"*Heartbeat*" Updates

Number 77 March, 2003

This *Heartbeat* will cover a recently released guideline and studies that will shed more light on some of our recent discussions. The first will be the American Heart Association (AHA) and the Centers for Disease Control and Prevention (CDC) new recommendations on testing for *hs*-CRP in clinical practice to give further validation and a review of our December 2002 *Heartbeat*.

The second discussion will center on a new hypertension trial that provides support for ACE inhibitors being the best anti-hypertensive agent right after the ALLHAT trial results (January 2003 *Heartbeat*), which concluded that diuretics are best.

The last two topics will give support to more appropriate usage of both beta-blockers and digoxin in heart failure (HF) to improve both compliance and outcomes.

New AHA/CDC recommendations for *hs*-CRP testing

The purpose of these recommendations is to provide a guide for clinical practice.[1] There has been an increasing amount of basic science and epidemiologic evidence making an impressive case that atherogenesis and atherothrombosis are essentially inflammatory processes. High sensitivity or cardiac CRP (*hs*-CRP) has been identified as a marker for this inflammation. The writing group concludes that it is reasonable to measure *hs*-CRP as an adjunct to other major risk factors to further assess absolute risk for coronary heart disease (CHD) primary prevention. The decision to use this study is optional, at the physician's discretion, and in this role, *this independent marker seems best used to detect enhanced risk where multiple risk factor scoring* has projected a 10-year CHD risk in the range of 10-20%.*

It is important to note that the benefits of using *hs*-CRP or any treatment based on this strategy remain uncertain. However, in primary prevention, the finding of a high-risk level *hs*-CRP may indicate the need to intensify risk-reduction therapies or may help motivate some patients to comply with Therapeutic Lifestyle Changes (TLC)—diet, exercise etc.

The writing group *recommends against hs-CRP testing of the general population.* It's utility is limited in secondary prevention because those who score at high-risk, >20% risk over 10 years, or who have known disease should already be receiving intensive treatment. Secondary preventive therapy with proven efficacy should not be dependent on *hs*-CRP levels. In addition, serial testing to follow response to treatment is not recommended.

The document recommends that *hs*-CRP be measured twice for better uniformity and accuracy with the average expressed in mg/L. The following cut points are advocated.

Cut points of risk for *hs*-CRP

Risk level	**Hs-CRP ***
Low	< 1
Average	1.0-3.0
High	> 3.0

*Levels of > 10mg/L should prompt the clinician to look for other signs of infection.

Those with high *hs*-CRP and low LDL-C are at higher risk then previously thought and are at higher risk for metabolic syndrome. They should have fasting glucose levels taken.

Everyone agrees that *hs*-CRP testing is "coming of age" but additional study is needed to evaluate the different strategies of using this in managing patients.

Are ACE inhibitors or Diuretics Best?

The main news in cardiology at the moment continues to revolve around the results from the largest hypertension trial ever conducted, the NHLBI sponsored ALLHAT trial, published in *JAMA* in December[2] and discussed in our January 2003 *Heartbeat*. ALLHAT concluded that diuretics were the most effective for blood-pressure control, and improved outcomes. Both the design of the trial and the interpretation of the results have continued to generate considerable controversy. Coincidently, the results of the new and large Second Australian National Blood Pressure Study (ANBP2) contradict those of ALLHAT. The findings demonstrate the superiority of ACE inhibitors over diuretics as first-line therapy in elderly hypertensive patients.[3]

So what are we to believe?

There is no place for absolute or categorical answers. We must equivocate and say probably both. Both sources are excellent. They were different studies using different diuretics and different ACE inhibitors in different populations. The trials used vastly different definitions of primary and secondary outcomes. This is the mental gymnastics of comparing apples to oranges. When the therapeutic tire meets the road, population-based studies help point the way but are not analogous to the care of individual patients. Treatment is complicated, requiring time, judgment and adjustment based on each individual patient's clinical history and response.

