

# Management of Advanced Heart Failure

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*Congestive heart failure (CHF) due to progressive systolic dysfunction has become a modern-day epidemic. Despite the increased incidence and prevalence, significant progress has been made in the past 10 to 15 years in the treatment of CHF at all stages. The current outlook for patients with newly diagnosed, mild heart failure is encouraging. It should be noted, however, that most of the morbidity and health care expenditure is incurred by a minority of patients diagnosed with CHF who are in the advanced stages of their disease. The thrust of this article will be to provide practical advice beyond current guidelines on the management of advanced CHF.*

As with all chronic diseases, the management of advanced congestive heart failure (CHF) requires a partnership between the patient and the health care provider, with the patient requiring as much understanding about the disease process and preventive measures as possible. From the physician's standpoint, the treatment of advanced heart failure requires an individualized approach with regard to

both patient education and pharmacologic treatment. Often very frequent and intense follow-up is necessary initially to stabilize and later to maintain a patient in optimal condition.

## MANAGEMENT OF ADVANCED HEART FAILURE

### Nonpharmacologic Measures

General, nonpharmacologic measures for the management of heart failure are as important to maintaining stability as the commonly used medications. These measures may be divided into physician-controlled and physician-directed, patient-controlled measures.

Efforts should be made to decrease the risk of new cardiac injury. These physician-directed measures include cessation of smoking, discontinuation of alcohol use, and weight reduction in obese patients. This also includes appropriate dietary

### KEY POINT

**As with all chronic diseases, the management of advanced CHF requires a partnership between the patient and the health care provider, with the patient requiring as much understanding about the disease process and preventive measures as possible.**

TABLE.	FACTORS POTENTIALLY CONTRIBUTING TO HEART FAILURE DECOMPENSATION
<p><b>Cardiovascular Factors</b></p> <ul style="list-style-type: none"> <li>● Superimposed ischemia or infarction</li> <li>● Uncontrolled hypertension</li> <li>● Unrecognized primary valvular disease</li> <li>● Worsening secondary mitral regurgitation</li> <li>● New onset or uncontrolled atrial fibrillation</li> <li>● Excessive tachycardia or bradycardia</li> <li>● Pulmonary embolism</li> </ul>	<p><b>Systemic Factors</b></p> <ul style="list-style-type: none"> <li>● Inappropriate medications</li> <li>● Superimposed infection</li> <li>● Anemia</li> <li>● Uncontrolled diabetes</li> <li>● Thyroid dysfunction</li> <li>● Electrolyte abnormalities</li> <li>● Pregnancy</li> </ul> <p><b>Patient-Related Factors</b></p> <ul style="list-style-type: none"> <li>● Medication noncompliance</li> <li>● Dietary indiscretion</li> <li>● Alcohol consumption</li> <li>● Substance abuse</li> </ul>

Adapted with permission from Stevenson LW, Massey BM, Francis GS. Optimizing therapy for complex or refractory heart failure: a management algorithm. *Am Heart J.* 1998;135:293–309.

measures to control hyperlipidemia and diabetes mellitus, if present. Physician-controlled measures include appropriate therapy for hypertension, hyperlipidemia, and diabetes mellitus, as well as advice and perhaps pharmacotherapy for smoking cessation and weight reduction. Other physician-controlled measures include avoidance of antiarrhythmic agents to suppress asymptomatic ventricular arrhythmias with complete avoidance of class I antiarrhythmics. With the exception of amlodipine, calcium channel blockers and nonsteroidal anti-inflammatory agents should also be avoided. Other recommendations for health maintenance include yearly influenza vaccine and pneumococcal immunization every 6 years.

Patient-controlled measures include restriction of daily dietary sodium intake to  $\leq 3$  grams, restricting fluids to 1 to 2 liters per day, and daily weight measurement to detect fluid retention so that early intervention may be initiated. A flexible diuretic regimen using increased doses of diuretics whenever weight increases more than 3 lbs in a 24-hour period may provide better control in appropriate patients. Diuretic doses must be individualized based on patient response. Patients should also be

encouraged to improve physical conditioning by engaging in moderate degrees of aerobic exercise, as tolerated.

