Heart Failure

Outpatient Management of Congestive Heart Failure

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Congestive heart failure (CHF) as a manifestation of systolic left ventricular dysfunction has become increasingly important as a clinical entity. In 1990, CHF affected 4.7 million patients in the United States.[1] Annually, the condition is newly diagnosed in 400,000 persons and the total cost of care exceeds $10 billion.[2,3] A 1993 analysis of data from the Framingham Heart Study revealed 5-year survival rates of 25% for men and 38% for women after diagnosis of congestive heart failure.[4] As our population ages and primary treatment of myocardial infarction improves, the number of patients with congestive heart failure will rise, which will present an increasing medical challenge and an increasing economic impact.

In recent years, our methods for managing congestive heart failure have gradually changed. Initially, management consisted of diuresis, which reduces fluid overload and relieves symptoms. Later attention was drawn to attempts to increase cardiac contractility through the use of inotropic drugs, but this approach resulted in devastating long-term mortality rates. More recently, cardiologists have begun to manage congestive heart failure by using vasodilators and beta blockers, agents that inhibit the deleterious effects of sympathetic neurotransmitters and vasoactive hormones.

Cardiologists continue to gain insights into the pathophysiology of congestive heart failure. With our new understanding of neurohormonal systems and the vascular endothelium, we have been able to derive rational approaches to clinical management and to the development of suitable medications to treat this chronic disease.

Vasodilators

In the mid 1970s, Cohn and associates[5] demonstrated that left ventricular function improved in patients with congestive heart failure who took vasodilators. In 1974, Franciosa and associates[6] reported that isosorbide dinitrate reduced right atrial and left ventricular filling pressures and increased cardiac output. Three years later, the same group[7] reported that the arterial dilator hydralazine reduced systemic vascular resistance and increased cardiac output but that it had little effect on right atrial and left ventricular filling pressures.

These discoveries led to the V-HeFT* trial, which investigated prazosin and a combination of hydralazine and isosorbide dinitrate as separate means of reducing arterial resistance and increasing venous capacitance.[8] In this study, mortality in both the placebo and the prazosin arms of the trial averaged 20% per year. However, the combination of hydralazine and isosorbide dinitrate resulted in a reduction of mortality to approximately 12% during the first year; over the follow-up period of 2.5 years, mortality rates continued to decrease. While this study demonstrated that the survival of patients with congestive heart failure could be improved by vasodilators, it also suggested that all such drugs might not be equally beneficial.

Calcium Channel Blockers

Because of their ability to relax smooth muscle and dilate peripheral vessels, calcium channel blockers have been considered for the management of congestive heart failure. However, in most cases, the vasodilatory potential of the calcium antagonists has been offset by their negative effects on myocardial contractility

*V-HeFT = Vasodilator-Heart Failure Trial

and by the propensity of these agents to activate the neuroendocrine system.[9,10] As a result, the calcium channel blockers tested to date are seldom viable options for the management of congestive heart failure (Table I).

The first-generation calcium channel blockers have demonstrated a tendency to worsen heart failure.[10] These drugs include nifedipine, diltiazem, and verapamil. Recently, the V-HeFT III study[11] showed that felodipine, a 2nd-generation calcium channel blocker, showed no significant beneficial effects in heart failure patients. The promising drug mibefradil was voluntarily withdrawn from the market by its manufacturer in June 1998.[12] Although investigators had hoped that the different action of this drug (which affected T-channel rather than L-channel transport) would limit complications, preliminary findings revealed that the combination of mibefradil and other common cardiovascular drugs increased the frequency and intensity of adverse effects.

Only in the PRAISE* Study, which tested the effects of amlodipine, has a calcium channel blocker been found to have beneficial effects on CHF.[13] Among patients with nonischemic cardiomyopathy, amlodipine decreased the combined risk of fatal and nonfatal events. However, among ischemic heart disease patients, amlodipine did not affect the incidence of death or hospitalization for major cardiovascular events; the overall decrease in morbidity and mortality following amlodipine treatment was nonsignificant. Additionally, the risk of pulmonary edema increased in the treated cohort. Further studies are pending to assess the role of amlodipine in the treatment of nonischemic dilated cardiomyopathy. Until these results are available, the use of calcium channel blockers in CHF should generally be avoided.

