

## Clinical Practice Guidelines for Heart Failure

*Based on a presentation by Kirkwood F. Adams, Jr., MD*

### **Presentation Summary**

Development of guidelines can be a difficult process; each organization or institution must establish the rules and criteria for including specific therapies and the level of complexity needed. Specific outcomes must be incorporated, including maintenance of comfort and functionality, freedom from hospitalization, and survival.

In existing guidelines for the management of heart failure, angiotensin-converting enzyme (ACE) inhibitor therapy is clearly the gold standard. However, there is

still a high mortality with ACE inhibitor therapy; the key may be choosing the right patients. Current guidelines reflect the uncertainty regarding digoxin before the Digitalis Investigation Group (DIG) trial; obviously, these guidelines should be revisited.

Clinical practice guidelines for the management of heart failure need to be revised to include a better consensus on beta-blockade, the new data on digoxin, emerging data on angiotensin II receptor antagonists, and current thinking on anti-coagulant therapy.

### **Development of Guidelines**

Clinical practice guidelines have emerged as an important strategy to optimize the care of patients with chronic disease. Unfortunately, the development of sound guidelines can be a difficult process for several reasons:

1. Can the major therapeutic goals for the chronic disease in question be identified and prioritized?

(a) The guidelines must be directed toward specific clinical outcomes.

(b) When multiple adverse outcomes are possible, controversy may arise concerning the relative importance of specific clinical events, such as mortality versus morbidity versus quality of life.

2. What rules of evidence and criteria justify specific therapies included in a practice guideline?

(a) What is sufficient evidence to prove the efficacy of a particular therapy? Although physicians are most comfortable when the evidence of efficacy is based on results of clinical trials, there are many limitations to using this type of data alone. What, then, is the role of clinical observation and consensual expert opinion?

(b) How much benefit is enough? If efficacy is established, what is the magnitude of a favorable drug effect?

(c) What is the cost/benefit ratio of the treatment in question? What is the risk/benefit ratio?

3. How complex and detailed should the guidelines be? Is it possible to generate recommendations that are so general they are of no value to the care of a particular patient? Naturally, complex and detailed guidelines are difficult to establish in a busy clinical practice that deals with many types of patients. The key to guideline development is to strike the proper balance between guidelines that are overly complex or too simplistic.

4. Increasingly, practice guidelines attempt to factor in the health economic aspects of the care plan proposed. This leads to guidelines that consider practical strategies for improving the efficiency of care to offset new costs related to the prolongation of chronic disease.

#### **Guidelines for Heart Failure**

The potential benefits of clinical practice guidelines seem to be especially evident for heart failure, a chronic disease in which mortality and morbidity is high and yet one in which a number of recent therapeutic advances may allow for an improved outcome. We will review these issues as they relate to the guidelines for this condition. The important first step is to identify the goals of heart failure management. Key outcomes include:

- Maintaining comfort and functionality in daily living
- Freedom from hospitalization
- Survival despite the chronic nature of the disease

Fortunately, much of the current pharmacologic therapy recommended for heart failure is supported by data from well-controlled clinical trials. There are, however, areas where expert opinion is necessary, particularly as potential new indications emerge for treatments that were originally intended for another condition like hypertension. An example would be the potential benefit of angiotensin receptor antagonists, which were originally developed to treat hypertension in patients who could not tolerate ACE inhibitors.

Digoxin therapy illustrates the complex interaction that exists between cost/benefit and risk/benefit ratios. With digoxin, the cost is low, so perhaps a less dramatic favorable benefit is needed to support the inclusion of this drug in a guideline. If the risk/benefit ratio for a particular drug is high, then perhaps a greater magnitude of benefit is needed before it is included in a guideline.

