More HF Therapy Above and Beyond

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Heart failure (HF) affects approximately five million Americans. There is no cure for this disease, and more than 50% of patients die within five years of diagnosis. African Americans suffer a disproportionate incidence of CVD, and for HF, they are affected at a rate almost twice that of the corresponding white population and are more likely to die from it. Based on data from the US Census Bureau and the Centers for Disease Control, an estimated 750,000 African Americans have been diagnosed with HF and the number is expected to grow to approximately 900,000 by 2010.

The traditional "life-saving" drugs (β-blockers and ACE inhibitors) we have used in HF, direct their activity at reestablishing neurohormonal balance, namely by antagonizing an over-activated renin angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS). African Americans may be more vulnerable to HF because of population-based variations in the mechanisms of HF. Hypertension studies have suggested that they have, on average, a less active RAAS and a lower bioavailability of nitric oxide than the white population. Augmenting nitric oxide may therefore be an alternative or supplemental approach to slow or possibly reverse progressive HF in blacks.

This *Heartbeat* will review the changing dynamic in the treatment of HF, some pathophysiology, the African-American Heart Failure Trial (A-HeFT) and the updated American College of Cardiology/ American Heart Association (ACC/AHA) 2005 HF Guidelines. These suggest that additional therapy which augments nitric oxide—isosorbide dinitrate (ISDN)-hydralazine (H) in combination with usual therapy (β-blockers and ACE inhibitors)—will further improve CV outcomes.

Changing Dynamic

It is interesting to note the changes in our treatment of HF over the years. Originally the heart was considered a hydraulic system—just a pump—and when it weakened, the result was low cardiac output and congestion. The treatment was to strengthen the pump (digoxin) and unload the pump (diuretics). Then dilators were added to decrease preload and afterload. Although this treatment made people feel better, it didn't seem to make any difference in outcomes. Once it was understood that deteriorating left ventricular structure and function were driven by an imbalance of vasoconstriction and vasodilatation, that outcomes began to improve (Figure 1).

Figure 1. Basic pathophysiology of Heart Failure: Imbalance between vasoconstriction and vasodilation.

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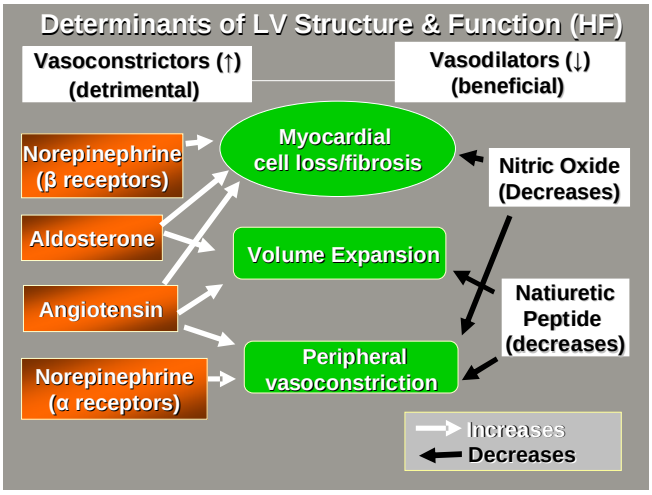


The key is the balance between vasoconstriction and vasodilation that affect the function and structure of the cardiovascular system. Over the past 10 years we've been very successful in the treatment of HF by antagonizing an overactive neurohormonal system which was negatively affecting myocardial structure and function through exaggerated vasoconstriction. The new evolving dynamic based on A-HeFT is to continue down-regulation of the RAAS and SNS with ACE inhibitors and β-blockers, but now add to that

nitric oxide enhancing therapy, attempting to up-regulate the other side of the equation (augmenting vasodilation) and to restore balance which will slow the progression of LV dysfunction and HF.

Combination ISDN plus hydrazaline

Clinical trial data have documented that nuerohormonal inhibitors [ACE inhibitors (blocking the RAAS), β-blockers (blocking the SNS) and aldosterone blockad], used alone or in combination, slow the progression of LV dysfunction. They retard the structural remodeling of the LV that characterizes chronic HF, thus reducing the rates of death and complications among patients with HF. Endothelial dysfunction, impaired bioavailability of nitric oxide, and increased oxidant stress also occur in patients with congestive heart failure and contribute to the remodeling process in experimental and clinical models of heart failure. Based on this information augmentation of nitric oxide was felt to be an alternative or supplemental approach to slow or reverse progressive heart failure.