When a patient is thought to have advanced CHF, based on chronic severity of symptoms or frequency of decompensation, the physician should reevaluate all aspects of the patient’s care. Failure to fully implement standard guidelines for care of the patient with mild to moderate heart failure often contributes to advanced disease with progressively worsening symptoms and prognosis. A thorough examination of the patient’s medical regimen should be performed, and if standard pharmacologic therapy has not been fully implemented, this should be the first priority. It is equally important to be aware of and tightly control comorbid conditions that may exacerbate heart failure symptoms. The **Table** lists several factors that may contribute to an episode of acute decompensation.

### Optimizing Standard Pharmacologic Therapy

Ideally, the patient with advanced heart failure should be maintained on an angiotensin-converting enzyme (ACE) inhibitor, a  $\beta$ -blocker, digitalis, loop

diuretics, and spironolactone. ACE inhibitors remain the mainstay of treatment of CHF at all levels of severity. Dosing of ACE inhibitors is often problematic in patients with profound CHF, and intolerance to even low doses of ACE inhibitors because of systemic hypotension is a very poor prognostic sign. Dosing should be increased as tolerated to equivalent doses used in large clinical trials (eg, enalapril 10 to 20 mg bid, captopril 25 to

### KEY POINT

**Failure to fully implement standard guidelines for care of the patient with mild to moderate heart failure often contributes to advanced disease with progressively worsening symptoms and prognosis.**

50 mg tid). Reasons to decrease the dosage or discontinue ACE inhibitors include cough (after pulmonary congestion has been ruled out), severe systemic hypotension (asymptomatic systolic blood pressure <80 mm Hg or symptomatic orthostatic hypotension when the patient is euvoletic), or progressive renal insufficiency with accompanying hyperkalemia. Renal insufficiency produced by ACE inhibitors is functional and generally reversible. Creatinine levels up to 3 to 3.5 mg/dL should be tolerated if hyperkalemia is not present.

Angiotensin II receptor blockers (ARBs) appear equivalent to ACE inhibitors with regard to survival in CHF and should be used if an ACE inhibitor is not tolerated because of cough (1). In equivalent doses, however, hypotension and renal insufficiency may remain problematic. There are no data showing superiority of combined ACE inhibition and angiotensin II receptor blockade; however, the combination may be useful in patients on an ACE inhibitor who can tolerate further afterload reduction.

With the exception of acutely decompensated class IV patients,  $\beta$ -blockers should be used in appropriate doses.  $\beta$ -Blockade is often difficult to initiate and maintain in the New York Heart

Association (NYHA) class III-B to IV patient. However, this class of medications has shown significant improvement in survival over and above that of ACE inhibitors. In severely decompensated patients, doses lower than the usual starting dose may be used with slow up-titration (every 4 weeks). This must be individualized since it depends on patient response. The choice of a selective  $\beta$ -blocker such as sustained-release metoprolol versus a nonselective  $\beta$ -blocker (carvedilol) is made based on several factors, including propensity toward orthostatic hypotension, coexistence of obstructive lung disease, and affordability. Currently, no  $\beta$ -blocker is recommended for use in patients with chronic class IV heart failure.

When one is up-titrating both an ACE inhibitor or ARB and a  $\beta$ -blocker, systemic hypotension often limits the optimal up-titration of the 2 medications. The recent Assessment of Treatment with Lisinopril and Survival (ATLAS) trial (2) comparing a low dose versus a high dose of lisinopril showed only an 8% relative decrease in mortality in the high-dose group, which was not statistically significant. By comparison, the various  $\beta$ -blocker trials have shown a 34% to 65% reduction in all-cause mortality when added to an ACE inhibitor. Given the known cross-regulation of the renin-angiotensin-aldosterone and the adrenergic nervous systems, it would seem appropriate to maintain patients on both an ACE inhibitor and  $\beta$ -blocker, even if only low doses of each are tolerated.

Digitalis has now, through 2 clinical trials, proved clinically useful in CHF. The Randomized Assessment of the Effects of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme (RADIANCE) trial (3) suggested that patients with more severe heart failure (NYHA functional class III and IV) are more likely to benefit from chronic digoxin therapy. In the Digitalis Investigation Group (DIG) trial (4), digoxin neither increased nor decreased mortality. However, more careful analysis of the data shows that digoxin therapy appeared to reduce mortality caused by worsening heart failure only to be offset by increased sudden (presumably arrhythmic) death. Posthoc analysis also showed a correlation between serum digoxin concentration and mortality, prompting many practitioners to

attempt to maintain the digoxin level between 0.5 and 1.0 ng/mL.

