resistance in heart failure. *Am J Med*. 1999;106(1):90–96.
 25. Brater DC. Pharmacology of diuretics. *Am J Med Sci*. 2000;319(1):38–50.
 26. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: Results of the Veterans Administration Cooperative Study. *N Engl J Med*. 1986;314(24):1547–1552.