Based on the results of ALLHAT and ANBP2 and many other studies it appears obvious that both diuretics and ACE inhibitors are extremely effective in lowering blood pressure and improving clinical outcomes. Furthermore, in both studies it was frequently necessary to prescribe a second or third medication to achieve adequate blood pressure goals. *Treatment of essential hypertension in African-Americans patients (ALLHAT) should probably begin with a diuretic, with the addition of an ACE inhibitor if needed. For Caucasian patients (ANBP2), the same treatment may be given in reverse*. The preferred combo will surely be a diuretic—"married" to an ACE inhibitor—to get the best results.[4] Once these drugs are used in combination, the racial differences in antihypertensive response are eliminated.[5] "When selecting appropriate therapy, choose a drug or combination of drugs for which there is strong evidence of effectiveness in persons with the type of problem found in the patient."[6] A treatment plan that takes all of these issues into account is summarized in Table 1.

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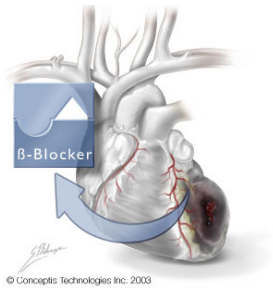
Table 1. Treatment Hypertension 2003

Comorbid Condition	Indicated Drugs*
Heart failure	ACE inhibitors, diuretics, B-blockers**, ARBs
DM with or without proteinuria	ACE inhibitors, ARBs or possibly B-blockers – all with a diuretic (Avoid dihydropyridine calcium antagonist alone)
Post-MI	B-blockers, ACE-inhibitors
Systolic hypertension (elderly)	Low dose ACE-inhibitor or ARB combined with a low dose diuretic (preferred), Alternative therapy: calcium channel blocker or B-blocker
Angina	B-blocker, calcium antagonist, ACE-inhibitor (not yet approved)
Pregnancy	Labetolol, methyldopa, calcium antagonists (ACEI contraindicated)
Prostatism	Alpha-blocker (not used alone)
Kidney insufficiency (non-diabetic)	ACE- inhibitor (ARB if ACEI not tolerated)

*****Three or more medications often necessary to achieve BP goal

******Carvedilol is preferred for hypertension and has been shown to improve proteinuria. Only two B-blockers are approved for HF (carvedilol and metoprolol XL/CR).

Focus on Beta-blocker Treatment Gap in HF



Beta-blockers prolong life and reduce the risk of disease progression in patients with chronic heart failure (HF) secondary to systolic dysfunction—resulting in decreased morbidity and mortality. Unfortunately, they remain underutilized in clinical practice—approximately 30-40% compliance—despite their established benefits. A lot of this underutilization is related to physician concerns about initiating treatment that is difficult in an asymtomatic patient. Patients can develop

symptomatic hypotension or worsening HF during the first few weeks of therapy. Physicians are afraid of precipitating a problem, even though the potential for benefit is huge. Furthermore, many physicians also have assumed that the beneficial effects may not become apparent for months. Other physicians may feel beta-blocker therapy is unimportant if not part of the discharge regimen.

Clearly a new strategy is needed to improve the use of beta-blockers in the broad HF population. In-hospital initiation of cardioprotective therapies has been demonstrated to markedly improve treatment utilization, long-term patient compliance and clinical outcomes in cardiovascular disease patients. HF guidelines recommend initiation of beta-blockers after adequate diuresis and generally following initiation of ACE inhibitor treatment, but they do not specify that initiation should take place in an outpatient setting.

It has become standard of practice to initiate and dose adjust ACE inhibitor therapy during hospitalization for HF. Implementing beta-blockers is usually done as an outpatient starting with their first post-discharge visit. Starting beta-blocker treatment during the hospitalization will improve their use because therapy won't be dependent on post-discharge follow-up or initiation by clinicians who may be reluctant to start treatment. The COPERNICUS trial demonstrated survival benefits with carvedilol in patients with severe HF and the safety of therapy during hospitalization in patients who are stabilized and euvolemic.[7] In addition, these benefits are seen early in the course of treatment—a few weeks.[8]

Late-breaking Results from the recently completed IMPACT-HF trial (Initiation Management Pre-discharge: process for Assessment of Carvedilol Therapy for Heart Failure) demonstrate that pre-discharge beta-blocker therapy is safe and resulted in a 90% rate of use at 60 days.[9]

Clinical implication: These findings should provide reassurance needed to encourage high levels of use that is warranted by the results of long-term clinical trials of beta-blockers for HF secondary to systolic dysfunction. *Early usage*, pre-hospital discharge—which takes advantage of the early window of opportunity—*is safe* and will result in earlier benefit and a much higher level of utilization and compliance with HF guidelines.