Diuretics have never been shown to improve mortality in CHF but are essential to maintaining patients free of pulmonary congestion and edema. Patients with so-called “wet” heart failure manifest volume overload primarily with orthopnea, dyspnea on minimal exertion, and dyspnea or cough immediately after reclining.

Generally, aggressive diuresis is accomplished with IV loop diuretics such as furosemide, bumetanide, or torsemide. Occasionally ethacrynic acid is used. In the acute setting with aggressive diuretic regimens, serum electrolytes should be assessed at least daily with potassium and magnesium measured twice daily with appropriate supplementation. In patients with advanced heart failure, loop diuretics are preferred because of their potency, with torsemide having better oral bioavailability in patients with chronically elevated right-sided filling pressures. Thiazide diuretics such as metolazone are often also used to augment loop diuretics by decreasing sodium reabsorption in the distal tubule. The addition of a thiazide must be accompanied by frequent and careful evaluation of serum electrolytes, as profound hypokalemia and hypomagnesemia may occur.

Spironolactone, though a weak diuretic, has now been accepted as part of standard therapy for patients with moderate to severe heart failure. The utility of this aldosterone antagonist was shown in the recently published Randomized Aldactone Evaluation Study (RALES) (5), which resulted in a 32% relative reduction in combined cardiovascular death and hospitalization with the use of even low doses of spironolactone.

The combination of hydralazine and nitrates has been shown to improve survival, but this combination was inferior to ACE inhibitors in the Veterans Administration Cooperative Vasodilator–Heart Failure Trial-II (V-HeFT-II). The combination remains useful in patients with intolerance to both ACE inhibitors and ARBs, as well as adjunctive therapy in the occasional patient with significant systemic hypertension despite maximum doses of an ACE inhibitor/ARB combination and  $\beta$ -blocker.

Currently, the only calcium channel blocker recommended for use in patients with CHF is amlodipine. Despite encouraging results in the Prospective Randomized Amlodipine Survival Evaluation-I (PRAISE-I) trial, the recently reported PRAISE-II trial failed to conclusively show a survival benefit in patients with nonischemic cardiomyopathy. Both trials did demonstrate the safe-

### KEY POINT

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ty of amlodipine with no increase in mortality in patients receiving the drug. Amlodipine is reserved for patients with recurrent angina pectoris and CHF and is used primarily as an antianginal in this setting. With a combination of hydralazine and nitrates, amlodipine may also be used for further afterload reduction in the occasional patient with persistent hypertension despite optimal therapy with other medications indicated for CHF.

### Role of Hemodynamic Monitoring

The role of invasive hemodynamic monitoring in the treatment of advanced CHF has been questioned since the report of worse survival in a patient population who had right heart catheterization during treatment in an intensive care unit setting (6). It must be noted, however, that only a minority of patients in this study had CHF as a primary diagnosis. Hemodynamic monitoring is indicated in the acutely decompensated patient in whom congestive symptoms cannot be easily relieved or when diuresis is limited by progressive renal insufficiency (serum creatinine  $\geq 2.5$  mg/dL) or hypotension (systolic blood pressure  $\leq 85$  mm Hg). Patients with comorbid conditions compounding the noninvasive assessment of clinical efficacy such as chronic obstructive pulmonary dis-

## KEY POINT

**Hemodynamic monitoring is indicated in the acutely decompensated patient in whom congestive symptoms cannot be easily relieved or when diuresis is limited by progressive renal insufficiency or hypotension.**

ease, renal failure, acute ischemic syndromes, or infection may also benefit. Failure to easily wean from IV inotropes that have been started empirically for acute decompensation is another indication. Lastly, the decision to declare a given regimen a therapeutic failure, implying the need for cardiac transplantation, or the futility of continued care should not be made without first attempting to tailor therapy based on objective hemodynamic measurement.

### Intravenous Inotropic Therapy

The role of IV inotropes (dobutamine, dopamine, and milrinone) in the therapeutic armamentarium for advanced CHF remains controversial. The controversy involving their use centers on the excess mortality reported with IV and oral inotropic agents. IV inotropic agents in current use fall into 2 distinct classes.