Health economic issues are particularly acute in the area of heart failure management. Desired outcomes may be realized only at a substantial economic cost. One area where there is obvious concurrence in treatment goals and financial consequences is the freedom from hospitalization; reductions in this area provide a positive benefit both clinically and economically. Comfort and functionality are important to the patient as well as from a clinical perspective; however, their economic benefit is less clear-cut, because work productivity is often not possible in this patient population. Paradoxically, survival, an obvious clinical benefit, may actually have a negative economic impact. If life is prolonged in heart failure, the use of other forms of medical treatment for conditions such as cancer or other forms of cardiovascular disease is likely to increase. Again, disease management strategies may enable cost-effective preventive measures and may offer more efficient ways to render care so as to lessen the costs of prolonging life in patients with chronic disease.

Excellent work by a number of heart failure specialists has led to a series of clinical practice guidelines that have substantially improved the care of patients with this syndrome.<sup>1,2</sup> Fortunately, the rapid pace of drug development in heart failure has resulted in a need to revisit these practice guidelines to accommodate new therapeutic developments. The remainder of this review will focus on specific pharmacologic therapy contained in the current guidelines from the standpoint of recent clinical trial results and consider

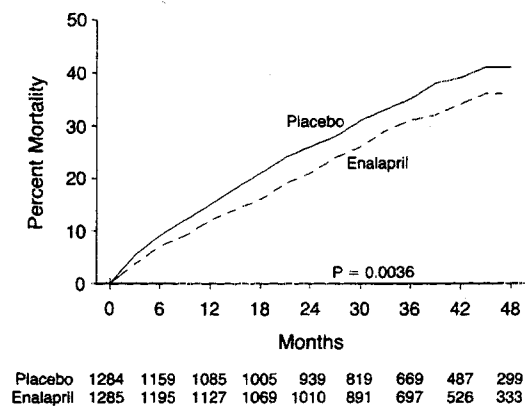
how these guidelines might be modified to accommodate new therapeutic approaches.

**Existing Guidelines:  
ACE Inhibitors**

ACE inhibitor therapy is clearly the gold standard of heart failure therapy in existing guidelines; such agents are of substantial therapeutic benefit in heart failure. Robust clinical trial data demonstrate decreased morbidity and hospitalization, as well as reduced mortality in symptomatic patients.<sup>3,4</sup> These benefits were seen despite a high rate of crossover to open-label ACE inhibitor therapy during the SOLVD [Study of Left Ventricular Dysfunction] trials. Although these clinical benefits are impressive, the limitations of ACE inhibitor therapy need to be considered as future guidelines are developed. For example, the mortality data from the treatment arm of the SOLVD trial (Figure 1)<sup>3</sup> indicates a significant difference in risk between ACE inhibitor and placebo-treated patients ( $P = 0.0036$ ); however, despite this beneficial effect, there is still a high residual risk of death in ACE inhibitor-treated patients.<sup>3</sup> As a result, even with the "gold standard" ther-

apy, many patients with chronic heart failure are not surviving long after this diagnosis. Data from the SOLVD treatment trial indicate that ACE inhibitor use was associated with a mortality reduction of 33% at 3 months, 29% at 6 months, but only 17% at 48 months. The reduction in death or hospitalization was 40% to 50% in the early stages and only 26% by the end of the study (Table 1).<sup>3</sup>

**Figure 1.** Mortality Due to Progressive Heart Failure



The numbers of patients alive in each group at the end of each period are shown at the bottom of the figure. See reference 3. Copyright ©1997 Massachusetts Medical Society. All rights reserved.

**Table 1.** Effect of Treatment on Mortality and Hospitalization for Congestive Heart Failure and Proportion of Patients Taking Angiotensin-Converting Enzyme Inhibitors after Various Periods\*

Months of Follow-up	Mortality			Death or Hospitalization For Heart Failure			Proportion Taking Inhibitors <sup>†</sup>	
	Placebo	Enalapril	Risk Reduction (95% CI)	Placebo	Enalapril	Risk Reduction (95% CI)	Placebo	Enalapril
	Number	Number	Percent	Number	Number	Percent	Percent	Percent
3	69	47	33 (2-53)	164	92	46 (30-57)	6	91
6	126	91	29 (8-46)	259	150	45 (33-55)	10	88
12	201	159	23 (5-37)	401	262	40 (30-48)	12	86
24	344	277	23 (10-34)	559	434	30 (21-38)	20	83
36	450	396	16 (4-27)	680	555	28 (19-35)	23	82
48	504	443	17 (5-27)	731	607	27 (18-34)	30	83
Overall <sup>‡</sup>	510	452	16 (5-26)	736	613	26 (18-34)	—	—