Angiotensin Converting Enzyme (ACE) Inhibitors

Studies dating from the mid-1970s demonstrated the effects of the renin-angiotensin-aldosterone system on the pathophysiology of congestive heart failure in non-human experimental subjects.[14] Recognition of the clinical significance of neurohormonal levels in patients with CHF led to clinical tests of drugs capable of altering the effects of neurohormones.[15]

Renin release is stimulated by a number of factors present in the setting of congestive heart failure, including reduction of renal blood flow, reduction of sodium delivery to the macula densa within the distal nephron, and activation of the renal sympathetic nerve endings.[16] The introduction of diuretics may also stimulate renin release.[17] The production of renin activates the conversion of angiotensinogen to angiotensin-1, which is then converted by angiotensin converting enzyme (ACE) to angiotensin-2. Angiotensin-2 binds specifically to cardiovascular receptors (AT_1 and AT_2), which leads both to arterial and venous constriction and to increased myocardial contractility and coronary vasoconstriction. Angiotensin-2 also increases the amount of circulating norepinephrine.[16] It is likely that the renin-angiotensin-aldosterone system interacts with endothelin and affects the release of aldosterone.[17,18] In the treatment of CHF, ACE inhibitors act primarily by impairing the conversion of angiotensin-1 to angiotensin-2. They may also decrease circulating catecholamines, impair the breakdown of bradykinin, and stimulate the synthesis of vasodilatory prostaglandins.[16]

Several clinical studies have demonstrated that ACE inhibitors may improve survival in patients with congestive heart failure. The first large clinical trial of ACE inhibitors was the 1987 CONSENSUS* trial,[19] which reported that enalapril improved the survival of patients with severe congestive heart failure. The mortality rate among placebo-treated patients in that trial was 54%; among patients treated with enalapril, mortality was reduced to 39%. A subsequent study, V-HeFT II, confirmed the benefits of hydralazine and isosorbide dinitrate but also demonstrated that treatment with enalapril further improved survival.[20] The observed survival benefit was primarily due to a decrease in sudden death rates among New York Heart Association (NYHA) functional class II patients; there was no evident benefit to patients in functional classes III and IV.

On the basis of these results, investigators suggested that additive benefits might accrue to patients treated with both hydralazine-isosorbide dinitrate and ACE inhibitors. The Hy-C Trial[21] compared tailored doses of hydralazine-isosorbide dinitrate with doses of captopril-isosorbide dinitrate in the treatment of patients with severe congestive heart failure. In that trial, survival increased in patients treated with captopril. The survival benefit was primarily the result of a decrease in sudden death, with no significant change in deaths due to the progression of CHF.

After an insult to the myocardium—for example, myocardial infarction, viral infection, or toxic exposure—the progression to congestive heart failure is marked by myocardial changes known as remodeling. Angiotensin-2 is thought to play a major role in the progression of adverse changes of myocytes, smooth muscle cells, fibroblasts, and endothelial cells.[22] These cellular changes result in dilation of the heart and alterations of cardiac geometry, as well as increases in interstitial fibrosis. In experiments with animals, early interruption of renin-angiotensin-

* PRAISE = Prospective Randomized Amlodipine Survival Evaluation; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study

TABLE I. Summary of Selected Calcium Channel Blocker Trials in the Treatment of Congestive Heart Failure

Trial (publication date)	Patient Population	Drug Studied	Target Dose (mg/day)	Duration	Outcome
MDPIT (1988)	Acute MI	diltiazem vs placebo	240	12-52 mos (mean, 25)	no overall effect on cardiac events/mortality*
DAVIT II (1990)	Acute MI	verapamil vs placebo	360	12-18 mos (mean, 16)	↓ mortality ↓ cardiac events no effect on patients with CHF
PRAISE I (1996)	NYHA FC IIIB-IV EF <30%	amlodipine vs placebo	10	6-33 mos (median, 13.8)	no effect on cardiac events/mortality**
V-HeFT III (1997)	Men CHF LVD limited exercise tolerance	felodipine vs placebo	10	3-39 mos (mean, 18)	↓ BP no effect on cardiac events/mortality
MACH I (incomplete)	NYHA FC II-IV EF <35%	mibefradil vs placebo	100+	2-3 y	*Preliminary results:* no effect serious negative interactions withdrawn from market

+ Used if tolerated. Patients also maintained at 50.

* ↓ cardiac events in patients without LVD; ↑ cardiac events in patients with LVD
** ↓ mortality and ↓ cardiac events in patients with nonischemic cardiomyopathy

BP = blood pressure; CHF = congestive heart failure; DAVIT = Danish Verapamil Infarction Trial; EF = ejection fraction; LVD = left ventricular dysfunction; MACH = Mortality Assessment in Congestive Heart Failure Trial; MDPIT = Multicenter Diltiazem Postinfarction Trial; MI = myocardial infarction; NHYA FC = New York Heart Association functional class; PRAISE = Prospective Randomized Amlodipine Survival Evaluation; V-HeFT = Vasodilator-Heart Failure Trial

aldosterone activation has been shown to limit left ventricular remodeling after myocardial infarction on both a cellular and an ultrastructural level.[23-25] Improvement in asymptomatic left ventricular dysfunction after treatment with ACE inhibitors may lead directly to improved survival rates among CHF patients.