Dobutamine and dopamine are  $\beta$ -adrenergic agonists. Dobutamine is the most frequently used inotropic agent in this class. It improves hemodynamics by its inotropic effect as well as by arteriolar and venous dilation, slightly decreasing both preload and afterload. It is generally dosed between 2 and 20  $\mu\text{g}/\text{kg}$  per minute as a continuous infusion but may be used intermittently. Tachyphylaxis can occur, usually over a period of days. Potential adverse effects include tachycardia, atrial and ventricular arrhythmias, and myocardial ischemia due to increased myocardial oxygen consumption. Dobutamine must be used cautiously in patients with ischemic cardiomyopathy. The ability of dobutamine to enhance contractility in “hibernating” myocardium with chronically poor coronary flow reserve may promote muscle cell death and arrhythmias.

The inotropic effect of dopamine is weak, as the drug acts indirectly by norepinephrine release from myocardial sympathetic nerve terminals. Tachyphylaxis occurs much more rapidly with dopamine than with dobutamine. Its primary use in the management of advanced heart failure is promotion of diuresis by its action on dopamine-specific receptors in the renal vasculature at low doses (1 to 3  $\mu\text{g}/\text{kg}$  per minute).

Phosphodiesterase-III inhibitors increase intracellular levels of cyclic adenosine monophosphate by inhibiting its breakdown. These agents also possess vasodilatory properties via the same mechanism in vascular smooth muscle and are often referred to as “inodilators.” Milrinone and amrinone are the 2 most widely used drugs in this class, though use of amrinone has declined significantly because of thrombocytopenia that is not apparent with the use of milrinone. Milrinone is generally dosed as a continuous infusion (0.375 to 0.75  $\mu\text{g}/\text{kg}$  per minute). Therapeutic levels are obtained in ~6 hours without bolus infusion. If therapeutic levels are required acutely, a bolus infusion of 50  $\mu\text{g}/\text{kg}$  over 10 minutes may be used. This must be done cautiously in the patient who is relatively hypotensive. The maintenance dosage of milrinone must be decreased empirically for renal insufficiency. Milrinone has been shown to decrease pulmonary vascular resistance as well as systemic vascular resistance and for this reason appears to be more useful with regard to the treatment of combined right and left heart failure than dobutamine. Milrinone does not increase myocardial oxygen consumption and therefore is preferred in patients with severe ischemic cardiomyopathy and CHF. Current consensus recommendations for the widespread use of  $\beta$ -blocker therapy in patients with CHF make milrinone a better choice for treating acute decompensation in patients taking  $\beta$ -blockers.

The FDA-approved indications for the use of IV inotropes include: (a) short-term in-hospital support for patients with heart failure due to low cardiac output; (b) short-term inotropic and hemodynamic support during major diagnostic or surgical procedures; and (c) maintenance therapy in patients waiting for more definitive therapy such as heart transplantation or placement of a ventricular

assist device. The choice to use an IV inotrope acutely in the hospital setting is based on patient presentation and known historic factors. Patients who present primarily with acute or subacute fluid overload because of dietary or medical noncompliance can generally be treated easily with reinstitution of their medications and an appropriate diet and IV diuretics. The patient who presents with significant low output symptoms regardless of volume status (evidence of poor end-organ perfusion such as Cheyne-Stokes respiration, cool extremities, and worsening liver or renal function) should benefit from the acute administration of an IV inotrope. Preliminary results of the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbation of Chronic Heart Failure (OPTIME-CHF) failed to show a beneficial effect on total length of hospital stay within 60 days of therapy, suggesting no benefit of routine use of this inotrope in patients hospitalized with CHF (7).\*

Use of chronic IV inotropic therapy either as a continuous or intermittent infusion remains highly controversial. Except as a bridge to more definitive therapy such as cardiac transplantation, chronic IV inotropic therapy must be viewed as palliative therapy in patients with advanced, end-stage CHF. If physician and patient agree on instituting chronic IV inotropic therapy, it should occur in the hospital setting, where hemodynamic monitoring can be provided. Intermittent IV inotropic therapy has been used in several centers to maintain patients' functional status. Patients receiving intermittent IV inotropic support should continue to have their oral medications optimized, and weaning attempts should be made at least every 6 months. Neither the patient nor the physician should rely on intermittent IV inotropic support to indefinitely maintain a better functional status.

## ADJUNCTIVE TREATMENT

### Antiarrhythmics

CHF can be significantly exacerbated by the presence of atrial fibrillation. Atrial fibrillation of new onset or of unknown duration requires control of ventricular rate and at least 1 attempt at cardioversion. In patients with advanced heart failure, diltiazem and high-dose  $\beta$ -blockers may exacerbate

congestive symptoms if used for rate control. Amiodarone is the drug of choice for both rate control and maintenance of sinus rhythm after cardioversion in this setting. After several days of IV therapy, cardioversion may be attempted provided the patient has been adequately anticoagulated.