$Z = 2.69; P = 0.0036$ 
 $Z = 5.65; P < 0.0001$

\*The 95% confidence intervals (CI) correspond to a two-sided  $P$  value of  $<0.05$  or a one-sided  $P$  value of  $<0.025$ . Risk reductions were calculated by the log-rank test from the data available at each specific time.

<sup>†</sup>Values shown for three and six months were based on data obtained after the visits at four and eight months, respectively. The inhibitors were angiotensin-converting enzyme inhibitors.

<sup>‡</sup>The total numbers of deaths were 518 and 458 when deaths after January 31, 1991, but before the patients' last visits, were included.

Although loss of treatment effect could be caused by crossover, it seems clear that ACE inhibitor therapy is not the final answer during chronic follow-up.

The SOLVD prevention trial remains the first and only major clinical trial to document the benefits of treatment in patients with asymptomatic left ventricular dysfunction.<sup>4</sup> Secondary prevention was achieved with ACE inhibitor therapy in these patients, as the occurrence of hospitalization and the development of heart failure were attenuated. Use of ACE inhibitors in asymptomatic patients with left ventricular dysfunction has not been widely promoted; yet certain subgroups of these patients appear to benefit substantially. Analysis of the benefit of enalapril in the SOLVD prevention trial patients who ranked in the lower third of the left ventricular ejection fraction spectrum reveals that development of heart failure was reduced by 49%, hospitalization for heart failure by 47%, and mortality by 16% in this subgroup. These data provide even stronger evidence for the value of ACE inhibitor therapy in patients with marked depression of ejection fraction, even in the absence of overt symptoms.

#### Existing Guidelines: Digoxin

These guidelines take a conservative position on the use of digoxin in heart failure. The recommendations issued in 1995 by the ACC/AHA [American College of Cardiology/American Heart Association] Task Force stated that "Uncertainty regarding the use of digitalis derives primarily from the lack of data regarding its effect on mortality. To remedy this uncertainty, the NHLBI [National Heart, Lung, and Blood Institute] and the VA [Veterans Administration] are currently conducting DIG, a large, placebo-controlled clinical trial. Until the results of this trial are released, controversy will persist regarding the appropriate role of digoxin in patients with heart failure who are in normal sinus rhythm."<sup>1</sup>

The AHCPR [Agency for Health Care Policy and Research] guidelines

raised many of the same issues and concerns about digoxin therapy.<sup>2</sup> These guidelines advocate adding digoxin to ACE inhibitors and diuretics in patients with severe heart failure and using a stepped approach in patients with mild to moderate heart failure, stating that patients who "become asymptomatic on optimal doses of ACE inhibitors and diuretics...do not require digoxin."

Therefore, existing guidelines for the use of digoxin in the treatment of heart failure have thus focused on several issues that suggest use of digoxin should be limited:

- The lack of mortality data
- The increase in mortality seen with other inotropic agents
- The emphasis on decreasing mortality from the ACE inhibitor literature
- The magnitude of benefit with digoxin
- The issue of digoxin toxicity

Completion and publication of the results of the DIG trial provide important new information that addresses many of these issues concerning the role of digoxin therapy in heart failure.<sup>5</sup> Recommendations concerning digoxin use in heart failure in existing guidelines need to be reconsidered in light of the DIG study for a couple of reasons. The DIG trial found a neutral effect of digoxin on mortality in patients who were treated with an ACE inhibitor and a diuretic. Although no survival benefit of digoxin therapy was evident, the neutral outcome allays concern that it might increase mortality in a manner similar to chronic therapy with other oral inotropic agents. The DIG results also demonstrate that digoxin therapy is associated with a significant reduction in hospitalization related to heart failure.