This hypothesis was supported by the results of the 1991 SOLVD* Treatment Trial.[26] In this study, enalapril significantly decreased mortality and hospitalization rates among congestive heart failure patients; this benefit was confined to patients in NYHA functional class II. However, patient improvement was not as pronounced in the later SOLVD Prevention Trial.[27] The development of clinical heart failure decreased after enalapril treatment among asymptomatic CHF patients with left ventricular dysfunction, but the survival benefit in the treated population overall was nonsignificant. Results from the recently published NETWORK trial, which differ from those of SOLVED[27] and CONSENSUS,[19] showed clinical improvement in patients treated with enalapril but no overall effect on heart failure, heart-failure-related hospitalization, or mortality.[28] The NETWORK trial, however, was not mortality-based but instead had a combined endpoint and, for the majority of patients, a lower target dosage of enalapril than did the other trials.

Although ACE inhibitors may reduce mortality and delay the progression of heart failure,[19,27] there is no evidence that these drugs result in improved myocyte function. Despite initial reduction of plasma norepinephrine levels in CHF patients after administration of ACE inhibitors, the levels of plasma norepinephrine ultimately increase again.[29]

Direct blockade of angiotensin-2 receptors (AT_1 and AT_2) as a supplement or alternative to ACE inhibitors may prove desirable in the management of congestive heart failure because angiotensin-2 may be formed by pathways other than those catalyzed by angiotensin converting enzyme. A large European study group, ELITE,* has recently reported im-

* SOLVD = Studies of Left Ventricular Dysfunction; ELITE = Evaluation of Losartan in the Elderly

proved survival of older patients with congestive heart failure treated with losartan, an angiotensin-2 inhibitor, when these patients were compared with patients on captopril.[30] Direct blockade of angiotensin-2 receptors may also avoid some of the side effects of ACE inhibitors. Additional studies are in progress to evaluate the potential of angiotensin-2 receptor blockade as a supplement to ACE inhibition. Whether ACE or angiotensin-2 inhibitors are used, renal function and serum potassium levels must be monitored.

The RESOLVD* trial, which combines neurohormonal blockade with ACE inhibitors, angiotensin II antagonists, and beta blockade, has recently completed follow-up in both stages (I and II). The results, which have not been published, will be used to design a mortality study. Through this study, investigators hope to define the role of neurohormonal blockade in the treatment of CHF.

Aspirin is frequently prescribed for patients with atherosclerotic disease to inhibit platelet function and intravascular thrombosis. Since atherosclerotic disease and heart failure often coexist, the effect of taking aspirin and ACE inhibitors concurrently has been considered. In a small cohort of patients, Guazzi and associates[31] reported attenuation of the antihypertensive effects of enalapril by 300 mg of aspirin daily, but not by 100 mg. The same investigators[32] tested the effect of aspirin given with enalapril or with the angiotensin-2 receptor blocker losartan. They reported lessened improvement in oxygen consumption when aspirin was given with enalapril but no adverse effect when aspirin was given with losartan. The CONSENSUS-II investigators reported that the effect of enalapril was less favorable at baseline among post-infarction patients taking aspirin than among those not taking aspirin.[33] In a small study comparing aspirin given with enalapril and ticlopidine given with enalapril, investigators found that enalapril reduced systemic vascular resistance more effectively when given in combination with ticlopidine than when given in combination with aspirin, most likely because ticlopidine does not interact on prostaglandin synthesis.[34] Clopidogrel, another platelet inhibitor that is structurally similar to ticlopidine, may be as effective as ticlopidine[35] and is associated with fewer side effects.

In a recent report based upon data from both arms of the SOLVD trial,[36] the use of antiplatelet agents was found to be associated with improved survival in patients with left ventricular dysfunction. The reduction in all-cause mortality and hospital admission was not dependent on the symptom status of the patients. However, the association between antiplatelet agents and improved survival rates was not seen in older patients or in the group randomized to enalapril, although an enalapril-related reduction continued in the combined endpoint of death or hospital admission for heart failure.[36]

A substantial number of patients are intolerant of ACE inhibitors. The most common side effect is cough, which occurs in up to 15% of patients receiving this class of drugs,[37,38] although taste disturbances and rash might also preclude use of ACE inhibitors. A rare side effect is angio-edema, which can prove fatal.[38] Neutropenia, nephrotic syndrome, and rash appear to be related to the sulfhydryl group present in some ACE inhibitors.[39] When ACE inhibitors are administered during the 2nd and 3rd trimesters of pregnancy, fetal abnormalities may occur.[40]

Dosage ranges and outcomes of various trials of ACE inhibitors in the management of congestive heart failure have been published previously (Tables II and III).

Beta Blockers

In 1975, Waagstein and associates in Sweden reported beneficial responses to beta blockade in patients with dilated cardiomyopathy.[41,42] Their findings predated reports that beta receptor density decreased in failing human hearts[43] and that plasma norepinephrine levels could be used as a prognostic indicator in congestive heart failure.[15] Waagstein's trials were based on clinical signs of a hyperadrenergic state in heart failure, particularly among patients with manifest tachycardia. Subsequently, a variety of small, poorly controlled studies of the effects of short-term beta blockade were published,[44-47] but none convincingly supported the use of beta blockade in standard management of congestive heart failure.

