Heart Failure:
New Insights, Practical Implications

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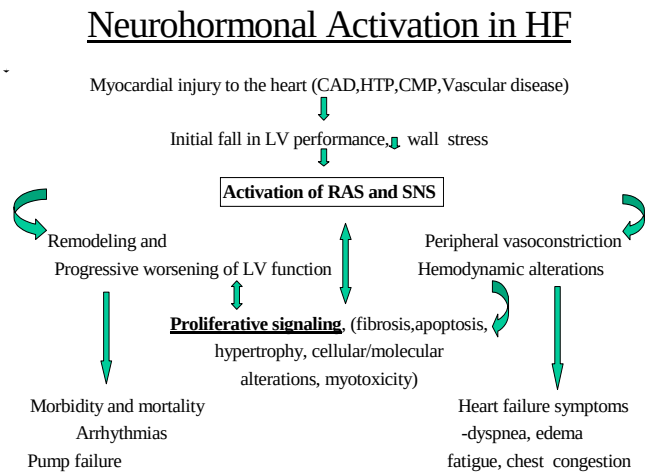
The purpose of this *Heartbeat* is to describe the scope of the heart failure (HF) problem, the current treatment and the implementation of this treatment in some common difficult scenarios.

Scope of the problem:

In the US today there are 4.8 million patients with symptomatic HF. Each year, HF is diagnosed in 400,000 to 700,000 new patients, and the incidence is increasing due to the increase in the median age of the population. The incidence is 1% to 3% in the general population and increases with age. It is reported to be 10% in elderly patients. A total of 3.5 million HF hospitalizations yearly contribute to an estimated $8-$15 billion spent annually for treatment, and the incidence is increasing. The readmission rate following hospitalization is ~ 30% 90 days after discharge, despite major advances in treatment. The optimum decreased hospitalization and survival advantage, with the use of ACE-inhibitors, digoxin and beta-blockers, has not been applied to daily clinical practice.

Current Treatment:

The modern treatment of systolic HF [LVEF<35%] is neurohormonal blockade. Dr. Arnold Katz said, "Before 1990, HF was viewed largely as a hemodynamic disorder. That's still true but the new paradigm is that the major underlying problem in HF is its progression." [1] To date, all the agents that inhibit progressive dilatation (remodeling) and slow deterioration of the failing heart, function at the neurohormonal level by blocking the activation of the renin-angiotensin system (RAS) and the sympathetic nervous system (SNS) (see figure), thus inhibiting proliferative signaling. These agents include ACE-inhibitors, beta–blockers and to a lesser extent, digitalis and spironolactone. Ironically, all of these agents were used in HF patients to improve hemodynamic alterations rather than to inhibit proliferative signaling.



The aims of treating HF are to improve symptoms, minimize side effects of treatment, decrease morbidity and prolong survival. An updated, evidence-based approach from our prior review[2] to the patient with systolic HF is outlined below.

1. **Diuretics** (to dry weight) **and nitrates**, in order to improve symptoms. Diuretics play a very important role in HF management by providing rapid resolution of symptoms and helping maintain euvolemia, which allows the initiation and maintenance of ACE inhibitors and beta-blockers.

   Once stable, delete the nitrates from the program. They have no proven survival advantage and can decrease the ability to add or increase other

survival-enhancing drugs because of hypotension. (Patients with angina would be the exception.)

Sometimes the diuretics can be discontinued.

2. **ACE-inhibitors** decrease mortality by >20%. All patients should receive them, titrated to goal dosage unless intolerant or have a contraindication.

   Start with low doses followed by doubling every 3-7 days. This titration schedule can be made faster or slower in individual patients as clinically appropriate. If hypotension or azotemia develops, always decrease the diuretic first if the patient appears to be at dry weight. (Patients with persistent azotemia have to be managed and monitored very closely.)