### KEY POINT

**Except as a bridge to more definitive therapy such as cardiac transplantation, chronic IV inotropic therapy must be viewed as palliative therapy in patients with advanced, end-stage CHF.**

Ventricular arrhythmias, particularly nonsustained ventricular tachycardia, are common in patients with advanced CHF. Most of the antiarrhythmics used to treat ventricular arrhythmias have either pro-arrhythmic or negative inotropic effects. There are no data to support the routine use of antiarrhythmic therapy for asymptomatic ventricular arrhythmias. Holter monitoring or a cardiac loop monitor may be useful in the patient with palpitations and mild intermittent dizziness. However, patients with near syncope or frank syncope and survivors of sudden cardiac death should undergo formal electrophysiologic testing with antiarrhythmic therapy (or device) directed by the results of this testing.

If an antiarrhythmic medication is called for, type-I antiarrhythmics should be avoided. The results of the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure (STAT-CHF) (8) showed amiodarone to be effective in suppressing ventricular arrhythmias in asymptomatic patients; however, there was no decrease in the overall survival or the rates of sudden death. The empiric use of amiodarone in asymptomatic patients with heart failure remains controversial and is currently being investigated.

### Lipid-Lowering Therapy

Many studies have now shown the utility of

3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in decreasing cardiovascular events in patients with coronary artery disease. Patients with advanced CHF of ischemic etiology should be maintained on this type of medication unless specifically contraindicated.

## Ultrafiltration

Ultrafiltration may be used to successfully control refractory volume overload and re-establish diuretic responsiveness in selected patients. Various methods of ultrafiltration may be used, including peritoneal dialysis, intermittent isolated ultrafiltration, continuous arteriovenous hemofiltration, or continuous venovenous hemofiltration. Of these, continuous venovenous hemofiltration has been used most successfully in patients with severely decompensated heart failure.

## WHEN TO REFER

Patients with advanced CHF should be referred to a general cardiologist for consultation whenever specific cardiologic diagnostic testing is thought necessary. Patients with persistent NYHA class III symptoms despite adequate conventional therapy and patients with other active primary or secondary cardiac problems such as angina pectoris, arrhythmias, and valvular disease should be followed concomitantly by a general cardiologist.

The continued increase in prevalence of advanced heart failure in the general population has prompted the establishment of specialized clinics for heart failure. Along with aggressive medical

management, patient education, including compliance with dietary, physical, and medication regimens, is repeatedly emphasized. Many of these clinics have access to investigational medications and devices. Patients should be referred to a specialized heart failure clinic when they demonstrate poor understanding of the importance of dietary, activity, and medication requirements; when NYHA functional class III-B or IV symptoms persist despite optimum medical management; and if they are subject to frequent hospitalizations for CHF.

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### KEY POINT

**Patients with persistent NYHA class III symptoms despite adequate conventional therapy and patients with other active primary or secondary cardiac problems such as angina pectoris, arrhythmias, and valvular disease should be followed concomitantly by a general cardiologist.**



## Dialogue Box

### ADVISORY BOARD

**Is the problem with use of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with advanced CHF due to renal effects or do NSAIDs have a cardiotoxic effect?**

#### VAN BAKEL

Most of the problem with the use of NSAIDs has to do with prostaglandin inhibition and the resultant effect on the kidney and its handling of sodium. These agents can cause patients to retain more fluid, making it more difficult to control edema. In my clinical practice, I've seen many patients with advanced CHF who are prescribed an NSAID for arthritis by another practitioner and within a week or so they are retaining a lot of fluid and end up in the hospital. The take-home message is that if you have patients with arthritis who need NSAIDs, it is important that you use these agents cautiously. Recognize that their diuretic need is likely to increase and that you may need to adjust their diuretic doses and follow their serum creatinine levels accordingly. The problem may be a little less with the cyclooxygenase-2 inhibitors.

### ADVISORY BOARD

**Would you elaborate on the theoretical advantage of the increased bradykinin production associated with ACE inhibition?**

#### VAN BAKEL

ACE inhibition results in increased levels of bradykinin, which is a vasodilator that will conceivably help a weak heart pump more effectively by reducing afterload. Whether higher levels of bradykinin translate into prolonged survival, less fibrosis, or less apoptosis of cardiac myocytes is unknown and is purely speculative at this point.