Although mortality did not differ significantly between the two groups, overall hospitalizations were reduced by 6% in the digoxin group, and there were fewer hospitalizations per patient for any reason in the digoxin group compared with the placebo group ( $P = 0.01$ ).

Hospitalizations for worsening heart failure were reduced 7.9% in the digoxin-treated patients ( $P < 0.001$ ), and the risk of the combined endpoint of death or hospitalization was significantly lowered in digoxin-treated patients (risk ratio, 0.75; 95% confidence interval, 0.69 to 0.82;  $P < 0.001$ ) (Figure 2).<sup>5</sup> The significant effect on hospitalization seen in this study argues for a continued role for digitalis in the treatment of heart failure. Interestingly, the DIG study results are in concert with those of the RADIANCE [Randomized Assessment of the Effect of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme] trial, which indicated less treatment failure in patients who were treated with the combination of ACE inhibitors, a diuretic, and digoxin rather than with ACE inhibitors and a diuretic alone.<sup>6</sup>

In addition to insights from the DIG study, new analyses of combined data from the PROVED [Prospective Randomized Study of Ventricular Failure and Efficacy of Digoxin] and RADIANCE trials, as well as the possible combination of digoxin with other agents, are changing the way digoxin therapy in heart failure is viewed.<sup>6,7</sup> Key points in the changing view of digoxin therapy for heart failure include:

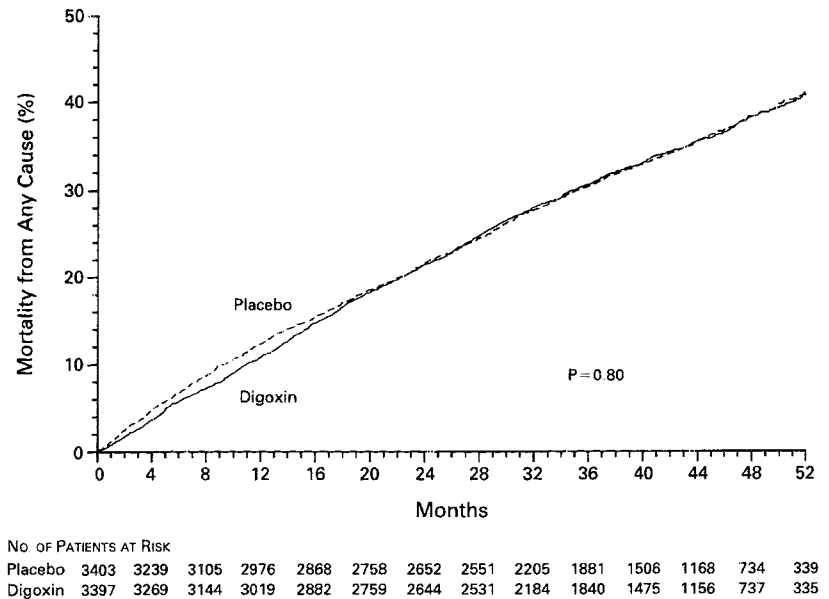
- New ideas concerning the serum concentration necessary for efficacy
- The role of digoxin therapy in patients with severe systolic dysfunction but mild clinical heart failure
- The role of potassium and magnesium, as well as that of aldosterone antagonists
- The possible benefits of combining digoxin and beta-blocker therapy

New ideas are emerging with regard to the dose and serum concentration for

digoxin.<sup>8</sup> Evidence from the PROVED and RADIANCE trials, which involved about 300 patients, suggests that clinical benefits can be obtained from low serum concentrations of digoxin. Treadmill exercise time was greater in patients who are continued on digoxin with either “low” (0.5 to 0.9 ng/mL), “moderate” (1.0 to 1.2 ng/mL) or high (>1.2 ng/mL) serum digoxin concentrations at randomization compared with patients who are withdrawn from digoxin (all  $P < 0.03$ ). Although this analysis has limitations—patients were not randomly assigned to different levels of digoxin serum concentration—the results support the concept that low digoxin serum concentrations offer clinical benefit, presumably with less risk of toxicity.