More recent clinical studies have reported increased ejection fractions and decreased left ventricular volumes in CHF patients treated by beta blockade.[48,49] Beta blockade acts in a number of ways that may benefit patients with congestive heart failure: up-regulation of beta receptors on myocytes, decreased myocardial energy requirements, antiarrhythmic effects, improved myocardial relaxation, decreased heart rate, protection against circulating catecholamines, and changes of myocyte isoform from fetal to adult. In patients taking beta blockers, improved left ventricular function may be seen after a treatment regimen of 1 to 3 months and may continue for several months thereafter. Generally, a reduction of left ventricular mass and a return to more normal ventricular geometry occurs only after 12 to 18 months of therapy.[50]

In contrast to experience with chronic inotropic treatment for congestive heart failure,[51] clinical, anatomic, and hemodynamic benefits have been docu-

*RESOLVD = Randomized Evaluation of Stategies for Left Ventricular Dysfunction

TABLE II. Summary of Selected Angiotensin Converting Enzyme Inhibitor Trials in the Treatment of Left Ventricular Dysfunction in Congestive Heart Failure

Trial (publication date)	Patient Population	Drug Studied	Target Dose (mg/day)	Duration	Outcome
CONSENSUS (1987)	NHYA FC IV	enalapril vs placebo	20	1 day-20 mos	↓ mortality ↓ CHF
SOLVD Treatment (1991)	Overt CHF (~90% in NYHA FC II-III) EF ≤35%	enalapril vs placebo	20	22-55 mos	↓ mortality ↓ CHF (no benefit to NYHA FC III-IV)
V-HeFT II (1991)	NYHA FC II-III EF <45% limited exercise tolerance	enalapril vs hydralazine c̄ isosorbide dinitrate	20 vs 300 (c̄ 160)	0.5-5.7 yrs	↓ mortality ↓ SDS
SOLVD Prevention (1992)	No overt CHF (NYHA FC I-II) EF ≤35%	enalapril vs placebo	20	14.6-62 mos	↓ CHF ↓ hospitalization no overall effect on mortality
Hy-C (1992)	NYHA FC III-IV mean EF 20%	captopril vs hydralazine c̄ isosorbide dinitrate	206±147*** vs 410±164***	12 mos	↓ mortality ↓ SDS
ATLAS (1998)	NHYA FC II-IV* EF ≤30%	high-dose lisinopril vs low-dose lisinopril	32.5-35 vs 2.5-5	3.5-5 yrs	↓ mortality/ hospitalization
NETWORK (1998)	NYHA FC II-IV	enalapril,** 2.5, 5, 10 mg b.i.d.	5, 10, 20	6 mos	no overall effect on CHF, CHF-related hospitalization, or mortality

* Background digitalis, diuretic, and angiotensin converting enzyme inhibitor therapy
** Blinded titration: if required, down-titrated (double blind)
*** Average doses. Range, 25-400 mg/day vs 100-600 mg/day, titrated to achieve hemodynamic goals.

ATLAS = Assessment of Treatment with Lisinopril and Survival Trial; CHF = congestive heart failure; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; EF = ejection fraction; Hy-C = Hydralazine versus Captopril Trial; NYHA FC = New York Heart Association functional class; SDS = sudden death syndrome; SOLVD = Studies of Left Ventricular Dysfunction; V-HeFT = Vasodilator Heart Failure Trial

mented in CHF patients treated with beta blocking agents. In the Metoprolol in Dilated Cardiomyopathy Trial Group, which included only 383 patients with idiopathic dilated cardiomyopathy, fewer patients in the group treated with metoprolol proceeded to heart transplantation, as compared with those in the group receiving placebo. Treated patients also had improved cardiac function and quality of life, although there was no significant effect on all-cause mortality.[52] Combined results of 4 carvedilol studies, however, reported a reduction in overall mortality in the treated group from 7.8% to 3.2%.[53] A reduction in the risk of hospitalization and in the combined risk of hospitalization or death among treated patients was also evident, although there was no effect on exercise performance. Carvedilol's unique features, e.g., its alpha blockade and antioxidant effect, may make it superior to other beta blockers.[53] Recently, carvedilol was approved by the Food and Drug Administration (FDA) for use in patients who are in NYHA functional class II or III. Use of carvedilol to treat functional class IV patients will be examined in the COPERNICUS* study.

* COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival

TABLE III. Summary of Selected Angiotensin Converting Enzyme Inhibitor Trials in Post-Infarction Treatment of Congestive Heart Failure

Trial (publication date)	Patient Population	Drug Studied	Target Dose (mg/day)	Duration	Outcome
SAVE (1992)	MI VLVF	captopril vs placebo	150	24-60 mos mean, 42±10	↓ mortality
CONSENSUS II (1992)	MI	enalaprilat/enalapril vs placebo	20+	41-180 days	no change in survival incomplete: early hypotension
AIRE (1993)	MI CHF	ramipril vs placebo	10	6 mos*	↓ mortality
GISSI-3 (1994)	MI	lisinopril vs open control	10	6 wks	↓ mortality
ISIS-4 (1995)	MI	captopril vs placebo	100	5 wks**	↓ mortality
TRACE (1995)	MI VLVF	trandolapril vs placebo	4++	24-50 mos	↓ mortality ↓ severe CHF
SMILE (1995)	MI	zofenopril vs placebo	60	6 wks	↓ mortality ↓ severe CHF

+ Used if tolerated. Range, 5-20. Begun by intravenous enalaprilat infusion.
++ Used if tolerated. Range, 1-4.
* Minimum. Average, 15 mos.
** Patients were followed to mortality or end of study (2 y 3 mos). 97% were followed to 5 wks.

AIRE = Acute Infarction Ramipril Efficacy; CHF = congestive heart failure; CONSENSUS II = Cooperative North Scandinavian Enalapril Survival Study II; GISSI-3 = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; ISIS-4 = The Fourth International Study of Infarct Survival; MI = myocardial infarction; SAVE = Survival and Ventricular Enlargement; SMILE = Survival of Myocardial Infarction Long-Term Evaluation; TRACE = Trandolapril Cardiac Evaluation Study Group; VLVF = very low ventricular function (TRACE, ejection fraction ≤35%; SAVE, ejection fraction ≤40%)

Many studies that demonstrate improved survival of CHF patients treated with beta blockade are limited by small size (the CIBIS* trial of bisoprolol)[54] or design (the carvedilol studies).[53] Pfeffer and Stevenson[55] described several shortcomings of the carvedilol trials, including relatively few patients and endpoints (only 53 deaths) and a relatively short median follow-up period (7 months), in comparison with the ACE inhibitor trials. In addition, patients who died or who could not tolerate carvedilol during the run-in period were not reported in the trial, and patients with the severest symptoms of heart failure comprised only 3% of the study population. The multicenter European CIBIS II study was the first randomized controlled clinical trial with sufficient power to address itself to all-cause mortality as its primary endpoint. The trial was prematurely terminated in March 1998 after all-cause mortality rates were shown to have significantly decreased in the bisoprolol treatment group; however, the study continued with an open-ended follow-up protocol.[56] Initial results, which were presented in August 1998,[57] showed that bisoprolol reduced all-cause mortality by 32% ($P<0.00005$), sudden death by 45% ($P<0.001$), and hospitalization for heart failure by 30% ($P<0.0005$). More data on the beneficial effects of beta blockade may be expected from other trials in progress, such as the Beta Blocker Evaluation Survival Trial.

Whether there are particular groups of heart failure patients (e.g., those with resting tachycardia) who are more likely to benefit from beta blockade or who are more likely to tolerate it remains to be seen. In any case, beta blockade should be introduced slowly into the therapeutic regimen, and patients should be carefully monitored during the introductory phase. Worsening of heart failure or severe bradyarrhythmias may require temporary intra-

* CIBIS = Cardiac Insufficiency Bisoprolol Study

venous inodilator support or discontinuation of the beta-blocking drug.

The accompanying table outlines the protocols and outcomes of several trials of beta blocking agents typically used in the management of congestive heart failure (Table IV).

Diuretics

Fluid retention and vascular congestion are not always the result of left ventricular dysfunction; they may result from other conditions such as renal failure. Nonetheless, systolic left ventricular functional impairment, as is often seen with chronic ischemic myocardial injury or idiopathic dilated cardiomyopathy, typically induces symptoms of pulmonary and systemic vascular congestion: dyspnea, increased abdominal girth, edema, fatigue, etc. Relief of these symptoms often depends on the initiation of effective diuresis, and chronic diuretic administration is necessary for many patients with congestive heart failure.

Although neuroendocrine factors may be activated by diuretic therapy, such treatment is likely to improve patients' long-term quality of life and has not been shown to adversely affect survival. Caution is necessary when adding ACE inhibitors to the regimen of patients already taking diuretics, because hypotension, renal hypoperfusion, hyperkalemia, and renal failure may ensue. It may be necessary to reduce the diuretic dose or discontinue diuretics briefly when an ACE inhibitor is introduced into the treatment regimen.

Patients with CHF should be kept as "dry" as is tolerable without inducing symptoms of hypotension and without inordinately raising blood urea nitrogen and creatinine levels. Some increase in BUN and creatinine may be tolerated if the alternative allows worsening symptoms of heart failure. Patients who need diuretics for management of congestive heart failure should be instructed to restrict and monitor fluid intake and to restrict dietary sodium intake.