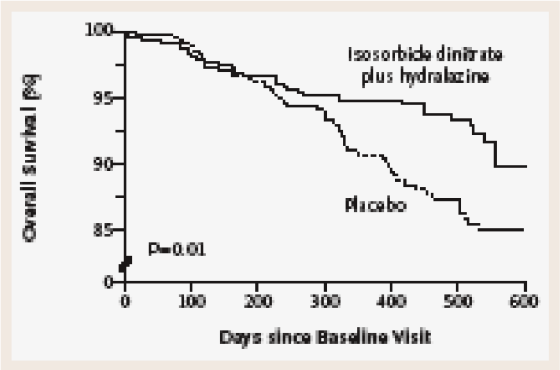
Retrospective analyses according to race in V-HeFT I and V-HeFT II have shown significant differences between blacks and whites in the response to pharmacotherapy for heart failure. The first Vasodilator Heart Failure Trial (V-HeFT I) demonstrated the benefit of combining the nitric oxide donor ISDN with the antioxidant H compared to placebo in black patients with mild-to-severe heart failure.[1] In V-HEFT II, ISDN + H was found to be equal in benefit to enalapril in the black but not the white population.[2] A-HeFT randomized 1050 self-reported black male or female patients to receive BiDil (ISDN 20mg/H 37.5mg) or placebo on top of standard medical therapy (Table 1).[3]

Table 1. Standard Therapy

Medication for HF (% of patients)	ISDN plus H N = 518	Placebo N = 532
Diuretic	88.0	91.5
ACE inhibitor	69.4	69.5
ARB	17.2	16.5
Carvedilol	55.2	55.8
Digoxin	58.5	60.7
Spironolactone	40.2	37.6

They were started on one tab 3x/day with a goal dosage of two tabs 3x/day. The trial was halted early when the data monitoring board observed a significant mortality increase in the placebo group. The study found a 43% drop in mortality and a 39% decrease in HF hospitalizations (the primary endpoints) among actively treated patients over an average of 10 months. The survival benefits emerged at 180 days and widened progressively thereafter (Figure 2).

Figure 2. Mortality reduction of 43% with nitric oxide enhancing therapy vs placebo added to standard therapy. Kaplan-Meir Estimates of Overall Survival.



Quality of life scores improved more in the BiDil group. Plasma brain natriuretic peptide (BNP) levels were decreased by 27% in the BiDil group vs. 13.4% in the placebo group.

Growing evidence supports the concept that nitric oxide protects against myocardial cell loss and fibrosis (both structural and vascular remodeling). ISDN is a vasodilator affecting both arteries and veins whose dilator properties result from the release of nitric oxide, subsequent activation of guanylyl cyclase, and ultimate smooth muscle relaxation. H is a selective dilator of arterial smooth muscle, and animal data suggests that it may decrease tolerance to nitrates. ISDN + H may serve as a nitric oxide donor, with H conferring protection against the degradation of nitric oxide induced by oxidative stress. The mechanism of action underlying the beneficial effect of BiDil in the treatment of HF has not been established. The data from A-HeFT support, but do not prove, the existence of a protective role of nitric oxide even in the presence of neurohormonal blockade.

Conclusion: This clinical trial, in which the study group was made up of black patients with heart failure, showed that the combination of ISDN and H (up-regulation of vasodilation) significantly improves survival, prolonged time to hospitalization for HF and improved patient reported functional status when added to standard therapy (down-regulation of

vasoconstriction) for heart failure. These results point to an anti-remodeling effect of this treatment over and above the already known benefits of ACE inhibitors and β-blockers. The new 2005 HF Guidelines from the ACC/AHA list this treatment as II (a) meaning that there is some conflicting evidence and divergence of opinion, but the weight of evidence/opinion is in favor of usefulness/efficacy.

Who should receive BiDil?

The following is the response from **Jay N. Cohn, MD,** Professor of Medicine, Cardiovascular Division, Department of Medicine, University of Minnesota Medical School; Director, Rasmussen Center for Cardiovascular Disease Prevention: "Anyone with heart failure, white or black, who has a dilated heart and who is not thriving and restored to full activity and comfort on existing therapy could be given a therapeutic trial with fixed-dose ISDN-H. White patients weren't studied in A-HeFT, so it would be an extrapolation beyond the trial to treat white patients. But the mechanism by which this drug works is not confined to African Americans or any other racial or demographic group. The response in black patients is so profound that it should be part of the standard regimen in these patients. But my assumption is that everybody will respond to this drug, to varying degrees. Since it's an effective therapy, I think it could be an option for every patient who remains symptomatic despite taking whatever other heart failure drugs they have taken."

ISDN+H should be added to anyone with LV dysfunction and hypertension after standard therapy has been optimized. ISDN+H should be used in patients determined to be high-risk and considered in those at intermediate risk based on a newly identified validated classification scheme for patients with acute decompensated HF (ADHF).[4] The risk stratification model uses admission BUN (>/= 43mg/dL), creatinine (>/= 2.75mg/dL) and systolic blood pressure [SBP] (< 115mm Hg) based on the ADHF National Registry (ADHERE) observational database. Risk groups and mortality are below:

- High-risk (All 3 risk factors present): 21.94 %.
- Intermediate-risk 1 (elevated BUN and reduced SBP but serum creatinine < 2.75: 12.42%.
- Intermediate-risk 2 (elevated BUN only): 6.41%.
- Intermediate-risk 3 (reduced SBP only): 5.49%.
- Low-risk group (none of the risk factors): 2.14%.