The effect of digoxin was examined in patients with significant systolic dys-

**Figure 2.** Mortality in the Digoxin and Placebo Groups



The number of patients at risk at each four-month interval is shown below the figure. See reference 5. Copyright ©1997 Massachusetts Medical Society. All rights reserved.

function but mild symptoms of heart failure.<sup>9</sup> Analysis of the combined PROVED and RADIANCE results indicated that the risk of treatment failure was greater when digoxin was withdrawn, even in patients with a low heart failure score at randomization.

Recent favorable results with beta receptor antagonists in heart failure and the approval of carvedilol by the FDA [Food and Drug Administration] for use in patients with mild to moderate systolic heart failure represent new advances in the care of patients with symptomatic ventricular dysfunction.<sup>10,11</sup> Future guidelines will have to address the role of these agents in the management of patients with systolic heart failure.

Several intriguing potential benefits of the combination of digoxin and beta-blocker therapy in patients with heart failure can be discussed.<sup>12</sup> The possibility exists that beta-blockade might limit or even prevent the adverse effects of digoxin related to cardiac arrhythmia and ischemia. Catecholamine-induced arrhythmia may account for sudden cardiac death caused by digoxin, which beta-blockade would be likely to antagonize.

Another potential benefit of digoxin therapy in which it is co-administered with a beta receptor antagonist relates to exercise tolerance. Clinical trials with digoxin have demonstrated favorable effects on exercise capacity in heart failure.<sup>5,6</sup>

By contrast, data from the MOCHA [Multicenter Oral Carvedilol Heart Failure Assessment] trial reveal the different aspects of carvedilol therapy in patients with this syndrome.<sup>13</sup> In this trial, dose-related reductions that increased ventricular function and decreased morbidity and mortality. By contrast, carvedilol had no beneficial effect on submaximal exercise (the 6-minute walk test) or more maximal exercise (the self-powered treadmill) compared with placebo. This reflects what has often been observed clinically: therapy may improve ventricular function, with no change in exercise capacity. Interestingly, early studies suggested that the

combination of digoxin and propranolol had favorable effects on exercise capacity in patients with poor ventricular function compared with propranolol alone.<sup>14</sup> Whether similar findings would be found with current third-generation beta-blockers in combination with digoxin deserves investigation.

### Summary

Clinical practice guidelines are of great potential value in optimizing the quality and efficiency of care in patients with heart failure. Initial guidelines for heart failure have great merit, but they must be adapted and updated to reflect new developments, including: a consensus on beta-blockade therapy for heart failure, consideration of new evidence concerning the efficacy of digoxin, and a review of emerging data on angiotensin II receptor antagonists.

Discussion of guidelines and recommendations for therapy are enlivened by the huge potential benefit of these approaches in heart failure. Although there are now many effective treatments, the challenge remains to develop and implement guidelines that change behavior and really improve outcome for patients.

### ... DISCUSSION HIGHLIGHTS ...

#### Clinical Practice Guidelines for Heart Failure

*Dr. Gheorghide:* I'd like to review the ACC/AHA Guidelines for the Evaluation and Management of Heart Failure (Table 2)<sup>16</sup> and discuss the managed care implications.

*Dr. Leider:* Heart failure is one of the few conditions where if we follow the guidelines, patients do better and costs go down quickly. What really counts is how effectively we implement the approaches in the guidelines.

*Dr. Adams:* There are actually two issues involved. The first issue is that

there are some problems with the way the guidelines are written, so the guidelines are going to be redone. The second issue is developing models for bringing that information down to the level of the patient.

**Dr. Gheorghiade:** I think it's clear that ACE inhibitors have been shown to reduce worsening heart failure and hospitalizations as well as mortality. However, the evidence for hydralazine and isosorbide dinitrate may not be as compelling.

