SJHG Heartbeat

Number 122 **November 2007**

The "Art & Science" of HF Management

The current polypharmacy approach to managing chronic systolic heart failure (HF) is difficult. However, when implemented, it is very successful in decreasing morbidity and mortality. This *Heartbeat* will discuss some ways to increase dosing compliance for the management of chronic HF and emphasize the importance of β-blockers in overall management.

In the past few years, several pivotal, large-scale, evidence based clinical trials have generated new information regarding HF management. As a result, ACC-AHA[1] updated their guidelines in 2005 and HFSA[2] in 2006 (Table 1).

Table 1. Staging System for HF and Recommended Interventions *

HF Stage	Examples	Recommended Interventions
A = high risk for HF	hypertension, T2DM, MetS, obesity, ASCVD	lifestyle modification; ACE inhibitors or ARBs
B = structural heart disease without signs/symptoms of HF	prior MI, LVH, and low LVEF, asymptomatic valvular disease	above measures plus ß-blockers
C = structural heart disease with prior or current signs/symptoms of HF	symptoms of HF (eg, fatigue, SOB, exercise intolerance)	above measures plus diuretics, aldosterone antagonists, digoxin, hydralazine/nitrates and ICD/CRT where indicated
D = refractory, end stage	marked symptoms at rest despite maximal therapy	above measures plus inotropes, transplant, mechanical support, experimental measures

* Modified from ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult—summary article. *J Am Coll Cardiol* 2005; 46:1116-43.

Table 2. Treatment Dosages of Inhibitors of RAAS.

Inhibitors of the Renin-Angiotensin-Aldosterone System and Beta-Blockers Commonly Used for the Treatment of Patients with Heart Failure and Low Ejection Fraction

Drug	Initial Daily Dose(s)	Maximum Dose(s)
ACE inhibitors		
Captopril	6.25 mg 3 times	50 mg 3 times
Enalapril	2.5 mg twice	10 to 20 mg twice
Fosinopril	5 to 10 mg once	40 mg once
Lisinopril	2.5 to 5 mg once	20 to 40 mg once
Perindopril	2 mg once	8 to 16 mg once
Quinapril	5 mg twice	20 mg twice
Ramipril	1.25 to 2.5 mg once	10 mg once
Trandolapril	1 mg once	4 mg once
Angiotensin receptor blockers		
Candesartan	4 to 8 mg once	32 mg once
Losartan	25 to 50 mg once	50 to 100 mg once
Valsartan	20 to 40 mg twice	160 mg twice
Aldosterone antagonists		
Spironolactone	12.5 to 25 mg once	25 mg once or twice
Eplerenone	25 mg once	50 mg once
Beta-blockers		
Bisoprolol	1.25 mg once	10 mg once
Carvedilol	3.125 mg twice	25 mg twice 50 mg twice for patients >85 kg
Metoprolol succinate extended release (metoprolol CR/XL)	12.5 to 25 mg once	200 mg once

ACE=angiotensin-converting enzyme; mg=milligrams; kg=kilograms

Compliance and Survival

That patients who don't take their drugs don't do well isn't very much of a surprise, but the fact that multiple drug prescriptions didn't equate to non-compliance was. A recent study showed that when polytherapy is started early, persistence with therapy and therefore outcomes were definitely improved.[3] The main message of the study is to start polypharmacy therapy early, preferably in the hospital, monitor for patient non-compliance and don't forget to safely up-titrate to the most effective dosages when possible (maximum dosages as listed in Table 2).

BNP Levels Can Help

Identifying useful strategies to facilitate HF monitoring and subsequent treatment is a very high priority, as the availability of multiple effective

therapeutic interventions now creates a need for 'guides' that will let us know when patients are adequately or inadequately treated.

The Systolic Heart Failure Treatment Supported by BNP (**STARS-BNP**) trial suggested that the biomarker-guided approach with BNP (science) was a good complement to traditional clinically driven management (art) and led to greater use of evidence-based medications (at higher, more beneficial doses)—Table 2—and fewer clinical events.[4] Clinicians prescribed more diuretics and especially ACE inhibitors (ACEI's) and β-blockers when they aimed dosage adjustments at the achievement of plasma brain-type natriuretic peptide (BNP) levels of <100 pg/mL, compared with guidance solely by clinical signs and symptoms. In addition, patients on BNP-guided management showed a significant decrease in the primary end point of death or unplanned hospitalization due to HF, fewer HF-related hospitalizations, and better event-free survival. There were no significant differences in all-cause mortality or all-cause hospitalization.

STARS-BNP randomized 220 patients in NYHA functional class 2-3 with an LVEF <45% to one of the two outpatient management strategies, BNP-guidance as a supplement to clinical judgment vs the traditional approach on its own. During the first three months, medical therapy was adjusted 134 times among the 110 patients in the BNP-guidance group—specifically in pursuit of the BNP target in 80%; medications were changed 66 times among the 110 clinically managed patients ($p<0.05$). In both groups, about 40% of the changes were to the diuretic dosage. But ACE-I/Angiotension receptor blockade (ARB) and β-blocker use increased more in the BNP-guidance group.

The benefits observed would probably be larger in routine clinical practice because in the trial, patients' care was led by HF specialists at dedicated heart-failure clinics, and at baseline all were on furosemide and virtually all were on a β-blocker and either an ACEI or an ARB at recommended dosage levels. These results are "interesting and provocative" but still need verification by larger trials that account for the full range of available treatment options for HF. Measuring BNP is established for the diagnosis of acute decompensated HF and prognostication of patients with HF. BNP also is quite helpful in the outpatient setting for the differential diagnosis of shortness of breath.[5]

Cardiac resynchronization therapy (CRT) causes a sustained reduction in BNP levels in patients with moderate-to-severe HF with cardiac dyssynchrony. This finding comes from the Cardiac Resynchronization-Heart Failure (CARE-HF) study.[6] Previous results from this study showed that CRT reduced morbidity and mortality and improved cardiac function in HF secondary to left ventricular systolic dysfunction and cardiac dyssynchrony.