The odds ratio of death was 10.4 when comparing the high-risk group with the low-risk group. Risk of mortality related to HF is also increased in male patients with HF and those with comorbid conditions such as anemia and dementia.

Safety Information

BiDil is contraindicated in those who are allergic to organic nitrates. Augmentation of the vasodilatory effects of ISDN by phosphodiesterase inhibitors (e.g. Viagra, Levitra and Cialis) could result in severe hypotension.

The most common side effects were headache (50%) and dizziness (32%). These symptoms were twice as frequent compared to placebo.

Potential problems

Race issue: This is probably a non-issue. Most large clinical trial data with outcomes benefits were performed in predominantly white populations. These treatment modalities have been applied to all races. As stated in the ACC/AHA 2005 HF Guidelines, the effect of ISDN + H in patients other than African Americans with HF who are undergoing standard therapy is not known because the population studied was limited to blacks, but there is no reason to believe that this benefit is limited to blacks. Variable response to treatment is always present. More study and genetic analysis are needed.

Compliance: The mere fact that we can walk into a patient and say we have a new therapy that really is especially effective in the African Americans should cancel out the negatives of too many pills and possible side effects. People want to feel better and live longer. Close monitoring of all the medications for these patients will be required, but, as with aldosterone antagonists, that is not a reason to withhold life-saving therapy.

Cost: BiDil is made from two inexpensive generic drugs, isosorbide dinitrate and hydrazaline hydrochloride, long used to dilate blood vessels for treatment of angina and hypertension respectively. For patients with insurance, NitroMed will ask prescription plans to pay $1.80 per pill, or as much as $200/month compared to generic costs of $.25 - $.30 per pill. The price is equivalent to Norvasc or Coreg. NitroMed's challenge is persuading insurers and Medicare to cover BiDil over the generics. Initially NitroMed is targeting uninsured patients with a

patient assistance program that will dispense BiDil free with just a one-page enrollment form.

How many drugs for HF?

1. ACE inhibitors: decrease mortality by > 20%.

	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

2. β-blockers: decrease mortality by another 30% to 50 % on top of ACE inhibitors. *Recent data has shown that starting β-blockers first is as good as, and possibly more beneficial, than starting ACE inhibitors first.*

	Start	Goal
Carvedilol**	3.125mg bid	25-50mg bid
Metoprolol CR/XL	12.5mg/day	150-200mg/day

** Beta blocker of choice

3. Aldosterone blockers: decrease mortality another 15% to 27% beyond ACE inhibitor and beta-blocker benefits. Close monitoring and careful patient selection is advised.[5]

	Start	Goal
spironolactone	25mg/day	50mg/day
eplerenone	25mg/day	50mg/day

4. Digoxin: decreases morbidity and probably mortality at appropriate low doses.

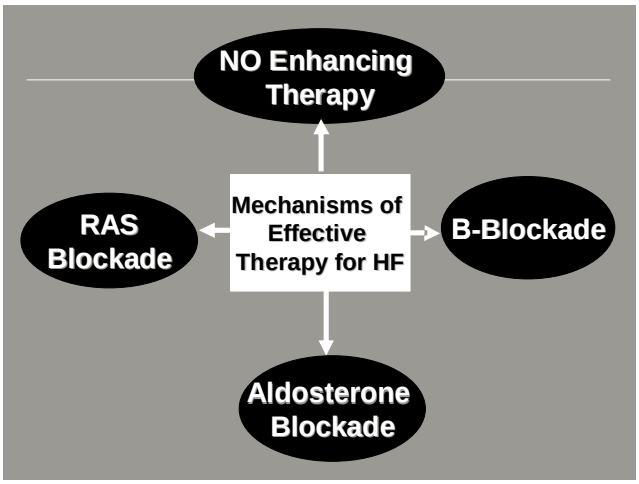
	Start	Goal level
digoxin	0.125mg/day	0.5 to 0.8 ng/ml

5. ARBS: Have been shown to be equally as beneficial as ACE inhibitors and possibly of some benefit on top of ACE inhibitors and β-blockers. ARBs are definitely indicated as an alternative if the patient is unable to tolerate an ACE inhibitor.

6. ISDN + H fixed combination: Offer a striking 43% mortality benefit on top of baseline treatment with ACE inhibitors, β-blockers, aldosterone antagonists and digoxin.

	Start	minimum	Goal
BiDil tabs 20mg/37.5mg	1 tab tid	½ tab tid	2 tabs tid

7. Diuretics (non-aldosterone antagonist): Not associated with outcomes benefit. Physicians are encouraged to regulate according to volume status. Treat to "dry weight" then discontinue.



Not surprisingly clinical data have documented those patients who are treated as per the guidelines and who take their medications as instructed—LIVE LONGER. HF is a serious disease and requires serious treatment.

On behalf of all of the staff and physicians of SJHG, I wish you all a Happy & Healthy Holiday Season!

Don't forget to register with your email address on our website.

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