### ADVISORY BOARD

**What guides the selection of the  $\beta$ -blockers used in a patient with CHF?**

#### VAN BAKEL

Whether the beneficial impact of  $\beta$ -blockers represents, as we think with ACE inhibitors, a class effect is still unclear. Based on clinical trials within the  $\beta$ -blocker class, we know that carvedilol, sustained-release metoprolol, and bisoprolol work and that nonsustained-release metoprolol has produced equivocal results in terms of survival. Part of the controversy stems from a recent clinical study called BEST ( $\beta$ -blocker Evaluation Survival Trial), in which the nonselective  $\beta$ -blocker bucindolol produced mixed results. What is interesting about this study was that, on subgroup analysis, white NYHA class III CHF patients did well but African American NYHA class III patients did poorly. In addition, NYHA class IV CHF patients in both of these groups did poorly. When the data were combined, there was a neutral effect. At least partially as a result of this study, the issue of race differences and the efficacy of these different drugs is just now coming onto the forefront.

### ADVISORY BOARD

**You discussed the importance of titrating up the dose of ACE inhibitors in patients with advanced CHF to the equivalent doses used in clinical trials as tolerated. What are the blood pressure parameters below which you get uncomfortable even if the patient denies any symptoms?**

#### VAN BAKEL

The numbers depend on the etiology of the patient's underlying disease. In an outpatient with dilated cardiomyopathy and normal coronary arteries, I think a systolic pressure of 80 mm Hg



## Dialogue Box

and a diastolic pressure of 50 mm Hg are fine, and in a patient with ischemic cardiomyopathy a systolic pressure in the mid-90s and a diastolic down to 60 mm Hg are fine.

### ADVISORY BOARD

**What doses do you aim for with  $\beta$ -blockers and what parameters do you monitor as you titrate the dose?**

#### VAN BAKEL

As I titrate up the dose I follow several parameters including heart rate, blood pressure, and whether or not the patients are wheezing. With regard to dosing, I've been pushing metoprolol succinate extended release to between 150 mg/d and 200 mg/d and carvedilol to 25 mg BID in patients with NYHA class III CHF. If the patients are still hypertensive or still tachycardic at that level, I'll push the carvedilol dosage up to 50 mg BID.

### ADVISORY BOARD

**With regard to  $\beta$ -blocker therapy, how do you deal with bundle branch blocks or higher blocks such as a first-degree atrioventricular (AV) block?**

#### VAN BAKEL

Bundle branch blocks don't really concern me. First-degree and higher AV blocks and sinus bradycardias are of more concern and are regarded as contraindications. In a patient with first-degree AV block, a  $\beta$ -blocker can be used but that patient needs to be followed more closely. The potential benefits of  $\beta$ -blockade in patients with severe heart failure should prompt consideration of placement of a demand pacemaker, if significant bradycardia or AV block would otherwise preclude its use.

### ADVISORY BOARD

**Since spironolactone is such a weak diuretic,**

**what accounts for its profound beneficial impact?**

#### VAN BAKEL

Theoretically, the beneficial effect of spironolactone stems from its ability to block the effects of aldosterone. Spironolactone may also help modulate the extracellular matrix and decrease cardiac fibrosis.

### ADVISORY BOARD

**In what situations would you favor the use of phosphodiesterase III inhibitors, such as milrinone, over  $\beta$ -adrenergic agonists, such as dobutamine, which have traditionally been used as inotropic agents?**

#### VAN BAKEL

I can think of 3 or 4 scenarios in which milrinone might be favored. First, milrinone is a better pulmonary vasodilator than dobutamine, thus you would get more bang for your buck by using milrinone in a patient with both right and left heart failure and pulmonary hypertension. Second, in the CHF patient who has been stabilized on a  $\beta$ -blocker at a moderate to high dose and is admitted with decompensated CHF, milrinone would actually work faster than dobutamine since you have to use much higher doses of dobutamine to overcome the antagonism of the  $\beta$ -receptor. Finally, studies have shown that milrinone in particular does not really increase myocardial oxygen consumption. So if you have someone with severe coronary disease in whom you are worried that dobutamine may provoke angina, milrinone might be a better first-line drug. In addition, I've also had occasion to use milrinone in patients who have become refractory to dobutamine, and the combination of low-dose dobutamine and milrinone seems to work a lot better in patients with refractory CHF.