	Start	Minimum	Goal
captopril	6.25mg Tid	50mg Tid	100mg Tid
enalapril	2.5mg Bid	10mg Bid	20 mg Bid
lisinopril	2.5mg/day	20mg/day	40mg/day
quinapril	5mg Bid	10mg Bid	20mg Bid
ramipril	2.5mg/day	5mg/day	10mg/day

3. **Beta-blockers** decrease mortality another 30-50% on top of the ACE benefit. All patients* with HF should receive beta-blockers unless intolerant or contraindicated.

   ***A recently released study[3] reported that the benefits of carvedilol, which have been known to help mild-to-moderate (Class II-III) HF, also benefit severe (Class IV) HF.**

   Treatment should be started when patients are at dry weight and feeling well, starting with small doses and titrating upward every two weeks.

	Start	Goal
Carvedilol**	3.125mg Bid	25-50mg Bid
Toprol	12.5mg/day	100-200mg/day

**** The first dose or any increased dose of carvedilol should be given at bedtime.**

These are the only two beta-blockers with proven mortality benefits and FDA approved for HF. Mortality benefits are seen with all doses but increase significantly with higher doses.

4. **Digoxin** decreases morbidity and probably mortality at appropriate low dosing level. It decreases diuretic use and recurrent hospitalizations in patients with advanced HF.

   Start at 0.125mg/day to get a blood level of 0.5-1.

5. **Spironolactone** decreases mortality by 27% in Class III-IV HF.

   Start at 25mg/day and increase or decrease depending on volume status and /or serum potassium. Every other day dosing still has significant mortality benefits.

General Measures:

- Frequent monitoring of electrolytes (especially potassium), renal function and magnesium until stable.
- Moderate salt restriction (<4gm/day).
- Avoid:
  1) anti-arrhythmic drugs for asymptomatic ventricular arrhythmias;
  2) most calcium antagonists; and
  3) non-steroidal anti- inflammatory agents.
- Prevention strategies are always the best treatment to decrease occurrence and reoccurrence or progression.
- Control hypertension, diabetes, and hyperlipidemia.
- Tobacco cessation.
- Cardiac Rehab (exercise) program.
- Correct anemia (usually it will require iron and erthropoietin supplementation--recommend hematology consult)[4].
- Daily weights (especially at home).

Question and Answer Session:

Why is there a 30% readmission rate within 90 days after discharge among HF patients?

The cause is multifactorial. The most important cause is non-compliance both among patients and physicians. Patients should have telemonitoring and a 2-week follow-up with either primary care physicians or cardiologists. This is to ensure that they are taking and tolerating their medications, complying with their diet, weighing themselves daily and to allow monitoring of their renal function and serum potassium levels.

Physicians have to know about the data, believe it and most importantly practice it. They have difficulty adding a medication or increasing the dosage of a medication in patients, who feel well, coupled with the perception that side effects in their patients are always higher than in the clinical trials, especially in the elderly and those with more advanced HF.

How is ideal body weight (IBW) determined for a HF patient?

To determine IBW a number of clinical parameters have to be assessed. Clinical symptoms of PND and orthopnea are two helpful indicators as to whether a patient is volume overloaded. Many patients will have SOB with exertion, since the beneficial effects of ACE inhibitors and beta-blockers occur over time. Physical signs, such as cervical venous distention, an S3 third heart sound, crepitant rales and pre-tibial or pedal edema would all suggest volume overload. Laboratory-wise the BUN/creatinine ratio can be factored in. If it isn't elevated, the patient's symptoms are improved, and he/she doesn't have any of the HF S/Ss mentioned above, then the patient can be considered euvolemic and the weight at this point to be IBW.

When using weights to monitor treatment, patients must be instructed to weigh themselves on the same scale at the same time every day. The comparison, going up or down, is more important than the actual number. A weight increase of 3 pounds or more is considered significant, and the HF nurse or attending physician should be called or a program to increase diuretic dosage should be in place.

What precautions should be taken to prevent hyperkalemia in a patient taking an ACE inhibitor and spironolactone?

Certain patients, such as those with diabetes or azotemia, are high-risk to develop hyperkalemia. Most patients, however, who are treated even with high dose ACE inhibitors and spironolactone don't usually develop hyperkalemia. Those identified as high-risk are started on 12.5mg of spironolactone, which at half the usual dosage has been shown to confer equal survival benefit. These patients should obviously be monitored more closely.