To successfully manage CHF, an understanding of the use of various types of diuretics is mandatory. Diuretics act at different levels in the nephron; therefore, judicious selection of diuretics permits enhancement of their favorable effects while mitigating less desirable ones. In a recent review,[58] Brater describes the bioavailability, routes of metabolism, and half-lives of the most common diuretics.

Loop Diuretics. The loop diuretics (furosemide, bumetanide, torsemide, and ethacrynic acid) actively affect sodium and chloride reabsorption in the ascending loop of Henle, producing passive removal of water from the descending loop of Henle and the collecting duct. The net results are increased fractional sodium excretion and increased free water clearance. All loop diuretics have similar pharmacologic properties. As a result, the minimal and maximal doses can be determined in individual patients by titrating the drug in order to find the amount needed to achieve a response at the transport site. Unfortunately, a long-acting loop diuretic has not been developed.

When administered intravenously to patients with acute onset of congestive heart failure, furosemide increases peripheral venous capacitance, decreases venous return to the heart, and lowers right atrial and pulmonary wedge pressures. These effects occur before the onset of diuresis, and the fall in pulmonary venous pressure and left ventricular filling pressure may produce early improvement of symptoms.[59] Similar hemodynamic changes occur when furosemide is given to patients with chronic heart failure.[60,61] The diuretic effect may be manifest within an hour of oral administration.

Loop diuretics are effective even in patients with decreased glomerular filtration rates. Their effects may be partially mediated by activation of the prostaglandin system.[62] In patients who have delayed gastric emptying or edematous bowel, the delayed absorption of the drugs administered orally may diminish their effect. Care must be taken to avoid intravascular hypovolemia, which may lead to alkalosis, azotemia, or hyperuricemia. Hyperuricemia, in turn, may occasionally precipitate gout.

Patients given loop diuretics must be monitored to ensure appropriate maintenance of potassium and magnesium levels. Like potassium, magnesium is an intracellular ion, which makes the measurement of total-body levels difficult. No accurate method of measurement is readily available to the clinician. Despite these limitations, serum magnesium levels (which represent less than 1% of total magnesium stores) should be measured in patients with congestive heart failure. If the serum level is low, a deficiency exists and patients should be given a magnesium supplement.

Thiazide Diuretics. Thiazide diuretics act at the distal tubule to inhibit sodium reabsorption and to stimulate potassium secretion. They are less effective than loop diuretics, especially in patients whose renal function is impaired. However, metolazone, one example of a thiazide diuretic, is a long-acting quinethazone derivative that is not affected by decreased renal function. Metolazone may be given as a single daily dose and may prolong and enhance the effects of loop diuretics taken concurrently. Serious complications of thiazide diuretics may include hypovolemia, hypotension, and potassium depletion.

Potassium-Sparing Diuretics. Potassium-sparing diuretics may be useful in treating patients with CHF. Spironolactone inhibits the effects of aldosterone,

TABLE IV. Summary of Selected Beta Blocker Trials in the Treatment of Congestive Heart Failure

Trial (publication date)	**Patient Population**	**Drug Studied**	**Target Dose** (mg/day)	**Duration**	**Outcome**
MDC (1993)	Idiopathic dilated cardiomyopathy EF <40%	metoprolol vs placebo	100-150+	12 mos	↓ morbidity ↓ need for transplant ↑ EF No significant effect on all-cause mortality
Bucindolol Investigators (1993)	NYHA FC II-III* EF ≤40%	bucindolol vs placebo	12.5, 50, 200++	12 wks	↓ deterioration of myocardial function ↑ EF
CIBIS (1994)	NYHA FC III-IV** EF <40%	bisoprolol vs placebo	5+++	1.9 yrs (mean)	↓ risk of hospitalization ↑ heart function no significant effect on mortality
US Carvedilol Heart Failure Study (1996)	*All protocol arms:* CHF ≥3 mos* EF ≤35%	*All protocol arms:* carvedilol vs placebo	*See protocols below*	*See protocols below*	↓ mortality ↓ risk of hospitalization
Colucci et al• (1997)	As above Mild CHF 6-min. walk dist.*** 425-550 m	As above	50-100++++	12 mos	↓ CHF ↓ cardiac events/mortality ↑ EF
PRECISE• (1996)	As above Moderate CHF 6-min. walk dist.*** 150-425 m	As above	50-100++++	6 mos	↓ hospitalization/mortality ↑ EF
MOCHA• (1996)	As above Moderate CHF 6-min. walk dist.*** 150-425 m	As above	12.5, 25, 50++	6 mos	*Dose-related:* ↑ EF ↓ mortality ↓ risk of hospitalization
Cohn et al• (1997)	As above Severe CHF 6-min. walk dist.*** <150 m	As above	46±12 vs 48±10+++++	6 mos	↑ EF
ANZ Heart Failure Trial (1997)	NYHA FC II-III; previous II-IV EF <45%	carvedilol vs placebo	50++++++	19 mos (mean)*****	↓ mortality ↓ risk of hospitalization ↑ EF ↓ LV ES dimension No effect on exercise performance
CIBIS II**** (1998)	NYHA FC II-IV EF <40%	bisoprolol vs placebo	10 (maximum)	1.4 y (mean)	↓ all-cause mortality ↓ SDS ↓ risk of hospitalization for CHF