Digoxin benefits are questioned

The original large digitalis trial, the Digitalis Investigation Group (DIG) trial, reported that digoxin provided no overall mortality benefit, but did show improved signs and symptoms and a significant reduction in the rate of hospitalizations (a secondary endpoint of the study).[10] A recent study, which was a post hoc analysis of DIG, found that females receiving digoxin had a rate of death that was more than 4% higher than women taking placebo, thus suggesting that digoxin may be harmful in women.[11]

Following this study the same authors reevaluated the data evaluating the relationship between serum digoxin concentrations (SDCs) and outcomes.

Table 2. Adjusted outcomes and hazard ratios by SDCs

Adjusted outcomes*	Placebo	HR** (95% CI) by SDC 0.5-0.8 ng/mL	HR (95% CI) by SDC 0.9-1.1 ng/mL	HR (95% CI) by SDC 1.2 ng/mL or greater
All-cause mortality	Referent	0.80 (0.68-0.94)	0.89 (0.74-1.08)	1.16 (0.96-1.39)
Cardiovascular mortality	Referent	0.86 (0.72-1.02)	0.93 (0.76-1.14)	1.21 (0.99-1.47)
Worsening heart failure	Referent	0.66 (0.49-0.89)	0.86 (0.63-1.17)	0.95 (0.69-1.31)
All-cause hospitalization	Referent	0.83 (0.74-0.93)	1.02 (0.89-1.18)	0.90 (0.77-1.04)
Hospitalization for worsening heart failure	Referent	0.56 (0.46-0.67)	0.74 (0.60-0.92)	0.65 (0.52-0.82)

*Adjusted for age; race; body mass index; LVEF; NYHA class; cardiothoracic ratio; number of HF signs and symptoms; systolic BP; heart rate; estimated glomerular filtration rate; duration of HF; primary cause of HF; history of MI, angina, diabetes, and hypertension; prior use of digoxin; and use of potassium-sparing diuretics, all other diuretics, ACE inhibitors, nitrates, hydralazine, and other vasodilators
**HR=hazard ratio

In this study they decided to restrict their analysis to men because SDCs were only available for a small number of women.[12] The findings demonstrated that higher SDCs were associated with increased mortality (Table 2) with HF secondary to systolic dysfunction. *Effectiveness of digoxin therapy along with improved outcomes may be optimized with SDCs of 0.5-0.8ng/ml.* The explanation for the different effects at different SDCs is that the neurohormonal benefits of digoxin are achieved at lower SDCs and do not increase with higher SDCs. The harmful effects are believed to reflect inotropic-associated increases in myocardial oxygen utilization and arrhythmogenisis at higher serum concentrations. The target levels in the DIG trial with average doses of 0.25-0.375mg were probably too high.

Clinical implication: "Given that no study has demonstrated any substantive clinical benefit for SDCs higher than 0.8ng/ml, prudent clinical practice would support a SDC of 0.5 to 0.8ng/ml as a revised therapeutic range," says senior author, Dr Harlan M Krumholz (Yale University, New Haven, CT). Digoxin doses of 0.125mg will more likely achieve this goal, but more frequent monitoring of SDCs will be necessary so that dosages can be adjusted to optimize benefits.

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Heartbeats can be found @ www.sjhg.salu.net under Patient Education—From Your Physician
mailto:maiese@dnamail.com

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* Coronary Heart Disease Risk Calculator is at the same site as *Heartbeats* above—26b.

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[8] Krum H et al. Effects of initiating carvedilol in patients with severe chronic heart failure. *JAMA* February 12 2003; 712-18.

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[10] Digitalis Investigation Group (DIG). Effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997; 336: 525-33.

[11] Rathore SS et al. Sex-based differences in the effect of digoxin for the treatment of heart failure. *N Eng J Med* October 31 2002; 347: 1403-11.

[12] Rathore SS et al. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA* February 19 2003; 289: 871-78.