For the others, the "Rule of 4" is a good guide. When the potassium is < 4mEq/L, adding an aldosterone antagonist to an ACE inhibitor is usually not a problem, especially if any potassium supplementation is eliminated. If potassium is > 4mEq/L, any potassium supplementation should be discontinued, and the potassium level should be rechecked in a week to get an accurate baseline. Spironolactone would be started at full dosage (25mg), but more frequent electrolyte checks are advised at 1 week and then again in a month to get "a feel" for direction.

Should ACE inhibitor dosage be "maximized" even in NYHA Class 1 HF, and at what blood pressure should ACE inhibitors be withheld?

When practicing evidence-based medicine the goal is to aim for the dosages used in the studies (as per the tables). Most experts would treat asymptomatic systolic dysfunction with the same high dose ACE inhibitor treatment.

When titrating the dose of these agents upward, the target is the goal dosage or the development of symptomatic hypotension as the limiting factor. Most patients don't get symptomatic until the BP gets below 80-90 mm Hg, with a very small group of patients remaining asymptomatic even at that blood pressure.

What about magnesium depletion?

Magnesium levels usually don't reflect true magnesium stores but still should be monitored. Levels usually parallel potassium levels. If the level is low, treatment with oral magnesium oxide starting at 400mg/d is recommended. If levels are normal, treatment isn't recommended unless the patient has myalgias, body aches, leg cramps or weakness, symptoms that strongly suggest depleted magnesium stores.

What heart rate would limit beta-blocker therapy?

Generally, a heart rate lower than 50 BPM should be avoided. If bradycardia or a conduction problem limits beta-blocker therapy, a pacemaker should be considered. Beta-blockers should be continued across the indication for the pacemaker because of their clinical and survival benefits in these patients.

Is it difficult to initiate beta-blocker in Class IV HF?

It can be difficult for all patients but especially for these patients because they usually have low systolic blood pressures. Most patients don't have to be hospitalized. First dose or an increase in dosage can be started at HS for carvedilol. Toprol XL and carvedilol are started at lowest dosages as per table. Volume status and blood pressure are the all important determinants of whether beta-blockers can be safely started.

Good beta-blocker treatment balances the initial decrease in LV function with the hope of improved function and survival later. That's why low dosage and careful titration are necessary to get past the first 4-6 weeks. Class IV patients with very low pressure may have to be hospitalized and placed on inotropic agents to get them through the beta-blocker loading and then weaned from the inotropic agents.

Conclusion:

There are a large number of patients who would benefit from appropriate HF therapy as outlined above. ACE inhibitors to goal dosage and beta-blocker treatment as described would increase the duration and quality of their lives. Mortality could be decreased by 30-50%.

News Flash

Increasing reports of fatal rhabdomyolysis, especially in combination with gemfibrozil, prompted Bayer to pull cerivastatin (Baycol) from the market last week. The FDA has received reports of 31 deaths with cerivastatin, 12 of which had concomitant gemfibrozil use.

The important message here is that even though serious rhabdomyolysis is almost 10x higher with cerivastatin, it does occur with other statins, especially in combination with gemfibrozil. This is a rare complication, but patients should be cautioned to discontinue their medication and consult their physician if they experience muscle pain.

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Heartbeats are available at
www.newsrounds.com under "cardiology".

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[1] Katz AM. Heart failure in 2001: a prophecy revisited. *Am J Cardiol* June 2001; 87(12): 1383-6

[2] Maiese ML. Heart Failure "Epidemic" and Management Strategy for CHF. *Heartbeat* April 1999; #37 newsrounds.com - Under cardiology.

[3] Packer M et al, for the Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med June 2001*; 334: 1651-58.

[4] Silverberg DS et al. The effect of correction of mild anemia in severe resistant CHF using subcutaneous erythropoietin and IV iron: A randomized controlled study. *J Am Coll Cardiol* June 2001; 37: 1775-80.