## Dialogue Box

Sporadic reports in the literature have shown that chronic IV milrinone can be used as a bridge to initiation of  $\beta$ -blockade. Once the patient is adequately stabilized on chronic home inotropic therapy with milrinone, an attempt should be made to initiate and slowly up-titrate  $\beta$ -blockade in an effort to eventually wean the patient off the inotrope.

**Editor's Note: The following questions were posed to Dr. Van Bakel as an update to this Dialogue Box.**

**Since the original publication of this article, what advances have been made in the treatment of advanced heart failure?**

### **VAN BAKEL**

Several studies have helped refine our use of standard therapy in this population. The COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) trial has shown good tolerability and equal efficacy of carvedilol in a population of people with severe heart failure. The benefit was equal to that seen in less severely ill patients. This expands the indication of  $\beta$ -blocker therapy to include patients with late NYHA class III and stabilized NYHA class IV symptoms.

Another study, the Val-HeFT (Valsartan Heart Failure Trial), comparing valsartan versus placebo in patients taking an ACE inhibitor and/or  $\beta$ -blocker, showed that patients taking valsartan plus an ACE inhibitor or valsartan plus a  $\beta$ -blocker did better. However, when valsartan, an ACE inhibitor, and a  $\beta$ -blocker were used concomitantly, survival was slightly worse. The reason for this finding is unclear; however, it does provide a cautionary note to multiple combination therapy.

Several studies have reported the efficacy of biventricular pacing, also called cardiac resyn-

chronization therapy. The theory behind these devices is that, as the QRS complex widens in heart failure, there is dyssynchrony in segmental left ventricular contraction that reduces overall cardiac output and contributes to mitral insufficiency. By pacing both the right ventricular apex and the posterior lateral wall via a lead placed through the coronary sinus, synchronized contraction of the entire left ventricle may be reestablished, thus decreasing mitral insufficiency and increasing cardiac output. Several studies are ongoing in an attempt to refine patient selection criteria and determine the efficacy of a combined biventricular pacer/defibrillator.

**What is BNP and how is it used clinically?**

### **VAN BAKEL**

BNP is brain natriuretic peptide, a 32-amino acid peptide that is secreted constitutively by the ventricles in response to stretch and increased wall stress. Its action is counterregulatory to many of the actions of the renin-angiotensin-aldosterone system and sympathetic nervous system in heart failure. The peptide binds to specific receptors in the vasculature, kidney, and other organs producing potent dose-related vasodilation with rapid onset and offset of action. At the cellular level vasodilation occurs by increasing levels of cyclic guanosine monophosphate.

**Is there a role for it in monitoring a patient's CHF and altering its treatment accordingly?**

### **VAN BAKEL**

BNP levels are variable within a narrow range within the normal population, increasing with age and with women tending to have higher levels than men. Several studies have shown significantly increased BNP levels in patients presenting



## Dialogue Box

with an acute exacerbation of CHF. A rapid point-of-care assay for BNP is now available (Biosite Diagnostics, San Diego, Calif). It has been extremely useful in differentiating dyspnea caused by CHF from other disease processes. BNP levels in patients with heart failure show dramatic increases with worsening severity of heart failure and have been shown to be prognostic for cardiovascular end points.

**In a patient with known CHF, is it ever possible to attain a normal BNP level and if so should it be a goal?**

### **VAN BAKEL**

It is possible to attain a normal BNP level though the more severe the heart failure the more elusive this goal becomes. Continued elevation of BNP levels on discharge from the hospital has been shown to be a marker for readmission, and despite observed clinical improvement, an argument has been made that normalization of BNP levels should be a goal of therapy. I suspect there will be some patients whose BNP levels will never

become satisfactory despite maximum tolerated treatment. These patients will have to be followed much more closely.

**What is nesiritide and when should it be used?**

### **VAN BAKEL**

Nesiritide is recombinant human BNP. This drug has been recently approved by the FDA for treatment of acute decompensated CHF. Its acute hemodynamic effects include significant dose-dependent reduction of right atrial, pulmonary artery, and pulmonary capillary wedge pressures as well as systemic and pulmonary vascular resistances, which cause an indirect increase in cardiac output and index and concomitant diuresis. Several studies have demonstrated clinical utility in the acute setting. In theory, this particular IV vasodilator may provide significant symptomatic relief without the attendant increase in mortality shown with other inotropes because it does not increase cyclic adenosine monophosphate and thus calcium flux within the myocyte.