**Dr. Adams:** One argument would be to use the combination of ARBs [adrenergic receptor blockers] plus nitrate.

**Dr. Brunton:** Where's the evidence for nitrates as part of the combination?

**Dr. Adams:** The theory is that nitrates may have an additive preload effect to ACE inhibitors, and that combination is used fairly often in patients who take ACE inhibitors, with a good clinical benefit.

**Table 2.** ACC/AHA Guidelines for Treatment of Heart Failure

<p><b>Pharmacologic Treatment of Left Ventricular Systolic Dysfunction</b></p> <p><i>Solid Evidence</i></p> <ol style="list-style-type: none"> <li>1. ACE inhibitors for all patients with significantly reduced left ventricular ejection fraction unless contraindicated</li> <li>2. Hydralazine and isosorbide dinitrate in patients who cannot take ACE inhibitors</li> <li>3. Digoxin in patients with heart failure caused by systolic dysfunction that is not adequately responsive to ACE inhibitors and diuretics</li> <li>4. Digoxin in patients with atrial fibrillation and rapid ventricular rates</li> <li>5. Diuretics for patients with fluid overload</li> <li>6. Anticoagulation in patients with atrial fibrillation or a previous history of systemic or pulmonary embolism</li> <li>7. Beta-blockers for high-risk patients after an acute myocardial infarction</li> </ol> <p><i>Some Evidence</i></p> <ol style="list-style-type: none"> <li>1. Digoxin for all patients with heart failure caused by left ventricular systolic dysfunction</li> <li>2. Addition of hydralazine and isosorbide dinitrate for patients who do not respond adequately to ACE inhibitors</li> <li>3. Beta-blockers for patients with dilated cardiomyopathy</li> <li>4. Anticoagulation in patients with sinus rhythm with a very low ejection fraction or intracardiac thrombi</li> <li>5. Outpatient low-dose dobutamine infusion for refractory heart failure</li> </ol> <p><i>Consensus-Based</i></p> <ol style="list-style-type: none"> <li>1. Calcium channel blockers in the absence of coexistent angina or hypertension</li> <li>2. Treatment of asymptomatic ventricular arrhythmias</li> </ol> <p><b>Pharmacologic Treatment of Left Ventricular Diastolic Dysfunction</b></p> <p><i>Solid Evidence</i></p> <ol style="list-style-type: none"> <li>1. Diuretics</li> <li>2. Nitrates</li> <li>3. Drugs suppressing A-V [atrioventricular] conduction to control ventricular rate in patients with atrial fibrillation</li> <li>4. Anticoagulation in patients with atrial fibrillation or previous systemic or pulmonary embolism</li> </ol> <p><i>Some Evidence</i></p> <ol style="list-style-type: none"> <li>1. Calcium channel blockers</li> <li>2. Beta-blockers</li> <li>3. ACE inhibitors</li> <li>4. Anticoagulation in patients with intracardiac thrombi</li> </ol> <p><i>Consensus-Based</i></p> <ol style="list-style-type: none"> <li>1. Drugs with a positive inotropic effect in the absence of systolic dysfunction</li> <li>2. Treatment of asymptomatic arrhythmias</li> </ol>
---

Reprinted with permission from *Circulation* 1995;92:2764-2784

**Dr. Gheorghide:** What about the third recommendation concerning digoxin?

**Dr. Adams:** I would end the statement after "systolic dysfunction."

**Dr. Brunton:** What we're really saying is to upgrade the recommendation from a class II recommendation, with some evidence, to a class I recommendation, with solid evidence.

**Dr. Bijou:** We need to remember that all these recommendations are for symptomatic patients only; there are no data for asymptomatic patients.