• Protocol arms included in the US Carvedilol Heart Failure Study.[53]

* Background diuretic (mandatory), angiotensin converting enzyme inhibitor (if tolerated), and digoxin (optional) therapy
** Background vasodilator and diuretic therapy
*** Protocols later amended: Mild, 450-550 m; Moderate, 150-450 m; Severe, <350 m
**** Measurements for outcomes included in table were made at 12 mos.
***** Background angiotensin converting enzyme inhibitor and diuretic therapy
****** Measurements for outcomes included in table were made at 12 mos.

\+ Dependent on body weight, age, heart rate, and blood pressure
++ Randomized
+++ 1.25, 2.5, 3.75, or 5 mg/day prescribed according to patients' clinical status
++++ As tolerated up to 50 mg/day for patients <85 kg, 100 mg/day for heavier patients
+++++ Average dose. 82% at target dose of 50 mg/day
++++++ Used if tolerated. Range, 12.5-50

ANZ = Australia–New Zealand; CHF = congestive heart failure; CIBIS = Cardiac Insufficiency Bisoprolol Study; CIBIS II = Cardiac Insufficiency Bisoprolol Study II; EF = ejection fraction; LV ES = left ventricular end-systolic; MDC = Metoprolol in Dilated Cardiomyopathy Trial; MOCHA = Multicenter Oral Carvedilol Heart Failure Assessment; NYHA FC = New York Heart Association functional class; PRECISE = Prospective Randomized Evaluation of Carvedilol in Symptoms and Exercise; SDS = sudden death syndrome

but its diuretic effect is modest when used alone. In combination with thiazide or loop diuretics, it may enhance diuresis while limiting potassium loss. Triamterene and amiloride, which block apical sodium channels,[56] are also useful with thiazide or loop diuretics. Their potassium-sparing effects are independent of aldosterone.

Carbonic Anhydrase Inhibitors. Carbonic anhydrase inhibitors such as acetazolamide inhibit hydrogen secretion from the proximal tubule and may serve as weak diuretics. They are primarily of value in patients who develop metabolic alkalosis due to chronic use of loop or thiazide diuretics.

Digitalis Glycosides

The use of digitalis glycosides in the treatment of congestive heart failure dates to the 18th century.[63] Although it has been generally accepted for use in the management of atrial fibrillation, digoxin is more effective in controlling ventricular rate at rest than at exercise. Studies have suggested that digoxin has beneficial effects on neuroendocrine mediators in congestive heart failure.[64] As neuroendocrine activity decreases, ejection fraction and exercise capacity improve. However, a minimum digoxin serum level necessary to achieve a therapeutic effect has not been determined.

Several clinical trials have studied the effects of digoxin in patients with CHF.

The large, prospective DIG* study[65] reported a modest decrease in morbidity and hospitalization rates for congestive heart failure among treated patients; however, the study gave no evidence of survival benefit. In the PROVED* and RADIANCE* trials,[66,67] congestive heart failure worsened when digoxin was withdrawn from patients' treatment regimens.

Major concerns regarding the use of digoxin arise from its potential for toxicity. In heart failure patients, this potential is particularly complicated by labile renal function and by the clinical necessity for the use of drugs that interact with digoxin. Serum digoxin levels may increase when digoxin is used with calcium channel blocking agents, amiodarone, or propafenone. When a patient exhibits hypokalemia or hypomagnesemia, the arrhythmogenic potential of digoxin is increased. Further, if creatinine clearance decreases as heart failure worsens, the digoxin dose needs to be lowered. Awareness of these factors and appropriate monitoring of serum digoxin levels will help minimize the drug's toxic effects.

*DIG = Digitalis Investigation Group; PROVED = Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin; RADIANCE = Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme

Arrhythmias or other harmful effects of digoxin can be ameliorated by the use of digoxin-immune antigen-binding fragments (Fab). After the administration of digoxin-immune Fab, the serum digoxin level increases and will not correlate with toxic potential, thereby making any measurement meaningless. Improvement of toxic symptoms can be expected within half an hour of administration of Fab; the clearance half-life in normal kidneys is 15 to 20 hours.[68] Multiple confounding factors, e.g., renal-function compromise, use of drugs that interact with digoxin, or conduction system impairment, make discontinuing digoxin a preferable choice under some circumstances. The use of digoxin simply to control heart rate in the setting of atrial fibrillation or flutter may not be necessary in a time when other drugs like amiodarone or propafenone can serve that purpose.