Application of BNP levels to optimize management of stable HF outpatients is a promising new application that we personally have found very helpful. Intuitively it makes a lot of sense, but it is still under intensive study.

Weight Monitoring in Heart Failure

We are all familiar with home glucose monitoring for diabetics and home blood pressure monitoring for hypertension. It is now time for home weight monitoring in patients with HF. Remote monitoring of daily weight substantiates the association of weight gain with hospitalization for HF. A recent case control study has demonstrated that the odds for HF hospitalization were associated with 2-3 fold increase in risk for weight gain between 2-5 lbs, 4-5 fold for 5-10 lbs and 7-8 fold for >10 lbs in the week preceding HF hospitalization.[7] Weight increase was not a feature of hospitalizations not associated with HF.

This evidence supports the common but unproven practice of monitoring weight in patients with HF, justifying and strengthening current practice guidelines and performance measures. This is a low-tech procedure and could easily be implemented in practice. My advice would be, ask your patients to give you a call if they gain 5 lbs or more in any given week. Raising the bar to 5 lbs per week is going to give you fewer false positives. Adding or increasing diuretic dosages would be the initial response followed by upward titration of other medications once *dry weight* is attained.

ACEIs or β-blockers First?

As new data emerge from clinical studies, it is crucial to update our clinical practices and treatment

guidelines, which may involve modifying old paradigms and perceptions and embracing new ones. ACEIs have long been recognized as the cornerstone in HF management, and as a result, these agents have typically been started before any other drugs.

However, many experienced HF specialists believe that if β-blockers had arrived at the scene first, ACEIs would now be viewed as second-line agents or as optional add-on therapy for patients on the background therapy of β-blockade, diuretic agents, spironolactone, and perhaps digoxin (with digoxin levels < then 0.8). In the past decade, our understanding of the role of β-blockers in the treatment of HF has made tremendous progress. These agents are now recognized as having the most impact on number of lives saved and reduced hospitalizations. Previous concerns limiting their use in various patient subsets have been alleviated with recent evidence, and the time has come to overcome these barriers and provide β-blockers at optimal dosages to all patients with HF.

In a scientifically humble, yet piercing report, β-blockers beat ACEIs in initial HF therapy. All of the measured end points (NYHA clinical classification, LV size and function, BNP and LVEF) were better in the 38 patient 'starting β-blockers first' group compared to the 40 patient 'starting ACEIs first' group.[8] There are a number of possible scientific and theoretical reasons the results of this study make sense. β-blockade blunts the hyperactivation and effects of the major neuroendocrine forces in HF, namely the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS). The ACE inhibitors mostly affect the latter. β-blockade reduces heart rate to a far greater degree, with a consequent fall in myocardial oxygen consumption, while augmenting coronary perfusion by increasing diastolic time. In addition, β-blockade alone impedes the direct toxic effects of elevated circulating catecholamines on the myocardium in HF.

The question of starting β-blockers before ACEIs, or vice versa, has occurred to all clinicians treating a patient on neither. Because of the greater benefits and greater degree of difficulty in early upward dosage titration of β-blockers, the recommendation is that β-blockers be started first, provided the patient is deemed clinically stable with no volume overload. Similarly, β-blocker dosages should be titrated upward regardless of whether ACEIs have reached target doses.

Often, a patient may experience an exacerbation of heart failure despite optimal pharmacotherapy; however, it is strongly recommended that β-blockers not be discontinued. Rather, adjustment in treatment with diuretics or ACEIs should be considered first, with temporary decreases in β-blocker dosage, only if necessary. When patients become hypotensive, dosages of diuretics should reduced first (assuming patients are at dry weight and possibly a little dehydrated), vasodilating agents should be reduced second if hypotension persists, with reductions in β-blocker dosages only as a last resort.

Similarly, reducing or discontinuing drugs that lower heart rate in patients with bradycardia should be considered before adjusting β-blocker dosages. Patients experiencing difficulty with initiation, upward dosage titration, or maintenance of β-blocker therapy because of bradycardia should be considered for pacemaker therapy providing "a floor" so β-blockers could be added and titrated to the most efficacious doses. This would be part of indicated therapy with an implantable cardiac defibrillator (ICD) or CRT. The importance of β-blocker treatment in systolic HF cannot be overemphasized.

Statins in HF

Although statins are not expressly indicated for HF per the recent updated guidelines, a few preliminary studies suggest they can improve outcomes in patients with HF.[9] [10] The efficacy and safety of statins in HF is still to be confirmed, and even if this is demonstrated, questions remain about dosage and treatment goals. Based on present data it is reasonable to add a statin to the treatment program for HF secondary to systolic dysfunction, especially in those with ischemic cardiomyopathy, but data seems to support usage in non-ischemic cardiomyopathy as well.[11]

Conclusions

The art of medicine is using optimal medical therapy (OMT) at the highest effective dosages. This improves both the quality and duration of patients' lives. Future randomized trials will clarify the *extent* to which monitoring certain parameters and basing interventions on the results (BNP levels, weight monitoring etc.) improves outcomes for patients with

HF. For now it appears that using both art and science are beneficial.

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***Heartbeat* is a South Jersey Heart Group publication.**

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