**Dr. Adams:** It depends on what you mean by symptoms. We have recently published our analysis of the relationship between symptoms and the response to digoxin withdrawal, based on the PROVED and RADIANCE data. Included in these trials is a prospective heart failure score, so we have an excellent idea of symptomatology in these patients at randomization. Given the stabilization phase included in the PROVED and RADIANCE data, it is not surprising that the heart failure scores were very low in most patients at the randomization visit. When the term "symptoms" is used, many people think that the patient has to have edema. In the PROVED and RADIANCE trials, many patients had dyspnea on exertion alone, and yet our analysis demonstrated a significant number of these patients deteriorated when digoxin was withdrawn.<sup>9</sup>

**Dr. Gheorghide:** I would say that any patient who has signs or symptoms of heart failure—from NS3 to JVD to cardiovascular to leg edema—should be a candidate for digoxin therapy. A patient with an ejection fraction (EF) of 25% and no symptoms probably should not receive digoxin therapy.

**Dr. Brunton:** This is where some of the confusion starts. We were talking earlier about triple therapy, and now

we're saying start with an ACE inhibitor and then add a diuretic or digoxin if the patient is symptomatic.

**Dr. Adams:** One of the issues with stepped care for patients is that by definition these patients are symptomatic. The current guidelines advocate starting with an ACE inhibitor and diuretic and then adding digoxin. The data from the DIG trial show that if we wait to add the digoxin, we will have a failure rate.

**Dr. Gheorghide:** Right. We have conclusive data that digoxin will prevent hospitalization. I don't think we should wait for the patient to be hospitalized and then start digoxin therapy.

We must remember that the guidelines are 3 to 4 years old, and they must be revisited in light of the new evidence we have.

**Dr. Bijou:** In looking at guidelines, we need to remember that medicine is dynamic and that things are changing very quickly. We also need to keep in mind who wrote the guidelines and their purpose. Finally, we must keep in mind the areas of controversy that remain: anticoagulation, cardiac rehabilitation, and digoxin.

#### ... REFERENCES ...

1. Guidelines for the evaluation and management of heart failure: Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Evaluation and Management of Heart Failure). *Circulation* 1995;92:2764-2784
2. Konstam MA, Dracup K, Baker DW et al. Heart Failure: Evaluation and care of patients with left ventricular systolic dysfunction. *J Cardiac Failure* 1995;1:183-187.
3. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302.
4. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients



with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685-691

5. Garg R, Gorlin R, Smith T, Yusuf S for the Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;336:525-533.

6. Packer M, Gheorghiade M, Young JB, et al. for the RADIANCE Study. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting enzyme inhibitors. *N Engl J Med* 1993;329:1-7.

7. Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: Results of the PROVED Trial. *J Am Coll Cardiol* 1993;22:955-962.

8. Young JB, Gheorghiade M, Packer M, Uretsky B, Hull H, on behalf of the PROVED and RADIANCE Investigators. Are low serum levels of digoxin effective in chronic heart failure? Evidence challenging the accepted guidelines for a therapeutic serum level of the drug (abstract) *J Am Coll Cardiol* 1993;21:378A.

9. Adams KF, Gheorghiade M, Uretsky BF, et al. Patients with mild heart failure worsen during withdrawal from digoxin therapy. *J Am Coll Cardiol* 1997;30:42-48.

10. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med* 1996;334:1349-1355.

11. Eichhorn EJ, Bristow MR. Medical therapies can improve the biological properties of the chronically failing heart. *Circulation* 1996;94:2285-2296.

12. Gheorghiade M, Pitt B, Digitalis Investigation Group (DIG) trial: A stimulus for further research. *Am Heart J* 1997;134:3-12.

13. Bristow M, Gilbert E, Abraham W, Adams K, Fowler M, Hershberger R, Kubo S, Narahara K, Ingersoll H, Drueger S, Young S, Shusterman N, for the MOCHA Investigators. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. *Circulation* 1996;94:2807-2816.

14. Crawford MH, LeWinter MM, O'Rourke RA, Karliner JS, Ross J Jr. Combined propranolol and digoxin therapy in patients with angina pectoris. *Ann Int Med* 1975;83:449-455.

15. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, Deedwania, Ney DE, Snaveley DB, Chang PI, on behalf of ELITE study investigators. Randomized trials of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;349:747-752.

16. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Guidelines for the evaluation and management of heart failure. *Circulation* 1995;92:2764-2784.