Anticoagulants

In patients with left ventricular dysfunction and normal sinus rhythm, the incidence of thromboembolic events is low, although an increased incidence has been noted in women with poor left ventricular ejection fractions.[69] Therefore, the use of anticoagulants in these patients is controversial[70,71] because of the associated increased risk of hemorrhage, especially in older patients. When data from all patient groups in the SOLVD trial were analyzed recently, warfarin use was found to be associated with improved survival and decreased morbidity, primarily a result of a decreased incidence of cardiac events.[71] However, only 13.2% of patients in both the treatment and prevention arms of the SOLVD trial were taking warfarin.[26,27] Patients who used warfarin had a higher percentage of atrial fibrillation and cerebrovascular disease, whereas nonusers of warfarin were more likely to have hypertension and ischemic heart disease and were more likely to be taking antiplatelet agents.

When currently available results are analyzed, anticoagulation appears to be indicated for patients with congestive heart failure who have a history of thromboembolism, episodes of atrial fibrillation, or evidence of detectable left atrial or ventricular thrombus on echocardiogram. Use of anticoagulants should be balanced with risk in older or otherwise debilitated patients, especially those with liver malfunction. Several studies[36,72,73] have shown low-dose aspirin to be beneficial in decreasing the incidence of thromboembolic episodes and to be associated with less risk of hemorrhage than anticoagulants. Certainly in patients with ischemic disease, antiplatelet agents are a rational choice. The WATCH trial (Warfarin and Antiplatelet Therapy in Chronic Heart Failure), which is now enrolling study centers, will evaluate warfarin anticoagulation and antiplatelet

therapy (clopidogrel and aspirin) in patients with chronic heart failure.

Natriuretic Peptides

Natriuretic peptides (brain, atrial, and C-type) may provide a new treatment therapy for patients with congestive heart failure. Brain (BNP) and atrial (ANP) natriuretic peptides have similar cardiovascular effects. They both induce diuresis and natriuresis and suppress the renin-angiotensin axis while dilating peripheral vascular beds.[74] Brain natriuretic peptide is found in the human brain but is much more prevalent in the ventricular myocardium. It is present in high concentrations in the plasma of patients with ventricular hypertrophy or congestive heart failure. Atrial natriuretic peptide is produced primarily in the atria and is also increased in hypervolemic patients.[75] C-type, which is found in the central nervous system as well as in renal and vascular endothelial cells, does not affect arterial pressure or salt or water excretion, although it does inhibit aldosterone secretion and is a more potent venous dilator. Its role in heart failure is unknown.[75]

Potential beneficial hemodynamic effects of ANP and BNP (decreased pulmonary capillary wedge pressure, increased cardiac index, decreased peripheral vascular resistance) have been demonstrated in CHF patients who received ANP[76-80] and BNP[81-83] infusions. Abraham and associates,[84] however, have cautioned that patients with severe heart failure may show renal resistance to BNP, possibly resulting from decreased sodium delivery "to the natriuretic peptide sensitive medullary collecting system, receptor downregulation, increased sympathetic tone, enhanced neutral endopeptidase activity, and development of cGMP deficiency secondary to enhanced phosphodiesterase activity."

Abraham[84] and others[85] also suggested inhibiting the metabolism (i.e., prolonging the half-life) of the natriuretic peptides in order to enhance their biologic activity. In one study, the diuretic effect of neutral endopeptidase inhibitor was minimal. However, there were desirable hemodynamic effects without stimulation of plasma renin activity; for example, pulmonary capillary wedge pressure decreased 40%.[85] Another study showed that the neutral endopeptidase inhibitor candoxatrilat significantly increased sodium excretion.[86]

Although more studies are needed, it is possible that neutral endopeptidase inhibitors will eventually provide another alternative to conventional vasodilation and diuretic therapy for patients with CHF. Levin and colleagues[75] have suggested that a combination of the 3 natriuretic peptides may improve cardiac function by decreasing cardiac hypertrophy.

Commentary

The goals of medical treatment of congestive heart failure are to reverse or forestall the disease process and to relieve symptoms. Patients and physicians must work together for optimal results, and patients must understand their disease processes well enough to develop skills of self-monitoring. When patients restrict sodium and fluid intake, medication management is simpler, which makes achieving fluid balance and compensating for congestive heart failure more likely. Patients who monitor their weight daily and recognize the early symptoms of CHF decrease their need for hospital inpatient care and increase the effectiveness of outpatient management.

Improved beta blockers and vasodilators that lessen the symptoms of the disease and allow patients a better quality of life are now being marketed. More studies are needed, however, to determine whether mortality rates are significantly affected by the new drugs. The use of antiarrhythmic drugs has also been studied and is discussed elsewhere in this issue. As we unravel all of the factors responsible for congestive heart failure, we will be able to develop even better treatments to manage this increasingly common disease. Patients who worsen to NYHA functional class III or IV may improve through very aggressive medical therapy; in some cases, though, the only alternatives are mechanical circulatory support or cardiac transplantation.

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